1

Basic pharmacokinetics

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Aims and learning outcomes

Pharmacokinetics is a fundamental scientific discipline that underpins applied therapeutics. Patients need to be prescribed appropriate medicines for a clinical condition. The medicine is chosen on the basis of an evidence-based approach to clinical practice and assured to be compatible with any other medicines or alternative therapies the patient may be taking.

The design of a dosage regimen is dependent on a basic understanding of the drug use process (DUP). When faced with a patient who shows specific clinical signs and symptoms, pharmacists must always ask a fundamental question: 'Is this patient suffering from a drug-related problem?' Once this issue is evaluated and a clinical diagnosis is available, the pharmacist can apply the DUP to ensure that the patient is prescribed an appropriate medication regimen, that the patient understands the therapy prescribed, and that an agreed concordance plan is achieved.

Pharmacists using the DUP consider:

- Need for a drug
- Choice of a drug
- Goals of therapy
- Design of regimen
  - Route
  - Dose and frequency
  - Duration
- Monitoring and review
- Counselling

Once a particular medicine is chosen, the principles of clinical pharmacokinetics are required to ensure the appropriate formulation of drug is chosen for an appropriate route of administration. On the basis of the patient's drug handling parameters, which require an understanding of

absorption, distribution, metabolism and excretion, the dosage regimen for the medicine in a particular patient can be developed. The pharmacist will then need to ensure that the appropriate regimen is prescribed to achieve optimal efficacy and minimal toxicity. Pharmacists then ensure that the appropriate monitoring is undertaken and that the patient receives the appropriate information to ensure compliance. Clinical pharmacokinetics is thus a fundamental knowledge base that pharmacists require to ensure effective practice of pharmaceutical care.

The aim of this chapter is to provide the practising clinical pharmacist with the appropriate knowledge and skills of applied clinical pharmacokinetics, which can be applied in everyday practice.

The objectives for this chapter are to enable the reader to:

- State the rationale for using therapeutic drug monitoring (TDM) to optimise drug therapy.
- Identify drugs that should be routinely monitored.
- Define first-order and zero-order kinetics.
- Apply one-compartment pharmacokinetics to single and multiple dosing following the intravenous and oral administration of drugs.
- Apply the basic principles of interpretation of serum drug concentrations in practice.
- Apply one-compartment pharmacokinetics to describe steady-state serum drug concentrations following oral slow-release dosing.
- Use the method of iteration to derive individualised pharmacokinetic parameters from serum drug concentration data.
- Apply nonlinear pharmacokinetics to describe steady-state plasma concentrations following parenteral and/or oral phenytoin therapy.

Introduction

Pharmacokinetics provides a mathematical basis to assess the time course of drugs and their effects in the body. It enables the following processes to be quantified:

Absorption
Distribution
Metabolism
Excretion

These pharmacokinetic processes, often referred to as ADME, determine the drug concentration in the body when medicines are prescribed. A fundamental understanding of these parameters is required to design an

Table 1.1 Drugs that should be routinely monitored

Therapeutic group	*Drugs*
Aminoglycosides	Gentamicin, tobramycin, amikacin
Cardioactive	Digoxin, lidocaine
Respiratory	Theophylline
Anticonvulsant	Phenytoin, carbamazepine, phenobarbital
Others	Lithium, ciclosporin

appropriate drug regimen for a patient. The effectiveness of a dosage regimen is determined by the concentration of the drug in the body.

Ideally, the concentration of drug should be measured at the site of action of the drug; that is, at the receptor. However, owing to inaccessibility, drug concentrations are normally measured in whole blood from which serum or plasma is generated. Other body fluids such as saliva, urine and cerebrospinal fluid (CSF) are sometimes used. It is assumed that drug concentrations in these fluids are in equilibrium with the drug concentration at the receptor.

It should be noted that the measured drug concentrations in plasma or serum are often referred to as drug *levels*, which is the term that will be used throughout the text. It refers to total drug concentration, i.e. a combination of bound and free drug that are in equilibrium with each other.

In routine clinical practice, serum drug level monitoring and optimisation of a dosage regimen require the application of clinical pharmacokinetics. A number of drugs show a narrow therapeutic range and for these drugs therapeutic drug level monitoring is required (Chapter 2). Table 1.1 identifies drugs that should be routinely monitored.

A variety of techniques is available for representing the pharmacokinetics of a drug. The most usual is to view the body as consisting of compartments between which drug moves and from which elimination occurs. The transfer of drug between these compartments is represented by rate constants, which are considered below.

Rates of reaction

To consider the processes of ADME the *rates* of these processes have to be considered; they can be characterised by two basic underlying concepts.

The rate of a reaction or process is defined as the velocity at which it proceeds and can be described as either *zero-order* or *first-order*.

Zero-order reaction

Consider the rate of elimination of drug A from the body. If the amount of the drug, A, is decreasing at a constant rate, then the rate of elimination of A can be described as:

$$\frac{dA}{dt} = -k^*$$

where k^* = the zero-order rate constant.

The reaction proceeds at a constant rate and is independent of the concentration of A present in the body. An example is the elimination of alcohol. Drugs that show this type of elimination will show accumulation of plasma levels of the drug and hence nonlinear pharmacokinetics.

First-order reaction

If the amount of drug A is decreasing at a rate that is proportional to A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

$$\frac{dA}{dt} = -kA$$

where k = the first-order rate constant.

The reaction proceeds at a rate that is dependent on the concentration of A present in the body. It is assumed that the processes of ADME follow first-order reactions and most drugs are eliminated in this manner.

Most drugs used in clinical practice at therapeutic dosages will show first-order rate processes; that is, the rate of elimination of most drugs will be first-order. However, there are notable exceptions, for example phenytoin and high-dose salicylates. In essence, for drugs that show a first-order elimination process one can show that, as the amount of drug administered increases, the body is able to eliminate the drug accordingly and accumulation will not occur. If you double the dose you will double the plasma concentration. However, if you continue to increase the amount of drug administered then all drugs will change from showing a first-order process to a zero-order process, for example in an overdose situation.

Pharmacokinetic models

Pharmacokinetic models are hypothetical structures that are used to describe the fate of a drug in a biological system following its administration.

One-compartment model

Following drug administration, the body is depicted as a kinetically homogeneous unit (see Figure 1.1). This assumes that the drug achieves instantaneous distribution throughout the body and that the drug equilibrates instantaneously between tissues. Thus the drug concentration–time profile shows a monophasic response (i.e. it is monoexponential; Figure 1.2a).

It is important to note that this does not imply that the drug concentration in plasma (C_p) is equal to the drug concentration in the tissues. However, changes in the plasma concentration quantitatively reflect changes in the tissues. The relationship described in Figure 1.2a can be plotted on a log C_p vs time graph (Figure 1.2b) and will then show a linear relation; this represents a one-compartment model.

Two-compartment model

The two-compartment model resolves the body into a central compartment and a peripheral compartment (see Figure 1.3). Although these compartments have no physiological or anatomical meaning, it is assumed that the central compartment comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin.

A two-compartment model assumes that, following drug administration into the central compartment, the drug distributes between that compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution, i.e. equilibration, between the two compartments.

The drug concentration–time profile shows a curve (Figure 1.4a), but the log drug concentration–time plot shows a biphasic response

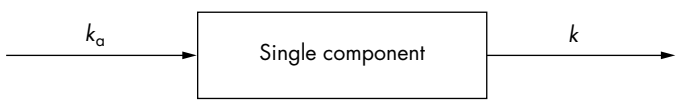

Figure 1.1 One-compartment model. k_a = absorption rate constant (h^{-1}), k = elimination rate constant (h^{-1}).

