THIRD EDITION

Clinical Pharmacy and Therapeutics

Edited by
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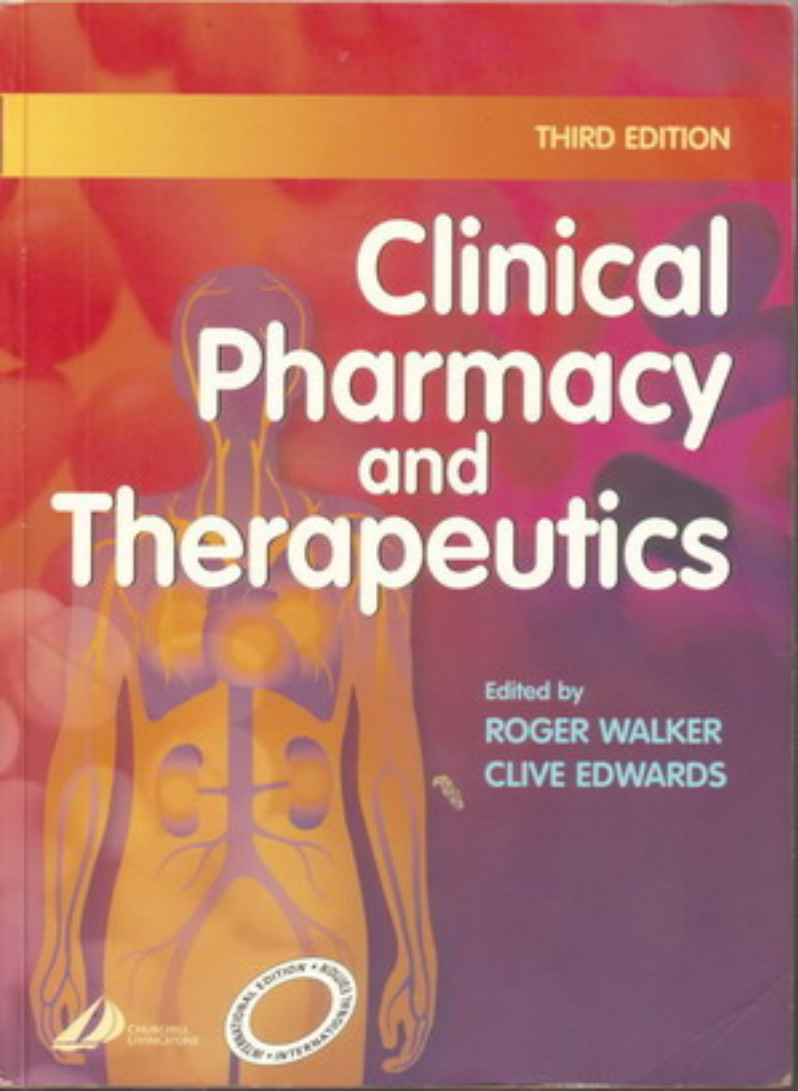
CLIVE EDWARDS



Clinical Pharmacy and Therapeutics

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Contents

Practical pharmacokinetics

1

R. Fitzpatrick

KEY POINTS

- Pharmacokinetics can be applied to a range of clinical situations with or without therapeutic drug monitoring (TDM).
- TDM can improve patient outcomes but is only necessary for drugs with a low therapeutic index, where there is a good concentration response relationship, and where there is no easily measurable physiological parameter.
- Sampling before steady state is reached or before distribution is complete leads to erroneous results.
- The volume of distribution can be used to determine the loading dose.
- The elimination half-life determines the time to steady state and the dosing interval.
- Kinetic constants determine the rate of absorption and elimination.
- Clearance determines the maintenance dose.
- Creatinine clearance can be reliably estimated from population values.
- Wherever possible use actual blood level data to assist dose adjustment. However, population pharmacokinetic values can be used for digoxin, theophylline, and gentamicin.
- Once daily dosing of gentamicin is a realistic alternative to multiple dosing.
- TDM is essential in the dose titration of lithium and phenytoin, but of little value for valproate, or the newer anticonvulsants.

Clinical pharmacokinetics may be defined as the study of the time course of the absorption, distribution, metabolism and excretion of drugs and their corresponding pharmacological response. In practice, pharmacokinetics makes it possible to model what may happen to a drug after it has been administered to a patient. Clearly, this science may be applied to a wide range of clinical situations, hence the term 'clinical pharmacokinetics'.

General applications

Clinical pharmacokinetics can be applied in daily practice for drugs with a low therapeutic index, even if drug level monitoring is not required.

Time to maximal response

By knowing the half-life of a drug, the time to reach a steady state may be estimated (Fig. 1.1), and thus when maximal therapeutic response is likely to occur, irrespective of whether drug level monitoring is needed.

Need for a loading dose

The same type of information can be used to determine whether a loading dose of a drug is necessary, since drugs with longer half-lives are more likely to require loading doses for acute treatment.

Dosage alterations

Clinical pharmacokinetics can be useful in determining dosage alteration if the route of elimination is impaired through end organ failure (e.g. renal failure) or drug interaction. Using limited pharmacokinetic information such as the fraction excreted unchanged (f_e value), which can be found in most pharmacology textbooks, quantitative dosage changes can be estimated.

Choosing a formulation

An understanding of the pharmacokinetics of absorption may also be useful in evaluating the appropriateness of particular formulations of a drug in a patient.

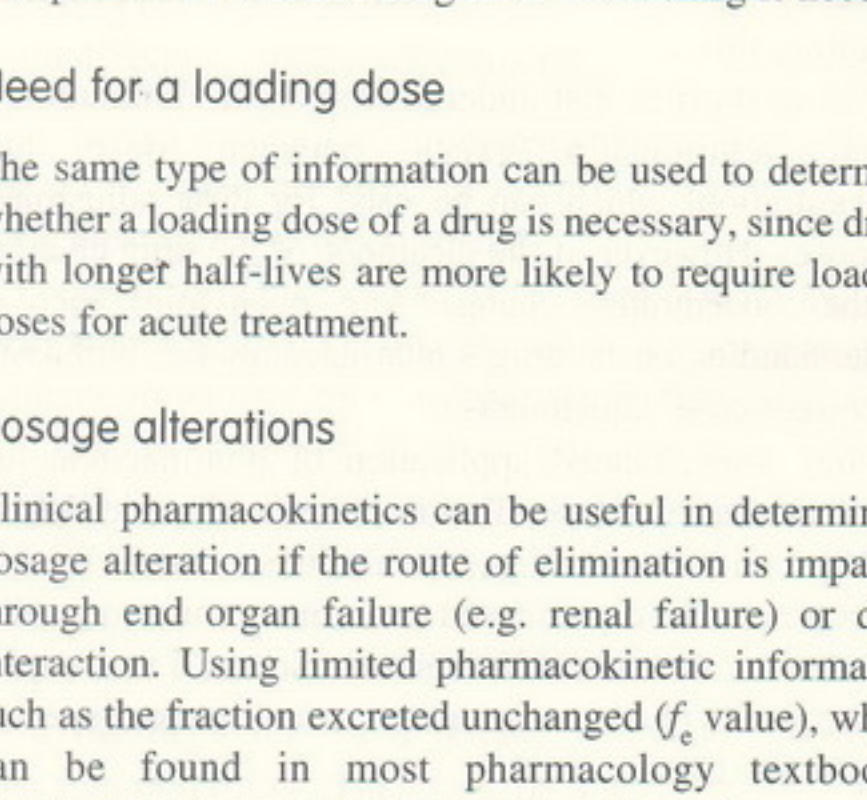


Figure 1.1 Time to steady state.

Application to therapeutic drug monitoring (TDM)

Clinical pharmacokinetics is usually associated with therapeutic drug monitoring (TDM), and its subsequent utilization. When TDM is used appropriately, it has been demonstrated that patients suffer fewer side-effects than those who were not monitored (Reid et al 1990). Although TDM is a proxy outcome measure, a study with aminoglycosides (Crist et al 1987) demonstrated shorter hospital stays for patients where TDM was used. Furthermore, a study on the use of anticonvulsants (McFadyen et al 1990) showed better epilepsy control in those patients where TDM was used.

There are various levels of sophistication for the application of pharmacokinetics to TDM. Knowledge of the distribution time and an understanding of the concept of steady state can facilitate determination of appropriate sampling times.

For most drugs that undergo first-order elimination, a linear relationship exists between dose and concentration, which can be used for dose adjustment purposes. However, if the clearance of the drug changes as the concentration changes (e.g. phenytoin), then an understanding of the drug's pharmacokinetics will assist in correct dose adjustments.

More sophisticated application of pharmacokinetics involves the use of population pharmacokinetic data to produce initial dosage guidelines, for example nomograms for digoxin and gentamicin, and to predict drug levels. Pharmacokinetics can also assist in complex dosage individualization using actual patient-specific drug level data.

Given the wide range of clinical situations in which pharmacokinetics can be applied, pharmacists must have a good understanding of the subject and how to apply it in order to maximize their contribution to patient care.

Basic concepts

Volume of distribution

The apparent volume of distribution (V_d) may be defined as the size of a compartment which will account for the total amount of drug in the body (A) if it were present in the same concentration as in plasma. This means that it is the apparent volume of fluid in the body which results in the measured concentration of drug in plasma (C) for a known amount of drug given, i.e.

$$C = \frac{A}{V_d}$$

This relationship assumes that the drug is evenly distributed throughout the body in the same concentration as in the plasma. However, this is not the case in practice, since many drugs are present in different concentrations in various parts of the body. Thus, some drugs such as digoxin have a very large apparent volume of distribution. This concept is better explained in Figure 1.2.

Apparent volume of distribution may be used to determine the plasma concentration after an intravenous loading dose:

$$C = \frac{\text{loading dose}}{V_d} \quad (1)$$

Conversely, if the desired concentration is known, the loading dose may be determined:

$$\text{loading dose} = \text{desired } C \times V_d \quad (2)$$

In the previous discussion, it has been assumed that after a given dose a drug is instantaneously distributed between the various tissues and plasma. In practice this

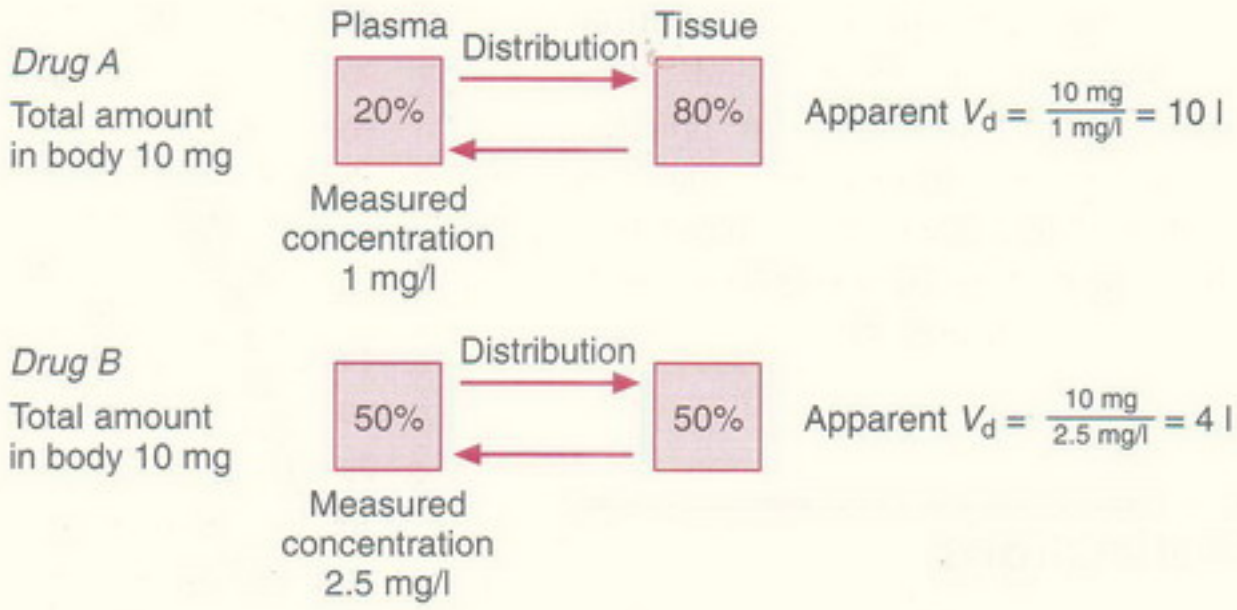


Figure 1.2 Distribution: more of drug A is distributed in the tissue compartment resulting in a higher apparent volume of distribution than drug B, where more remains in the plasma.

From equation (1) we can determine the change in plasma concentration ΔC immediately after a single dose:

$$\Delta C = \frac{S \times F \times \text{dose}}{V_d} \quad (10)$$

where F is bioavailability, and S is the salt factor, which is the fraction of active drug when the dose is administered as a salt (e.g. aminophylline is 80% theophylline, therefore $S = 0.8$).

Conversely, to determine a loading dose:

$$\text{loading dose} = \frac{\text{desired change in } C \times V_d}{S \times F} \quad (11)$$

At the steady state it is possible to determine maintenance dose or steady state plasma concentrations from a modified equation (4):

$$\text{rate in} = \frac{S \times F \times \text{dose}}{T} = CL \times \text{average } C^{ss} \quad (12)$$

where T is the dosing interval.

Peak and trough levels

For oral dosing and constant intravenous infusions, it is usually adequate to use the term 'average steady state plasma concentration' (average C^{ss}). However, for some intravenous bolus injections it is sometimes necessary to determine peak and trough levels (e.g. gentamicin).

At the steady state, the change in concentration due to the administration of an intravenous dose will be equal to the change in concentration due to elimination over one dose interval:

$$\Delta C = \frac{S \times F \times \text{dose}}{V_d} = C_{max} - C_{min}$$

Within one dosing interval the maximum plasma concentration (C^{ss}_{max}) will decay to the minimum plasma concentration (C^{ss}_{min}) as in any first-order process.

Substituting C^{ss}_{max} for C_1 and C^{ss}_{min} for C_2 in equation (7):

$$C^{ss}_{min} = C^{ss}_{max} \times e^{-k_e \times t}$$

where t is the dosing interval.

If this is substituted into the preceding equation:

$$\frac{S \times F \times \text{dose}}{V_d} = C^{ss}_{max} - C^{ss}_{min} \times e^{-k_e \times t}$$

Therefore:

$$C^{ss}_{max} = \frac{S \times F \times \text{dose}}{V_d [1 - e^{-k_e \times t}]} \quad (13)$$

$$C^{ss}_{min} = \frac{S \times F \times \text{dose}}{V_d [1 - e^{-k_e \times t}]} \times e^{-k_e \times t} \quad (14)$$

Interpretation of drug concentration data

The availability of the technology to measure the concentration of a drug in serum should not be the reason for monitoring. There are a number of criteria that should be fulfilled before therapeutic drug monitoring is undertaken. These are:

- the drug should have a low therapeutic index
- there should be a good concentration–response relationship
- there are no easily measurable physiological parameters.

In the absence of these criteria being fulfilled, the only other justification for undertaking TDM is to monitor compliance or to confirm toxicity. When interpreting TDM data a number of factors need to be considered.

Sampling times

In the preceding sections, the time to reach the steady state has been discussed. When TDM is carried out as an aid to dose adjustment, the concentration should be at the steady state. Therefore, approximately five half-lives should elapse after initiation or changing a maintenance regimen, before sampling. The only exception to this rule is when toxicity is suspected. When the steady state has been reached, it is important to sample at the correct time. It is clear from the discussion above that this should be done when distribution is complete (see Fig. 1.3).

Dosage adjustment

Under most circumstances, providing the preceding criteria are observed, adjusting the dose of a drug is relatively simple, since a linear relationship exists between the dose and concentration if a drug follows first-order elimination (Fig. 1.5A). This is the case for most drugs.

Capacity limited clearance

If a drug is eliminated by the liver, it is possible for the metabolic pathway to become saturated, since it is an enzymatic system. Initially the elimination is first order, but once saturation of the system occurs, elimination becomes zero order. This results in the characteristic dose–concentration graph of Figure 1.5B. For the majority of drugs eliminated by the liver, this effect is not seen at normal therapeutic doses and only occurs at very high supra-therapeutic levels, which is why the kinetics of some drugs in overdose is different from normal. However, one important exception is phenytoin, where saturation of the enzymatic pathway occurs at

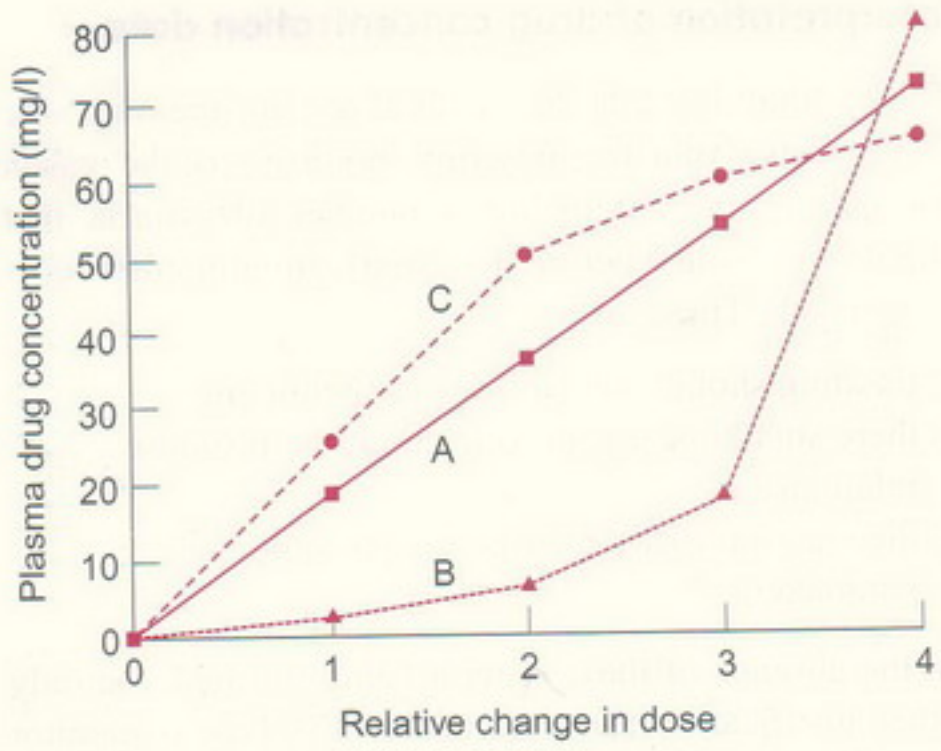


Figure 1.5 Dose-concentration relationships. **A** First-order elimination. **B** Capacity-limited clearance. **C** Increasing clearance.

therapeutic doses. This will be dealt with in the section on phenytoin.

Increasing clearance

The only other situation where first-order elimination is not seen is where clearance increases as the serum concentration increases (Fig. 1.5C). Under normal circumstances, the plasma protein binding sites available to a drug far outnumber the capacity of the drug to fill those binding sites, and the proportion of the total concentration of drug which is protein bound is constant. However, this situation is not seen in one or two instances (e.g. valproate and disopyramide). For these particular drugs, as the concentration increases the plasma protein binding sites become saturated, and the ratio of unbound drug to bound drug increases. The elimination of these drugs increases disproportionately to the total concentration, since elimination is dependent on the unbound concentration.

Therapeutic range

Wherever TDM is carried out, a therapeutic range is usually used as a guide to the optimum concentration. The limits of these ranges should not be taken as absolute. Some patients may respond to levels above or below these ranges, whereas others may experience toxic effects within the so-called therapeutic range. These ranges are only adjuncts to dose determination, which should always be done in the light of clinical response.

Clinical applications

Estimation of creatinine clearance

Since many drugs are renally excreted, and the most practical marker of renal function is creatinine clearance, it is often necessary to estimate this in order to undertake dosage adjustment in renal impairment. The usual method is to undertake a 24-hour urine collection coupled with a serum creatinine measurement. The laboratory then estimates the patient's creatinine clearance. The formula used to determine creatinine clearance is based upon the pharmacokinetic principles in equation (3).

The rate of elimination is calculated from the measurement of the total amount of creatinine contained in the 24-hour urine sample divided by 24, i.e.

$$\frac{\text{amount of creatinine}}{24} = \text{rate of excretion (mg/h)}$$

Using this rate of excretion and substituting the measured serum creatinine for C^{ss} in equation (4), the creatinine clearance can be calculated.

However, there are practical difficulties with this method. The whole process is cumbersome and there is an inevitable delay in obtaining a result. The biggest problem is the inaccuracy of the 24-hour urine collection.

An alternative approach is to estimate the rate of production of creatinine (i.e. rate in) instead of the rate of elimination (rate out). Clearly this has advantages, since it does not involve 24-hour urine collections and requires only a single measure of serum creatinine. There are data in the literature relating creatinine production to age, weight and sex, since the primary source of creatinine is the breakdown of muscle.

Therefore, equations have been produced which are rearrangements of equation (4), i.e.

$$\text{creatinine clearance} = \frac{\text{rate of production}}{C^{ss}}$$

Rate of production is replaced by a formula which estimates this from physiological parameters of age, weight and sex.

It has been shown that the equation produced by Cockcroft & Gault (1976) appears to be the most satisfactory. A modified version using SI units is shown below:

$$\frac{\text{creatinine clearance (ml/min)}}{} = \frac{F \times [(140 - \text{age in years}) \times \text{weight (kg)}]}{\text{serum creatinine } (\mu\text{mol/l})}$$

where $F = 1.04$ (females) or 1.23 (males).

