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Introduction to Clinical Pharmacokinetics

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Abstract

Clinical pharmacokinetics is the study of the relationships between drug dosage regimens and concentration–time profiles. The three fundamental parameters that control these relationships are: clearance – the volume of fluid completely cleared of drug per unit time; volume of distribution – the apparent volume into which the drug has distributed to produce the measured concentration; and elimination half-life – the time taken for 50% of the drug to be eliminated. Knowledge of distribution volume can be used to calculate a loading dose so as to achieve a target concentration quickly, while knowledge of clearance can be used to calculate the dose rate required to maintain a target concentration. Elimination half-life determines the time taken for a dose of drug to be eliminated from the body and the time taken to reach steady state, and can be used to calculate the optimal dosage interval to produce the target peak-to-trough difference.

Key words: Pharmokinetics – Paediatrics – Dosage regimen design

Introduction

In clinical practice, pharmacokinetic principles are used to characterise the relationships between drug dosage regimens and drug concentration–time profiles. Attainment of the correct dosage regimen is of fundamental importance: low doses are likely to be ineffective, whereas excessive doses are likely to produce toxic effects. However, it may be difficult to identify clearly the relationship between drug dose and therapeutic response because drug handling can vary widely between different individuals, and this leads to a broad range of concentrations being achieved for a given dose. In such circumstances, exploration of the concentration–effect relationship may be more useful, even when there is a time-lag between the attainment of the maximum concentration and the development of the maximum effect (as often occurs with intravenous dosing). In this context, more sophisticated data analysis techniques may be required to characterise the relationships between dose, concentration and effect[1,2].

While the identification of a 'target' or 'therapeutic' concentration range may be important, the shape of the concentration–time profile can also be relevant for some drugs. For example, high carbamazepine peaks are liable to produce toxic effects, whereas low troughs may lead to a loss of efficacy. The target, therefore, is a 'flat' profile with little fluctuation in concentration between doses. In contrast, the target profile for an aminoglycoside antibiotic requires high peaks to optimise antimicrobial activity and low troughs to reduce the potential for toxicity, and, potentially, to facilitate drug action[3]. The response to the cancer chemotherapeutic agent cisplatin depends on the patient's overall 'exposure' to the drug[4], whereas the shape of the etoposide concentration–time profile influences the response. Splitting the etoposide dose into small daily amounts is more effective than giving the total amount as a single dose[5].

The primary requirement, therefore, is to identify the ideal concentration–time profile. This requires a detailed knowledge of the *typical* pharmacokinetic parameters, and their variability in the target population, such that dosage regimens can be calculated that achieve these ideal profiles in the majority of patients. Correspondingly, knowledge of *individual* pharmacokinetic parameters allows manipulation of dosage regimens to achieve target profiles within a specific patient.

The principles of pharmacokinetics are introduced in the following sections to show how clearance

and volume of distribution can be used to design these dosage regimens.

Absorption

The bioavailability of a drug formulation, i.e. *F*, the fraction absorbed, is the proportion of the administered dose that reaches the systemic circulation. Although particularly relevant for oral therapy, a bioavailability of < 100% also occurs when drugs are given by routes of administration such as intramuscularly, subcutaneously, intranasally or transdermally. According to convention, bioavailability is determined by comparing the area under the concentration–time curve (AUC) after the test route of administration with the AUC after intravenous administration. The AUC ratio, corrected for any differences in dose, provides an estimate of *F* (assuming there is no change in drug elimination between administrations).

Factors that influence bioavailability include the physicochemical characteristics of the drug and its formulation; the extent of 'first-pass' metabolism in the gut wall and liver; concomitant drug therapy; blood flow and gut motility; and vomiting and diarrhoea. In general, the absorption of drugs with a low bioavailability tends to be more variable among patients and is more likely to be affected by disease states and drug or food interactions. As an illustrative example, toxicity associated with elevated concentrations of both cyclosporin and terfenadine has been linked to the inhibition of gut wall metabolism by grapefruit juice[6].

The rate at which drugs are absorbed into the systemic circulation often depends on the formulation. Oral liquids are generally absorbed more quickly than tablets and, in turn, tablet formulations are often deliberately manipulated to flatten the concentration–time profile. This modification, which can reduce the potential for toxicity and extend the duration of action, has been undertaken for a number of drugs, such as theophylline, nifedipine and diltiazem.