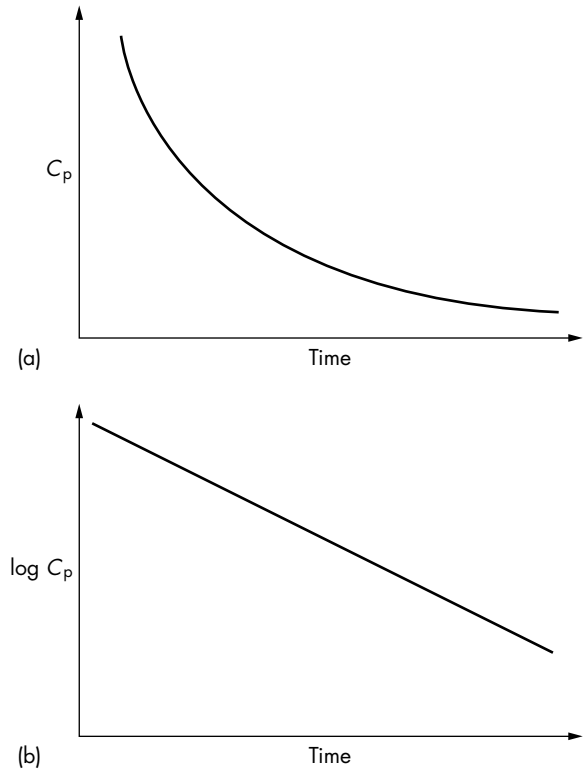

Figure 1.2 (a) Plasma concentration (C_p) versus time profile of a drug showing a one-compartment model. (b) Time profile of a one-compartment model showing log C_p versus time.

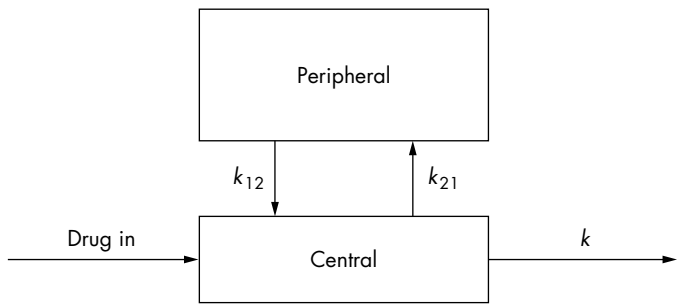

Figure 1.3 Two-compartment model. k_{12}, k_{21} and k are first-order rate constants: k_{12} = rate of transfer from central to peripheral compartment; k_{21} = rate of transfer from peripheral to central compartment; k = rate of elimination from central compartment.

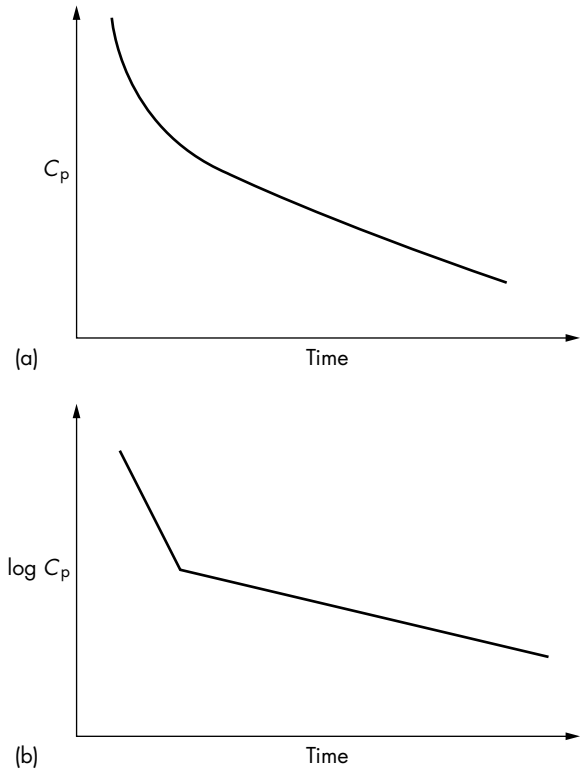

Figure 1.4 (a) Plasma concentration versus time profile of a drug showing a two-compartment model. (b) Time profile of a two-compartment model showing log C_p versus time.

(Figure 1.4b) and can be used to distinguish whether a drug shows a one- or two-compartment model.

Figure 1.4b shows a profile in which initially there is a rapid decline in the drug concentration owing to elimination from the central compartment and distribution to the peripheral compartment. Hence during this rapid initial phase the drug concentration will decline rapidly from the central compartment, rise to a maximum in the peripheral compartment, and then decline.

After a time interval (t), a distribution equilibrium is achieved between the central and peripheral compartments, and elimination of the drug is assumed to occur from the central compartment. As with the one-compartment model, all the rate processes are described by first-order reactions.

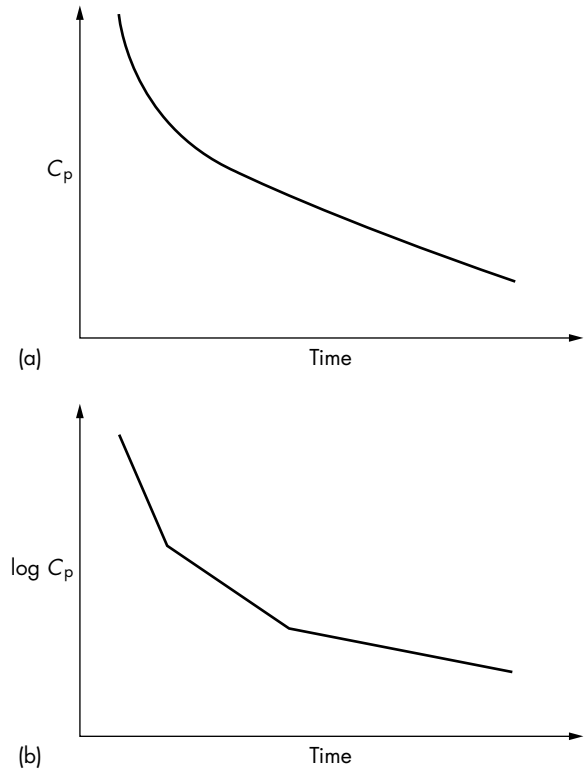

Figure 1.5 (a) Plasma concentration versus time profile of a drug showing multicompartment model. (b) Time profile of a multicompartment model showing log C_p versus time.

Multicompartment model

In this model the drug distributes into more than one compartment and the concentration–time profile shows more than one exponential (Figure 1.5a). Each exponential on the concentration–time profile describes a compartment. For example, gentamicin can be described by a three-compartment model following a single IV dose (see Figure 1.5b).

Pharmacokinetic parameters

This section describes various applications using the one-compartment open model system.

Elimination rate constant

Consider a single IV bolus injection of drug X (see Figure 1.2). As time proceeds, the amount of drug in the body is eliminated. Thus the rate of elimination can be described (assuming first-order elimination) as:

$$\frac{dX}{dt} = -kX$$

Hence

$$X = X_0 \exp(-kt)$$

where X = amount of drug X, X_0 = dose and k = first-order elimination rate constant.

Volume of distribution

The volume of distribution (V_d) has no direct physiological meaning; it is not a 'real' volume and is usually referred to as the *apparent volume of distribution*. It is defined as *that volume of plasma in which the total amount of drug in the body would be required to be dissolved in order to reflect the drug concentration attained in plasma*.