Digoxin

Action and uses

Digoxin is the most widely used of the digitalis glycosides. Its primary actions on the heart are those of increasing the force of contraction and decreasing conduction through the atrioventricular node. Currently, its main role is in the treatment of atrial fibrillation by slowing down the ventricular response although it is also used in the treatment of heart failure in the presence of sinus rhythm. The primary method of monitoring its clinical effect in atrial fibrillation is by measurement of heart rate but knowledge of its pharmacokinetics can be helpful in predicting a patient's dosage requirements.

Serum concentration–response relationship

- < 0.5 micrograms/litre: no clinical effect
- 0.7 micrograms/litre: some positive inotropic and conduction blocking effects
- 0.8–2 micrograms/litre: optimum therapeutic range
- 2–2.5 micrograms/litre: increased risk of toxicity, although tolerated in some patients
- > 2.5 micrograms/litre: gastrointestinal, cardiovascular system and central nervous system toxicity.

Distribution

Digoxin is widely distributed and extensively bound in varying degrees to tissues throughout the body. This results in a high apparent volume of distribution. Digoxin volume of distribution can be estimated using the equation 7.3 l/kg (lean body weight (BWt)) which is derived from population data. However, distribution is altered in patients with renal impairment, and a more accurate estimate in these patients is given by:

$$V_d = 3.8 \times \text{lean BWt} + (3.1 \times \text{creatinine clearance (ml/min)})$$

A two-compartment model best describes digoxin disposition (see Fig. 1.3) with a distribution time of 6–8 hours. Clinical effects are seen earlier after intravenous doses, since the myocardium has a high blood perfusion and affinity for digoxin. Sampling for TDM must be done no sooner than 6 hours post-dose, otherwise an erroneous result will be obtained.

Elimination

Digoxin is eliminated primarily by renal excretion of unchanged drug (60–80%), but some hepatic metabolism occurs (20–40%). The population average value for digoxin clearance is:

$$\text{digoxin clearance (ml/min)} = 0.8 \times \text{BWt} + (\text{creatinine clearance (ml/min)})$$

However, patients with severe congestive heart failure have a reduced hepatic metabolism and a slight reduction in renal excretion of digoxin:

$$\text{digoxin clearance (ml/min)} = 0.33 \times \text{BWt} + (0.9 \times \text{creatinine clearance (ml/min)})$$

Lean body weight should be used in these equations.

Absorption

Digoxin is poorly absorbed from the gastrointestinal tract, and dissolution time affects the overall bioavailability. The two oral formulations of digoxin have different bioavailabilities:

$$F \text{ (tablets)} = 0.65$$

$$F \text{ (liquid)} = 0.8$$

Practical implications

Using population averages it is possible to predict serum concentrations from specific dosages, particularly since the time to reach the steady state is long. Population values are only averages, and individuals may vary. In addition, a number of diseases and drugs affect digoxin disposition.

As can be seen from the preceding discussion, congestive heart failure, hepatic and renal disease all decrease the elimination of digoxin. In addition, hypothyroidism increases the serum concentration (decreased metabolism and renal excretion) and increases the sensitivity of the heart to digoxin. Hyperthyroidism has the opposite effect. Hypokalaemia, hypercalcaemia, hypomagnesaemia and hypoxia all increase the sensitivity of the heart to digoxin. There are numerous drug interactions reported of varying clinical significance. The usual cause is either altered absorption or clearance.

Theophylline

Theophylline is an alkaloid related to caffeine. It has a variety of clinical effects including mild diuresis, central nervous system stimulation, cerebrovascular vasodilatation, increased cardiac output and bronchodilatation. It is the latter which is the major therapeutic effect of theophylline. Theophylline does have some serious toxic effects. However, there is a good serum concentration–response relationship.

Serum concentration–response relationship

- < 5 mg/l: no bronchodilatation*

* Some patients exhibit a clinical effect at these levels which has been attributed to possible anti-inflammatory effects.

- 5–10 mg/l: some bronchodilatation and possible anti-inflammatory action
- 10–20 mg/l: optimum bronchodilatation, minimum side-effects
- 20–30 mg/l: increased incidence of nausea, vomiting* and cardiac arrhythmias
- > 30 mg/l: cardiac arrhythmias, seizures.

Distribution

Theophylline is extensively distributed throughout the body, with an average volume of distribution based on population data of 0.48 l/kg.

Theophylline does not distribute very well into fat, and estimations should be based on lean body weight. A two-compartment model best describes theophylline disposition, with a distribution time of approximately 40 minutes.

Elimination

Elimination is a first-order process primarily by hepatic metabolism to relatively inactive metabolites.

The population average for theophylline clearance is 0.04 l/h/kg, but this is affected by a number of diseases/drugs/pollutants. Therefore, this value should be multiplied by:

- 0.5 where there is cirrhosis, or when cimetidine, erythromycin or ciprofloxacin are being taken concurrently
- 0.4 where there is congestive heart failure with hepatomegaly
- 0.8 where there is severe respiratory obstruction ($FEV_1 < 1$ l)
- 1.6 in patients who smoke (defined as more than 10 cigarettes per day), since they metabolize theophylline more quickly.

Neonates metabolize theophylline differently, with 50% being converted to caffeine. Therefore, when it is used to treat neonatal apnoea of prematurity a lower therapeutic range is used (usually 5–10 mg/l), since caffeine contributes to the therapeutic response.

Product formulation

Aminophylline (the ethylenediamine salt of theophylline) is only 80% theophylline. Therefore, the salt factor *(S)* is 0.8. Most sustained-release (SR) preparations show good bioavailability but not all SR preparations are the same. The absorption rate constant (k_a) provides a good guide to slow-release characteristics. Generally, the lower the k_a value the better the slow-release capabilities.

Practical implications

Intravenous bolus doses of aminophylline need to be given slowly (preferably by short infusion) to avoid side-effects due to transiently high blood levels during the distribution phase. Oral doses with slow-release preparations can be estimated using population-average pharmacokinetic values and titrated proportionately according to blood levels and clinical response. In most circumstances, slow-release preparations may be assumed to provide 12 hours' cover. However, more marked peaks and troughs are seen with fast metabolizers (smokers and children). In these cases, the slow-release preparation with the lowest k_a value may be used twice daily (e.g. Theo-Dur ($k_a = 0.18$) or Uniphyllin ($k_a = 0.22$)). Alternatively, thrice-daily dosage is required if a standard ($k_a = 0.3$–0.4) slow-release product is used (e.g. Phyllocontin ($k_a = 0.37$) or Nuelin SA ($k_a = 0.33$)).

Gentamicin

Clinical use

The spectrum of activity of gentamicin is similar to other aminoglycosides but its most significant activity is against *Psuedomonas aeruginosa.* It is still regarded by many as first choice for this type of infection.

Therapeutic range

Gentamicin has a low therapeutic index, producing dose-related side-effects of nephro- and ototoxicity. The use of TDM to aid dose adjustment is essential if these toxic effects which appear to be related to peak and trough serum levels are to be avoided. It is generally accepted that the peak level (drawn 1 hour post-dose after an intravenous bolus or intramuscular injection) should not exceed 12 mg/l and the trough level (drawn immediately pre-dose) should not exceed 2 mg/l.

The above recommendations relate to multiple daily dosing of gentamicin. If once daily dosing is to be used, then different monitoring and interpretation parameters apply as described at the end of this section.

Distribution

Gentamicin is relatively polar and distributes primarily into extracellular fluid. Thus, the apparent volume of distribution is only 0.25 l/kg. Gentamicin follows a two-compartment model with distribution being complete within 1 hour.

* Nausea and vomiting can occur within the therapeutic range.

Elimination

Elimination is by renal excretion of the unchanged drug. Gentamicin clearance is approximately equal to creatinine clearance.

Practical implications

Since the therapeutic range is based on peak (1 hour post-dose to allow for distribution) and trough (pre-dose) concentrations, it is necessary to be able to predict these from any given dosage regimen.

Initial dosage. This may be based on the patient's physiological parameters. Gentamicin clearance may be determined directly from creatinine clearance. The volume of distribution may be determined from lean body weight. The elimination constant k_e may then be estimated using these parameters in equation (6). By substituting k_e and the desired peak and trough levels into equation (7), the optimum dosage interval can be determined (add on 1 hour to this value to account for sampling time). Using this value (or the nearest practical value) and the desired peak or trough value substituted into equation (13) or (14) it is possible to determine the appropriate dose.

Changing dosage. This is not as straightforward as for theophylline or digoxin, since increasing the dose will increase the peak and trough levels proportionately. If this is not desired, then use of pharmacokinetic equations is necessary. By substituting the measured peak and trough levels and the time between them into equation (7), it is possible to determine k_e (and the half-life from equation (8) if required). To estimate the patient's volume of distribution from actual blood level data, it is necessary to know the C^{ss}_{max} immediately after the dose (time zero), not the 1-hour value which is measurred. To obtain this, equation (7) may be used, this time substituting the trough level for C_2 and solving for C_1. Subtracting the trough level from this C^{ss}_{max} at time zero, the volume of distribution may be determined from equation (10). Using these values for k_e and V_d, derived from actual blood level data, a new dose and dose interval can be determined as before.

Once daily dosing. There are theoretical arguments for once-daily dosing of gentamicin, since aminoglycosides display concentration-dependent bacterial killing, and a high enough concentration to mean inhibitory concentration (MIC) ratio may not be achieved with multiple dosing. Furthermore, aminoglycosides have a long post-antibiotic effect. Aminoglycosides also accumulate in the kidneys, and once daily dosing could reduce renal tissue accumulation. There have been a number of clinical trials comparing once-daily administration of aminoglycosides with conventional administration. A small number of these trials have shown less nephrotoxicity, no difference in ototoxicity, and similar efficacy with once-daily administration. Initial dosage for a once-daily regimen is 5–7 mg/kg/day for patients with a creatinine clearance of >60 ml/min. This is subsequently adjusted on the basis of blood levels. However, monitoring of once-daily dosing of gentamicin is different to multiple dosing. One approach is to take a blood sample 6–14 hours after the first dose and plot the time and result on a standard concentration-time plot (the Hartford nomogram, Nicolau et al 1995; Fig. 1.6). The position of the individual patient's point in relation to standard lines on the nomogram indicate what the most appropriate dose interval should be (either 24, 36 or 48 hours). Once-daily dosing of gentamicin has not been well studied in children, pregnant or breastfeeding women, patients with major burns, renal failure, endocarditis or cystic fibrosis. Therefore, it cannot be recommended in these groups and multiple daily dosing should be used.

Lithium

Lithium is effective in the treatment of acute mania and in the prophylaxis of manic depression. The mechanism of action is not fully understood, but it is thought that it may substitute for sodium or potassium in the central nervous system. Lithium is toxic, producing dose-dependent and dose-independent side-effects. Therefore, TDM is essential in assisting in the management of the dosage.

Dose-dependent effects

The serum concentration–response relationship derived on the basis of the 12-hour standardized lithium level (measured 12 hours after the evening dose of lithium) is shown below:

- < 0.4 mmol/l: little therapeutic effect
- 0.4–1.0 mmol/l: optimum range for prophylaxis
- 0.8–1.2 mmol/l: optimum range for acute mania
- 1.2–1.5 mmol/l: causes possible renal impairment
- 1.5–3.0 mmol/l: causes renal impairment, ataxia, weakness, drowsiness, thirst, diarrhoea
- 3.0–5.0 mmol/l: causes confusion, spasticity, dehydration, convulsions, coma, death. (Levels above 3.5 mmol/l are regarded as a medical emergency.)

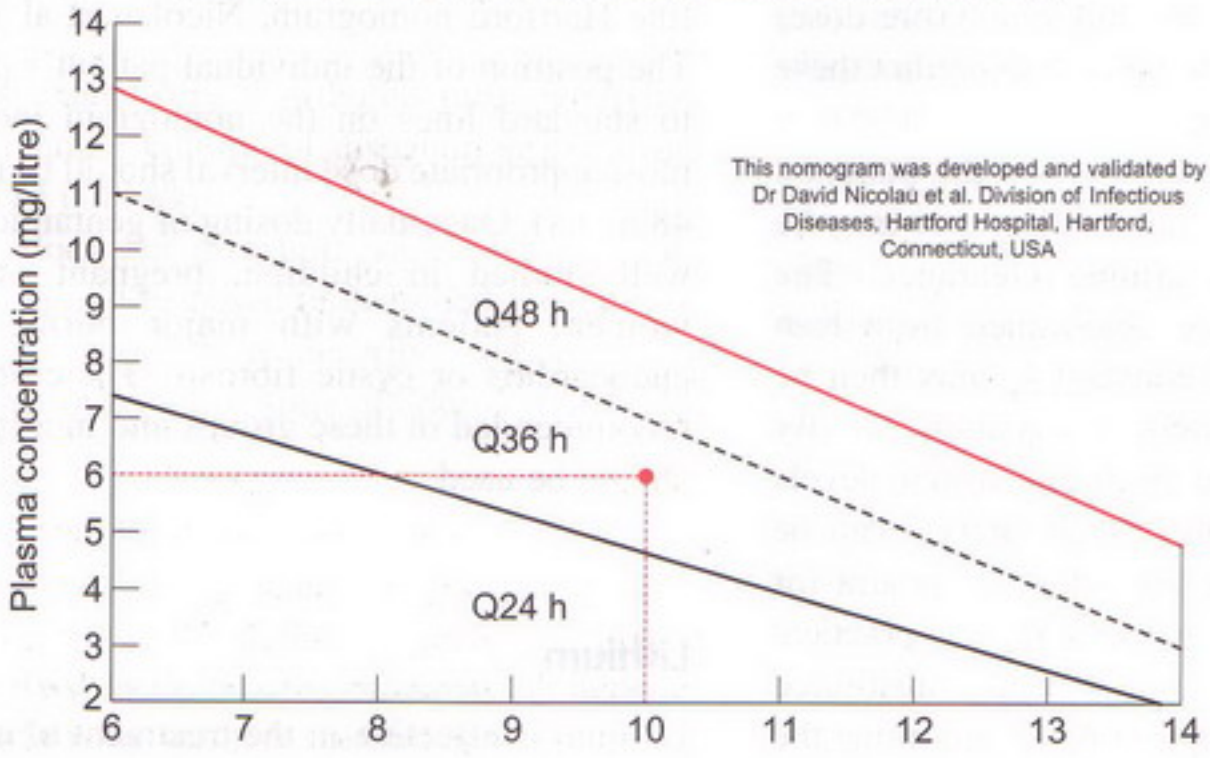
Dose-independent effects

These include tremor, hypothyroidism (approximately 10% of patients on chronic therapy), nephrogenic diabetes insipidus, gastrointestinal upset, loss in bone density, weight gain (approximately 20% of patients gain more than 10 kg) and lethargy.

If result available within 24 h

- Use graph below to select dose interval. Use plasma concentration and time interval between start of infusion and sample to plot intercept (see example given on graph).
- Give next dose (7 mg/kg by infusion as above) after interval indicated by graph.
  If result falls above upper limit for Q48 h, abandon once daily regimen. Measure gentamicin concentration after another 24 h and adopt multiple daily dose regimen if result <2 mg/l
  If result falls on Q24 h sector it is not necessary to recheck gentamicin concentration within 5 days unless patient's condition suggests renal function may be compromised.

- **Graph:** Use values of plasma concentration and time interval to find intercept
  (Example given of 6 mg/l after 10 h yields dose interval of 36 h)



This nomogram was developed and validated by Dr David Nicolau et al. Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut, USA

MONITORING

- Repeat U&E daily. Calculate creatinine clearance from serum creatinine to check dose interval has not changed.
- If dose interval has to be changed, check gentamicin concentration 6–14 h after start of next infusion note time of start of infusion and time of sampling and use graph to verify correct dose interval.

This protocol is based on that used at the Tayside area hospitals, Scotland

Figure 1.6 Nomogram for adjustment of once daily gentamicin dosage (Nicolau et al 1995).

Distribution

Lithium is unevenly distributed throughout the body, with a volume of distribution of approximately 0.5–1 l/kg. Lithium follows a two-compartment model (see Fig. 1.3) with a distribution time of 8 hours (hence, 12-hour sampling criterion).

Elimination

Lithium is excreted unchanged by the kidneys. Lithium clearance is approximately 20% of creatinine clearance, since there is extensive reabsorption in the renal tubules.

In addition to changes in renal function, dehydration, diuretics (particularly thiazides), angiotensin-converting enzyme inhibitors (ACE inhibitors) and non-steroidal anti-inflammatory drugs (NSAIDs) (except aspirin and sulindac) all decrease lithium clearance.

Conversely, aminophylline and sodium loading increase lithium clearance.

Notwithstanding the above factors, there is a wide inter-individual variation in clearance, and the lithium half-life in the population varies between 8 and 35 hours with an average of approximately 18 hours. Lithium clearance shows a diurnal variation, being slower at night than during the day.

Practical implications

In view of the narrow therapeutic index, lithium should not be prescribed unless facilities for monitoring serum lithium concentrations are available. Since lithium excretion is a first-order process, changes in dosage result in a proportional change in blood levels. Blood samples should be drawn 12 hours after the evening dose, since this will allow for distribution and represent the slowest excretion rate. Population pharmacokinetic data (particularly the volume of distribution) cannot be relied upon to make initial dosage predictions, although

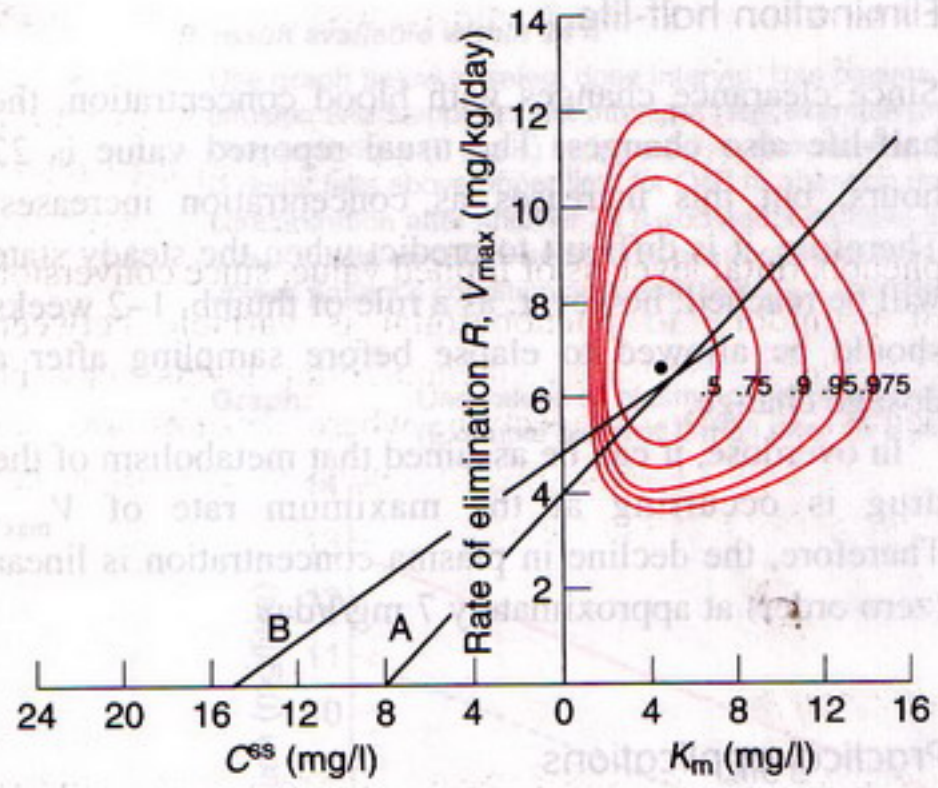


Figure 1.7 Orbit graph. The most probable values of V_{max} and K_m for a patient may be estimated using a single steady-state phenytoin concentration and a known dosing regimen. The eccentric circles or 'orbits' represent the fraction of the sample patient population whose K_m and V_{max} values are within that orbit. (1) Plot the daily dose of phenytoin (mg/kg/day) on the vertical line (rate of elimination). (2) Plot the steady-state concentration (C^{ss}) on the horizontal line. (3) Draw a straight line connecting C^{ss} and daily dose through the orbits (line A). (4) The coordinates of the mid point of the line crossing the innermost orbit through which the line passes are the most probable values for the patient's V_{max} and K_m. (5) To calculate a new maintenance dose, draw a line from the point determined in Step 4 to the new desired C^{ss} (line B). The point at which line B crosses the vertical line (rate of elimination) is the new maintenance dose (mg/kg/day). The line A represents a C^{ss} of 8 mg/l on 276 mg/day of phenytoin acid (300 mg/day of sodium phenytoin) for a 70 kg patient. Line B has been drawn assuming the new desired steady-state concentration was 15 mg/l (μg/ml). The original figure is modified so that R and V_{max} are in mg/kg/day of phenytoin acid (modified from Evans et al 1992).

Serum concentration–response relationship

- < 4 mg/l: little therapeutic benefit
- 4–12 mg/l: optimum therapeutic range for monotherapy
- > 9 mg/l: possible side-effects of nystagmus, diplopia, drowsiness and ataxia, particularly if patients are on other anticonvulsant therapy
- > 12 mg/l: side-effects common, even on monotherapy.