Volume of Distribution

Volume of distribution (*V*) can be defined as a proportionality constant that links the amount of drug in the body to the measured plasma concentration. As a general rule, *V* does not represent a physiological volume but an *apparent* volume into which the drug would have to distribute to achieve the measured concentration. For example, if the body is considered to be a large bucket of fluid into which a known amount of drug is dropped, the volume of fluid in the bucket can be determined by measuring the drug concentration in the bucket, i.e.

$$\text{Volume (litre)} = \frac{\text{Amount (mg)}}{\text{Concentration (mg/l)}}$$

Figure 1 illustrates this principle. Single 100 mg doses of drug A, drug B and drug C are dropped into three identical 'buckets', each containing the same total volume of fluid. However, when the 'blood' in the centre of the bucket is sampled, the measured drug concentrations vary from 1 mg/l to 100 mg/l and the corresponding volume estimates range from 100 litre to 1 litre. This is caused by differences in the way each drug distributes throughout the bucket. Drug A is evenly distributed, while Drug B binds extensively to proteins in the 'blood compartment' and is only able to cross the semipermeable membrane into the 'tissue compartment' to a very limited extent. This leads to a high concentration when the blood is sampled and consequently a low volume of distribution. In contrast, Drug C binds extensively to proteins in the tissue compartment, and hence the blood concentration is low and the volume estimate is high.

The volume of distribution is therefore mainly determined by the ratio of plasma to tissue binding and by how much of the total amount of drug in the body is outside the sampling compartment (i.e. the blood). Other factors, such as lipid and water solubility, may also be important. For example, the volume of distribution of chloroquine, which accumulates in several tissues, is 204 litre/kg[7], while gentamicin, which is water soluble, has a volume of distribution that approximates to the extracellular fluid volume[8].

Differences in the volume of distribution between paediatric and adult patients reflect differences in body composition. Neonates and young children have a higher proportion of body water per kilogram of body weight and a larger surface area to body weight ratio. As extracellular fluid volume is more closely correlated with body surface area, the volume of distribution of gentamicin, which averages 0.25–0.3 litre/kg in adults, is higher in neonates, at around 0.5 litre/kg[8,9].

Furthermore, in contrast to adults, infants and children have lower concentrations of the principal plasma binding proteins albumin and α_1-acid glycoprotein. The importance of these differences lies in the interpretation of drug concentration measurements. In routine practice, total (bound plus free) drug concentrations are measured, rather than the free, active component. If protein binding is reduced, the same total concentration will result in a higher free concentration. For example, a total phenytoin concentration of 5 mg/l (20 µmol/l) in an infant in whom 20% of the drug is free, will be

equivalent to a total concentration of 10 mg/l (40 µmol/l) in an adult in whom 10% of the drug is free. In both cases, the free concentration would be 1 mg/l (4 µmol/l). These potential differences should also be acknowledged in drug development and paediatric drug research and, if possible, free drug concentrations should be measured.

In clinical practice, knowledge about volume of distribution can be applied to determine the loading dose D_L required to reach a target concentration and, correspondingly, the expected concentration produced by a given loading dose. The loading dose can simply be calculated from the product of target concentration and volume of distribution V_D. For example, the gentamicin dose required to achieve a peak gentamicin concentration of 10 mg/l in a neonate weighing 1 kg would be 10 mg/l × 0.5 litre/kg × 1 kg = 5 mg. Additional correction factors may be required: for example, salt correction factor (s) if the drug is formulated as a salt, molar correction factor (m) if concentrations are reported in molar units and bioavailability (F) if the drug is not administered intravenously. If some drug is already present, the 'target concentration' is adjusted by subtracting the initial concentration. A general expression for calculating loading dose is therefore:

$$D_L = \frac{V_D \times (\text{Target conc.} - \text{Measured conc.})}{Fsm}$$

Clearance

Clearance represents the irreversible removal of a drug from the body and determines the average steady state concentration achieved with a regular maintenance dose. Clearance can be defined as the volume of fluid that is completely cleared of drug per unit time and is the product of *extraction ratio* and blood (or serum) *flow rate*.

Extraction ratio (Figure 2) describes the efficiency with which an organ of elimination (e.g. liver, kidney, etc) removes a drug from the blood. It can be determined by measuring the concentration entering (C_{in}) and leaving (C_{out}) the organ. If $C_{out} = 0$, the drug will be totally removed and the extraction ratio will be 1. However, if $C_{out} = C_{in}$, there is no drug removal and the extraction ratio will be 0. The extraction ratio generally lies somewhere between these two values.

Flow rate determines the rate of drug delivery to the eliminating organ and the units of clearance are therefore volume/time (e.g. litre/h or ml/min).