The body is not a homogeneous unit, even though a one-compartment model can be used to describe the plasma concentration–time profile of a number of drugs. It is important to realise that the concentration of the drug (C_p) in plasma is not necessarily the same in the liver, kidneys or other tissues.

Thus C_p in plasma does not equal C_p or amount of drug (X) in the kidney or C_p or amount of drug (X) in the liver or C_p or amount of drug (X) in tissues. However, changes in the drug concentration in plasma (C_p) are proportional to changes in the amount of drug (X) in the tissues. Since

$$C_p \text{ (plasma)} \propto C_p \text{ (tissues) i.e. } C_p \text{ (plasma)} \propto X \text{ (tissues)}$$

Then

$$C_p \text{ (plasma)} = V_d \times X \text{ (tissues)}$$

where V_d is the constant of proportionality and is referred to as the volume of distribution, which thus relates the total amount of drug in the body at any time to the corresponding plasma concentration. Thus

$$V_d = \frac{X}{C_p}$$

and V_d can be used to convert drug amount X to concentration. Since

$$X = X_0 \exp(-kt)$$

then

$$\frac{X}{V_d} = \frac{X_0 \exp(-kt)}{V_d}$$

Thus

$$C_{pt} = C_p^0 \exp(-kt)$$

This formula describes a monoexponential decay (see Figure 1.2), where C_{pt} = plasma concentration at any time t.

The curve can be converted to a linear form (Figure 1.6) using natural logarithms (ln):

$$\ln C_{pt} = \ln C_p^0 - kt$$

where the slope = $-k$, the elimination rate constant; and the y intercept = $\ln C_p^0$. Since

$$V_d = \frac{X}{C_p}$$

then at zero concentration (C_p^0), the amount administered is the dose, D, so that

$$C_p^0 = \frac{D}{V_d}$$

If the drug has a large V_d that does not equate to a real volume, e.g. total plasma volume, this suggests that the drug is highly distributed in tissues. On the other hand, if the V_d is similar to the total plasma volume this will suggest that the total amount of drug is poorly distributed and is mainly in the plasma.

Half-life

The time required to reduce the plasma concentration to one half its initial value is defined as the *half-life* ($t_{1/2}$).

Consider

$$\ln C_{pt} = \ln C_p^0 - kt$$

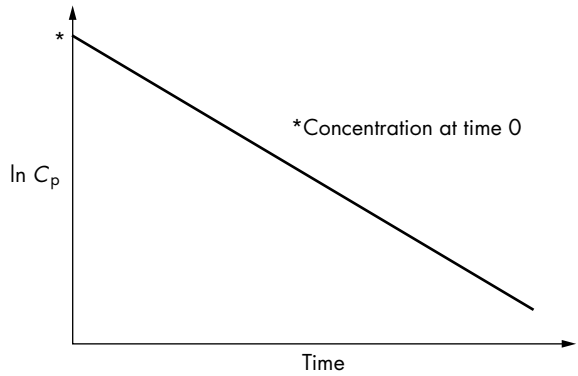

Figure 1.6 Ln C_p versus time profile.

Let C_p^0 decay to $C_p^0/2$ and solve for $t = t_{1/2}$:

$$\ln(C_p^0/2) = \ln C_p^0 - kt_{1/2}$$

Hence

$$kt_{1/2} = \ln C_p^0 - \ln(C_p^0/2)$$

and

$$t_{1/2} = \frac{(\ln 2)}{k}$$

$$t_{1/2} = \frac{0.693}{k}$$

This parameter is very useful for estimating how long it will take for levels to be reduced by half the original concentration. It can be used to estimate for how long a drug should be stopped if a patient has toxic drug levels, assuming the drug shows linear one-compartment pharmacokinetics.

Clearance

Drug clearance (CL) is defined as the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion. Clearance for a drug is constant if the drug is eliminated by first-order kinetics. Drug can be cleared by renal excretion or by metabolism or both. With respect to the kidney and liver, etc., clearances are additive, that is:

$$CL_{total} = CL_{renal} + CL_{nonrenal}$$

Mathematically, clearance is the product of the first-order elimination rate constant (k) and the apparent volume of distribution (V_d). Thus

$$CL_{total} = k \times V_d$$

Hence the clearance is the elimination rate constant – i.e. the fractional rate of drug loss – from the volume of distribution.

Clearance is related to half-life by

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$

If a drug has a CL of 2 L/h, this tells you that 2 litres of the V_d is cleared of drug per hour. If the C_p is 10 mg/L, then 20 mg of drug is cleared per hour.

Pharmacokinetic applications

This section describes how pharmacokinetics can be used in clinical practice.

Single IV administration

Decay from a toxic level

For example, patient D has a potentially toxic digoxin level of 4.5 μg/L. Given that the half-life of digoxin in this patient is 60 h, and assuming that renal function is stable and absorption is complete, for how long should the drug be stopped to allow the level to fall to 1.5 μg/L?

(a) Calculate elimination rate constant (k):

$$k = \frac{0.693}{60}$$
$$= 0.0116\ h^{-1}$$

(b) Time for decay (t) from C_{p1} to C_{p2}

$$t = \frac{\ln C_{p1} - \ln C_{p2}}{k}$$
$$t = \frac{\ln 4.5 - \ln 1.5}{0.0116}$$
$$= 94.7\ h$$

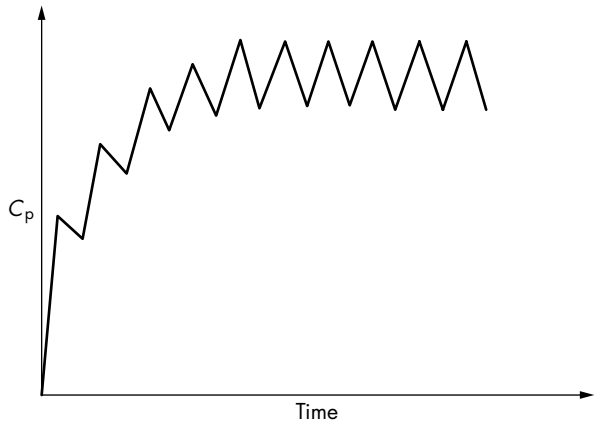

Figure 1.7 Time profile of multiple IV doses.

Hence

$$t = 4 \text{ days}$$

Multiple doses

Some drugs may be used clinically on a single-dose basis, although most drugs are administered continually over a period of time. When a drug is administered at a regular dosing interval (orally or IV), the drug accumulates in the body and the serum concentration will rise until steady-state conditions have been reached, assuming the drug is administered again before all of the previous dose has been eliminated (see Figure 1.7).

Steady state

Steady state occurs when the amount of drug administered (in a given time period) is equal to the amount of drug eliminated in that same period. At steady state the plasma concentrations of the drug (C_p^{ss}) at any time during any dosing interval, as well as the peak and trough, are similar. The time to reach steady-state concentrations is dependent on the half-life of the drug under consideration.

Effect of dose

The higher the dose, the higher the steady-state levels, but the time to achieve steady-state levels is independent of dose (see Figure 1.8). Note that the fluctuations in $C_{p\,max}$ and $C_{p\,min}$ are greatest with higher doses.