Distribution

Carbamazepine is distributed widely in various organs, with the highest concentration found in liver and kidneys. Carbamazepine is 70–80% protein bound and shows a wide variation in the population-average apparent volume of distribution (0.8–1.9 l/kg). This wide variation is thought to be due to variations in absorption (since there is no parenteral form) and protein binding.

Elimination

Carbamazepine is eliminated almost exclusively by metabolism, with less than 2% being excreted unchanged in the urine. Elimination is a first-order process, but carbamazepine induces its own metabolism. Therefore, at the beginning of therapy, clearance is 0.01–0.03 l/h/kg, rising to 0.05–0.1 l/h/kg on chronic therapy. Auto-induction begins in the first few days of commencing therapy and is maximal at 2–4 weeks.

Since clearance changes with time, so does half-life, with reported values as long as 35 hours after a single dose, decreasing to 5–7 hours on regular dosing.

Absorption

Absorption after oral administration is slow, with peak concentrations being reached 2–24 hours post-dose (average 6 hours). Absorption is incomplete, with bioavailability estimated at approximately 80% (F = 0.8).

Practical implications

Use of pharmacokinetic equations is limited, due to the auto-induction effect. However, there are a number of important practical points:

- Blood samples should not be drawn before the steady state, which will not be achieved until 2–4 weeks after starting therapy or 3–4 days after subsequent dose adjustments.
- When sampling, the trough level should be measured because of the variable absorption pattern.
- Complex calculations are not helpful, but as a rule of thumb each 100 mg dose will increase the plasma concentration at the steady state by approximately 1 mg/l in adults.
- A number of other drugs (including phenytoin) when given concurrently will affect carbamazepine metabolism and subsequent blood levels.

Phenobarbital

Phenobarbital is effective in the treatment of tonic–clonic and partial seizures, and is also useful in the treatment of febrile seizures. Although there is a clear concentration–response relationship, routine serum concentration monitoring is less useful than for other drugs, since tolerance occurs.

Serum concentration–response relationship

- < 15 mg/l: little therapeutic effect
- 15–40 mg/l: optimum range
- 40–50 mg/l: sedation, confusion (elderly), although may be tolerated by some patients
- > 60 mg/l: serious toxic effect of ataxia, lethargy, stupor, coma.

The sedation which commonly manifests early on in therapy becomes less with continued therapy.

Distribution

Phenobarbital readily distributes into most body tissues and is 50% protein bound. The population-average volume of distribution is 0.7–1 l/kg.

Elimination

Phenobarbital is primarily (80%) metabolized by the liver, with approximately 20% being excreted unchanged in the urine. Elimination is a first-order process, but is relatively slow with a population-average clearance of approximately 0.004 l/h/kg. However, as with theophylline, clearance in children is increased. In the case of phenobarbital, the adult clearance value is doubled in children. Applying equations (6) and (8) to these population values gives an estimate of the half-life of the order of 5 days. This is much shorter in children and longer in the elderly.

Practical application

In view of the long half-life, single daily dosage is possible with phenobarbital. Samples for therapeutic monitoring may be drawn any time during a dose interval, since concentration fluctuation between doses is minimal. However, the patient should be at the steady state, which takes 2–4 weeks (1–2 weeks in children). The pharmacokinetics of phenobarbital may be altered by liver and (less markedly) renal disease, but are not affected by the concurrent administration of other anticonvulsants.

Primidone

Like phenobarbital, primidone is effective in the treatment of tonic–clonic and partial seizures. Much of the anticonvulsant activity of primidone is due to the metabolites phenobarbital and phenylethylmalonamide. Therefore, primidone serum concentrations are only useful to confirm transient toxicity. Toxic manifestations such as sedation, nausea and ataxia are seen at concentrations greater than 15 mg/l. The plasma concentration should be drawn approximately 3 hours post-dose, which corresponds to the peak concentration.

Phenylethylmalonamide assays are not available routinely, although this metabolite probably contributes to anticonvulsant activity. Measurement of phenobarbital levels is of limited value, since conversion of primidone to phenobarbital is variable between individuals. However, phenobarbital levels may be helpful in dosage selection, where seizures are not adequately controlled despite regular dosage, or where there is suspected toxicity.

Valproate

Sodium valproate as valproic acid in the bloodstream has a broad spectrum of anticonvulsant activity, being useful in generalized absence, generalized tonic–colonic and partial seizures.

Serum concentration–response relationship

There is no clear concentration–response relationship for valproate, although a range of 50–100 mg/l is often quoted as being optimal. Levels exceeding this range do not confer any additional therapeutic benefits. Although there is no clear relationship between serum levels and toxic effects, the rare hepatotoxicity associated with valproate appears to be related to very high levels of over 150 mg/l.

Distribution

Valproate is extensively bound to plasma protein (90–95%), and unlike other drugs, it can saturate protein-binding sites at concentrations greater than 50 mg/l, altering the free fraction of drug. Therefore, the apparent volume of distribution of valproate varies from 0.1 to 0.5 l/kg.

Elimination

Elimination of valproate is almost entirely by hepatic metabolism, with less than 5% being eliminated by the kidneys.

As a result of the saturation of protein-binding sites and the subsequent increase in the free fraction of the drug, clearance of the drug increases at higher concentrations. Therefore, there is a non-linear change in plasma concentration with dose (illustrated in Fig. 1.5C).

Practical implications

In view of the lack of a clear concentration/response relationship and the variable pharmacokinetics, there are limited indications for the measurement of valproate

levels. In most cases, dosage should be based on clinical response. However, in a few cases where seizures are not controlled at high dosage, a serum level may be helpful in confirming treatment failure. If monitoring is to be undertaken, levels should be drawn at steady state (2–3 days). A trough sample will be the most useful, since wide fluctuations of blood levels may occur during a dose interval.

Lamotrigine, vigabatrin, gabapentin, tiagabine and topiramate

These newer anticonvulsants are indicated for the treatment of a range of types of epilepsy. All are used as adjunctive treatment with other anticonvulsants, with only lamotrigine indicated for monotherapy.

Serum concentration–response relationship

There is no clear relationship between serum concentration and response for these newer anticonvulsants. The situation is further complicated by the fact that these preparations are usually used as an add-on therapy with other anticonvulsants.

Practical implications

While these newer anticonvulsants have narrow therapeutic indices and inter- and intra-individual variation in pharmacokinetics, there is not enough evidence to support routine TDM, and dosage should be titrated to clinical response.

Ciclosporin

Ciclosporin is a neutral lipophilic cyclic endecapeptide extracted from the fungus *Tolypocladium inflatum gams.* It is a potent immunosuppressive agent, used principally to reduce graft rejection after kidney, heart, heart–lung, liver, pancreas and bone marrow transplants. The drug has a low therapeutic index, with a number of toxic effects including nephrotoxicity, hepatotoxicity, gastrointestinal intolerance, hypertrichosis and neurological problems. Efficacy in reducing graft rejection as well as the main toxic effect of nephro- and hepatotoxicity appear to be concentration related.

Serum concentration–response relationship

With all drugs that are monitored the therapeutic range is a window with limits, which are not absolute. It is even more difficult to define a therapeutic range for ciclosporin, since there are a number of influencing factors. First, the measured concentration varies depending on sampling matrix (i.e. whole blood, plasma or serum). Second, it depends on whether the assay is specific for ciclosporin alone or non-specific to include metabolites. A target concentration range of 200–400 micrograms/litre is generally accepted for the immediate postoperative phase following renal transplants. Levels below the lower limit of this window are associated with an increased incidence of graft rejection. Levels above the upper limit are associated with an increased incidence of nephrotoxicity and hepatotoxicity, although an upper limit of 800 micrograms/litre has also been suggested. This target range can be reduced to 100–200 micrograms/litre 3–6 months post-transplant. These target ranges are based on assays specific for the ciclosporin parent compound.

Distribution

Ciclosporin is highly lipophilic and is distributed widely throughout the body with a volume of distribution of 4–8 l/kg. There is variable distribution of ciclosporin within blood, since the whole blood concentration is approximately twice the plasma concentration. Within plasma, ciclosporin is 98% protein bound.

Elimination

Ciclosporin is eliminated primarily by hepatic metabolism, with wide inter-individual variation in clearance (0.1–2 l/h/kg). In children these values are approximately 40% higher, with a .resulting increased dosage requirement on a milligram per kilogram basis. In elderly patients or patients with hepatic impairment a lower clearance rate has been observed.

Practical implications

In addition to the wide inter-patient variability in distribution and elimination pharmacokinetic parameters, absorption of standard formulations of ciclosporin is variable and incomplete ($F = 0.2–0.5$ in normal subjects). In transplant patients this variation in bioavailability is even greater, and increases during the first few months after transplant. Furthermore, a number of drugs are known to interact with ciclosporin. All these factors suggest that therapeutic drug monitoring will assist in optimum dose selection, but the use of population averages in dose prediction is of little benefit, due to wide inter-patient variation. When using TDM with ciclosporin a number of practical points need to be considered:

- The sampling matrix should be whole blood, since there is a variable distribution of ciclosporin between blood and serum.
- Samples should represent trough levels and be drawn at the steady state, which is achieved 2–3 days after initiating or changing the dosage (average half-life is 9 hours).

- Ciclosporin concentration monitoring should be undertaken every 2–3 days in the immediate postoperative phase until the patient's clinical condition is stable. Thereafter, monitoring can be undertaken every 1–2 months.
- TDM should be performed when changing brands of ciclosporin, since there are marked differences in the bioavailability of different brands.

Summary pharmacokinetic data for drugs with therapeutic serum concentrations are listed in Table 1.1.

CASE STUDIES

Case 1.1

Mr B. is a 55-year-old 65 kg man with chronic obstructive airways disease (COAD). He has been taking Nuelin SA 250 mg tablets in a dose of two tablets twice a day for many years. He has been admitted to hospital with congestive heart failure (CHF). On examination he has ankle oedema, hepatomegaly and raised jugular venous pressure (JVP).

Three days after admission Mr B. starts fitting and anticonvulsants are considered. You suggest that high theophylline levels can cause this but unfortunately (this is late Friday) there is no possibility of obtaining a level quickly.

Questions

1. If theophylline is the cause of the fitting, why has this occurred now since he has been on the medicine for some time?
2. Estimate Mr B.'s theophylline level at the time of the fitting.
3. How long after stopping Nuelin will Mr B.'s theophylline be within the therapeutic range (assume first-order elimination)?

Answers

1. Development of severe congestive heart failure reduces theophylline clearance by 50% therefore it is the same as doubling Mr B.'s current dose.
2. Using population averages, the normal clearance for a man of his weight would be 65 kg × 0.04 l/h = 2.6 l/h. However, his clearance is reduced by 50% as a result of his CHF. Therefore, CL = 1.3 l/h. Applying equation (12), assuming F=1, S=1, then his predicted C^{ss} is 32 mg/l.
3. You first need an estimate of V_d which from population data = 0.48 l/kg × 65 kg = 31.2 l. Assuming the value of clearance calculation in the previous section and applying equation (6) we find $CL = k_e \times V_d$. Therefore 1.3 l/h = 31.2 l × K_e.

Table 1.1 Summary of pharmacokinetic data[a]

Drug	Therapeutic range of serum concentrations	V_d(l/kg)	CL(l/h/kg)	Half-life (h)
Digoxin	0.8–2.0 micrograms/litre 1–2.6 nmol/l	7.3	See text	36
Theophylline	10–20 mg/l 55–110 μmol/l	0.48	0.04	8
Gentamicin	Peak 5–12 mg/l, trough < 2 mg/l	0.25	1 × CL (creatinine)	2
Lithium	0.4–0.8 mmol/l	0.5–1	0.2 × CL (creatinine)	18
Phenytoin	10–20 mg/l 40–80 μmol/l	1	K_m = 6 mg/l V_{max} = 7 mg/kg/day	
Carbamazepine	4–12 mg/l 17–50 μmol/l	0.8–1.9	0.05–1	
Phenobarbital	15–40 mg/l 65–172 μmol/l	0.7–1	0.004	120
Primidone	< 15 mg/l < 69 μmol/l	0.6		
Valproate	< 100 mg/l < 693 μmol/l			
Ciclosporin	200–400 micrograms/litre			9

[a] Estimates based on the average patient. See text for variability.

Therefore $k_e = 0.042\ h^{-1}$. Applying equation (8) using this k_e value gives a half-life of 16.5 h. It will take one half-life (16.5 h) for the theophylline level to fall to 16 mg/l, which is within the therapeutic range.

Case 1.2

Miss J.M. is a 50 kg woman taking phenytoin at a dose of 100 mg three times a day for the last 2 months and is seen at out-patients complaining of blurred vision and exhibiting nystagmus. Her phenytoin level is 25 mg/l.

Questions

1. Calculate V_{max} and K_m values for this patient.
2. Calculate the dose required to achieve a level of 12 mg/l.
3. Check your answer using the orbit graph.
4. How long will it take for the level to fall within the therapeutic range?

Answers

1. From population data V_{max} = 7 mg/day/kg × 50 kg = 350 mg/day. Substitute this into equation (15) using the measured C^{ss} of 25 mg/l and her current dose of 300 mg/day, and assuming S = 0.9 Solve for K_m = 7.4 mg/l.
2. Substitute these *K*m and V_{max} values into equation (15) with a desired C^{ss} of 12 mg/l and assume S = 0.9. This gives a dose of 240 mg day. This could be rounded up to 250 mg per day. (Note: to half the level does not mean halving the dose since phenytoin exhibits non-linear kinetics.)
3. Using the orbit graph (Fig. 1.7) the new dosage would be 250 mg/day after correcting for *S*.
4. At supra-therapeutic levels it can be assumed that metabolism is occurring at V_{max}. By dividing V_{max} (amount eliminated from the body per day) by V_d (volume of distribution) you can calculate rate of fall of blood level; V_d can be calculated from population data V_d = 1 l/kg × 50 kg = 50 l. Therefore, concentration falls at a rate of

$$\frac{350\ \text{mg/day}}{50\ \text{l}} = 7\ \text{mg/l per day}$$

Therefore, withhold dosage for 1 day to allow the levels to fall from 25 mg/l to 25 – 7 = 18 mg/l, before starting new regimen.

Case 1.3

A 35-year-old 55 kg patient is commenced on gentamicin i.v. in a dose of 80 mg every 8 hours. Unfortunately, the hospital guidelines have not been followed and the blood levels taken 1 hour and 4 hours after the first dose are 4.5 mg/l and 2.3 mg/l, respectively. Your advice is sought on an appropriate regimen.

Questions

1. Calculate the patient's pharmacokinetic parameters of K_e, half-life and V_d.
2. Calculate a new regimen to achieve a peak level of 9 mg/l and a trough level of 1 mg/l.

Answers

1. Since you have blood level data taken after effectively a single dose, you can use this to calculate the patient's parameters. Substitute the two blood levels and the time between them (3 h) into equation (7) and solve for k_e

$$2.3\ \text{mg/l} = 4.5\ \text{mg/l} \times e^{-k_e \times 3}$$
$$\ln 2.3 = \ln 4.5 - k_e \times 3$$
$$0.83 = 1.5 - k_e \times 3$$

Therefore $K_e = 0.22\ h^{-1}$.

Substitute this into equation (8) to obtain half-life = 3.15 hours. To find V_d we need to know the blood level immediately after the dose was given (you cannot use the 1 h value). Therefore, substitute either the 1 h level or the 4 h level as C_2 into equation (7) with the appropriate time (1 or 4 h) and the k_e (0.22 h^{-1}) to find C_1 which is the concentration at time 0 = 5.6 mg/l. Substitute this into equation (10) to find V_d = 14.2 l.

2. The first part of the regimen is the time interval. Substitute the desired peak and trough (9 and 1) into equation (7) with K_e calculated in the previous section (0.22 h^{-1}) and solve for t = 10 h. This is the time between the peak and trough. The peak is measured 1 h post-dose, therefore the dose interval is 11 h. The nearest practical dose interval would be 12 h.

   We now need to calculate the actual C^{ss}_{max} immediately after the dose is given. Substitute 9 mg/l (the desired 1 h post-dose level) as C_2 in equation (7) where t = 1 and solve for C_1.

   This will give a C^{ss}_{max} of 11.25 mg/l.

   Substitute this into equation (13) with a dose interval of 12 h and solve for dose = 148 mg. Check C^{ss}_{min} using equation (14). A practical dose would be 140 mg 12 hourly.

Case 1.4

Mr E.F., a 77-year-old 67 kg man, is admitted in uncontrolled atrial fibrillation. The doctor decides to commence him on digoxin, but is unsure of the dosage in view of his age. He seeks your views. The patient has a serum creatinine level of 140 μmol/l.

Questions

1. Calculate a suitable loading dose for this patient.
2. Calculate a suitable maintenance dose for this patient.

Answers

1. Since the patient is elderly, first calculate his creatinine clearance using the Cockroft & Gault (1976) equation, since this will be used in calculation of both volume of distribution and maintenance dose.

$$CL(\text{creatinine}) = \frac{1.23 \times [(140 - 77) \times 67]}{140}$$
$$= 37.1\ \text{ml/min}$$

Since renal function is relatively low, use V_d = 3.8 × Lean Bwt + (3.1 × creatinine clearance).

Therefore V_d = 254 + 115 = 369 l (compare this V_d to that calculated from body weight only).

To calculate the appropriate loading dose substitute 369 l into equation (11) where desired concentration is 1.5 micrograms/litre using F for digoxin tablets = 0.65. Solve for dose = 850 micrograms. A practical dose of 750 micrograms will suffice. Check using equation (10) to show it will produce a level of 1.32 micrograms/litre.

2. To calculate maintenance dose substitute the estimated creatinine clearance 37.1 ml/min into the equation.

Digoxin clearance = 0.8 × Bwt + creatinine clearance which gives a value of 90.7 ml/min. Convert into l/h = 5.44 l/h. Substitute this into equation (12) and solve for dose (F = 0.65, T = 24 h, and desired C^{ss} is 1.5 micrograms/litre) which gives a dose of 299 micrograms per day. The nearest practical dose is 312.5 (1 × 250 micrograms and 1 × 62.5 microgram tablet). 250 micrograms per day would also suffice to produce a level of 1.24 micrograms/litre.

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with drug–drug interactions which have the potential to adversely affect patient care.

Epidemiology

It is difficult to give an accurate estimate of the incidence of drug interactions, mainly because published studies have frequently used different criteria for definition, particularly in distinguishing between clinically significant and non-significant interactions. Some of the early studies uncritically compared prescribed drugs with lists of possible drug interactions without taking into account their potential clinical significance. A review of nine studies of the epidemiology of drug–drug interactions in hospital admissions found that the reported incidence ranged from 0% to 2.8% (Jankel & Fitterman 1993). However, the authors considered all studies reviewed to be flawed to some extent. In the Harvard Medical Practice study of adverse events, 20% of events in acute hospital in-patients were drug related. Of these, 8% were considered to be due to a drug interaction, suggesting that interactions are responsible for fewer than 2% of adverse events in this patient group (Leape et al 1992). Few studies have attempted to quantify the incidence of drug–drug interactions in the community. A US community pharmacy study revealed a 4.1% incidence of interactions (Rupp et al 1992), while in a Swedish study the incidence was 1.9% (Linnarsson 1993). Although the overall incidence of adverse drug interactions is probably quite low (< 1%), it is still a considerable problem in terms of the global number of patients at risk and the potential for morbidity and mortality.

Susceptible patients

Certain patients are at increased risk of drug interactions. Polypharmacy is common, and the more drugs a patient takes the greater is the likelihood of an ADR. One hospital study found an ADR rate of 7% in patients taking 6–10 drugs, increasing to 40% in those taking 16–20 drugs (Smith et al 1969). This exponential rise is partly due to drug interactions. Drug interactions are more likely to have serious consequences when they affect elderly or seriously ill patients. Patients at particular risk include those with hepatic or renal disease, those on long-term therapy for chronic disease, for example those with human immunodeficiency virus (HIV) infection, epilepsy or diabetes, those in intensive care, transplant recipients, patients undergoing complicated surgical procedures and those with more than one prescribing doctor. Critically ill and elderly patients are at increased risk not only because they take more medicines, but also because of impaired homoeostatic mechanisms that might otherwise counteract some of the unwanted effects. Interactions may occur in some individuals but not in others. The effects of interactions involving drug metabolism may vary greatly in individual patients because of differences in the rates of drug metabolism and in susceptibility to microsomal enzyme induction. Certain drugs are frequently implicated in drug interactions and require careful attention. These are listed in Table 2.1.

Mechanisms of drug interactions

Drug interactions are conventionally discussed according to the mechanisms involved. There are some situations where drugs interact by unique mechanisms, but certain mechanisms are encountered time and time again. These mechanisms can be conveniently divided into those with a pharmacokinetic basis and those with a pharmacodynamic basis. Drug interactions often involve more than one mechanism.

Pharmacokinetic interactions

Pharmacokinetic interactions are those which can affect the processes by which drugs are absorbed, distributed, metabolized or excreted. There is marked inter-individual variability in these processes, and although these interactions may be expected, their extent cannot easily be predicted. Such interactions may result in a change in the drug concentration at the site of action with subsequent toxicity or decreased efficacy.