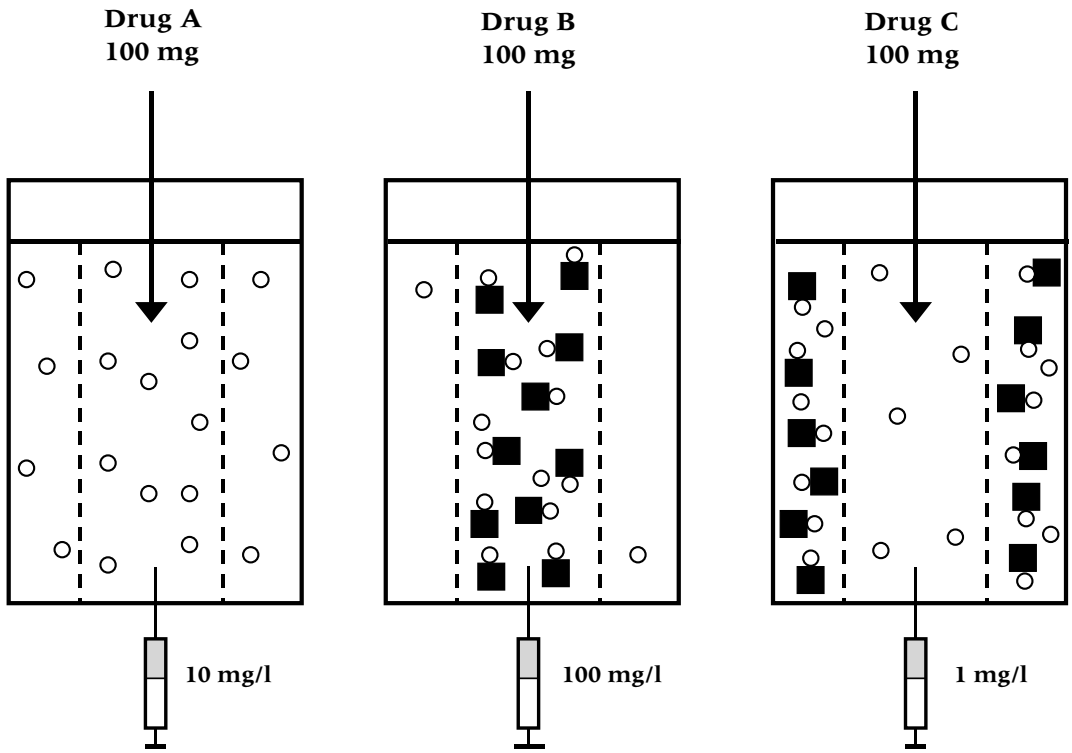
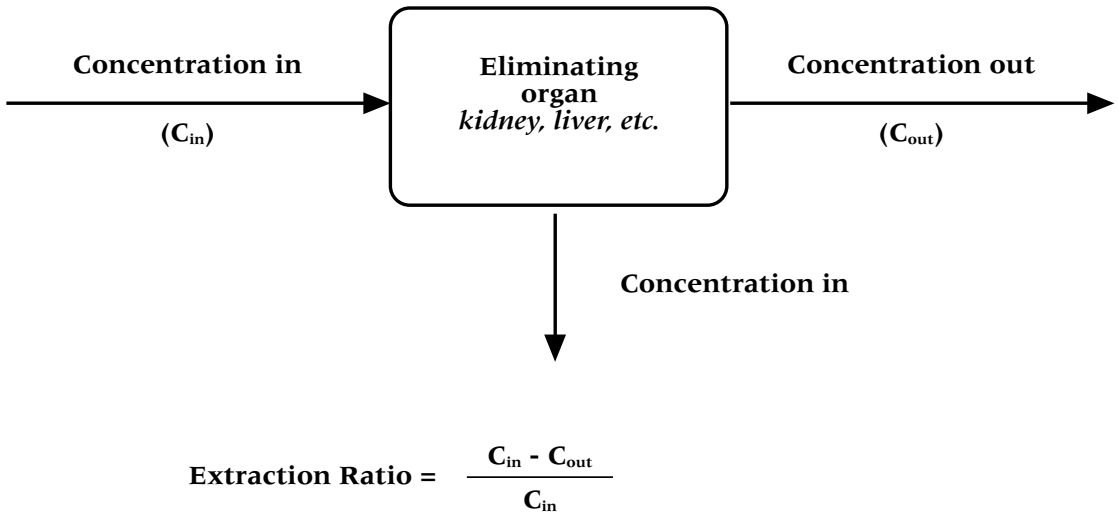


Figure 1. The principle of volume of distribution.
With Drug A, the measured concentration in the sampling compartment is 10 mg/l, therefore the volume is estimated at 10 litre (100 mg/10 mg/l). Drug B is highly bound to plasma proteins, therefore the measured concentration of 100 mg/l results in an estimated volume of 1 litre. Drug C is extensively distributed into the tissues and the measured concentration of 1 mg/l gives an apparent volume of 100 litre.



$$\text{Extraction Ratio} = \frac{C_{in} - C_{out}}{C_{in}}$$

Figure 2. Extraction ratio.
As the drug passes through the organ of removal it can be extracted and removed from the body. The extraction ratio represents the proportion removed and this lies between 0 and 1. An extraction ratio of zero means that none of the drug is removed, while a ratio of 1 means that all of the drug is removed.