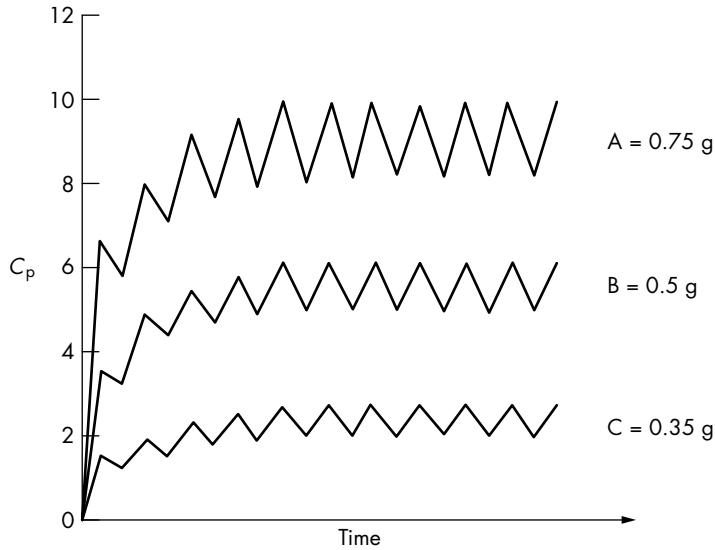

Figure 1.8 Time profiles of multiple IV doses – reaching steady state using different doses.

Effect of dosing interval

Consider a drug having a half-life of 3 h. When the dosing interval, τ, is less than the half-life, $t_{1/2}$, greater accumulation occurs, i.e. higher steady-state levels are higher and there is less fluctuation in $C_{p\ max}$ and $C_{p\ min}$ (see Figure 1.9, curve A). When $\tau > t_{1/2}$, then a lower accumulation occurs with greater fluctuation in $C_{p\,max}$ and $C_{p\,min}$ (see Figure 1.9, curve C).

If the dosing interval is much greater than the half-life of the drug, then $C_{p\ min}$ approaches zero. Under these conditions no accumulation will occur and the plasma concentration–time profile will be the result of administration of a series of single doses.

Time to reach steady state

For a drug with one-compartment characteristics, the time to reach steady state is independent of the dose, the number of doses administered, and the dosing interval, but it is directly proportional to the half-life.

Prior to steady state

As an example, estimate the plasma concentration 12 h after therapy commences with drug A given 500 mg three times a day.

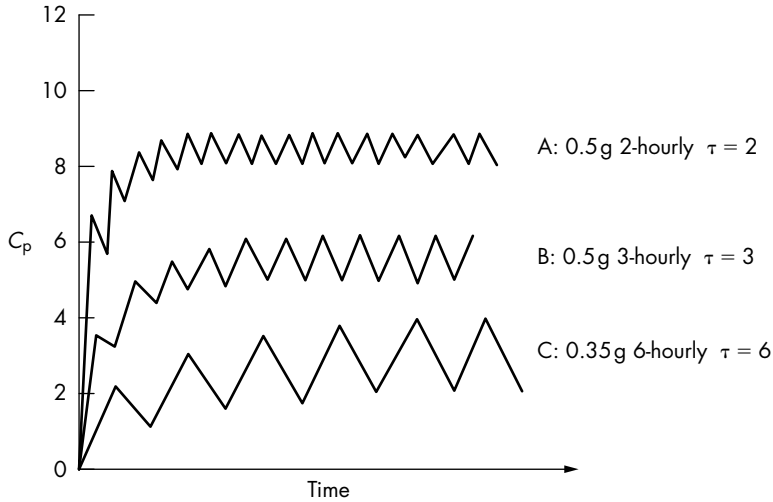

Figure 1.9 Time profiles of multiple IV doses – reaching steady state using different dosing intervals.

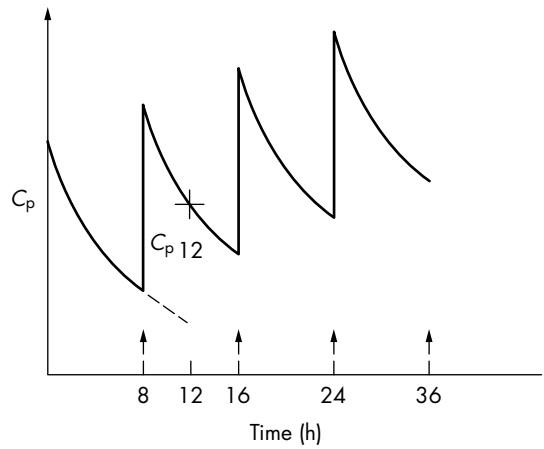

Figure 1.10 Multiple intravenous doses prior to steady state.

Consider each dose as independent and calculate the contribution of each dose to the plasma level at 12 h post dose (see Figure 1.10).

From the first dose:

$$C_{p1} = C_p^0 \exp(-k \times 12)$$

From the second dose:

$$C_{p2} = C_p^0 \exp(-k \times 4)$$

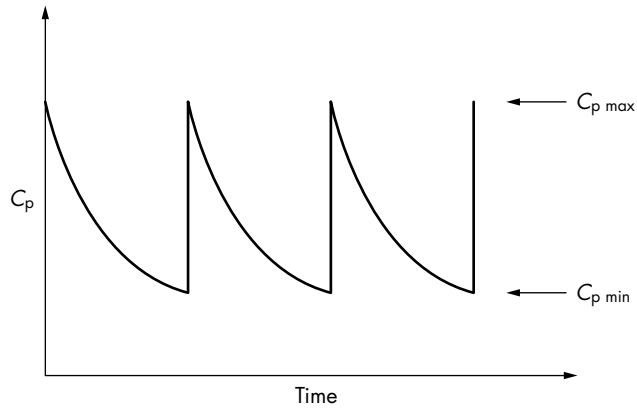

Figure 1.11 Time profile at steady state and the maximum and minimum plasma concentration within a dosage interval.

Thus, total C_{pt} at 12 h is

$$C_{pt} = C_p^0 \exp(-k \times 12) + C_p^0 \exp(-k \times 4)$$

Remember that $C_p^0 = D/V_d$.

This method uses the principle of superposition. The following equation can be used to simplify the process of calculating the value of C_p at any time t after the nth dose:

$$C_{pt} = \frac{D \times [\exp(-kn\tau) \times [\exp(-kt)]}{V_d \times [1 - \exp(-k\tau)]}$$

where n = number of doses, τ = dosing interval and t = time after the nth dose.

At steady state

To describe the plasma concentration (C_p) at any time (t) within a dosing interval (τ) at steady state (see Figure 1.11):

$$C_{pt} = \frac{D \times [\exp(-kt)]}{V_d \times [1 - \exp(-k\tau)]}$$

Remember that $C_p^0 = D/V_d$. Alternatively, for some drugs it is important to consider the salt factor (S). Hence, if applicable, $C_p^0 = SD/V_d$ and:

$$C_{pt} = \frac{S \times D \times [\exp(-kt)]}{V_d \times [1 - \exp(-k\tau)]}$$

To describe the maximum plasma concentration at steady state (i.e. $t = 0$ and $\exp(-kt) = 1$):

$$C_{\text{p max}} = \frac{D \times 1}{V_{\text{d}} \times [1 - \exp(-k\tau)]}$$

To describe the minimum plasma concentration at steady state (i.e. $t = \tau$):

$$C_{\text{p min}} = \frac{D \times [\exp(-k\tau)]}{V_{\text{d}} \times [1 - \exp(-k\tau)]}$$

To describe the average steady-state concentration, C_{p}^{ss} (this notation will be used throughout the book):

$$C_{\text{p}}^{\text{ss}} = \frac{D}{\text{CL} \times \tau} \quad \text{or} \quad C_{\text{p}}^{\text{ss}} = \frac{S \times D}{\text{CL} \times \tau}$$