Table 2.1 Some drugs with high risk of interaction

Concentration dependent toxicity
Digoxin
Lithium
Aminoglycosides
Cytotoxic agents
Warfarin
Steep dose-response curve
Verapamil
Sulphonylureas
Levodopa
Patient dependent on therapeutic effect
Immunosuppressives, e.g. ciclosporin, tacrolimus
Glucocorticoids
Oral contraceptives
Antiepileptics
Antiarrhythmics
Saturable hepatic metabolism
Phenytoin
Theophylline

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Immunosuppressives, e.g. ciclosporin, tacrolimus
Glucocorticoids
Oral contraceptives
Antiepileptics
Antiarrhythmics
Saturable hepatic metabolism
Phenytoin
Theophylline

Absorption

Most drugs are given orally for absorption through the mucous membranes of the gastrointestinal tract. Most of the interactions which occur within the gut result in reduced rather than increased absorption. It is important to recognize that the majority result in changes in the absorption rate, although in some instances the total amount (i.e. the extent) of drug absorbed is affected. For drugs which are given chronically on a multiple dose regimen (for example the oral anticoagulants) the rate of absorption is usually unimportant provided the total amount of drug absorbed is not markedly altered. On the other hand, delayed absorption can be clinically significant where the drug affected has a short half-life, or where it is important to achieve high plasma concentrations rapidly, as may be the case with analgesics or hypnotics. Drug absorption interactions can often be avoided if an interval of 2–3 hours is allowed between the administration of the interacting drugs.

Changes in gastrointestinal pH. The absorption of a drug across mucous membranes depends on the extent to which it exists in the non-ionized, lipid-soluble form. The ionization state depends on the pH of its milieu, the pKa of the drug and formulation factors. Weakly acidic drugs, such as the salicylates, are better absorbed at low pH because the unionized form predominates. An alteration in gastric pH due to antacids, histamine H_2 antagonists or proton pump inhibitors therefore has the potential to affect the absorption of other drugs. The clinical significance of antacid-induced changes in gastric pH is not certain, particularly since relatively little drug absorption occurs in the stomach. Changes in gastric pH tend to affect the rate of absorption rather than the total bioavailability, provided that the drug is acid labile. Theoretically antacids could be expected markedly to influence the absorption of other drugs via this mechanism, but in practice there are very few clinically significant examples. Antacids, histamine H_2 antagonists and omeprazole can significantly decrease the bioavailability of ketoconazole and itraconazole, as both require gastric acidity for optimal absorption. The absorption of fluconazole, however, is not significantly altered by changes in gastric pH. The alkalinizing effects of antacids on the gastrointestinal tract are transient and the potential for interaction may be minimized by leaving an interval of 2–3 hours between the antacid and the potentially interacting drug.

Adsorption, chelation and other complexing mechanisms. Certain drugs react directly within the gastrointestinal tract to form chelates and complexes which are not absorbed. The drugs most commonly implicated in this type of interaction include tetracyclines and the quinolone antibiotics which can complex with iron, and antacids containing calcium, magnesium and aluminium. Tetracyclines can chelate with divalent or trivalent metal cations such as calcium, aluminium, bismuth and iron to form insoluble complexes, resulting in greatly reduced serum tetracycline concentrations.

Bisphosphonates such as etidronate are often co-prescribed with calcium supplements in the treatment of osteoporosis. If these are ingested concomitantly, the bioavailability of both is significantly reduced with the possibility of therapeutic failure (Fogelman et al 1986).

The absorption of some drugs may be reduced if they are given with adsorbents such as charcoal or kaolin, or anionic exchange resins such as colestyramine or colestipol. The absorption of propranolol, digoxin, warfarin, tricyclic antidepressants, ciclosporin and thyroxine is reduced by colestyramine. Acarbose, an agent used in the management of diabetes mellitus, inhibits intestinal alpha glucosidase, thereby delaying the digestion and absorption of starch and sucrose. Case reports suggest that this drug can significantly decrease plasma concentrations of digoxin. Digoxin levels increased to within the therapeutic range after acarbose was discontinued (Ben-Ami et al 1999). Patients taking both acarbose and digoxin should separate dosing by an interval of at least 6 hours. Most chelation and adsorption interactions can be circumvented by separating doses of the interacting drugs by a period of several hours.

Drug effects on the gastrointestinal flora. Bacterial flora predominate in the large bowel, and are present in much smaller numbers in the stomach and small bowel. Thus drugs which are well absorbed from the small bowel are less likely to be affected by changes in gut flora. In about 10% of individuals a substantial amount of digoxin is inactivated by gut bacteria, and the introduction of a broad-spectrum antibiotic may lead to substantially increased plasma digoxin concentrations. Antibiotics may also prevent the intestinal bacterial hydrolysis of drug conjugates secreted into bile and thus reduce reabsorption of the active parent drug. In this way, antibiotics may reduce the enterohepatic circulation of ethinylestradiol in oral contraceptives, leading to reduced circulating oestrogen levels with the potential for therapeutic failure. This is likely to be an extremely rare interaction; the enterohepatic circulation of ethinylestradiol is probably of very minor importance in most people, as judged from data from women with ileostomies.

Effects on gastrointestinal motility. Since most drugs are largely absorbed in the upper part of the small intestine, drugs which alter the rate at which the stomach empties its contents can affect absorption. Anticholinergic drugs delay gastric emptying. These drugs are commonly used in the control of movement disorders but they have been shown to reduce the bioavailability of levodopa by as much as 50% and to reduce plasma chlorpromazine concentrations significantly. Other drugs with anticholinergic effects

that might influence gastrointestinal motility include tricyclic antidepressants, phenothiazines, and some antihistamines.

Opioids such as diamorphine and pethidine strongly inhibit gastric emptying and greatly reduce the absorption rate of paracetamol. Codeine, however, has no significant effect on paracetamol absorption. Morphine and diamorphine have been shown to reduce the absorption of antiarrhythmics such as mexiletine in patients with myocardial infarction. Metoclopramide increases gastric emptying and increases the absorption rate of paracetamol, an effect which is used to therapeutic advantage in the treatment of migraine. It also accelerates the absorption of propranolol, mefloquine, lithium, and ciclosporin. In general, this type of interaction is rarely clinically significant (Greiff & Rowbotham 1994).

Drug displacement (protein-binding) interactions

Once absorbed a drug is distributed to its site of action and during this process it may interact with other drugs. In practice the main mechanism behind such interactions is displacement from protein-binding sites. A drug displacement interaction is defined as a reduction in the extent of plasma protein binding of one drug caused by the presence of another drug, resulting in an increased free or unbound fraction of the displaced drug. Many drugs and their metabolites are highly bound to plasma proteins. Albumin is the main plasma protein to which acidic drugs such as warfarin are bound, while basic drugs, such as tricyclic antidepressants, lidocaine (lignocaine), disopyramide and propranolol, are generally bound to α_1-acid glycoprotein. Displacement from these proteins can be demonstrated in vitro for many drugs and in the past it was thought to be an important mechanism underlying many interactions. Current evidence suggests that, for most drugs, if displacement occurs, then the concentration of free drug will rise temporarily, but metabolism and distribution will return the free concentration to its previous level. The time this takes will depend on the half-life of the displaced drug. The biological significance of the short-term rise of free concentration is generally of minor importance but may need to be taken into account in therapeutic drug monitoring. For example, if a patient taking phenytoin is given a drug which displaces some phenytoin from its binding sites, the total (i.e. free plus bound) plasma phenytoin concentration will fall even though the free (active) concentration remains the same. There are few examples of clinically important interactions which are entirely due to protein-binding displacement. It has been postulated that a sustained change in steady state free plasma concentration could arise with the parenteral administration of some drugs which are extensively bound to plasma proteins and non-restrictively cleared (i.e. the efficiency of the eliminating organ is high). Drugs meeting these criteria include alfentanil, fentanyl, hydralazine, lidocaine (lignocaine), midazolam and verapamil. However, no documented cases of problems in clinical practice as a result of such interactions have been found (Rolan 1994, Sansom & Evans 1995).

Drug metabolism

Most clinically important interactions involve the effect of one drug on the metabolism of another. Metabolism refers to the process by which drugs and other compounds are biochemically modified to facilitate their degradation and subsequent removal from the body. The liver is the principal site of drug metabolism although other organs, such as the gut, kidneys, lung, skin and placenta, are involved. Drug metabolism consists of phase I reactions, such as oxidation, hydrolysis and reduction, and phase II reactions, which primarily involve conjugation of the drug with substances such as glucuronic acid and sulphuric acid. Phase I metabolism generally involves the hepatic CYP450 mixed function oxidase system.

Cytochrome P450 isoenzymes. The cytochrome P450 system comprises about 40–50 isoenzymes, each derived from the expression of an individual gene. As there are many different isoforms of these enzymes a classification for nomenclature has been developed (Anon 2000, Slaughter & Edwards 1995, Horsmans 1997). Four main subfamilies of P450 isoenzymes are thought to be responsible for most (about 90%) of the metabolism of commonly used drugs in humans, CYP1, CYP2, CYP3 and CYP4. Individual isoenzymes that have been specifically identified are given a further number (e.g. CYP2D6; this is the most extensively studied isoenzyme, debrisoquine hydroxylase). Although there is overlap, each CYP isoenzyme tends to metabolize a discrete range of substrates. Of the many isoenzymes, just a few (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A3, and CYP3A4) seem to be responsible for the metabolism of most commonly used drugs. The genes which encode specific CYP isoenzymes can vary between individuals and, sometimes, ethnic groups. These variations (polymorphisms) may affect metabolism of substrate drugs. For example, some people have CYP2D6 isoenzymes with decreased or absent activity and so have reduced capacity to metabolize drugs, such as nortriptyline, that are substrates for this enzyme, leading to their accumulation during therapy and an increased risk of adverse effects.

The effect of a CYP isoenzyme on a particular substrate can be altered by interaction with other drugs. Drugs may be themselves substrates for a CYP isoenzyme and/or may inhibit or induce the isoenzyme. In most instances, oxidation of a particular drug is brought about by several

CYP isoenzymes and results in the production of several metabolites. So, inhibition or induction of a single isoenzyme would have little effect on plasma levels of the drug. However, if a drug is metabolized primarily by a single CYP isoenzyme, inhibition or induction of this enzyme would have a major effect on the plasma concentrations of the drug. For example, if erythromycin (an inhibitor of CYP3A4) is taken by a patient being given carbamazepine (which is extensively metabolized by CYP3A4), this may lead to toxicity due to higher concentrations of carbamazepine. Table 2.2 gives examples of some drug substrates, inducers and inhibitors of the major CYP450 isoenzymes.

Enzyme induction. The most powerful enzyme inducers in clinical use are the antibiotic rifampicin and antiepileptic agents such as barbiturates, phenytoin and carbamazepine, the last being able to induce its own metabolism (autoinduction) (see also Table 2.2). Cigarette smoking, chronic alcohol use and the herbal preparation St John's wort can also induce drug-metabolizing enzymes. Since the process of enzyme induction requires new protein synthesis, the effect usually develops over several days or weeks after starting an enzyme inducing agent. Similarly, the effect generally persists for a similar period following drug withdrawal. Enzyme inducing drugs with short half-lives

Table 2.2 Some drug substrates, inducers, and inhibitors of the major cytochrome P450 enzymes

P-450 isoform	Substrate	Inducer	Inhibitor
CYP1A2	Amitriptyline Imipramine Theophylline *R*-warfarin	Omeprazole Cigarette smoke	Fluvoxamine Ciprofloxacin Cimetidine
CYP2A6	Halothane	Phenytoin	Tranylcypromine
CYP2C9	Diazepam Diclofenac Fluvastatin Losartan *S*-warfarin	Barbiturates Carbamazepine Dexamethasone Primidone Rifampicin St John's wort	
CYP2C19	Citalopram Omeprazole	Rifampicin	Omeprazole Tranylcypromine
CYP2D6	Amitriptyline Codeine Dihydrocodeine Flecainide Fluoxetine Haloperidol Imipramine Nortriptyline Olanzapine Propranolol Risperidone Thioridazine Venlafaxine	Quinidine	Amiodarone Cimetidine Ritonavir SSRIs (selective serotonin reuptake inhibitors)
CYP2E1	Enflurane Halothane	Alcohol (chronic) Isoniazid	Cimetidine Disulfiram
CYP3A4	Amiodarone Terfenadine Ciclosporin Corticosteroids Oral contraceptives Tacrolimus *R*-warfarin	Carbamazepine Phenytoin Barbiturates Dexamethasone Primidone Rifampicin St John's wort	Erythromycin Itraconazole Cimetidine Ketoconazole Fluconazole Ritonavir
CYP4A1	Testosterone	Clofibrate	

(e.g. rifampicin) will induce metabolism more rapidly than inducers with longer half-lives (e.g. phenytoin) because they reach steady state concentrations more rapidly. Enzyme induction usually results in a decreased pharmacological effect of the affected drug, except perhaps in the case of drugs with active metabolites. The effects of enzyme induction vary considerably between patients, and are dependent upon age, genetic factors, concurrent drug treatment and disease state. There is evidence that the enzyme-induction process is dose dependent, although some drugs may induce enzymes at any dose. Some examples of interactions due to enzyme induction are shown in Table 2.3.

Enzyme inhibition. Enzyme inhibition is an extremely common mechanism behind drug interactions. Just as some drugs can stimulate the activity of CYP450 enzymes, there are many which have the opposite effect and act as inhibitors. The rate of metabolism of drugs given concurrently can be reduced and they begin to accumulate within the body. Some enzyme inhibitors are shown in Table 2.4. Enzyme inhibition appears to be dose-related; inhibition of metabolism of the affected drug begins as soon as sufficient concentrations of the inhibitor appear in the liver, and the effects are usually maximal when the new steady state plasma concentration is achieved. Thus, for drugs with a short half-life, the effects may be seen within a few days of administration of the inhibitor. The effects are not seen until later for drugs with a long half-life. The clinical significance of this type of interaction depends on various factors, including dosage (of both drugs), alterations in pharmacokinetic properties of the affected drug, such as a half-life, and patient characteristics such as disease state. Interactions of this type are again most likely to affect drugs with a narrow therapeutic range, such as theophylline, ciclosporin, oral anticoagulants and phenytoin. For example, the initiation of treatment with an enzyme inhibitor such as ciprofloxacin or cimetidine in a patient taking chronic theophylline could result in a doubling of plasma concentrations. The ability to inhibit drug metabolism may be related to specific chemical structures. For example, a number of known enzyme inhibitors contain an imidazole ring, including cimetidine, ketoconazole, itraconazole, metronidazole and omeprazole. Some examples of interactions due to enzyme inhibition are shown in Table 2.5.

Predicting interactions involving metabolism. Predicting drug interactions is not easy because individual drugs in the same class may have different effects on an isoenzyme. For example, the quinolone antibiotics ciprofloxacin and norfloxacin inhibit CYP1A2 and have been reported to increase plasma theophylline levels, whereas lomefloxacin is a much weaker inhibitor and appears not to interact in this way. The relationship between drugs and the cytochrome P450 system is often tested early in drug development using in vitro techniques. Increasingly, the resulting information about potential drug interactions is included in manufacturers' summaries of product characteristics. However, the clinical significance of these interactions is often unknown. Pharmacists should be aware of the key sources of information on interactions and should use them to help predict and tackle clinically important interactions.

Drug transportation

P-glycoprotein (P-gp) is now known to have a role in drug interactions. A recognized cause of multiple drug resistance in malignant disease, more recent work indicates that P-gp also mediates the transcellular transport of many drugs. It acts as a drug transporter pump in the gut, kidneys and many other organs. There have been several published case reports of macrolide antibiotics increasing blood concentrations of digoxin. Initially the underlying mechanism was not understood as digoxin is renally excreted and not significantly metabolized by the liver. It is now known that digoxin is transported by, and macrolides inhibit, P-gp. If the transport pump is inhibited,

Table 2.3 Some examples of interactions due to enzyme induction

Drug affected	Inducing agent	Clinical outcome
Oral contraceptives	Rifampicin Rifabutin Modafinil	Therapeutic failure of contraceptive Additional contraceptive precautions required Increased oestrogen dose required
Ciclosporin	Phenytoin Carbamazepine St John's wort	Decreased ciclosporin levels with possibility of transplant rejection
Paracetamol	Alcohol (chronic)	In overdose, hepatotoxicity may occur at lower doses
Corticosteroids	Phenytoin Rifampicin	Increased metabolism with possibility of therapeutic failure

Table 2.4 Some enzyme inhibitors frequently implicated in interactions

Antibacterials	**Cardiovascular drugs**
Ciprofloxacin	Amiodarone
Erythromycin	Diltiazem
Isoniazid	Quinidine
Metronidazole	Verapamil
Antidepressants	**Gastrointestinal drugs**
Fluoxetine	Cimetidine
Fluvoxamine	Omeprazole
Nefazodone	
Paroxetine	
Sertraline	
Antifungals	**Anti-rheumatic drugs**
Fluconazole	Allopurinol
Itraconazole	Azapropazone
Ketoconazole	Phenylbutazone
Miconazole	
Antivirals	**Other**
Indinavir	Disulfiram
Ritonavir	Propoxyphene
Saquinavir	Sodium valproate

Table 2.5 Some examples of interactions due to enzyme inhibition

Drug affected	Inhibiting agent	Clinical outcome
Anticoagulants (oral)	Ciprofloxacin Clarithromycin	Anticoagulant effect increased and risk of bleeding
Azathioprine	Allopurinol	Enhancement of effect with increased toxicity
Carbamazepine	Cimetidine	Antiepileptic levels increased with risk of toxicity
Phenytoin		
Sodium valproate		
Sildenafil	Ritonavir	Enhancement of sildenafil effect with risk of hypotension

the result will be an increased concentration of the substrate drug in the body. Many, but not all, of the drugs transported by P-gp are also metabolized by CYP3A4 which can confuse the interpretation of interactions. Other common substrates for P-gp are ciclosporin, fluoroquinolones, protease inhibitors, lignocaine, quinidine and ranitidine. Common inhibitors are diltiazem, verapamil and macrolide antibiotics.

Elimination interactions

Most drugs are excreted either in the bile or in the urine. Blood entering the kidneys is delivered to the glomeruli of the tubules where molecules small enough to pass across the pores of the glomerular membrane are filtered through into the lumen of the tubules. Larger molecules, such as plasma proteins and blood cells, are retained. The blood then flows to other parts of the kidney tubules where drugs and their metabolites are removed, secreted or reabsorbed into the tubular filtrate by active and passive transport systems. Interactions can occur when drugs interfere with kidney tubule fluid pH, active transport systems, or blood flow to the kidney thereby altering the excretion of other drugs.

Changes in urinary pH. As with drug absorption in the gut, passive reabsorption of drugs depends on the extent to which the drug exists in the non-ionized lipid-soluble form. Only the unionized form is lipid soluble and able to diffuse back through the tubule cell membrane. Thus, at alkaline pH weakly acidic drugs

(pKa 3.0–7.5) largely exist as unionized lipid-insoluble molecules which are unable to diffuse into the tubule cells and will therefore be lost in the urine. The renal clearance of these drugs is increased if the urine is made more alkaline. Conversely, the clearance of weak bases (pKa 7.5–10) is higher in acid urine. Strong acids and bases are virtually completely ionized over the physiological range of urine pH and their clearance is unaffected by pH changes.

This mechanism of interaction is of very minor clinical significance since most weak acids and bases are inactivated by hepatic metabolism rather than renal excretion. Furthermore, drugs that produce large changes in urine pH are rarely used clinically. Urine alkalinization or acidification has been used as a means of increasing drug elimination in poisoning with salicylates and amphetamines respectively.

Changes in active renal tubule excretion. Drugs which use the same active transport system in the kidney tubules can compete with one another for excretion. Such competition between drugs can be used to therapeutic advantage. For example, probenecid may be given to increase the serum concentration of penicillins by delaying their renal excretion. Increased methotrexate toxicity, sometimes life-threatening, has been seen in some patients concurrently treated with salicylates and some other non-steroidal anti-inflammatory drugs (NSAIDs). The development of toxicity is more likely in patients treated with high dose methotrexate and those with impaired renal function. The mechanism of this interaction may be multifactorial, but competitive inhibition of methotrexate's renal tubular secretion is likely to be involved. If salicylates or NSAIDs are essential in patients treated with methotrexate for malignancy, the dose of methotrexate should be halved. Patients taking low doses for rheumatoid arthritis may take concurrent NSAIDs, but close monitoring for bone marrow toxicity is vital (Brouwers & de Smet 1994).

Changes in renal blood flow. Blood flow through the kidney is partially controlled by the production of renal vasodilatory prostaglandins. If the synthesis of these prostaglandins is inhibited (e.g. by indometacin), the renal excretion of lithium is reduced with a subsequent rise in serum levels. The mechanism underlying this interaction is not entirely clear, as serum lithium levels are unaffected by some potent prostaglandin synthetase inhibitors (e.g. aspirin). If a NSAID is prescribed for a patient taking lithium the serum levels should be closely monitored.

Pharmacodynamic interactions

Pharmacodynamic interactions generally involve additive, synergistic or antagonistic effects of drugs acting on the same receptors or physiological systems. These interactions are much less easy to classify than those with a pharmacokinetic basis.

Antagonistic interactions

It is to be expected that a drug with an agonist action at a particular receptor type will interact with antagonists at that receptor. For example, the bronchodilator action of a selective β_2 adrenoreceptor agonist such as salbutamol will be antagonized by β adrenoreceptor antagonists. There are numerous examples of interactions occurring at receptor sites, many of which are used to therapeutic advantage. Specific antagonists may be used to reverse the effect of another drug at receptor sites; examples include the opioid antagonist naloxone and the benzodiazepine antagonist flumazenil. Alpha-adrenergic agonists such as metaraminol and methoxamine may be used in the management of priapism arising due to excessive α-adrenergic antagonism by phentolamine and related compounds.