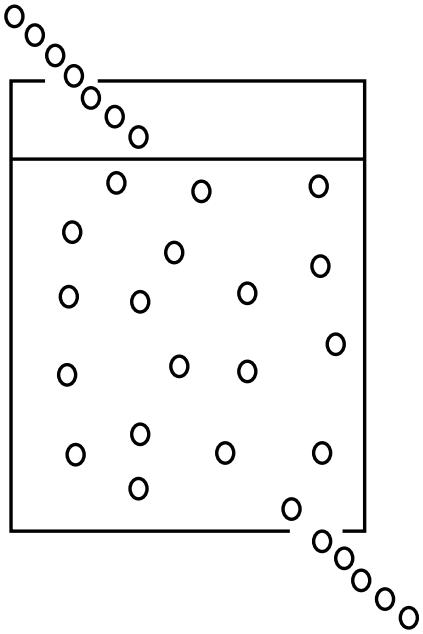


Figure 3. The principle of steady state.
If the drug input rate matches the output rate, the steady state concentration will be maintained.

These theoretical relationships are of limited value for designing dosage regimens in clinical practice but the principles of clearance are fundamentally important. If the 'bucket' in Figure 1 develops a leak, the level can only be maintained if the input rate exactly matches the output rate (Figure 3). Clearance relates the input rate to the level that is maintained.

When a drug is administered as a constant rate infusion, the concentration will gradually increase until the infusion rate is balanced by the elimination rate. From this point onwards the concentration will remain constant. This is known as *steady state* and clearance is the constant that links the dosing rate to the steady state concentration. Consequently, whereas knowledge of volume of distribution allows

calculation of the drug *dose* required to achieve a *target concentration*, knowledge of clearance allows calculation of the *dose rate* required to maintain a *target steady state concentration* (C_{ss}), i.e.

$$\text{Doserate (mg / h)} = \text{Target } C_{ss} \text{ (mg / l)} \times \text{Clearance (litre / h)}$$

This means that if the dose is altered, the steady state concentration will change in direct proportion to the change in dose. Figure 4 illustrates this principle. When the infusion rate is doubled, the steady state concentration also doubles.

The same rules apply to all modes of administration. For multiple oral doses, infusion rate is replaced by dosing rate, i.e. dose/dosage interval, and C_{ss} is replaced by C_{ss} average (the average steady state concentration over the dosage interval). Figure 5 shows a typical oral steady state profile and identifies the peak, trough and average steady state concentrations. C_{ss} average is the most useful measurement for the purposes of dose adjustment, and, if the profile is flat, the sampling time will be less critical such that a trough concentration measurement is often acceptable. Once again, steady state concentrations will change in direct proportion to changes in dose rate and a general expression can be derived that takes into account bioavailability, salt and molar correction factors. Pharmacokinetic convention uses the Greek symbol τ to denote dosage interval.

$$\text{Maintenance dose rate} = \frac{\text{Target } C_{ss} \text{ average} \times \text{Clearance}}{Fsm}$$

Therefore

$$\text{Maintenance dose} = \frac{\text{Target } C_{ss} \text{ average} \times \text{Clearance} \times \tau}{Fsm}$$

Many clinical factors influence clearance and, depending on the therapeutic index of the drug, potentially alter dose requirements. Since clearance generally increases with weight, drugs are often dosed on a milligram per kilogram basis, although body surface area may be a more useful index of the relationship between clearance and 'size'[10]. Most drugs are cleared from the body by hepatic metabolism, renal excretion or a combination of these mechanisms, and so renal impairment and hepatic disease are important determinants of drug dosage requirements. Other clinical conditions that affect the function of these organs, such as cardiac or respiratory disease, may also alter clearance.

When total drug concentrations are measured, clearance will apparently increase if protein binding is reduced (for example, following drug displacement