Since

$$t_{1/2} = \frac{0.693 \times V_{\text{d}}}{\text{CL}}$$

then

$$C_{\text{p}}^{\text{ss}} = \frac{1.44 \times D \times t_{1/2}}{V_{\text{d}} \times \tau}$$

Steady state from first principles

At steady state the rate of drug administration is equal to the rate of drug elimination. Mathematically the rate of drug administration can be stated in terms of the dose (D) and dosing interval (τ). It is always important to include the salt factor (S) and the bioavailability (F). The rate of drug elimination will be the clearance of the plasma concentration at steady state:

$$\text{Rate of drug administration} = \frac{S \times F \times D}{\tau}$$

$$\text{Rate of drug elimination} = \text{CL} \times C_{\text{p}}^{\text{ss}}$$

At steady state:

$$\frac{S \times F \times D}{\tau} = \text{CL} \times C_{\text{p}}^{\text{ss}}$$

Table 1.2 In practice, steady state is assumed to be reached in 5 half-lives. If we assume a patient is receiving 100-mg doses and half the total amount is eliminated at each half life, the table shows the time to reach steady-state concentration in the body

Dose (mg)	*Amount in the body (mg)*	*Amount eliminated (mg)*	*Number of half lives*
100	100	50	1
100	150	75	2
100	175	87.5	3
100	187.5	93.75	4
100	197.5	98.75	5
100	198.75	99.37	6
100	199.37[a]	99.68	7

[a] Continuing at this rate of dosage, the amount of drug in the body will remain the same.

Rearranging the equation:

$$C_{\mathrm{p}}^{\mathrm{ss}} = \frac{S \times F \times D}{\mathrm{CL} \times \tau}$$

In practice, steady state is assumed to be reached in 4–5 half-lives. If we assume that a patient is receiving a 100-mg dose and half the total amount is eliminated at each half-life, Table 1.2 shows the time to reach a steady-state concentration in the body.

Intravenous infusion

Some drugs are administered as an intravenous infusion rather than as an intravenous bolus. To describe the time course of the drug in plasma during the infusion prior to steady state (see Figure 1.12), one can use:

$$C_{\mathrm{p}t} = \frac{R[1 - \exp(-kt)]}{\mathrm{CL}}$$

where

$$R = \frac{D}{\tau}$$

or

$$R = \frac{S \times D}{\tau}$$

if a salt of the drug is given.

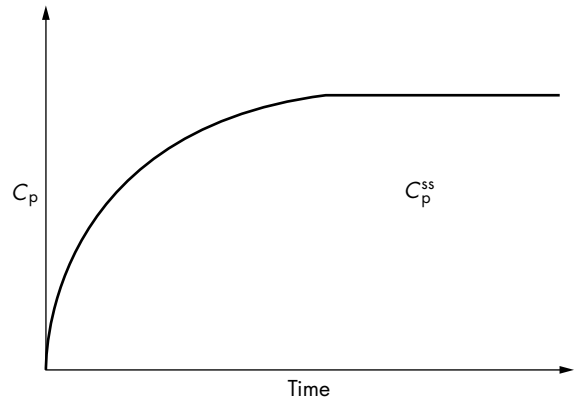

Figure 1.12 Time profile after IV infusion.

Following a continuous infusion, the plasma concentrations will increase with time until the rate of elimination (rate out) equals the rate of infusion (rate in) and will then remain constant. The plateau concentration, i.e. C_p^{ss}, is the steady-state concentration. Steady state will be achieved in 4–5 times the $t_{1/2}$. If one considers the previous equation, which describes the plasma concentration during the infusion prior to steady state, then at steady state,

$$\exp(-kt) = 0$$

As rate in = rate out at steady state,

$$R = \mathrm{CL} \times C_p^{ss}$$

$$C_p^{ss} = \frac{D}{\tau \times \mathrm{CL}}$$

where $R = D/\tau$ = infusion rate (dose/h).

When a constant infusion is stopped, the drug concentrations in the plasma decline in an exponential manner, as illustrated in Figure 1.13.

To estimate the plasma concentration, C_p' at t' one must describe the decay of C_p^{ss} at time t to C_p' at time t'. Thus, from the above:

$$C_p^{ss} = \frac{D}{\tau \times \mathrm{CL}}$$

To describe the decay of C_p from t to t', one uses the single-dose IV bolus equation

$$C_{pt} = C_p^0[\exp(-kt)]$$

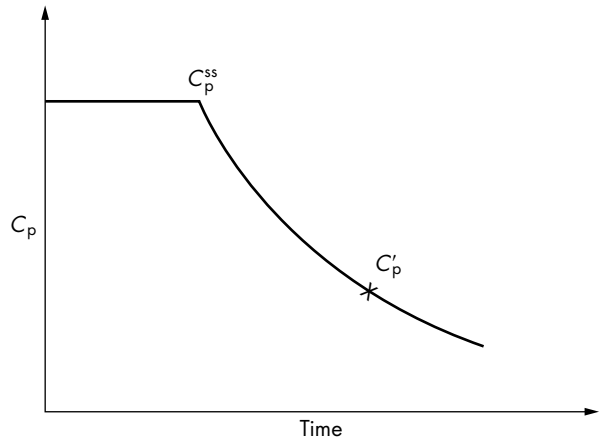

Figure 1.13 Profile following discontinuation of an infusion.

Since C_p^0 is C_p^{ss}, then from the above,

$$C'_p = \frac{D \exp[-k(t' - t)]}{\tau \times \mathrm{CL}}$$

Loading dose

The time required to obtain steady-state plasma levels by IV infusion will be long if a drug has a long half-life. It is, therefore, useful in such cases to administer an intravenous loading dose to attain the desired drug concentration immediately and then attempt to maintain this concentration by a continuous infusion.

To estimate the loading dose (LD), where C_p^{ss} is the final desired concentration, use

$$\mathrm{LD} = V_d \times C_p^{ss}$$

If the patient has already received the drug, then the loading dose should be adjusted accordingly:

$$\mathrm{LD} = V_d \times (C_p^{ss} - C_p^{\mathrm{initial}})$$

or

$$\mathrm{LD} = \frac{V_d \times (C_p^{ss} - C_p^{\mathrm{initial}})}{S}$$

if the salt of the drug (salt factor S) is used.

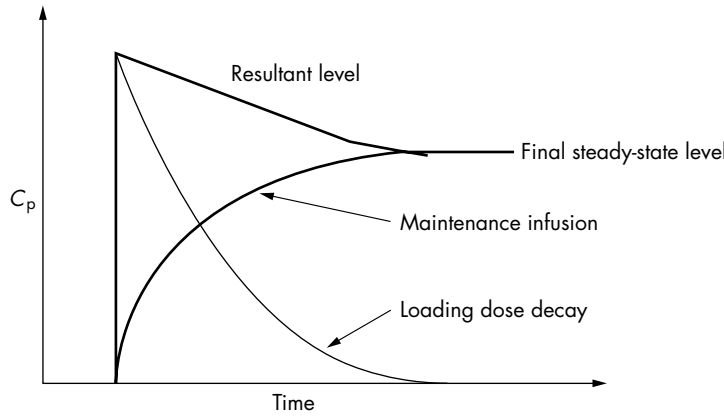

Figure 1.14 Profile following a loading dose and maintenance infusion.