Additive or synergistic interactions

If two drugs with similar pharmacological effects are given together, the effects can be additive (see Table 2.6). Although not strictly drug interactions, the mechanism frequently contributes to adverse drug reactions. For example, the concurrent use of drugs with central nervous system (CNS) depressant effects, such as antidepressants, hypnotics, antiepileptics and antihistamines, may lead to excessive drowsiness, yet such combinations are frequently encountered. Combinations of drugs with arrhythmogenic potential, for example antiarrhythmics, neuroleptics, tricyclic antidepressants, and those producing electrolyte imbalance (e.g. diuretics) may lead to ventricular arrhythmias and should be avoided. Another example which has assumed greater importance of late is the risk of ventricular tachycardia and torsade de pointes associated with the concurrent use of more than one drug with the potential to prolong the QT interval on the electrocardiogram (see Chapter 3, Case 3.2).

Interactions due to changes in drug transport mechanisms

The antihypertensive effect of adrenergic neurone blocking drugs such as bethanidine and debrisoquine is prevented or reversed by indirectly acting amines and the tricyclic antidepressants, though these antihypertensives are now seldom used. Tricyclic antidepressants also prevent the re-uptake of noradrenaline (norepinephrine) into peripheral adrenergic neurones so that its pressor effects are increased.

Table 2.6 Some additive or synergistic interactions	
Interacting drugs	Pharmacological effect
NSAID and warfarin	Increased risk of bleeding
ACE inhibitors and K-sparing diuretic	Increased risk of hyperkalaemia
Verapamil and β-adrenergic antagonists	Bradycardia and asystole
Neuromuscular (NM) blockers and aminoglycosides	Increased NM blockade
Alcohol and benzodiazepines	Increased sedation
Thioridazine and halofantrine	Increased risk of QT interval prolongation
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

Interactions due to disturbances in fluid and electrolyte balance

Changes in electrolyte balance may alter the effects of drugs, particularly those acting on the myocardium, neuromuscular transmission and the kidney. An important interaction is the potentiation of the effects of cardiac glycosides such as digoxin by diuretics and other drugs which decrease plasma potassium concentrations. Similarly, diuretic induced hypokalaemia increases the risks of ventricular arrhythmias associated with antiarrhythmic drugs such as sotalol, procainamide, quinidine and amiodarone. Angiotensin-converting enzyme (ACE) inhibitors have a potassium sparing effect, such that the concurrent use of potassium supplements or potassium sparing diuretics may lead to dangerous hyperkalaemia. Coadministration of tacrolimus with potassium sparing diuretics and potassium supplements can also lead to life-threatening hyperkalaemia, especially in patients with renal failure.

Lithium intoxication can be precipitated by the use of diuretics, particularly thiazides and metolazone, and ACE inhibitors. NSAIDs can also precipitate lithium toxicity, mainly due to NSAID inhibition of prostaglandin-dependent renal excretion mechanisms. NSAIDs also impair renal function and cause sodium and water retention, effects which can predispose to interactions. Many case reports describe the antagonistic effects of NSAIDs on diuretics and anti-hypertensive drugs. The combination of triamterene and indometacin appears particularly hazardous as it may result in acute renal failure. NSAIDs may also interfere with the beneficial effects of diuretics and ACE inhibitors in heart failure. It is not unusual to see patients whose heart failure has deteriorated in spite of increased doses of furosemide (frusemide) who are also concurrently taking an NSAID.

Indirect pharmacodynamic interactions

There are many indirect pharmacodynamic interactions of potential clinical significance. In insulin-dependent diabetics the normal recovery from an episode of hypoglycaemia may be impaired to some extent by propranolol. In addition, the hypoglycaemic effects of the sulphonylureas may occasionally be reduced by β-adrenoreceptor antagonists. Non-selective β-blockers block the mobilization of glucose from the liver so that recovery from hypoglycaemia is delayed. They can also block β_2 receptors in the pancreas that mediate insulin release, preventing the effects of the sulphonylureas. These interactions have been well studied and marked effects on blood glucose control appear to be unusual. Patients whose diabetes is controlled by insulin or oral hypoglycaemics can be treated with selective β-blockers, but they should be aware that the familiar warning signs of hypoglyacaemia may be masked and blood glucose should be carefully monitored.

Monoamine-oxidase inhibitors. Monoamine-oxidase inhibitors (MAOIs) reduce the breakdown of noradrenaline (norepinephrine) in the adrenergic nerve ending. This leads to the nerve ending having large stores of noradrenaline (norepinephrine) which can be released into the synaptic cleft in response to either a neuronal discharge or an indirectly acting amine. The action of directly acting amines – adrenaline (epinephrine), isoprenaline, noradrenaline (norepinephrine) – appears to be unchanged or only moderately increased in patients taking MAOIs, although in patients with underlying cardiovascular disease there may be some adverse consequences. In contrast, the concurrent use of MAOIs and indirectly acting sympathomimetic amines (e.g. amphetamines, tyramine, methylenedioxymethamfetamine (MDMA),

phenylpropanolamine, pseudoephedrine) can result in a potentially fatal hypertensive crisis. Some of these compounds are contained in proprietary cough and cold remedies. Tyramine is normally present in foodstuffs (e.g. cheese and red wine) and is metabolized in the gut wall by MAO to inactive metabolites. In patients taking MAOIs, however, tyramine will be absorbed intact. If patients taking MAOIs also take these amines there may be a massive release of noradrenaline (norepinephrine) from adrenergic nerve endings with a resulting syndrome of sympathetic overactivity characterized by hypertension, headache, excitement, hyperpyrexia, and cardiac arrhythmias. Fatal intracranial haemorrhage and cardiac arrest may result. The risk of interactions continues for several weeks after the MAOI is stopped as new MAO enzyme must be synthesized. Patients taking irreversible MAOIs should not take any indirectly acting sympathomimetic amines. All patients must be strongly warned about the risks of cough and cold remedies, illicit drug use and the necessary dietary restrictions.

Serotonin syndrome. Serotonin syndrome is a rare condition which is becoming increasingly well recognized in patients receiving combinations of serotonergic drugs (Sporer 1995, Lane & Baldwin 1997). It can occur when two or more drugs affecting serotonin are given at the same time or after one serotonergic drug is stopped and another started. The syndrome is characterized by symptoms including confusion, disorientation, abnormal movements, exaggerated reflexes, fever, sweating, diarrhoea and hypotension or hypertension. Diagnosis is made when three or more of these symptoms are present and no other cause can be found. Symptoms usually develop within hours of starting the second drug but occasionally they can occur later.

Drug-induced serotonin syndrome is generally mild and resolves when the offending drugs are stopped. However, it can be severe and deaths have occurred. A large number of drugs have been implicated including tricyclic antidepressants, monoamine-oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), pethidine, lithium, and dextromethorphan (Gravlin 1997). The most severe type of reaction has occurred with the combination of selective serotonin re-uptake inhibitors and monoamine-oxidase inhibitors. Both non-selective MAOIs such as phenelzine and selective MAOIs such as moclobemide and selegiline have been implicated.

Serotonin syndrome is best prevented by not using serotonergic drugs in combination. Special care is needed when changing from an SSRI to an MAOI and vice versa. The SSRIs, particularly fluoxetine, have long half-lives and serotonin syndrome may occur if a sufficient wash-out period is not allowed before switching from one to the other. When patients are being switched between these two groups of drugs the guidance in manufacturers' summaries of product characteristics should be followed.

Conclusions

It is impossible to remember all drug interactions of potential clinical significance. Practitioners should be continually alert to the possibility of drug interactions and take appropriate steps to minimize their occurrence. In general, where the combination of potentially interacting drugs is unavoidable, the dose of any drug likely to have increased effects as a result of the interaction should be reduced (e.g. by one-third to one-half) and the patient monitored for toxic effects using clinical variables or plasma drug levels for at least 2 weeks or until these are stable. For drugs that are likely to have reduced effects as a result of the interaction, the patient similarly should be monitored for therapeutic failure for at least 2 weeks or until stable, and the dose increased if necessary. Alternatively, it may be appropriate to switch one of the treatments to one which does not interact. Patients should be advised to seek guidance about their medication if they plan to stop smoking or start a herbal remedy, as they may need close monitoring during the transition.

CASE STUDIES

Case 2.1

A 19-year-old woman is well-controlled on carbamazepine 400 mg twice daily for the treatment of epilepsy. When visiting the local community pharmacy to collect her repeat prescription she mentions that she has recently begun taking St John's wort.

Question

What is the nature of the potential drug interaction and what advice do you give?

Answer

St John's wort, a herbal remedy commonly taken for depression, induces activity of CYP1A2, CYP2C9 and CYP3A4, thereby increasing the metabolism and reducing the plasma concentrations of drugs such as warfarin, theophylline, ciclosporin, antiepileptics, oral contraceptives, protease inhibitors, non-nucleoside reverse transcriptase inhibitors and SSRIs. Most herbal remedies are unlicensed and the amount of the active ingredients unregulated, and so the extent of any effect of St John's wort on other drugs is unpredictable. Carbamazepine is a substrate of the CYP3A4 isoenzyme, so its effect may be reduced if St John's wort is taken concurrently and the patient placed at increased risk of seizures.

The UK Committee on Safety of Medicines has issued guidance on the problem of drug interactions between St John's wort and prescribed medicines. This states that a clinically important interaction with carbamazepine is likely and that the combination should not be used. It also suggests that patients already taking the combination should stop the St John's wort and the carbamazepine level should be checked.

Case 2.2

A consultant cardiologist would like to prescribe orlistat for weight reduction for a 56-year-old patient who received a heart transplant several months ago. He is taking amlodipine, fluconazole, atorvastatin, ciclosporin, prednisolone and aciclovir.

Questions

1. Are there likely to be any clinically significant drug interactions?
2. What advice do you give?

Answers

1. There is a potential interaction with ciclosporin. Orlistat inhibits fat absorption and it is possible that it reduces the bioavailability of ciclosporin, a highly lipid-soluble drug. There have been occasional reports of subtherapeutic ciclosporin blood concentrations occurring after initiation of orlistat therapy.
2. Although the effect of separating doses of ciclosporin from orlistat is not known, it would be prudent to give ciclosporin 2 hours before or several hours after the orlistat. If the combination is used, plasma levels of ciclosporin should be carefully monitored when orlistat is initiated, discontinued, or if the dose is changed.

Case 2.3

A customer in the pharmacy asks to buy some cimetidine tablets for dyspepsia. When asked about other medicines she tells you that she is also taking an oral contraceptive and that she is midway through a prescribed course of bupropion (amfebutamone) to help her stop smoking.

Question

Is the sale of over-the-counter (OTC) cimetidine appropriate in this situation?

Answer

No. Bupropion (amfebutamone) has recently been made available as a therapy for smoking cessation and its considerable potential for interaction with other medicines has since been recognized. The main concern relates to a dose-related risk of seizures and an increase of seizures occurring in the presence of factors which lower the seizure threshold.

Cimetidine is known to be a potent inhibitor of the CYP450 enzyme system and it could allow bupropion (amfebutamone)to accumulate in the body if given concurrently. Famotidine and ranitidine do not inhibit liver enzymes and either would be a better choice of H_2 antagonist in this patient.

Case 2.4

A general practitioner asks your advice about prescribing the non-steroidal anti-inflammatory drug celecoxib for osteoarthritis in a 68-year-old man who is also taking warfarin, atenolol and levothyroxine (thyroxine).

Question

Do you anticipate any problems with the addition of celecoxib?

Answer

The combination of celecoxib and warfarin is best avoided as bleeding and increased prothrombin time have been reported. Both celecoxib and warfarin are metabolized through the same cytochrome P450 pathway (CYP2C9) so it is possible that a competitive inhibition could occur, resulting in decreased elimination of either or both drugs. If treatment with celecoxib is considered essential in a patient already taking warfarin the international normalized ratio (INR) should be checked frequently at the start of treatment.

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Adverse drug reactions 3

A. Lee S. H. L. Thomas

KEY POINTS

- Adverse drug reactions (ADRs) are an important cause of morbidity and mortality. They are responsible for a considerable number of hospital admissions and significantly increase health care costs.
- The World Health Organization defines an adverse drug reaction as any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy.
- Adverse drug reactions can be classified as either type A or type B. Type A (augmented) reactions are normal pharmacological effects which are undesirable. They are usually dose-dependent and fairly predictable. They are an important cause of morbidity, but death is unusual.
- Type B (bizarre) reactions are effects unrelated to the known pharmacology of a drug. These reactions are rare, unpredictable and generally unrelated to dose. Reactions are often severe or fatal.
- Important predisposing factors to adverse drug reactions include extremes of age, polypharmacy, intercurrent disease and genetic factors. Mechanisms of reactions may be pharmaceutical, pharmacokinetic or pharmacodynamic.
- Early recognition of potential adverse drug reactions is critical. Type B reactions are unlikely to be detected during clinical trials. Post-marking surveillance, including spontaneous reporting of suspected adverse drug reactions, is essential for monitoring drug safety.
- The pharmacist should always ensure that medicines are used safely, and should endeavour to minimize the impact of adverse drug reactions on pharmaceutical care. The pharmacist also has an important role in pharmacovigilance procedures.

An adverse drug reaction (ADR) is any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use (Pirmohamed et al 1998). It has been recognized since the earliest times that drug therapy can be a significant cause of morbidity and mortality. About 400 BC Hippocrates warned of the dangers of drugs, recommending that they should never be prescribed unless the patient had been thoroughly examined. In 1785, when William Withering described the benefits of digitalis, he also described the vomiting, alteration of vision, bradycardia, convulsions and death it could cause. In the 20th century great therapeutic advances were accompanied by a growing awareness of the problem of adverse reactions to medicines among both health care professionals and consumers. In particular, the thalidomide tragedy in the late 1950s and early 1960s was the seminal event leading to the development of modern drug regulation. Thalidomide, prescribed as a 'safe' hypnotic to many thousands of pregnant women, caused a severe form of limb abnormality known as phocomelia in many of the babies born to these women.

Drug-induced disease is rarely specific and almost invariably mimics naturally occurring disease. Few adverse drug reactions are associated with diagnostic clinical or laboratory findings which demarcate them from the features of a spontaneous disease. Moreover, many of the subjective effects frequently attributed to drugs (such as headache, nausea and dizziness) occur commonly in healthy individuals taking no medication and in patients taking a placebo. Pharmacists have a key role in minimizing the occurrence of adverse drug reactions. This requires some knowledge of the adverse effects of drugs, including their frequency and severity, the most common predisposing factors, and the relationship to dosage and duration of treatment. There is a huge literature on adverse drug reactions, including several comprehensive textbooks, and this chapter is no more than an introduction to the subject. It concentrates on the epidemiology, mechanisms and classification of adverse drug reactions, important predisposing factors, and how adverse reactions are identified and evaluated.

Epidemiology

Many studies have attempted to determine the incidence of adverse drug reactions in a variety of settings. The estimates of incidence vary widely and this reflects differences in the methods used to detect suspected reactions and differences in the definition of an ADR. Nevertheless, several important studies in the 1960s helped establish the epidemiological basis of drug-induced disease. One of these was the Boston Collaborative Drug Surveillance Program (BCDSP), which made a great impact in the field; data were

collected on over 50 000 consecutive patients admitted to medical wards over a 10-year period (Borda et al 1968). This allowed much original research on the association between short-term drug exposure and acute ADRs to be carried out. In an interim analysis of 19 000 patients monitored there were approximately 171 000 drug exposures and an adverse reaction rate of 30% (Jick 1974). However, many ADRs were minor and the author concluded that drugs were 'remarkably non-toxic'. Detailed analysis of the data provided much information on patient characteristics predisposing to ADRs and allowed some established adverse effects of drugs, such as excessive drowsiness or 'hangover' with flurazepam, to be quantified.

The Harvard Medical Practice study showed that in 1984, 3.7% of 30 195 patients admitted to acute non-psychiatric hospitals experienced adverse reactions during their stay (Brennan et al 1991). Further data from this group suggested a 6% incidence of adverse drug events and a 5% incidence of potential adverse drug events among 4031 medical and surgical admissions over a 6-month period (Bates et al 1995). Of all events observed, 1% were fatal, 12% life-threatening, 30% serious and 57% significant. Of observed adverse drug events, 28% were considered preventable, with a greater proportion of the life-threatening and serious reactions in that category. The drug classes most frequently implicated in those reactions were analgesics, antibiotics, sedatives, cytotoxics, cardiovascular drugs, anticoagulants, antipsychotics, antidiabetics and electrolytes. A recently published study of adverse events in hospital in-patients in Colorado and Utah in 1992 found a similar frequency and type of adverse events to those observed in the Harvard study (Thomas & Brennan 2000). A review of data on nearly 15 000 patients discharged from 28 hospitals in the two states identified adverse events (not necessarily drug related) associated with 2.9% of hospitalizations in each state. Adverse drug reactions were the second most common type of adverse event, accounting for 19.3% of those identified. A quarter (24.9%) of the ADRs were associated with antibiotics, 17.4% with cardiovascular agents, 8.9% with analgesics and 8.6% with anticoagulants. More than a third of the ADRs were considered avoidable and nearly 1 in 10 caused irreversible harm. UK data from a study carried out in Oxford suggested that 7% of over 20 000 medical in-patients experienced an ADR during their stay in hospital (Smith et al 1996).

Adverse reactions to drugs are responsible for a significant number of hospital admissions, with reported rates ranging from 0.3% to as high as 11% (Beard 1992, Lazarou et al 1998). Overall, the incidence of ADR-induced admissions, as estimated from large early studies, is of the order of 3% of medical admissions. For ADRs occurring in the community, the reported incidence ranges from 2.6% to 41% of patients, but this is a much more difficult area to study and there are fewer well-designed studies (Martys 1979, Mulroy 1973). Despite the problems with definition and incidence studies, ADRs undoubtedly increase hospital admission rates, increase morbidity and mortality, and have a significant impact on health care costs. Two recent US studies showed that the length of hospital stay was significantly greater in patients who experienced an ADR while in hospital (Classen et al 1997, Bates et al 1997). Both studies estimated substantial cost implications: the Classen study estimated that the occurrence of an ADR increased the cost of patient care by $2262 per patient and Bates et al estimated the cost of preventable ADRs in a 700-bed hospital to be $2.8 million per annum.

Definition and classification

An adverse drug reaction has been defined by the World Health Organization as 'any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy'.There are several ways of classifying adverse reactions, but the simplest is to separate them into types A and B as proposed by Rawlins and Thompson in 1977 (Table 3.1). Type A reactions are the result of an exaggerated, but otherwise normal, pharmacological action of a drug given in the usual therapeutic doses. Examples include bradycardia with a β adrenoreceptor blocker, haemorrhage with anticoagulants or hypoglycaemia with a sulphonylurea. Type A reactions are predictable from a drug's known pharmacology. They are usually dose-dependent and their incidence and morbidity are generally high. Their mortality, however, is usually (but not invariably) low. Some type A adverse reactions have a long latency. Examples include teratogenicity, chloroquine retinopathy, and delayed effects such as the vaginal clear-cell adenocarcinoma which may occur in the daughters of women who received diethylstilbestrol during pregnancy.

In contrast, type B reactions are aberrant effects that are not to be expected on the basis of a drug's pharmacology. Examples include malignant hyperthermia of anaesthesia, acute porphyria and many immunological reactions. Type B reactions are generally unrelated to dosage and, although comparatively rare, they often cause serious illness and death. These reactions are often not observed during conventional pharmacological and toxicological screening programmes and consequently they account for many drug withdrawals from the market.

It has been suggested that the type A and B classification be extended by adding types C (chronic, long-term effects), D (delayed effects), E (end of use or

Table 3.1 Comparison between type A and type B adverse drug reactions (Rawlins & Thompson 1977, Rawlins & Thomas 1998)

	Type A augmented response	Type B (bizarre response)
Pharmacologically predictable	Yes	No
Dose-dependent	Yes	No
Incidence	High	Low
Morbidity	High	Low
Mortality	Low	High
Management	Dosage adjustment often appropriate	Stop

withdrawal effects) and F (failure of therapy) (Edwards & Aronson 2000). In our view these additional classes do not assist in understanding either the mechanisms of ADRs or their management.

Predisposing factors

Factors predisposing to ADRs may relate either to the properties of the drug or to the characteristics of the patient.

Multiple drug therapy

The incidence of adverse drug reactions and interactions has been shown to increase sharply with the number of drugs taken. This suggests that the effects of multiple drug use are not simply additive. There is likely to be a synergistic effect, but the concept of confounding by multiple disease states must be borne in mind.