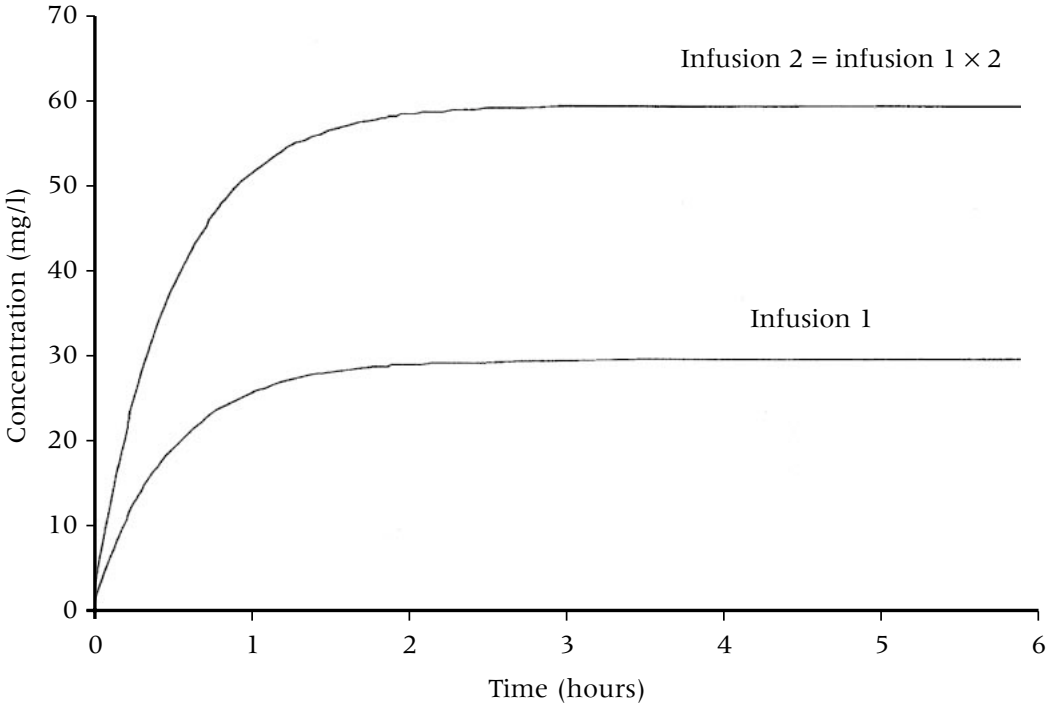


Figure 4. Concentration–time profiles during a constant rate intravenous infusion. The steady state concentration changes in direct proportion to the change in infusion rate. Since the second infusion rate is twice the first, the steady state concentration increases from 30 mg/l to 60 mg/l.

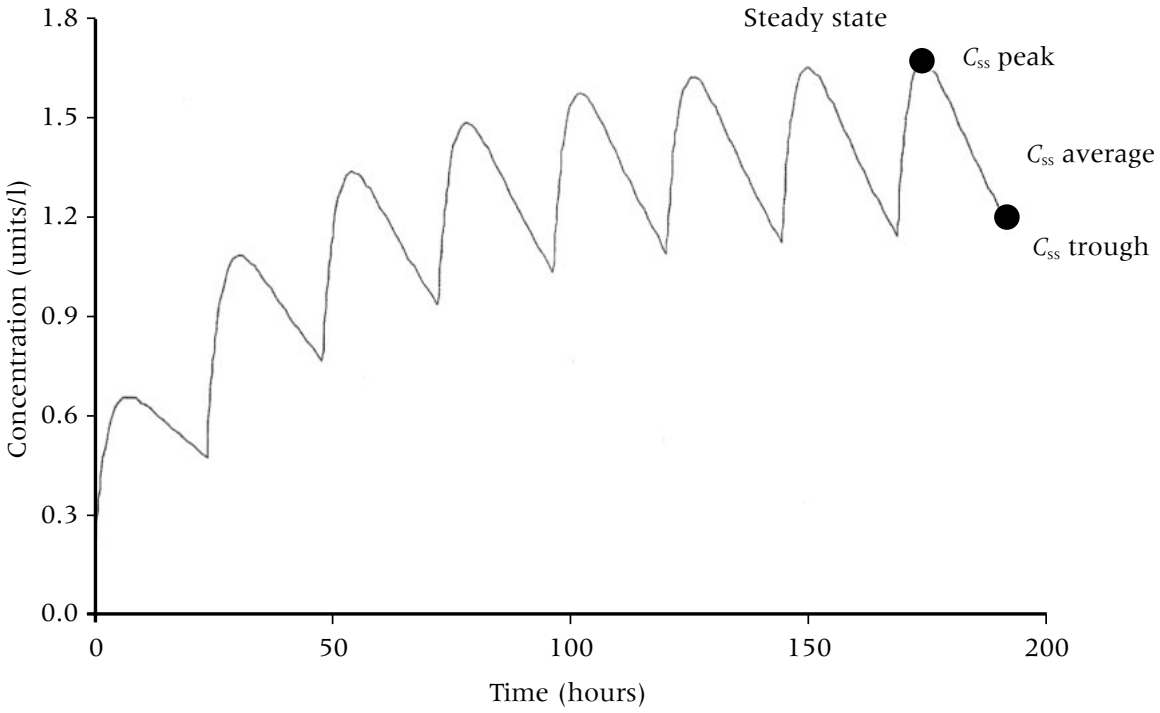


Figure 5. Oral steady state concentration–time profile showing peak, trough and average steady state concentrations.

interactions). However, unless there is also a change in the free drug clearance, steady state free drug concentrations will be unchanged and dosage adjustments are not necessary. Nevertheless, care must be taken in the interpretation of total drug concentration measurements under these circumstances, especially if drug handling is being compared in different patient groups.

Clearance itself may be altered by the addition or removal of concomitant drug therapy. Enzyme inducers such as rifampicin and carbamazepine can increase the clearance of other drugs, while inhibitors such as cimetidine, ciprofloxacin, verapamil and many of the new antidepressants, compete for the metabolic enzymes, leading to a reduction in clearance and increase in the concentration of other drugs. Recent advances in the understanding of the isoenzymes responsible for drug metabolism has led to an increased awareness of the potential for drug interactions and greater ability to predict those that are likely to have clinical significance[11].