Now consider the plasma concentration–time profile following a loading dose and maintenance infusion (see Figure 1.14). The equation to describe the time course of the plasma concentrations of drug following simultaneous administration of an IV loading dose (LD) and initiation of infusion (D) is the sum of the two equations describing these two processes individually:

$$C_p = \frac{\text{LD} \exp(-kt)}{V_d} + \frac{D[1 - \exp(-kt)]}{\tau \times \text{CL}}$$

The final plasma concentration achieved is not the 'true' steady-state concentration, since that will still require about 4 half-lives to be reached, but depending on the accuracy of the loading dose it will be fairly close. However, this regimen allows the concentration somewhere near steady state to be achieved more rapidly. If the salt is used:

$$C_p = \frac{S \times \text{LD} \exp(-kt)}{V_d} + \frac{S \times D[1 - \exp(-kt)]}{\tau \times \text{CL}}$$

Single oral dose

The plasma concentration–time profile of a large number of drugs can be described by a one-compartment model with first-order absorption and elimination.

Consider the concentration versus time profile following a single oral dose (Figure 1.15). Assuming first-order absorption and first-order

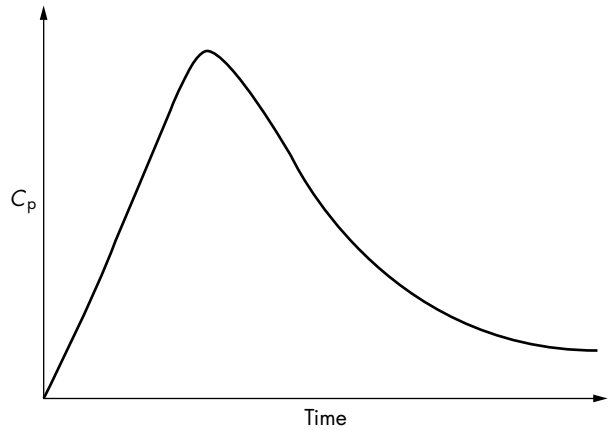

Figure 1.15 Single oral dose profile.

elimination, the rate of change of amount of drug (X) in the body is described by:

$$\frac{dX}{dt} = k_a X_a - kX$$

where k_a = absorption rate constant; k = elimination rate constant; X = amount of drug in the body; and X_a = amount of drug at the absorption site (X_0 if all is available). Following integration:

$$X = \frac{X_0\ k_a\ [\exp(-kt) - \exp(-k_a t)]}{k_a - k}$$

To convert X to C_p one uses the apparent volume of distribution (V_d). Furthermore, following oral administration, the bioavailability (F) and salt factor (S) (see below) must be considered.

Fractional bioavailability, F

F is the fraction of an oral dose that reaches the systemic circulation, which following oral administration may be less than 100%. Thus, if $F = 0.5$ then 50% of the drug is absorbed. Parenteral dosage forms (IM and IV) assume a bioavailability of 100%, and so $F = 1$; it is therefore not considered and is omitted from calculations.

If the loading dose is to be administered orally, then the bioavailability term (F) needs to be introduced. Thus:

$$\text{LD} = \frac{V_d \times C_p}{F}$$

Salt factor, S

S is the fraction of the administered dose, which may be in the form of an ester or salt, that is the active drug. Aminophylline is the ethylenediamine salt of theophylline, and S is 0.79. Thus 1 g aminophylline is equivalent to 790 mg theophylline.

Accordingly, S needs to be incorporated along with F into the oral loading dose equation and the equation that describes the plasma concentration C_p at any time t following a single oral dose. Thus,

$$\text{LD} = \frac{V_d \times C_p}{S \times F}$$

and

$$C_{pt} = \frac{SFD}{V_d} \times \frac{k_a[\exp(-kt) - \exp(-k_a t)]}{k_a - k}$$

N.B. The S factor may need to be considered during IV infusion administration.

Multiple oral dosing

Prior to steady state

Consider a patient on medication prescribed three times a day. The profile shown in Figure 1.16 shows the administration of three doses. If we consider a time 28 h into therapy, all three doses would have been administered.

To calculate C_p at 28 h post dose, use the single oral dose equation and consider the contributions of each dose:

Contribution from dose 1; $t_1 = 28$ h:

$$C_{p1} = \frac{SFD}{V_d} \times \frac{k_a[\exp(-kt_1) - \exp(-k_a t_1)]}{k_a - k}$$

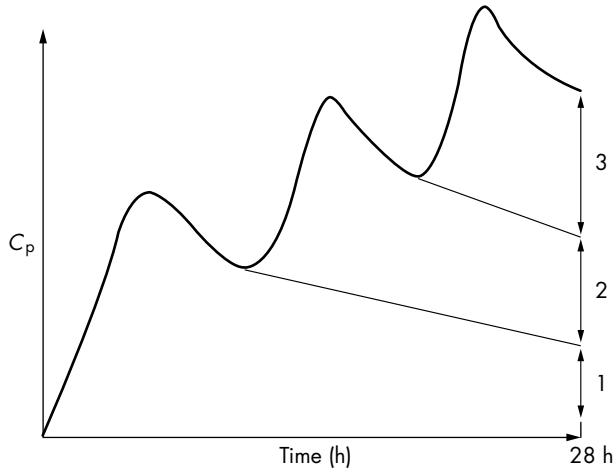

Figure 1.16 Multiple dosing prior to steady state.

Contribution from dose 2, $t_2 = 18$ h:

$$C_{p2} = \frac{SFD}{V_d} \times \frac{k_a[\exp(-kt_2) - \exp(-k_a t_2)]}{k_a - k}$$

Contribution from dose 3; $t_3 = 8$ h:

$$C_{p3} = \frac{SFD}{V_d} \times \frac{k_a[\exp(-kt_3) - \exp(-k_a t_3)]}{k_a - k}$$

Thus,

$$C_{p28h} = C_{p1} + C_{p2} + C_{p3}$$

The above method uses the principle of superposition to calculate the C_p at any time t after the nth dose. The following equation can simplify the process.

$$C_{pt} = \frac{SFDk_a}{V_d(k_a - k)} \times \left\{ \frac{[1 - \exp(-nk\tau)](\exp(-kt))}{1 - \exp(-k\tau)} - \frac{[1 - \exp(-nk_a\tau)](\exp(-k_a t))}{1 - \exp(-k_a\tau)} \right\}$$

where n = number of doses, τ = dosage interval and t = time after the nth dose.

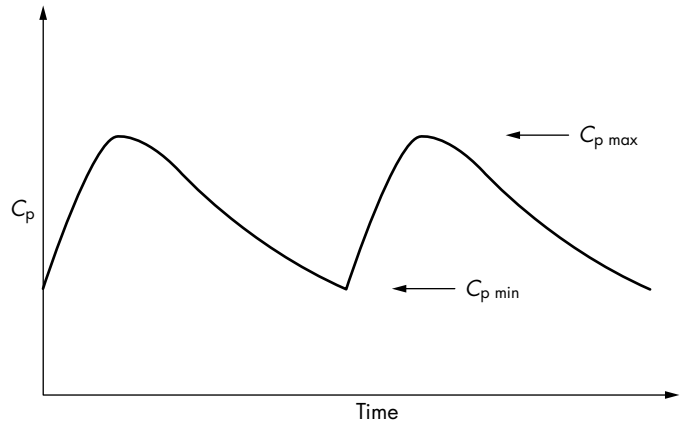

Figure 1.17 Multiple dosing at steady state.

At steady state

At steady state the plasma concentration–time profile can be described by

$$C_{pt} = \frac{SFDk_a}{V_d(k_a - k)} \times \left\{ \frac{\exp(-kt)}{1 - \exp(-k\tau)} - \frac{\exp(-k_a t)}{1 - \exp(-k_a \tau)} \right\}$$

The plasma concentration at steady state fluctuates between a maximum ($C_{p\ max}$) and a minimum ($C_{p\ min}$) concentration, within a dose interval (see Figure 1.17).