Age

The very old and the very young are more susceptible to adverse drug reactions. The elderly often have multiple and chronic disease and are major consumers of medicines. They are particularly vulnerable to the adverse effects of drugs because of the physiological changes that accompany ageing. Most studies have shown a positive correlation between age and the number of adverse drug reactions but this is a complex issue (Castleden & Pickles 1988, Lawson 1998, Thomas & Brennan 2000). It is difficult to determine whether age alone renders these patients more susceptible to ADRs or whether this simply reflects increased drug exposure, multiple disease states and age-related pharmacokinetic changes. Drug metabolism is impaired in the elderly. In fit elderly people, changes in the rates of drug metabolism are mainly due to the age-related decrease in liver blood flow and liver mass. Consequently there is greater systemic exposure to drugs which normally undergo substantial biotransformation in the liver during absorption. In the frail elderly there appears to be, in addition, a reduction in the intrinsic hepatic drug-metabolizing activity, which increases their vulnerability to type A reactions (Kinirons & Crome 1997). There is also evidence that age-related pharmacodynamic changes make the elderly more sensitive to the effects of some drugs. Adverse reactions in elderly patients often present in a vague, non-specific fashion. Mental confusion, constipation, hypotension and falls may be the presenting features of illness but may also suggest ADRs. Drugs which commonly cause problems in elderly patients include hypnotics, diuretics, non-steroidal anti-inflammatory drugs, antihypertensives, psychotropics and digoxin.

All children, and particularly neonates, differ from adults in the way they handle and respond to drugs. Some drugs are particularly likely to cause problems in neonates but are generally well tolerated in older children, for example morphine. Others are associated with an increased risk of problems in children of any age, for example sodium valproate. Hazardous drugs for neonates include chloramphenicol, morphine and antiarrhythmics. Specific examples of concern in children are Reye's syndrome with aspirin and hepatotoxicity with sodium valproate (Choonara et al 1996).

Gender

Women may be generally at greater risk of ADRs than men; increased drug exposure does not seem to account for this difference. Women are reputed to be more

susceptible to blood dyscrasias with phenylbutazone and chloramphenicol, to histaminoid reactions to neuromuscular blocking drugs, to reactions involving the gastrointestinal tract and to drug-induced prolongation of the QT interval on the electrocardiogram (Lawson 1998).

Intercurrent disease

Patients with impaired renal or hepatic function are at substantially increased risk of developing ADRs to drugs eliminated by these organs. There are, however, specific disease states which may predispose to adverse drug reactions, such as human immunodeficiency virus (HIV)-positive patients who suffer an increased incidence of the adverse effects of co-trimoxazole. Immune deficiency is a complex clinical area with multiple drug exposures, multiple illness events and consequent difficulty in interpreting drug toxicity data.

Race and genetic polymorphism

Inherited factors that affect the pharmacokinetics of numerous drugs are of great importance in determining an individual's risk of ADR. The discipline of pharmacogenetics deals with those variations in drug response that are under hereditary control. Genetic variations in genes for drug metabolizing enzymes, drug receptors and drug transporters have been associated with individual variability in the efficacy and toxicity of drugs (Meyer 2000). These genetic polymorphisms of drug metabolism produce the phenotypes of 'poor metabolizers' or 'rapid metabolizers' of numerous drugs. Polymorphisms in the cytochrome P450 enzymes in the liver can have a profound effect on drug efficacy. In poor metabolizers the genes encoding specific cytochrome P450 enzymes often contain inactivating mutations, which result in a complete lack of active enzyme and a severely compromised ability to metabolize drugs.

All pharmacogenetic variations studied to date occur at different frequencies among sub-populations of different ethnic or racial origins. This ethnic diversity implies that ethnic origin has to be considered in pharmacogenetic studies and in pharmacotherapy.

Mechanisms of type A adverse drug reactions

The individual response to drugs shows great variation. This is manifest either as different doses being required to produce the same pharmacological effect, or as different responses to a defined dose. Such inter-individual variation is the basis of type A adverse reactions. Dose-related adverse reactions may occur because of variations in the pharmaceutical, pharmacokinetic or pharmacodynamic properties of a drug, and are often due to the underlying disease state or pharmacogenetic characteristics of the patient (Rawlins & Thomas 1998). In some cases a combination of these causes may be responsible.

Pharmaceutical causes

Adverse reactions can occur due to pharmaceutical aspects of a dosage from either because of alterations in the quantity of drug present, or in its release characteristics. As a result of stringent requirements laid down by regulatory authorities, such reactions are now rare in developed countries. In 1983 a rate-controlled preparation of indometacin (Osmosin) was withdrawn following the receipt of a significant number of reports of gastrointestinal bleeding and haemorrhage. This was probably due to the irritant effects of a very high concentration of the active ingredient on a localized area of intestinal mucosa.

Pharmacokinetic causes

Quantitative alterations in the absorption, distribution, metabolism and elimination of drugs may lead to alterations in the concentration of a drug at its site of action with corresponding changes in its pharmacological effects. Such alterations may produce either an exaggerated response or therapeutic failure as a consequence of abnormally low drug concentrations.

Absorption

Differences in both the rate and extent of drug absorption may cause adverse effects. Factors which can influence the extent of absorption of a drug include dosage, pharmaceutical factors, gastrointestinal tract motility, the absorptive capacity of the gastrointestinal mucosa, and first-pass metabolism in the liver and gut wall before it reaches the systemic circulation. The rate of absorption of orally administered drugs is largely determined by the rate of gastric emptying, which is influenced by factors including the nature of the gastric contents, disease and concomitant drugs. The majority of adverse reactions resulting from changes in drug absorption are reduced therapeutic efficacy or therapeutic failure.

Distribution

The distribution of drugs to various tissues and organs is dependent on factors including regional blood flow, plasma protein and tissue binding. Changes in how a drug is distributed may, theoretically, predispose to adverse effects, although the clinical importance of such mechanisms is unclear.

Elimination

Most drugs are excreted in the urine or bile or metabolized by the liver to yield metabolites which are then excreted by the kidneys. Changes in drug elimination rates are probably the most important cause of type A adverse drug reactions. Reduced elimination leads to drug accumulation, with potential toxicity due to increased plasma and tissue levels. Conversely, enhanced elimination leads to reduced plasma and tissue drug levels, resulting in therapeutic failure.

Renal excretion

Impaired glomerular filtration leads to reduced elimination of drugs which undergo renal excretion. Individuals with reduced glomerular filtration (such as patients with intrinsic renal disease, the elderly and neonates) are liable to develop type A adverse reactions to 'normal' therapeutic doses of drugs which are mainly excreted by the kidney. Some of the most potentially toxic drugs in this respect are digoxin, ACE inhibitors, aminoglycoside antibiotics, some class I antiarrhythmic agents (disopyramide, flecainide), and many cytotoxic agents. The occurrence of these ADRs may be minimized by adjusting the dosage given to individual patients on the basis of their renal function.

Drug metabolism

Lipid-soluble agents are frequently metabolized to water-soluble compunds which then undergo excretion by the kidney. Metabolism occurs predominantly in the liver, although the kidney, lungs, skin and gut also have some metabolizing capacity. In man, drug metabolism can be divided into two phases. Phase I (oxidation, reduction or hydrolysis) exposes functionally reactive groups or adds them to the molecule. Phase II (sulphation, glucuronidation, acetylation or methylation) involves conjugation of the drug at a reactive site produced during phase I. Drugs that already have reactive groups undergo phase II reactions only. Others are sufficiently water-soluble after phase I metabolism to be eliminated by renal excretion.

Inter-individual differences or alterations in the rate at which drugs are metabolized result in appropriate variations in elimination rates. Reduced rates of metabolism may lead to drug accumulation and an increased risk of type A adverse drug reactions, while enhanced rates of metabolism may result in therapeutic failure. There is wide inter-individual variation in some routes of metabolism, even among normal individuals, because of genetic and environmental influences. This particularly applies to oxidation, hydrolysis and acetylation. Competition for glucuronidation may occur when two drugs metabolized by this pathway are given concurrently.

Microsomal oxidation

Drug oxidation occurs mainly in the smooth endoplasmic reticulum of the liver by the cytochrome P450 enzyme system. It is mediated by a group of enzymes known as the cytochrome P450 superfamily. Four main subfamilies of P450 isoenzymes are thought to be responsible for most (about 90%) of the metabolism of commonly used drugs in humans, CYP1, CYP2, CYP3 and CYP4. Individual isoenzymes that have been specifically identified are given a further number (e.g. CYP2D6, which is the most extensively studied isoenzyme, debrisoquine hydroxylase). Although there is overlap, each CYP isoenzyme tends to metabolize a discrete range of substrates. Of the many isoenzymes, just a few (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A3 and CYP3A4) seem to be responsible for the metabolism of most commonly used drugs. The genes which encode specific CYP isoenzymes can vary between individuals and, sometimes, ethnic groups.

Inter-individual variability in debrisoquine metabolism is well-recognized. Poor metabolizers tend to have reduced first-pass metabolism, increased plasma levels, and exaggerated pharmacological response to this drug, resulting in postural hypotension. By contrast, rapid metabolizers may require considerably higher doses for a standard effect. The antidepressants nortriptyline and desipramine are metabolized by similar mechanisms to those of debrisoquine and as a result the steady state plasma levels reached with these drugs are dependent on the individual's phenotype. The enzyme showing polymorphism in this situation is debrisoquine hydroxylase or CYP2D6. This enzyme is inactive in about 6% of white people. In the UK several million people are thus at risk of compromised metabolism or ADRs when prescribed drugs that are CYP2D6 substrates. Many such drugs are used in the treatment of psychiatric, neurological and cardiovascular diseases. Clinical problems can also arise from the co-administration of drugs that inhibit or compete for CYP2D6. A drug may interact with and inhibit CYP2D6 to the extent that it is no longer functionally active, resulting in a patient responding like a poor metabolizer even though he or she has an extensive metabolizer genotype. Thus quinidine, a powerful CYP2D6 inhibitor, may exaggerate the effects of other drugs that are prescribed concomitantly or may prevent the metabolic activation of drugs such as codeine by CYP2D6. Genotyping the CYP2D6 enzyme to assist individual dose selection for psychiatric drugs is currently the most widely accepted application of pharmacogenetic testing.

The potential effects of enzyme induction and inhibition on other drugs are discussed in the chapter on drug interactions (see Chapter 2).

Hydrolysis

Suxamethonium apnoea is the best-known example of an alteration in drug response due to individual variation in drug hydrolysis. The neuromuscular blocking effects of suxamethonium are usually short lived, as the drug is rapidly inactivated in plasma by hydrolysis. The hydrolysis is catalysed by plasma pseudocholinesterase which exists in several different genetically determined forms. Individuals homozygous for the atypical gene (about 1 in 2500 of the UK population) may develop prolonged neuromuscular blockade. Suxamethonium apnoea may also be somewhat prolonged in individuals who are heterozygous for the gene (i.e. who possess both the usual and the atypical gene). The frequency of the atypical genes shows marked racial variation. Phenotypic studies of patients who develop prolonged neuromuscular blockade after suxamethonium do not always reveal recognizable genetic abnormalities. In some instances these type A reactions are secondary to liver or renal disease, both of which can influence the activity of plasma cholinesterase.

Acetylation

A number of drugs are metabolized by acetylation including dapsone, isoniazid, hydralazine, phenelzine, procainamide and many sulphonamides. Acetylation is under genetic control and shows a polymorphism such that individuals may be phenotyped as either 'slow' or 'rapid' acetylators. The variability is due to differences in the activity of the liver enzyme N-acetyltransferase. In the UK about half the population are rapid acetylators, but there are considerable racial differences. The incidence of rapid acetylation is highest among the Japanese and among Canadian Inuit.

Slow acetylators are at increased risk of developing type A adverse reactions. Thus, isoniazid-induced peripheral neuropathy, the haematological adverse effects of dapsone, and the adverse effects of sulfapyridine are more likely to occur in these individuals. Slow acetylators of hydralazine and procainamide are also at greater risk than fast acetylators of developing systemic lupus erythematosus.

Glucuronidation

Several drugs commonly used in clinical practice (e.g. morphine, paracetamol, and ethinylestradiol) are eliminated at least partly by glucuronide conjugates. There is evidence that, like the CYP450 enzyme system, glucuronyltransferases exist in multiple forms with many drugs acting as substrates for more than one isoenzyme. Glucuronyltransferases are also inducible and the administration of an inducing drug can lead to loss of efficacy of combined oral contraceptives.

Pharmacodynamic causes

Many, if not most, type A ADRs have a pharmacokinetic basis. Some, however, are due to enhanced sensitivity of target organs or tissues. Moreover, in some individuals, ADRs may result from a combination of the two mechanisms. The reasons why tissues from different individuals should respond differently to drugs are still largely unknown, but evidence is accumulating to show that target organ sensitivity is influenced by the drug receptors themselves, by physiological homoeostatic mechanisms and by disease (Rawlins & Thomas 1998).

Mechanisms of type B adverse drug reactions

Type B reactions are inexplicable in terms of the normal pharmacology of the drug. The cause may be pharmaceutical or pharmacokinetic, or may lie in target organ response (pharmacodynamic).

Pharmaceutical causes

Pharmaceutical apects of the medicine itself may be the cause of type B adverse reactions. Such reactions can occur due to the presence of degradation products of the active constituents, the effects of the non-drug components of the formulation, such as excipients and other compounds (i.e. colourings, preservatives and antioxidants), or the actions of synthetic by-products of the active constituents. In most cases the administration of a decomposed drug will result in therapeutic failure, but in some cases the decomposition product may be toxic and potentially lethal (e.g. earlier formulations of tetracycline). Adverse reactions have resulted from the incorporation of clearly toxic substances such as diethylene glycol (which caused 105 deaths in the USA in 1937 when it was used as a solvent in sulphanilamide elixir); the use of certain excipients in susceptible patient groups, such as asthmatics or neonates; and the alteration of an excipient mixture resulting in changes in the bioavailability of drugs such as digoxin and phenytoin. A number of adverse reactions caused by pharmaceutical excipients are recognized.

Nowadays, with stringent manufacturers' controls and monitoring by regulatory authorities, it is extremely unusual for pharmaceutical preparations to be adulterated with synthetic by-products. A relatively recent example is the potentially fatal syndrome of eosinophilia and myalgia associated with L-tryptophan, which was probably due to a contaminant, although genetic factors may have been involved.

Pharmacokinetic causes

There are no documented type B adverse reactions that can be attributed to abnormalities of absorption or distribution. However, there is, emerging evidence that to suggest that the bioactivation of drugs to yield reactive species is responsible for a significant proportion of type B adverse effects (Knowles et al 2000). Binding of such reactive metabolites may result in either direct or immune-mediated toxicity (Pirmohamed et al 1994). Examples of type B reactions postulated to occur as a result of bioactivation to reactive metabolites include tacrine (hepatotoxicity), clozapine (agranulocytosis), halothane (hepatotoxicity) and carbamazepine (hypersensitivity reactions). The reasons why only some individuals develop such type B reactions remains unclear. Suspectible people may have overactive or underactive specific bioinactivation pathways, or immunological characteristics that render them more responsive to haptogens or immunogens.

Pharmacodynamic causes

Individual patients vary widely in their responses to drugs. Even after allowance has been made for the patient's age, gender, bodyweight, disease state and concurrent drug regimens there is still variation between individuals. Qualitative differences in the target organ response to drugs may be considered as genetic, immunological, neoplastic or teratogenic.

Genetic causes for abnormal response

Many type B adverse reactions have been labelled as idiosyncratic reactions that were assumed to be due to some qualitative abnormality in the patient. Until recently, drug 'idiosyncrasies' have tended to form a 'dustbin' category for ADRs that could not be classified under any other heading. This situation is now changing slowly as their underlying mechanisms are better understood and it is becoming apparent that many have a genetic basis (Table 3.2 gives some examples).

Erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency

A well known example of qualitative difference in the response to drugs is G6PD deficiency, which affects between 100 and 400 million people worldwide. G6PD is an enzyme required for the stability of red blood cells. Individuals with a sex-linked inherited deficiency in this enzyme have weakened red cell membranes and are predisposed to haemolysis due to oxidant drugs such as primaquine, sulphonamides and sulphones, and nitrofurantoin. There are many variants of G6PD and not all are associated with drug-induced haemolysis. The frequency of the enzyme deficiency also varies widely between and within various populations. The African type G6PD (A^-) is characterized by mild enzyme deficiency with a mean activity of 8–20% of normal. The Mediterranean type, on the other hand, is characterized

Table 3.2 Examples of genetically determined adverse reactions

Condition	Drug	Effects
Erythrocyte enzyme deficiencies		
• Glucose-6-phosphate dehydrogenase	Oxidant drugs (see Table 3.3)	Haemolytic anaemia
• Methaemoglobin reductase	Oxidant drugs (see Table 3.3)	Methaemoglobinaemia
Haemoglobin variants		
• Haemoglobin H, Zurich, Torino	Oxidant drugs (see Table 3.3)	Haemolytic anaemia
• Haemoglobin Zurich	Sulphonamides	Haemolytic anaemia
Porphyria (hepatic)	Barbiturates, sulphonamides, griseofulvin	Preciptates attack of porphyria
Malignant hyperthermia	General anaesthetics (halothane) Muscle relaxants	Hyperthermia with prolonged muscle rigidity, acidosis
Genetic predisposition to raised intraocular pressure	Topical corticosteroids	Increased intraocular pressure
Familial dysautonomia (Riley–Day syndrome)	General anaesthetics Parasympathomimetics	Exaggerated reponse

by severe enzyme deficiency (0–4% enzyme activity). Consequently, a potentially haemolytic drug is likely to produce only mild haemolysis in patients with the African type, but it may have severe and potentially fatal effects in patients with the Mediterranean type. Many drugs have been associated with haemolysis in G6PD deficiency, but the severity of the reaction varies between drugs and also depends on the type of enzyme deficiency. Haemolytic episodes can be provoked by drugs or illness in G6PD-deficient individuals and some drugs have been wrongly implicated as a cause of haemolysis. The number of currently available medicines with proven haemolytic potential in G6PD-deficient individuals is relatively small; primaquine is probably the best-known example. Drugs that should be avoided in G6PD deficiency are shown in Table 3.3.

Hereditary methaemoglobinaemias

An inherited deficiency of methaemoglobin reductase in erythrocytes renders affected individuals susceptible to the development of methaemoglobinaemia and cyanosis in response to oxidant drugs. Drugs that are oxidizing agents, nitrites, and all of the drugs listed in Table 3.3 may have this effect.

Porphyrias

The porphyrias are a heterogeneous group of inherited disorders of haem biosynthesis. The disorders are transmitted as autosomal dominants, with the exception of the rare congenital porphyria, which is recessive. The effects of drugs are of most importance in patients with acute porphyrias, in whom certain commonly prescribed agents may precipitate life-threatening attacks. Other trigger factors include alcohol and endogenous and exogenous steroid hormones. In the acute porphyrias, patients develop abdominal and neuropsychiatric disturbances, and they excrete in their urine excessive amounts of the porphyrin precursors 5-aminolaevulinic acid (ALA) and porphobilinogen. A number of drugs may induce excess porphyrin synthesis. However, it is extremely difficult to predict whether or not a drug will cause problems in patients with porphyria and the only factors shown to be clearly linked with porphyrinogenicity are lipid solubility and membrane fluidization (i.e. the ability to disrupt the phospholipid bilayer of the cell membrane). A number of commonly used drugs induce ALA synthetase in the liver, but there is wide variation between porphyric patients in their sensitivity to drugs which may trigger attacks. Thus, whereas a single dose of a drug may be sufficient to trigger an acute attack in one patient, another may require a number of relatively large doses of the same drug to produce any clinically significant effect. Lists of drugs which are known to be unsafe and drugs which are thought to be safe for use in acute porphyria are available in the British National Formulary.

Table 3.3 Drugs to be avoided in G6PD deficiency

Dapsone
Niridazole
Methylthioninium chloride (Methylene blue)
Primaquine
Quinolones (including ciprofloxacin, nalidixic acid, norfloxacin and ofloxacin)
Sulphonamides (including co-trimoxazole)

Malignant hyperthermia

Malignant hyperthermia is a rare but potentially fatal condition in which there is a rapid rise in body temperature (at least 2°C per hour) occurring without obvious cause after administration of anaesthetics or muscle relaxants. The condition usually follows the administration of an inhalational general anaesthetic, often halothane, in combination with suxamethonium. In addition to the temperature rise, the syndrome is characterized by stiffness of skeletal muscles, hyperventilation, acidosis, hyperkalaemia and signs of increased activity of the sympathetic nervous system. It is likely that the condition is triggered by an abnormal release of intracellular ionized calcium, which may be due to an inherited defect of cellular membranes. The condition is associated with a mortality rate of up to 40%.

Glucocorticoid glaucoma

In genetically predisposed individuals, glucocorticoids can cause a rise in intraocular pressure leading to blindness. Development of increased intraocular pressure appears to be correlated with dosage, and may persist for several months after stopping steroid treatment. It is important to remember that this complication may arise in patients treated with glucocorticoid eye drops.

Cholestatic jaundice induced by oral contraceptives

Oral contraceptives are known to cause jaundice in some women, especially during the first month of medication; this recovers rapidly on discontinuation of treatment. Available evidence suggests that a genetic component is important for the development of the reaction. The underlying mechanism for this reaction is unclear, but it

is likely that oestrogen-induced changes in the composition of the hepatocyte membrane are involved.

Immunological reasons for abnormal response

Some drugs (e.g. peptides of foreign origin such as streptokinase) are immunogenic and may cause immunological reactions in their own right (Assem 1998). Drug allergy is the most frequently encountered type of immunological adverse reaction. True allergic reactions are immunologically mediated effects. The features of these reactions are:

- there is no relation to the usual pharmacological effects of the drug
- there is often a delay between the first exposure to the drug and the occurrence of the subsequent adverse reaction
- very small doses of the drug may elicit the reaction once allergy is established
- the reaction disappears on withdrawal of the drug
- the illness is often recognizable as a form of immunological reaction.