Elimination Rate Constant and Elimination Half-life

When a drug is administered as a constant rate infusion, the steady-state concentration–time profile is flat, as illustrated in Figure 4. However, if bolus intravenous doses are given at regular intervals, the concentration will fluctuate between the peak and the trough. The difference between the peak and trough concentrations depends on the dosage interval and the rate of drug elimination. Following other modes of administration, the observed concentration–time profile will be influenced by other factors, such as the duration of a 'pulsed' infusion or the rate of absorption of an oral dose. Figure 6 illustrates how alteration of absorption and elimination rates can influence concentration–time profiles and peak-to-trough ratios.

For most drugs, the rate of elimination from the body is proportional to the amount of drug present. This means that a constant *fraction* of the drug is removed per unit time (e.g. 10% per hour) and the shape of the decline in concentration with time is therefore exponential. Figure 7 shows a typical concentration–time profile for a drug after a single intravenous bolus dose, assuming that the drug distributes instantaneously throughout its volume of distribution. The proportion eliminated per time is known as the elimination rate constant (k) and depends on two parameters – the volume of fluid cleared per time (clearance) and the volume to be cleared (volume of distribution), i.e.

$$k = \frac{\text{Clearance (litre/h)}}{\text{Volume (litre)}}$$

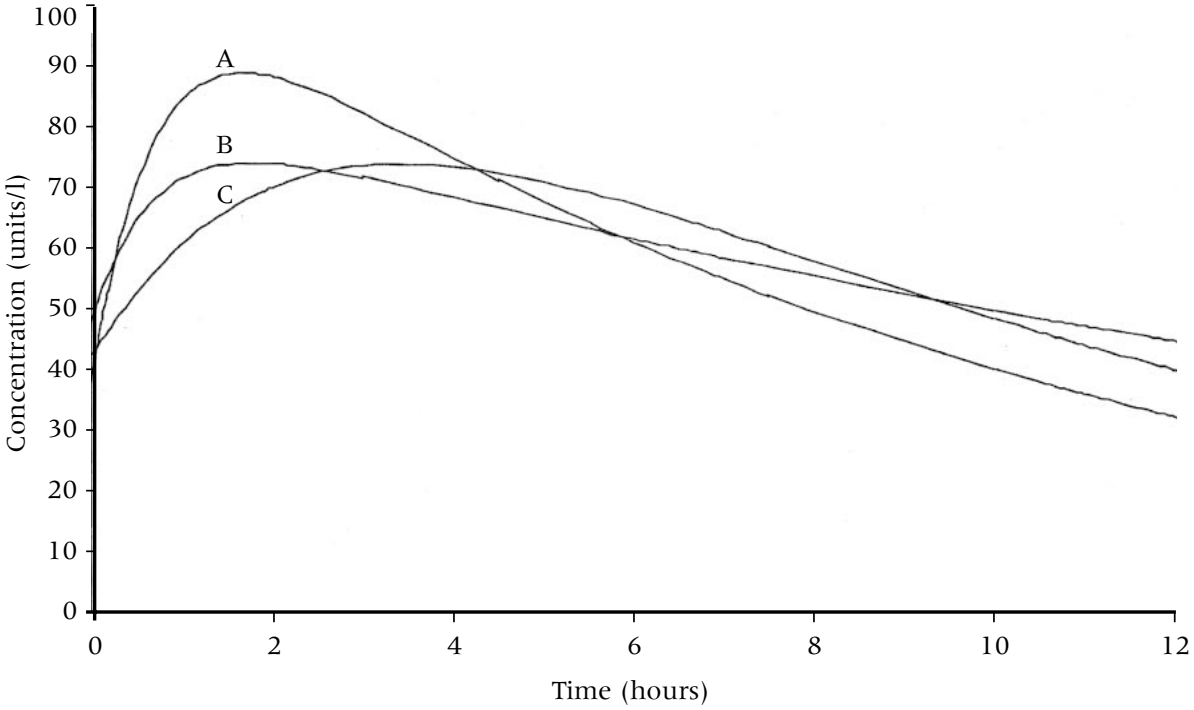


Figure 6. Oral steady state concentration–time profiles illustrating the influence of absorption and elimination rate.
Key:
***A* = absorption rate constant 1.5/h, elimination rate constant 0.1/h. *B* = absorption rate constant 1.5/h, elimination rate constant 0.05 /h. *C* = absorption rate constant 0.4/h, elimination rate constant 0.1/h.**