To estimate $C_{p\ max}$, one first needs to estimate time to peak (t_{pk}):

$$t_{pk} = \frac{1}{k_a - k} \times \ln \frac{k_a[1 - \exp(-k\tau)]}{k[1 - e(-k_a\tau)]}$$

Note that t_{pk} is independent of the dose administered. Thus,

$$C_{p\,max} = \frac{SFDk_a}{V_d(k_a - k)} \times \left\{ \frac{\exp(-kt_{pk})}{1 - \exp(-k\tau)} - \frac{\exp(-k_a t_{pk})}{1 - \exp(-k_a \tau)} \right\}$$

The minimum plasma concentration at steady state occurs just before the next dose, i.e., when $t = \tau$. So

$$C_{p\,min} = \frac{SFDk_a}{V_d(k_a - k)} \times \left\{ \frac{\exp(-k\tau)}{1 - \exp(-k\tau)} - \frac{\exp(-k_a \tau)}{1 - \exp(-k_a \tau)} \right\}$$

When using these formulae, individual values should be calculated, since they are often used more than once.

When the half-life of a drug is long, the fluctuations between the peak and trough are small, and the equation derived above under Intravenous infusion (p. 18) can be used to describe the average steady-state concentration:

$$C_p^{ss} = \frac{D}{T \times CL}$$

Clinical case studies

CASE STUDY 1.1 Multiple IV bolus

Patient D receives Drug Code XR2, 100 mg every 8 h. At steady state, two plasma concentrations are measured:

Sample 1 is taken at 1 h post dose: *Conc = 9.6 mg/L*

Sample 2 is taken pre dose: *Conc = 2.9 mg/L*

See Figure 1.18

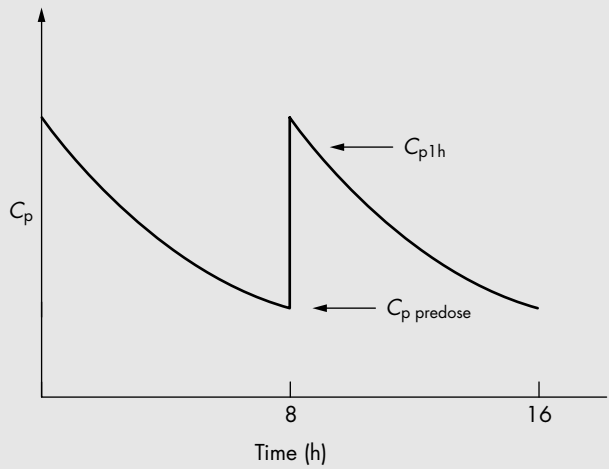

Figure 1.18 Two plasma concentrations measured at steady state, $C_{p\ 1h}$ and $C_{p\ predose}$.

Since the samples were taken at steady state, the pre-dose sample represents the trough concentration. $C_{p\ max}$, C_{pt} and $C_{p\ min}$ will be the same within each dosing interval.

→

CASE STUDY 1.1 (continued)

Calculate the elimination rate constant (*k*)

$$k = \frac{\ln C_{p1} - \ln C_{p2}}{t_2 - t_1}$$

Now C_{p1} is 9.6 mg/L and C_{p2} is 2.9 mg/L, and sample times are 1 h and 8 h (extrapolated). Thus

$$t_2 - t_1 = 7\,\text{h}$$

So

$$k = \frac{\ln 9.6 - \ln 2.9}{7} = \frac{1.197}{7}$$

$$k = 0.171\,\text{h}^{-1}$$

and the half-life ($t_{1/2}$) is

$$t_{1/2} = \frac{0.693}{0.171} = 4.1\,\text{h}$$

Calculate the volume of distribution (V_d)
The volume can be calculated from either the 1 h post- or pre-dose samples.

From the 1 h post-dose sample
The following equation describes the plasma concentration 1 h post dose at steady state:

$$C_{p1} = \frac{D \times \exp(-kt)}{V_d[1 - \exp(-k\tau)]}$$

Thus

$$V_d = \frac{D \times \exp(-kt)}{C_{p1}[1 - \exp(-k\tau)]}$$

$$V_d = \frac{100\ e^{-0.1710\times1}}{9.6(1 - e^{-0.1710\times8})}$$

$$= \frac{100 \times 0.8428}{9.6 \times 0.7454}$$

$$= 11.8\ \text{L}$$

→

CASE STUDY 1.1 (continued)

From the pre-dose sample
The following equation describes $C_{p,min}$ at steady state:

$$C_{p\ min} = \frac{D \times \exp(-k\tau)}{V_d[1 - \exp(-k\tau)]}$$

$$V_d = \frac{D \times \exp(-k\tau)}{C_{p\ min}[1 - \exp(-k\tau)]}$$

$$V_d = \frac{100\ e^{-0.1710\times 8}}{2.9(1 - e^{-0.1710\times 8})}$$

$$= \frac{100 \times 0.2546}{2.9 \times 0.7454}$$

$$= 11.8\ L$$

Calculate clearance

$$CL = k \times V_d$$
$$= 0.171 \times 11.8$$
$$= 2.02\ L/h$$

Individualised pharmacokinetic parameters
The patient's individual parameters are as follows:

Elimination rate constant (k)	$0.171\ h^{-1}$
Volume of distribution (V_d)	11.8 L
Clearance (CL)	2.02 L/h
Half-life ($t_{1/2}$)	4.1 h
Time to steady state (t_{ss})	18.5 h

CASE STUDY 1.2 Oral dose

Patient H, aged 40 years and weighing 60 kg, receives an oral dose of Drug Code XR4, 500 mg every 12 h. The patient is at steady state. A plasma level is measured at 10 h post dose and is reported to be 18.2 mg/L.

→

CASE STUDY 1.2 (continued)

Assume one-compartment kinetics, all doses were given and $F = 1$. Estimate patient H's individualised pharmacokinetic data.
Data given:

$V_d = 0.4\,\text{L/kg}$

$\text{CL} = 0.05\,\text{L/h/kg}$

$k_a = 0.4\,\text{h}^{-1}$

$S = 1$

Use population data to obtain starting parameters

$V_d = 0.4 \times 60 = 24\,\text{L}$

$\text{CL} = 0.05 \times 60 = 3.0\,\text{L/h}$

$k = 0.125\,\text{h}^{-1}$

$t_{1/2} = 5.5\,\text{h}$

Estimate C_{pt} at sampling time (i.e. $C_{p\ \text{predicted}}$), t = 10 h

$$C_{pt} = \frac{SFDk_a}{[V_d(k_a - k)]} \times \frac{\exp(-kt)}{1 - \exp(-k\tau)} \times \frac{\exp(-k_a t)}{1 - \exp(-k_a\tau)}$$

Now

$$SFDk_a = 1 \times 1 \times 500 \times 0.4$$

and

$$V_d(k_a - k) = 24(0.4 - 0.125)$$

and the exponential part is

$$\frac{(e^{-0.125\times10})}{(1 - e^{-0.125\times12})} - \frac{(e^{-0.4\times10})}{(1 - e^{-0.4\times12})}$$

Thus

$$C_{pt} = \frac{200}{6.6}\left(\frac{0.2865}{0.7768} - \frac{0.0183}{0.9918}\right)$$

$$= 10.6\,\text{mg/L}$$

→

CASE STUDY 1.2 (continued)

Compare $C_{p\ predicted}$ with $C_{p\ measured}$

Assess whether the patient is 'clearing' the drug faster or slower than the initial population data estimate. Assume the volume of distribution is fixed. From the data, the predicted concentration, 10.6 mg/L, when compared with the measured value of 8.2 mg/L, does suggest that the patient's clearance is faster than population data.