Allergic reactions vary from rash, serum sickness and angio-oedema to life-threatening bronchospasm and hypotension associated with anaphylaxis. Many factors influence the development of allergic reactions. Patients with a history of atopic or allergic disorders are at greatest risk. Table 3.4 lists some examples of adverse reactions with an immunological basis.

Delayed adverse effects of drugs

A number of adverse effects may only become apparent after long-term treatment, for example the relatively harmless melanin deposits in the lens and cornea that are seen after years of phenothiazine treatment and which should be distinguished from pigmentary retinopathy, a dose-related adverse effect occurring within several months of initiation of treatment. Other examples include the development of vaginal carcinoma in the daughters of women given diethylstilbestrol during pregnancy for the treatment of threatened abortion, and immunosuppressives and chemotherapeutic agents which can induce malignancies that may not be apparent until years after treatment has been given.

Adverse effects associated with drug withdrawal

Some drugs cause symptoms when treatment is stopped abruptly, for example the benzodiazepine withdrawal syndrome, rebound hypertension following discontinuation of antihypertensives such as clonidine and the acute adrenal insufficiency that may be precipitated by the abrupt withdrawal of corticosteroids. These are all type A reactions.

Detection and monitoring of adverse drug reactions

By the time a drug receives a marketing authorization it will usually have been given to an average of 1500 people, and it is likely that clinical trials will have detected only the most common adverse drug reactions. It follows that type B reactions, particularly those with an incidence of 1 in 500 or less, are unlikely to have been identified before the drug appears on the market. It is only after much wider use that rare reactions or those which occur predominantly in certain subgroups within populations, such as the elderly, are detected. It is therefore essential to monitor safety once a drug has been marketed. Some methods used commonly in post-marketing surveillance are described below.

Case reports

The publication of single case reports, or case series, of adverse drug reactions in the medical literature is an important means of detecting new and serious reactions, particularly type B reactions. In the past, case reports

Table 3.4 Immunological mechanisms of adverse drug reactions (according to the Coombs and Gell classification, 1968)

Immunological reaction	Immunological mechanism	Clinical manifestation	Drugs
Type I	IgE mediated	Anaphylaxis	Penicillin
Type II	Humoral cytotoxic	Haemolysis	Methyldopa
Type III	Humoral immune complex (IgM, IgG) mediated	Serum sickness Acute glomerulonephritis Systemic lupus erythematosus	Streptokinase Hydralazine
Type IV	Cell-mediated injury	Morbilliform skin eruptions	Amoxicillin

have been vital in alerting the professions to several serious adverse reactions, for example the oculomucocutaneous syndrome associated with practolol and halothane-induced hepatitis. In recent years, published single case reports have become less important with the emergence of formalized spontaneous reporting systems.

Cohort studies

Cohort studies are prospective studies which study the fate of a large group of patients taking a particular drug. The best studies compare adverse event rates in groups of patients taking the drug of intent with a comparative group. Cohort studies include ad hoc investigations set up to investigate specific problems (e.g. the Royal College of General Practitioners' oral contraceptive study), studies sponsored by pharmaceutical companies, prescription event monitoring (PEM), and a variety of record linkage schemes.

Case–control studies

Case–control studies compare drug usage in a group of patients with a particular disease with use among a matched control group who are similar in potentially confounding factors, but who do not have the disease. The prevalence of drug taking is then compared between the groups and a significant excess of drug takers in the disease group may be evidence of an association with the drug. This is a useful retrospective method which can provide valuable information on the incidence of type B reactions and the association between drugs and disease. Examples of associations which have been established by case–control studies are Reye's syndrome and aspirin, and the relationship between maternal diethylstilbestrol ingestion and vaginal adenocarcinoma in female offspring. The case–control method is an effective means for confirming whether or not a drug causes a given reaction once a suspicion has been raised. It is not capable of detecting previously unsuspected adverse reactions.

Spontaneous reporting schemes

The thalidomide tragedy led to the institution, in many countries, of national schemes for the voluntary collection of adverse drug reaction reports. In the UK the Committee on Safety of Medicines (CSM) adverse reactions reporting scheme ('yellow card'scheme) has been operating for more than 30 years. The scheme has received over 300 000 reports of suspected adverse reactions. Doctors and pharmacists are asked to report all suspected serious adverse reactions, and all suspected reactions to newer products (marked with an inverted black triangle symbol in product information and in the British National Formulary). Spontaneous reporting schemes cannot provide estimates of risk because the true number of cases is invariably underestimated, and the denominator (i.e. the total number of patients treated with the drug in question) is not known. However, the CSM's spontaneous reporting scheme has been shown to provide valuable early warnings or signals of possible adverse drug reactions and to enable the study of associated factors. The main advantages of the scheme are:

- it is easily available for all doctors and pharmacists to report
- it covers all therapeutic agents, including vaccines and herbal medicines
- it is capable of detecting both rare and common reactions
- it is relatively inexpensive to operate.

The main disadvantage of the scheme is the level of under-reporting of reactions; it is likely that fewer than 10% of serious reactions are notified. The scheme operates on the basis that reports should be made despite uncertainty about a causal relationship, irrespective of whether or not the reaction is well recognized, and regardless of other drugs having been given concurrently.

Identification of adverse drug reactions

The establishment of a causal relationship between a specific drug and a clinical event is a fundamental problem in adverse reaction assessment. First, adverse drug reactions frequently mimic other diseases and, second, many of the symptoms attributed to them occur commonly in healthy individuals taking no medication. Thus clinicians may fail to recognize the features of an adverse drug reaction because they do not fit into a clearly defined pattern.

When a suspected adverse reaction has occurred, it may be helpful to try to assess whether it is definitely, probably or possibly due to the drug. This process, known as causality assessment, is fraught with difficulties, although some decision on the likelihood that a drug caused a particular reaction is usually taken, perhaps subconsciously in some cases. Various systematic approaches, or algorithms, have been developed in an attempt to rationalize causality assessment of adverse reactions, but these are of limited value.

Factors taken into account when assessing the likelihood of an adverse drug reaction

Where an adverse drug reaction is suspected, a full history – in particular details of other drugs taken by the patient,

including over-the-counter and herbal medicines – is important (Gruchalia 2000). The patient should be asked about the nature and timing of the symptom or event, and whether such effects have occurred in the past. The temporal relationship of a suspected adverse drug reaction is important. It is relatively easy to recognize an adverse reaction that occurs soon after drug administration and an event predating prescription is clearly unlikely to be drug related. However, once more than a few weeks have elapsed the association between the drug and the event is more difficult. This is well illustrated by the practolol syndrome. There are very few cases where it is certain that a given drug caused a particular reaction in a specific patient, even though the drug is known to cause the reaction in some recipients. Unlike other conditions in medicine, adverse drug reactions rarely produce characteristic physical signs and laboratory investigations. It is reassuring to find that an adverse reaction resolves once a drug is stopped, but this may take time. Occasionally the adverse reaction is irreversible, as in tardive dyskinesia which may actually deteriorate when the offending drug is withdrawn. Rechallenge sometimes occurs inadvertently but is only rarely justified clinically to confirm a diagnosis. Positive rechallenge is often taken as proof of a causal relationship, but this may not always be the case, particularly where the suspected reaction is subjective in nature.

Patients and adverse drug reactions

There is some evidence that patients themselves are capable of correctly distinguishing probable adverse drug reactions from other types of adverse clinical event (Mitchell et al 1994, Egberts et al 1996). An increasing proportion of patients and their carers wish to be involved in decisions about medication. In an investigation of the attitudes of patients with ankylosing spondylitis, 47% reported serious adverse drug reactions associated with their medication. They regarded insufficient information and inadequate monitoring by the doctor as important causes of adverse drug reactions (O'Brien et al 1990). A recent US study of 2500 hospital out-patients attempted to determine whether patients believed the physician should use discretion in the amount of information given to them on potential adverse drug reactions. It found that most individuals wanted to be told of all possible adverse effects and did not favour physician discretion (Ziegler et al 2001). It seems reasonable to expect that providing education for patients about their drug therapy could assist in preventing or minimizing ADRs. Such intervention needs to be carefully constructed and balanced, with risks and benefits being kept in perspective. This type of educational initiative is costly but it could turn out to be money well spent in the long term by reducing ADRs and associated morbidity.

The pharmacist's role

Ensuring that medicines are used safely is fundamental to the pharmacist's role. Pharmacists' involvement in patient care should result in prevention of some, and early detection of other ADRs. Recent studies have demonstrated that pharmacist involvement with patients averted a large number of potential adverse reactions (Lesar at al 1997, Leape et al 1999). Based on knowledge of relevant patient and medication factors, pharmacists can ensure that prescribing is as safe as reasonably possible. Medication counselling should include alerting the patient to potential adverse effects. The pharmacist also has a significant role in the education of other health care professionals about the prevention, detection and reporting of ADRs.

Regulatory authorities in many countries accept reports of adverse reactions from pharmacists; in the USA, pharmacists initiate most reports submitted to the Food and Drug Administration (FDA) via the Medwatch system. In the UK, the involvement of hospital pharmacists has been shown to increase the number of yellow cards submitted to the CSM with no discernible difference in the quality of reports submitted from hospital doctors and hospital pharmacists (Lee et al 1997). Similarly, yellow card reports from community pharmacists have been shown to be comparable to those received from GPs (Davis & Coulson 1999). All pharmacists in the UK are now able to contribute to yellow card reporting. Community pharmacists are well placed to assist in monitoring for problems with over-the-counter medicines, complementary therapies and new medicines.

Conclusion

Adverse drug reactions are an inevitable risk associated with the use of modern medicines. However, careful attention to dosage, taking into account factors such as age and renal function, will minimize the risk of type A reactions in many patients. Genetic status should be taken into account in the few cases where this is appropriate, and it is now possible to genotype individuals, using recombinant DNA methods, for some of the known polymorphisms.

CASE STUDIES

Case 3.1

A 45-year-old black man presented at the accident and emergency department with extreme swelling of his lips and surrounding face. His current medication comprised ramipril 5 mg daily, bendroflumethiazide (bendrofluazide) 2.5 mg daily and reboxetine 4 mg twice daily. He had been taking ramipril and bendroflumethiazide (bendrofluazide) for about 6 months and reboxetine for the last 2 months.

Questions

1. What drug-induced complication do these symptoms suggest?
2. How should it be managed?

Answers

1. Angioedema is the term used to describe soft tissue swelling of the eyes, lips and hands; it is a severe form of urticaria. In severe cases the mouth and larynx can be involved. Angioedema is a recognized problem with all angiotensin-converting enzyme (ACE) inhibitors. The estimated incidence is 0.1–0.5% in Caucasians but may be higher in other racial groups.

   In most cases the reaction occurs in the first week of treatment, often within hours of the initial dose. However, in some cases it has developed after prolonged therapy of up to several years. The mechanism of ACE inhibitor-induced angioedema is thought to involve bradykinin, but angiotensin-II receptor antagonists, which do not affect this substance, can also induce angioedema.
2. Treatment of ACE inhibitor-induced angioedema is governed by the severity of the reaction. ACE inhibitors should be withdrawn immediately in any patient presenting with angioedema. In mild cases, with no airway obstruction, withdrawal of the ACE inhibitor may be sufficient. More serious cases may require stabilization of the airway and administration of i.v. corticosteroids, subcutaneous adrenaline (epinephrine) and antihistamines. Affected patients should not receive further treatment with ACE inhibitors. An alternative drug from a different class (not an angiotensin II antagonist) should be substituted. Angioedema has been described in association with angiotensin II antagonists in patients who have previously experienced this problem with an ACE inhibitor. Angiotensin II anatagonists should therefore be used with extreme caution in such patients.

Case 3.2

A 58-year-old woman was admitted to hospital for investigation after several episodes of syncope. On admission she was taking tibolone 2.5 mg daily, indapamide 2.5 mg daily, sumatriptan and co-codamol, as necessary, for migraine and mizolastine 10 mg daily for hayfever. The ECG showed a prolonged QT interval (the corrected QT interval, QTc, measured 550 ms). All electrolyte concentrations were normal.

Questions

1. Could any of the current medication have contributed to the patient's problem?
2. How should QT interval prolongation be managed?

Answers

1. A number of drugs have the potential to prolong the QT interval on the electrocardiogram (ECG). The QT interval is an indirect measure of the duration of the ventricular action potential and ventricular repolarization. Prolongation of ventricular repolarization can cause arrhythmias, the most characteristic of which is torsade de pointes (twisting of the points), a specific form of ventricular tachycardia. The name describes the characteristic 'twisting'of the QRS complexes around the electrical axis on the ECG, which can appear as an intermittent series of rapid spikes lasting a few seconds during which the heart fails to pump effectively. This is usually a self-limiting arrhythmia that may cause dizziness or syncope, but it can lead to ventricular fibrillation which can cause sudden death. The cause of malfunction may be genetic (congenital long QT syndrome (LQTS)) or related to metabolic disturbance or drug therapy (acquired LQTS). Drugs are thought to prolong repolarization either by blocking potassium channels and thus delaying potassium outflow, or by enhancing inward sodium or calcium currents. QT prolongation is usually assumed to be present when the QT interval corrected for changes in the heart rate (QTc) is greater than 450 ms (men) or 470 ms (women), although arrhythmias are most often associated with values of 550 ms or more.

   The antihistamine mizolastine has a weak potential to prolong the QT interval in a few individuals. The degree of prolongation is described as modest and cardiac arrhythmias have not been reported. This patient is also taking the diuretic indapamide; diuretic use, independent of electrolyte concentrations, is a known risk factor for torsade de pointes.
2. If a patient is suspected to have drug-induced prolongation of the QT interval, the drug(s) implicated should be stopped immediately. In this case, the patient's syncopal episodes may have been related to an arrhythmia. Some patients with torsade de pointes may be asymptomatic, while others experience dizziness, light-headedness, syncope, collapse, irregular heart beat and palpitations. The arrhythmia should be controlled by accelerating the heart rate, either by atrial pacing or by an isoprenaline infusion. Electrolyte abnormalities should be corrected and magnesium sulphate infusion may effectively terminate the arrhythmia, even in the presence of normal magnesium levels. Antiarrhythmic drugs may worsen the problem and should be avoided. Torsade de pointes that degenerates to ventricular fibrillation requires DC shock for termination.

Case 3.3

A 25-year-old woman presents with a prescription for fexofenadine 120 mg daily for an itchy rash. Patient medication records show that she has been taking carbamazepine 200 mg three times daily for the past 3 months.

Question

What action should be taken?

Answer

Carbamazepine causes skin eruptions in about 3% of patients. Eruptions include erythematous, morbilliform, urticarial or purpuric rashes. Toxic epidermal necrolysis and exfoliative dermatitis are well recognized. The time to onset for these reactions after the initiation of carbamazepine is variable, but is generally 6 months or less.

In this case, it may be that the prescriber has overlooked carbamazepine as a possible cause of the rash. The woman should be questioned about the nature of the rash, whether she has a history of skin disease or allergic reactions, and about other potential trigger factors. The prescriber should be contacted to discuss whether the rash may be drug related. If so, carbamazepine should be stopped.

Case 3.4

A consultant psychiatrist asks your advice about a 49-year-old woman who is taking olanzapine 10 mg daily for schizophrenia. The patient has type 2 diabetes which is managed by diet only. Within 6 weeks of starting olanzapine, the patient noted a deterioration in her blood glucose control. Her fasting blood glucose levels before treatment was started were generally in the range 6–9 mmol/l but have now increased to around 12 mmol/l. The patient has gained 2.5 kg in weight since olanzapine was started.

Questions

1. Is olanzapine likely to have worsened diabetic control in this patient?
2. If so, which alternative antipsychotics may be used?

Answers

1. All atypical antipsychotics are associated with weight gain. Olanzapine has been reported to cause or exacerbate diabetes in several published case reports. The exact cause of glucose dysregulation with olanzapine is unclear, but weight gain does not seem to be the sole aetiology.

   It has been postulated that serotonin ($5\text{-}HT_{IA}$) antagonism may decrease the responsiveness of the pancreatic beta cells. This would result in inappropriately low insulin secretion and hyperglycaemia. Further examination of the incidence and aetiology of this problem is needed.
2. Olanzapine is not contraindicated in patients with diabetes, but should be used with careful monitoring of blood glucose control. In this case, where the patient's diabetic control has worsened during therapy, it would be reasonable to discontinue olanzapine and switch to another antipsychotic. Risperidone or quetiapine are alternative atypical antipsychotics not associated with problems in diabetic patients.

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4 Laboratory data

H. A. Wynne C. Edwards

KEY POINTS

- Biochemical and haematological tests provide useful information for the diagnosis, screening, management, prognosis and monitoring of disease.
- Reference ranges are important guides which represent the test values from 95% of the healthy population (mean ± 2 standard deviations).
- A series of values, rather than a single test value, is often required to ensure clinical relevance and to eliminate erroneous values due to patient variation or to analytical or sampling errors.
- A wide variety of intracellular enzymes may be released into the blood following damage to tissues such as cardiac muscle, hepatocytes and skeletal muscle. These can be measured in serum to provide useful diagnostic information.
- Commonly requested biochemical test profiles include so-called 'U and Es', (urea and electrolytes), liver function tests and cardiac enzymes.
- Commonly requested haematological test profiles include full blood count, differential white cell count, erythrocyte sedimentation rate (ESR), serum folate and vitamin B_{12} and iron status.
- Drug therapy can induce abnormal test results.

This chapter will consider the common biochemical and haematological tests that are of clinical and diagnostic importance. For convenience, each individual test will be dealt with under a separate heading and a brief review of the physiology and pathophysiology will be given where appropriate to explain the basis of biochemical and haematological disorders.

It is usual for a reference range to be quoted for each individual test (Table 4.1). This range is based on data obtained from a sample of the general population which is assumed to be disease-free. Many test values have a normal distribution and the reference values are taken as the mean ± 2 standard deviations (SD). This includes 95% of the population. The 'normal' range must always be used with caution since it takes little account of an individual's age, sex, weight, height, muscle mass or disease state, many of which variables can influence the value obtained. Although reference ranges are valuable guides, they must not be used as sole indicators of health and disease. A series of values rather than a simple test value may be required in order to ensure clinical relevance and to eliminate erroneous values caused, for example, by spoiled specimens or by interference from diagnostic or therapeutic procedures. Furthermore, a disturbance of one parameter often cannot be considered in isolation without looking at the pattern of other tests within the group.

Further specific information on the clinical and therapeutic relevance of each test may be obtained by referral to the relevant chapter in this book.

Table 4.1 Biochemical data: typical normal adult reference values measured in serum (or plasma)

Laboratory test	Reference range
Urea and electrolytes	
Sodium	135–145 mmol/l
Potassium	3.5–5.0 mmol/l
Calcium (total)	2.15–2.46 mmol/l
Calcium (ionized)	1.19–1.37 mmol/l
Phosphate	0.80–1.44 mmol/l
Creatinine	50–110 μmol/l
Urea	3.0–8.0 mmol/l
Glucose	
Fasting	3.3–6.0 mmol/l
Non-fasting	< 11.0 mmol/l
Glycated haemoglobin	< 5.5%
Liver function tests	
Albumin	38–50 g/l
Bilirubin (total)	< 19 μmol/l
Bilirubin (conjugated)	< 4 μmol/l
Enzymes	
Alanine transaminase	< 60 U/l
Aspartate transaminase	< 35 U/l
Alkaline phosphatase	35–130 U/l
γ-glutamyl transpeptidase	< 70 U/l
Cardiac markers	
Cardiac troponin (cTnT)	< 0.1 microgram/l
Creatine kinase	< 175 U/l
Lactate dehydrogenase	< 430 U/l
Other tests	
Osmolality	282–295 mmol/kg
Uric acid	0.15–0.47 mmol/l

Biochemical data

The homeostasis of various elements, water and acid–base balance are closely linked, both physiologically and clinically. Standard biochemical screening includes several measurements which provide a picture of fluid and electrolyte balance and renal function. These are commonly referred to colloquially as 'U and Es' (urea and electrolytes) and the major tests are described below.

Sodium and water balance

Sodium and water metabolism are closely interrelated both physiologically and clinically, and play a major role in determining the osmolality of serum.

Water constitutes approximately 60% of body weight in men and 55% in women (women have a greater proportion of fat tissue which contains little water). Approximately two-thirds of body water is found in the intracellular fluid (ICF) and one-third in the extracellular fluid (ECF). Of the ECF 75% is found within interstitial fluid and 25% within serum (Fig. 4.1).

In general, water permeates freely between the ICF and the ECF. Cell walls function as semipermeable membranes, with water movement from one compartment to the other being controlled by osmotic pressure: water moves into the compartment with the higher osmotic concentration. The osmotic content of the two compartments is generally the same, i.e. they are isotonic. However, the kidneys are an exception to this rule.

The osmolality of the ECF is largely determined by sodium and its associated anions, chloride and bicarbonate. Glucose and urea have a lesser but nevertheless important role in determining ECF osmolality. Protein (especially albumin) makes only a small (0.5%) contribution to the osmolality of the ECF but is a major factor in determining water distribution between the two compartments. The contribution of proteins to the osmotic pressure of serum is known as the colloid osmotic pressure, or oncotic pressure.

The major contributor to the osmolality of the ICF is potassium.