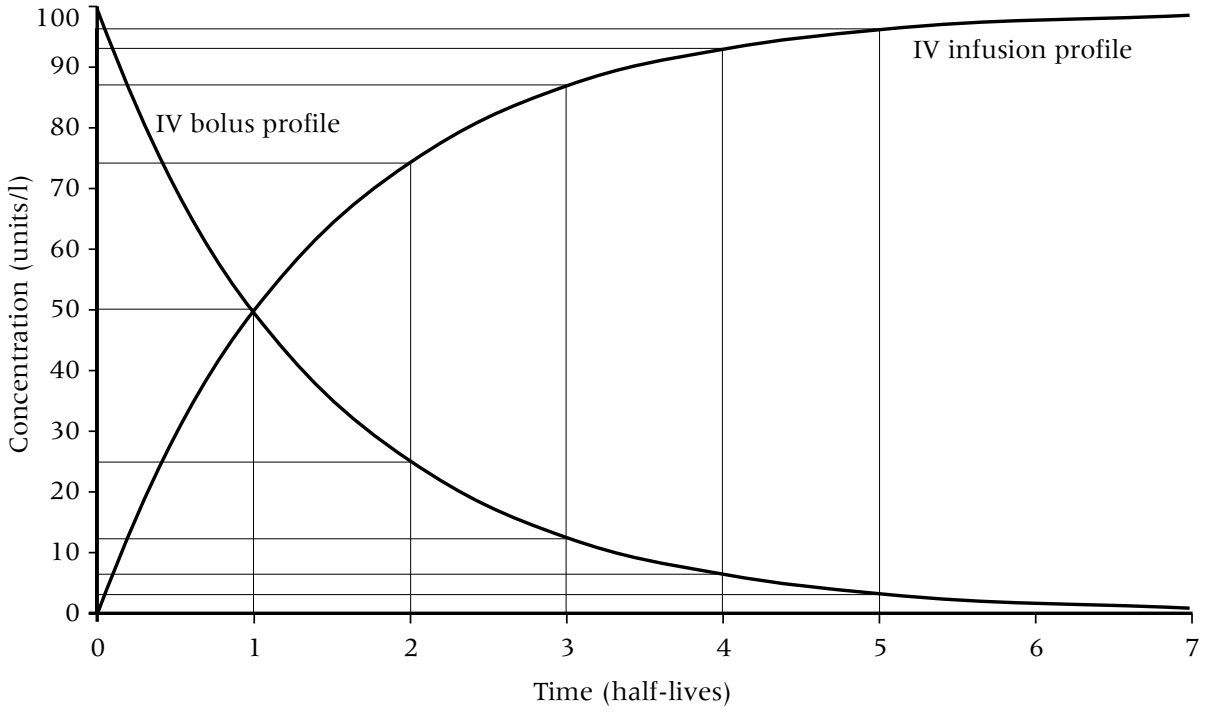


Figure 7. Concentration–time profiles following a single intravenous bolus dose and during a constant rate infusion.
Time is shown in half-lives. 97% of the drug is eliminated and 97% of steady state is achieved in five half-lives.

An associated parameter, elimination half-life, also determines the speed at which a drug is removed from the body. The elimination half-life is defined as the time it takes for the concentration to fall to half its original value: thus, 50% of the dose will be eliminated in one half-life, 75% in two half-lives and 97% after five half-lives (Figure 7). Since the decline is exponential, the relationship between two concentration measurements, C_1 and C_2 taken at times t_1 and t_2, is:

$$C_2 = C_1 \exp[-k(t_2 - t_1)]$$

In one half-life, C_2 will be 50% of C_1, therefore $C_2/C_1 = 0.5$. An expression for the half-life can be obtained by taking the natural logarithm of both sides of the equation, i.e.

$$0.5 = \exp[-kt_{½}]$$
$$\Downarrow$$
$$\ln 0.5 = -k \times t_{½}$$
$$\Downarrow$$
$$-0.693 = -k \times t_{½}$$
$$\Downarrow$$
$$t_{½} = 0.693 / k$$

The time taken to achieve steady state on multiple dosing also depends on the half-life. As illustrated by the infusion profile in Figure 7, 50% of steady state is reached after one half-life, 75% after two half-lives and 97% after five half-lives. Sampling after 4–5 half-lives of therapy therefore gives a good indication of the eventual steady state concentration.

Half-life can be used to determine the appropriate dosage interval to achieve a target concentration–time profile. If a flat profile is desired, the drug must be given at an interval that is less than one half-life, to avoid the concentration fluctuating by 50% or more. In contrast, if the aim is to achieve a high peak and a low trough, e.g. a gentamicin peak above 8 mg/l and a trough < 1 mg/l, the drug needs to be given every 3–4 half-lives to achieve the desired profile (8 ➔ 4 ➔ 2 ➔1 ➔ 0.5). Although drug half-lives are quoted widely in the literature, it should be remembered that these represent average values, often measured in healthy adults. In addition, because elimination half-life depends on both clearance and volume of distribution, changes in half-life may represent either a change in clearance or a change in volume. Conversely, if elimination half-life is unaltered, it is possible that both clearance and volume of distribution have changed by the same proportion. Knowledge about elimination half-life is therefore limited because it offers little guidance on loading or maintenance doses.

Non-linear Pharmacokinetics

For many drugs, both the proportion of an oral dose that is absorbed into the systemic circulation, and the clearance, are relatively constant and not influenced by the dose amount. Under these circumstances, the drug's pharmacokinetics are said to be linear, i.e. if the maintenance dose is doubled, the average steady state concentration will also double. However, not all drugs or drug formulations are characterised by linear pharmacokinetics and the relationships between dose and concentration may be more complex. For example, if drug absorption depends on a carrier transport mechanism, increasing the dose may saturate the transport, leading to a lower than expected increase in concentration. Changing to a smaller dose given more frequently may solve this problem. Other factors that cause non-linearity, or unpredictability in the relationship between dosage regimen and steady state concentration, include enzyme induction or inhibition, non-linear protein binding and changes in clinical status.

Non-linearity caused by dose-dependent changes in clearance occurs with drugs that are cleared by hepatic metabolism, but this is rarely detected in practice because the doses are usually too low. However, clinical doses of phenytoin are close to those that saturate the metabolising enzymes and there is consequently a disproportionate elevation of the steady state concentration as the maintenance dose is increased. This is illustrated in Figure 8 where estimates of the maximum rate of metabolism (V_{max}) and the concentration at half V_{max} (K_m) are used to show how dosage increases would alter C_{ss} average. At low doses, the increase in C_{ss} is essentially linear, but as concentrations of around 10 mg/l are reached, a small increase in dose produces a large increase in C_{ss}. The relationships between dose rate, C_{ss}, V_{max} and K_m are controlled by the Michaelis-Menten equation, i.e.

$$C_{ss}\,(\text{mg/l}) = \frac{K_m\,(\text{mg/l}) \times \text{Dose rate (mg/day)}}{V_{max}\,(\text{mg/day}) - \text{Dose rate (mg/day)}}$$

Maintenance doses of phenytoin must always be below V_{max} (the maximum amount of phenytoin eliminated per day), otherwise concentrations would continue to accumulate and steady state would never be reached. Saturation and 'zero order pharmacokinetics' – where a constant *amount* of drug is eliminated per unit time – therefore only occur at very high concentrations.

Summary

To achieve optimal drug dosage regimens, knowledge of the relationship between the

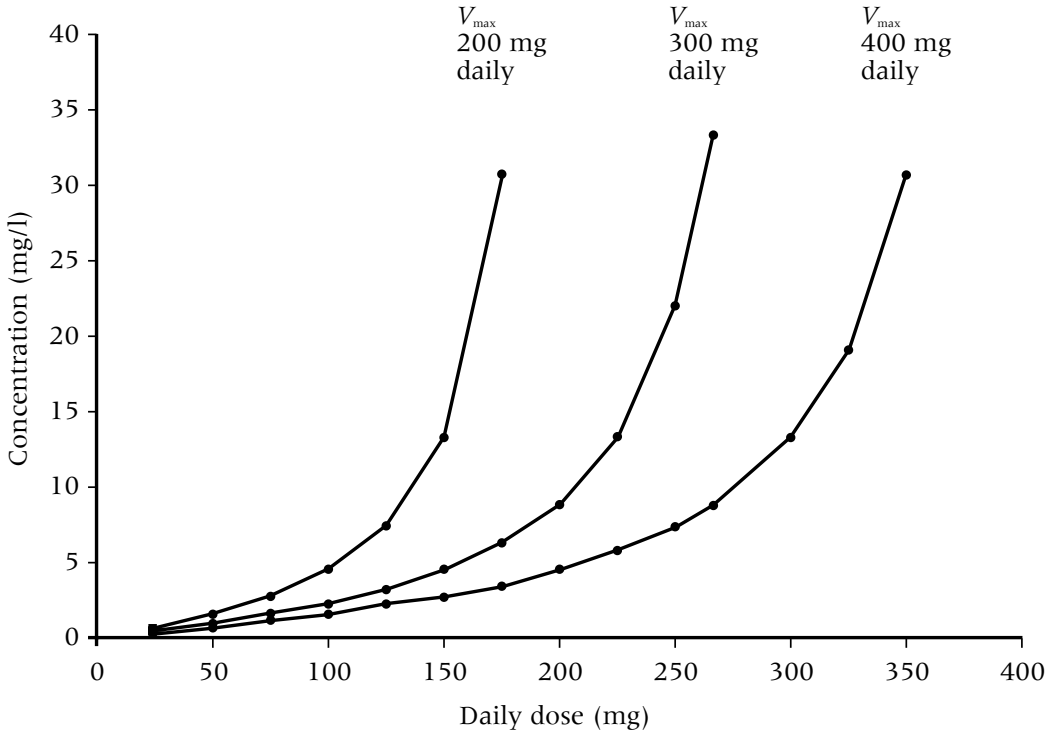


Figure 8. Steady state phenytoin concentrations versus dose for a range of V_{max} values.

concentration–time profile and the therapeutic response is necessary. However, once the target profile has been identified, knowledge of the principal pharmacokinetic parameters – bioavailability, volume of distribution and clearance – can be used to determine the appropriate loading and maintenance doses. Thereafter, elimination rate constant and elimination half-life, which control the rate of decline in concentration, can be used to calculate the optimal dosage interval.

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