The amount of water taken in and lost by the body depends on intake, diet, activity and the environment. Over time the intake of water is normally equal to that lost (Table 4.2). The minimum daily intake necessary to maintain this balance is approximately 1100 ml. Of this, 500 ml is required for normal excretion of waste products in urine, while the remaining volume is lost via the skin in sweat, via the lungs in expired air, and in faeces.

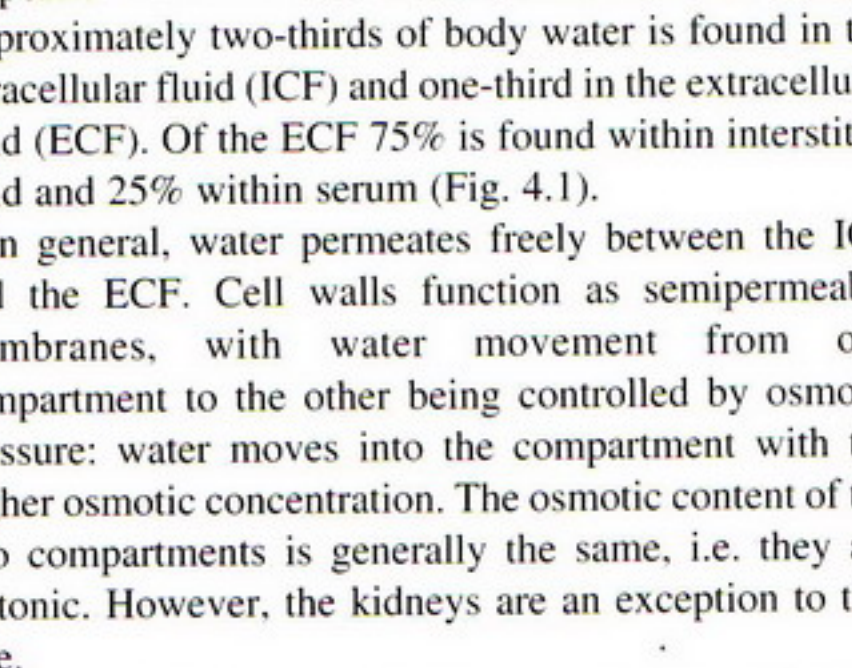

Figure 4.1 Approximate distribution of water in a 70 kg man.

Water depletion

Water depletion will occur if intake is inadequate or loss excessive. Excessive loss of water through the kidneys is unusual except in diabetes insipidus or following the overenthusiastic use of diuretics.

Patients with fever will lose water through the skin and ventilated patients will lose it through the lungs. Diarrhoea causes water depletion. Water loss is usually compensated for if the thirst mechanism is intact or can be responded to, but this may not occur in patients who are unconscious, have swallowing difficulties or are disabled. Severe water depletion may induce cerebral dehydration, causing confusion, fits and coma, and circulatory failure can occur.

The underlying cause for the water depletion should be identified and treated. Replacement water should be given orally where possible, or by nasogastric tube, intravenously or subcutaneously if necessary. About two-thirds of the deficit should be corrected within 24 hours and the remainder during the following 24 hours.

Water excess

Water excess is usually associated with an impairment of water excretion such as that caused by renal failure or the

Table 4.2 Typical daily water balance for a healthy 70 kg adult

	Input (ml)	Output (ml)	
Oral fluids	1400	Urine	1500
Food	700	Lung	400
Metabolic oxidation	400	Skin	400
		Faeces	200
Total	2500		2500

syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This syndrome has several causes including chest infections and some tumours. Excess intake is rarely a cause of water excess since the healthy adult kidney can excrete water at a rate of up to 2 ml/min. Patients affected usually present with signs consistent with cerebral overhydration, although if it is of gradual onset, over several days, they may be asymptomatic. Hyponatraemia is usually present.

Water and ECF osmolality

If the body water content changes independently of the amount of solute, osmolality will be altered (the normal range is 282–295 mmol/kg of water). A loss of water from the ECF will increase its osmolality and result in the movement of water from the ICF to ECF. This increase in ECF osmolality will stimulate the hypothalamic thirst centres to promote a desire to drink while also stimulating the release of vasopressin or antidiuretic hormone (ADH). ADH increases the permeability of the renal collecting ducts to water and promotes water reabsorption with consequent concentration of urine.

If the osmolality of the ECF falls, there is no desire to drink and no secretion of ADH. Consequently a dilute urine is produced which helps restore ECF osmolality to normal.

The secretion of ADH is also stimulated by angiotensin II, arterial and venous baroreceptors, volume receptors, stress (including pain), exercise and drugs such as morphine, nicotine, tolbutamide, carbamazepine and vincristine. If blood volume decreases by more than 10% the hypovolaemia stimulates ADH release and overrides control based on osmolality.

Sodium distribution

The body of an average 70 kg man contains approximately 3000 mmol of sodium. Most of this sodium is freely exchangeable and is extracellular. The normal serum range is 135–145 mmol/l. In contrast, the ICF concentration of sodium is only about 10 mmol/l.

Each day approximately 1000 mmol of sodium is secreted into the gut and 25 000 mmol filtered by the kidney. The bulk of this is recovered by reabsorption from the gut and renal tubules. It should be clear therefore that partial failure of homeostatic control can potentially have major consequences.

Sodium and ECF volume

The ECF volume is dependent upon total body sodium since sodium is almost entirely restricted to the ECF, and water intake and loss are regulated to maintain a constant concentration of sodium in the ECF compartment.

Sodium balance is maintained by renal excretion. Normally, 70% of filtered sodium is actively reabsorbed in the proximal tubule, with further reabsorption in the loop of Henle. Less than 5% of the filtered sodium load reaches the distal tubule where aldosterone can stimulate further sodium reabsorption.

Other factors such as natriuretic peptide hormone can also affect sodium reabsorption. This hormone is secreted by the cardiac atria in response to atrial stretch following a rise in atrial pressure associated with, say, volume expansion. It is natriuretic (increases sodium excretion in urine) and, among other actions, reduces aldosterone concentration.

Sodium depletion

Inadequate oral intake of sodium is rarely the cause of sodium depletion although inappropriate parenteral treatment may occasionally be implicated. Sodium depletion commonly occurs with water depletion, resulting in dehydration or volume depletion. The normal response of the body to the hypovolaemia includes an increase in aldosterone secretion (which stimulates renal sodium reabsorption) and an increase in ADH secretion if ECF volume depletion is severe.

The serum sodium level can give an indication of depletion, but it must be borne in mind that the serum sodium may be:

- increased – e.g. where there is sodium and water loss but with predominant water loss, as occurs in excessive sweating
- normal – e.g. where there is isotonic sodium and water loss, as occurs from burns or a haemorrhage
- decreased – e.g. sodium loss with water retention as would occur if an isotonic sodium depletion were treated with a hypotonic sodium solution.

Sodium excess

Sodium excess can be due to either increased intake or decreased excretion. Excessive intake is not a common cause although iatrogenic hypernatraemia can be associated with excessive intravenous saline infusion.

Sodium excess is usually due to impaired excretion. It may also be caused by a primary mineralocorticoid excess (for example Cushing's syndrome or Conn's syndrome), but is often due to a secondary hyperaldosteronism associated with, for example, congestive cardiac failure, nephrotic syndrome, hepatic cirrhosis with ascites, or renal artery stenosis. Sodium and water retention causes oedema.

Hypernatraemia

The signs and symptoms of hypernatraemia include muscle weakness and confusion.

Drug-induced hypernatraemia is often the result of a nephrogenic diabetes insipidus-like syndrome whereby the renal tubules are unresponsive to ADH. The affected patient presents with polyuria, polydipsia or dehydration. Lithium and phenytoin are the most commonly implicated drugs.

- The diabetes insipidus-like syndrome with lithium has been reported after only 2 weeks of therapy. The syndrome is usually reversible on discontinuation. While affected, however, many patients are unresponsive to exogenous ADH.
- Demeclocycline can also cause diabetes insipidus and has been used in the management of patients with the syndrome of inappropriate ADH secretion (SIADH).
- Phenytoin generally has a less pronounced effect on urinary volume than lithium or demeclocycline, and does not cause nephrogenic diabetes insipidus. It inhibits ADH secretion at the level of the central nervous system.

Hypernatraemia can be caused by a number of other drugs (Table 4.3) and by a variety of mechanisms; for example, hypernatraemia secondary to sodium retention is known to occur with corticosteroids while the administration of sodium-containing drugs parenterally in high doses also has the potential to cause hypernatraemia.

Table 4.3 Examples of drugs known to cause hypernatraemia

Adrenocorticotrophic hormone
Anabolic steroids
Androgens
Carbenoxolone
Clonidine
Corticosteroids
Diazoxide
Lactulose
Methyldopa
Oestrogens
Oral contraceptives
Phenylbutazone
Sodium bicarbonate

Hyponatraemia

A fall in the serum sodium level can be the result of sodium loss, water retention in excess of sodium, or a combination of both factors. A number of drugs have also been implicated as causing hyponatraemia (Table 4.4).

The inappropriate secretion of ADH is the mechanism underlying many drug-induced hyponatraemias. In this syndrome the drug may augment the action of endogenous ADH (e.g. chlorpropamide), increase the release of ADH (e.g. carbamazepine), or have a direct ADH-like action on the kidney (e.g. oxytocin). Hyponatraemia can also be induced by mechanisms different from those described above. Lithium may cause renal damage and a failure to conserve sodium. Likewise the natriuretic action of diuretics can predispose to hyponatraemia.

Table 4.4 Examples of drugs known to cause hyponatraemia

Aminoglutethimide
Amitriptyline and other tricyclic antidepressants
Amphotericin
Captopril and other angiotensin-converting enzyme (ACE) inhibitors
Carbamazepine
Chlorpropamide
Cisplatin
Clofibrate
Cyclophosphamide
Diuretics
Heparin
Lithium
Miconazole
Non-steroidal anti-inflammatory drugs (NSAIDs)
Opiates
Oxcarbazepine
Tolbutamide
Vasopressin
Vincristine

Potassium

The total amount of potassium in the body, like sodium, is 3000 mmol. About 10% of the body potassium is bound in red blood cells, bone and brain tissue and is not exchangeable. The remaining 90% of total body potassium is free and exchangeable with the vast majority having an intracellular location. Only 2% of the exchangeable total body potassium is in the ECF, the compartment from which the serum concentration is sampled and measured. Consequently, the measurement of serum potassium is not an accurate index of total body potassium, but together with the clinical status of a patient it permits a sound practical assessment of potassium homeostasis.

The serum potassium concentration is controlled mainly by the kidney with the gastrointestinal tract normally having a minor role. The potassium filtered in the kidney is almost completely reabsorbed in the proximal tubule. Potassium secretion is largely a passive process in response to the need to maintain membrane potential neutrality associated with active reabsorption of sodium in the distal convoluted tubule and collecting duct. The extent of potassium secretion is determined by a number of factors, including:

- the amount of sodium available for exchange in the distal convoluted tubule and collecting duct
- the availability of hydrogen and potassium ions for exchange in the distal convoluted tubule or collecting duct
- the ability of the distal convoluted tubule or collecting duct to secrete hydrogen ions
- the concentration of aldosterone
- tubular fluid flow rate.

As described above, both potassium and hydrogen can neutralize the membrane potential generated by active sodium reabsorption and consequently there is a close relationship between potassium and hydrogen ion homeostasis. In acidosis, hydrogen ions are normally secreted in preference to potassium – i.e. hyperkalaemia is often associated with acidosis (except in renal tubular acidosis). In alkalosis fewer hydrogen ions will be present and potassium is excreted – i.e. hypokalaemia is often associated with alkalosis.

The normal daily dietary intake of potassium is of the order of 60--200 mmol, which is more than adequate to replace that lost from the body. It is unusual for a deficiency of normal intake to account for hypokalaemia. A transcellular movement of potassium into cells, loss from the gut or excretion in the urine are the main causes of hypokalaemia.

Hypokalaemia

Transcellular movement into cells. The shift of potassium from the serum compartment of the ECF into cells accounts for the hypokalaemia reported following intravenous or, less frequently, nebulized administration of β-adrenoceptor agonists such as salbutamol. Parenteral insulin also causes a shift of potassium into cells, and is used for this purpose in the acute management of patients with hyperkalaemia.

Loss from the gastrointestinal tract. Although potassium is secreted in gastric juice, much of this, together with potassium ingested in the diet, is reabsorbed in the small intestine. Stools do contain some potassium, but in a patient with chronic diarrhoea or a fistula considerable amounts of potassium may be lost and precipitate hypokalaemia. Likewise, the abuse of laxatives increases gastrointestinal potassium loss and may precipitate hypokalaemia. Analogous to the situation with diarrhoea, the potassium secreted in gastric juice may be lost following persistent vomiting and can also contribute to hypokalaemia.

Loss from the kidneys. Mineralocorticoid excess, whether it be due to primary or secondary hyperaldosteronism or Cushing's syndrome, can increase urinary potassium loss and cause hypokalaemia. Likewise, increased excretion of potassium can result from renal tubular damage. Nephrotoxic antibiotics such as gentamicin have been implicated in this.

Many drugs which can induce hypokalaemia do so by affecting the regulatory role of aldosterone upon potassium–sodium exchange in the distal tubule and collecting duct. Administered corticosteroids mimic aldosterone and can therefore increase potassium loss.

Perhaps the most commonly used groups of drugs that can cause hypokalaemia are thiazide and loop diuretics. Both groups of drugs increase the amount of sodium delivered and available for reabsorption at the distal convoluted tubule and collecting duct. Consequently, this will increase the amount of potassium excreted from the kidneys. Some of the drugs known to cause hypokalaemia are shown in Table 4.5.

Clinical features. The patient with moderate hypokalaemia may be asymptomatic, but the symptoms of more severe hypokalaemia include muscle weakness, hypotonia, paralytic ileus, depression and confusion. Arrhythmias may occur. Typical changes on the electrocardiogram (ECG) are of ST depression, T wave depression/inversion and prolonged P–R interval. Insulin secretion in response to a rising blood glucose concentration requires potassium and this mechanism may be impaired in hypokalaemia. Rarely there may be impaired renal concentrating ability with polyuria and polydipsia.

Hypokalaemia is managed by giving either oral potassium or intravenous potassium, depending on its severity.

Hyperkalaemia

Hyperkalaemia may arise from excessive intake, decreased elimination or shift of potassium from cells to

Table 4.5 Examples of drugs known to cause hypokalaemia

Amphotericin
Aspirin
Corticosteroids
Diuretics
Gentamicin
Glucose
Insulin
Laxatives
Benzylpenicillin (penicillin G) (sodium salt)
Piperacillin + tazobactam
Salicylates
Sodium bicarbonate
Sodium chloride
Terbutaline
Ticarcillin + clavulanate

Table 4.6 Examples of drugs known to cause hyperkalaemia

Angiotensin-converting enzyme (ACE) inhibitors
Antineoplastic agents (e.g. cyclophosphamide, vincristine)
Non-steroidal anti-inflammatory drugs (NSAIDs)
β-adrenoceptor blocking agents
Ciclosporin
Digoxin (in acute overdose)
Diuretics, potassium sparing (amiloride, triamterene, spironolactone)
Heparin
Isoniazid
Lithium
Penicillins (e.g. potassium salt)
Potassium supplements
Succinylcholine chloride
Tetracycline

the ECF. It is rare for excessive oral intake to be the sole cause of hyperkalaemia. The inappropriate use of parenteral infusions containing potassium is probably the most common iatrogenic cause of excessive intake. Hyperkalaemia is a common problem in patients with renal failure due to their inability to excrete a potassium load.

The combined use of potassium-sparing diuretics such as amiloride, triamterene or spironolactone with an angiotensin-converting enzyme (ACE) inhibitor, which will lower aldosterone, is a recognized cause of hyperkalaemia, particularly in the elderly. Mineralocorticoid deficiency states such as Addison's disease where there is a deficiency of aldosterone also decrease renal potassium loss and contribute to hyperkalaemia.

The majority of body potassium is intracellular. Severe tissue damage, catabolic states or impairment of the energy-dependent sodium pump, caused by hypoxia or diabetic ketoacidosis, may result in apparent hyperkalaemia due to potassium moving out of and sodium moving into cells. Table 4.6 gives examples of some drugs known to cause hyperkalaemia.

Haemolysis during sampling or a delay in separating cells from plasma will result in potassium escaping from red blood cells into plasma and causing an artefactual hyperkalaemia.

Clinical features. Hyperkalaemia can be asymptomatic but fatal. An elevated potassium level has many effects on the heart, notably the resting membrane potential is lowered and the action potential shortened. Characteristic changes of the ECG precede ventricular fibrillation and cardiac arrest.

In emergency management of a patient with hyperkalaemia (>6.5 mmol/l ± ECG changes), intravenous calcium gluconate (or chloride) at a dose of 10 ml of 10% solution is given intravenously over 5 minutes. This does not reduce the potassium concentration but antagonizes the effect of hyperkalaemia on cardiac tissue. Immediately thereafter, glucose 50 g with 20 units soluble insulin, for example, by intravenous infusion, will lower serum potassium levels within 30 minutes by increasing the shift of potassium into cells.

If acidosis is present, bicarbonate administration may be considered.

The long-term management of hyperkalaemia may involve the use of oral or rectal polystyrene cation-exchange resins which remove potassium from the body.

Chronic hyperkalaemia in renal failure is managed by a low potassium diet.

Calcium

The body of an average man contains about 1 kg of calcium and 99% of this is bound to bone. Calcium is present in serum bound mainly to the albumin component of protein (46%), complexed with citrate and phosphate (7%), and as free ions (47%). Only the free ions of calcium are physiologically active. Calcium metabolism is regulated by parathyroid hormone (PTH) which is inhibited by increased serum concentrations of calcium ions. PTH is secreted in response to low calcium concentrations and increases serum calcium by actions on osteoclasts, kidney and gut.

The serum calcium level is often determined by measuring total calcium, i.e. that which is free and bound, but the measurement of free or ionized calcium offers advantages in some situations.

In alkalosis, hydrogen ions dissociate from albumin, and calcium binding to albumin increases, together with an increase in complex formation. If the concentration of ionized calcium falls sufficiently, clinical symptoms of hypocalcaemia may occur despite the total serum calcium concentration being unchanged. The reverse effect (i.e. increased ionized calcium), occurs in acidosis.

Changes in serum albumin also affect the total serum calcium concentration independently of the ionized concentration. A variety of equations are available to estimate the calcium concentration. A commonly used formula is shown in Figure 4.2. Caution must be taken when using such a formula in the presence of disturbed blood hydrogen ion concentrations.

Hypercalcaemia

Hypercalcaemia may be caused by a variety of disorders, the most common being hyperparathyroidism and malignancy. Hypercalcaemia of malignancy is seen in multiple myeloma and carcinomas which metastasize in bone. It is also seen in squamous carcinoma of the bronchus, as a result of a peptide with PTH-like activity, produced by the tumour. Hypercalcaemia also occurs in thyrotoxicosis, vitamin A and D intoxication, renal transplantation and acromegaly.

Thiazide diuretics, lithium, tamoxifen and calcium supplements used in the management of osteoporosis are examples of some of the drugs which can cause hypercalcaemia.

An artefactual increase in total plasma calcium may sometimes be seen as a result of a tourniquet being applied during venous sampling. The resulting venous stasis may cause redistribution of fluid from the vein into the extravascular space, and the temporary haemoconcentration will affect albumin levels.

Management of hypercalcaemia involves correction of any dehydration with normal saline followed by furosemide (frusemide) which inhibits tubular reabsorption of calcium. Bisphosphonates are used to inhibit bone turnover.

For albumin < 40 g/l:

Corrected calcium = [Ca] + 0.02 × (40 – [alb]) mmol/l

For albumin > 45 g/l:

Corrected calcium = [Ca] – 0.02 ([alb] – 45) mmol/l

Figure 4.2 Formula for correction of total plasma calcium concentration for changes in albumin concentration: albumin concentration = [alb] (albumin units = g/l); calcium concentration = [Ca] (total calcium units = mmol/l).

Hypocalcaemia

Hypocalcaemia can be caused by a variety of disorders including hypoalbuminaemia, hypoparathyroidism, pancreatitis and those that cause vitamin D deficiency, e.g. malabsorption, reduced exposure to sunlight, liver disease and renal disease. In alkalaemia (for instance as may occur when a patient is hyperventilating) there is an increase in protein binding of calcium, which can result in a fall in plasma levels of ionized calcium, manifesting itself as paraesthesiae or tetany.

Drugs that have been implicated as causing hypocalcaemia include phenytoin, phenobarbital, aminoglycosides, phosphate enemas, calcitonin, mithramycin and furosemide (frusemide).

Phosphate

About 80% of body phosphate is in bone, 15% in intracellular fluid and only 0.1% in extracellular fluid. Its major function is in energy metabolism. Plasma levels are regulated by absorption from the diet, which is partly under the control of vitamin D, and PTH which controls its excretion by the kidney.

Hypophosphataemia

Excessive use of antacids may result in binding of dietary phosphate in the gut. Phosphate moves into cells as a result of increased glycolysis such as occurs in alkalosis and insulin treatment during diabetic ketoacidosis promotes cellular uptake of the anion. Hypophosphataemia is also seen in renal failure, parenterally fed patients and chronic alcohol abuse.

Clinical features. Severe hypophosphataemia can cause muscle weakness and wasting and some skeletal wasting.