Alter *k* accordingly by the process of iteration

Let $k = 0.10\,h^{-1}$. Thus

$$CL = 2.4\,L/h$$

Predict C_{pt} at 10 h post dose using the above information; k_a remains the same:

$$V_d(k_a - k) = 24(0.4 - 0.10)$$

and the exponential part is

$$\frac{e^{-0.10\times10}}{1 - e^{-0.4\times10}} - \frac{e^{-0.10\times12}}{e^{-0.4\times12}}$$

Thus

$$C_{p10\,h} = 14.1\,mg/L$$

Still $C_{p\ predicted}$ is less than $C_{p\ measured}$.

Let $k = 0.08\,h^{-1}$. Thus

$$CL = 1.92\,L/h$$

Predict C_{pt} at 10 h post dose:

$$V_d(k_a - k) = 24(0.4 - 0.08)$$

and the exponential part is

$$\frac{e^{-0.08\times10}}{1 - e^{-0.4\times12}} - \frac{e^{-0.08\times10}}{1 - e^{-0.4\times12}}$$

Thus

$$C_{p10\,h} = 18.4\,mg/L$$

Now $C_{p\ predicted}$ is very close to $C_{p\ measured}$.

→

CASE STUDY 1.2 (continued)

Summary

k (h^{-1})	CL (L/h)	$C_{p\ predicted}$ (mg/L)
0.125	3.0	10.6
0.10	2.4	14.1
0.08	1.92	18.4

Hence using $k = 0.08\,h^{-1}$ the predicted concentration is 18.4 mg/L, which is similar to the observed concentration of 18.2 mg/L.

The patient's observed pharmacokinetic parameters

$CL = 1.92\,L/h$

$V_d = 24\,L$

$k = 0.08\,h^{-1}$

$t = 8.6\,h$

Note that the volume of distribution of 0.4 L/kg is assumed to be constant.

Assessment of individualised data

In practice the glossary of equations described (p. 37) can be used to simulate plasma concentration vs time profiles for a dosage regimen using different routes of administration. The important issue is to utilise mean pharmacokinetics parameters derived from research that match the clinical and demographic data of the patient. Basic data can be obtained from original research papers or from the pharmaceutical industry for the specific drug. Where possible the equations that describe the average steady state concentration (C_p^{ss}) can be used to estimate the levels in the patient. Pharmacokinetic interpretation and estimation of a patient's actual pharmacokinetic data, e.g. CL, relies on plasma concentrations measured at a specific time following drug administration where this depicts the average plasma concentration.

The basic questions to be asked when determining which set of equations to use follows the algorithm described in Figure 1.22.

To determine whether the data are acceptable, see monographs on individual drugs because, for TDM, the individual parameters must be

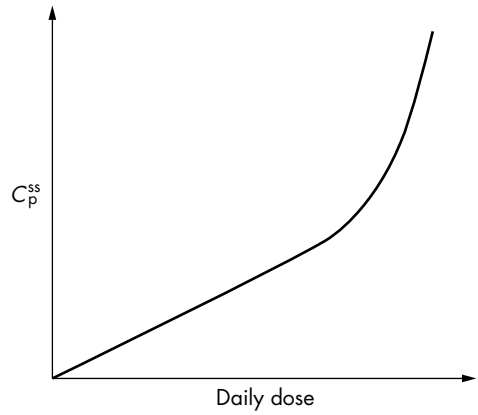

Figure 1.19 C_p^{ss} profile following different doses of phenytoin.

interpreted in light of the patient's dosage details, clinical status, and so on (see individual drug monographs in the following chapters).

Nonlinear pharmacokinetics: Basic parameters

Drugs such as phenytoin will show nonlinear drug handing. The process of metabolism are nonlinear and the rate of metabolism shows zero order. In practice, Michaelis–Menten pharmacokinetics are applied, and the equations are summarised below.

If a patient receives different doses of phenytoin, e.g. 200 mg/day, 250 mg/day, 300 mg/day or 400 mg/day, the steady-state plasma concentration varies exponentially with time; that is, a small change in the total daily dose of phenytoin shows a disproportionate increase in the steady-state concentration (C_p^{ss}) (Figure 1.19).

Figure 1.20 describes the profile of the rate of metabolism of phenytoin given at different dosages. As the dose of phenytoin increases, the rate of elimination increases until it reaches a plateau where the rate of elimination is constant despite increases in the total daily dose of the drug. The profile can be described as follows.

Rate of elimination:

$$\frac{-dX}{dt} = \frac{V_m \times C_p^{ss}}{K_m + C_p^{ss}}$$

Hence the model that appears to fit the pattern for the metabolic elimination of phenytoin is not linear and is the one proposed by Michaelis and

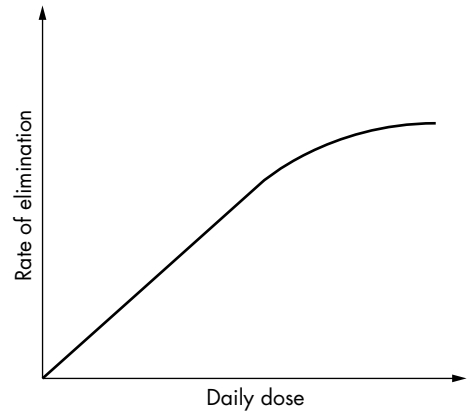

Figure 1.20 Profile of elimination following phenytoin administration.

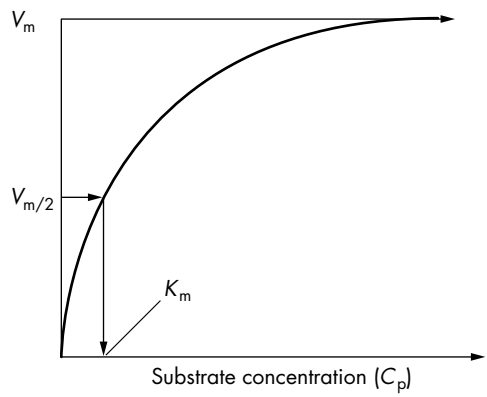

Figure 1.21 Relationship between rate of metabolism (V) versus substrate concentration (C_p) for a drug showing nonlinear pharmacokinetics.

Menten. The velocity (V) or rate at which an enzyme can metabolise a substrate (C_p) can be described by the following equation:

$$V = -\frac{V_m \times C_p}{K_m + C_p}$$

where V is the rate of metabolism, V_m (sometimes referred to as V_{max}) is the maximum rate of metabolism and K_m is the substrate concentration (C_p) at which V will be half V_m, i.e. when half the total enzyme is complexed with the substrate. (See Figure 1.21.)

At steady state we know that the rate of administration is equal to the rate of elimination; hence, in the clinical situation, the daily dose (R, or D) is substituted for velocity (V), and the steady-state phenytoin concentration (C_p^{ss}) is substituted for substrate concentration (S). Further equations can be described for steady-state concentrations.

At steady state the rate of administration is equal to the rate of elimination. The rate of administration can be expressed as SFD/τ where D/τ can equal R. Hence

$$RSF = \frac{V_m \times C_p^{ss}}{K_m + C_p^{ss}}$$

V_m is the maximum metabolic capacity, i.e. the total amount of drug that can be eliminated at saturation. K_m is the Michaelis constant, which by definition is the concentration at which the metabolism is operating at half the maximum capacity.

All drugs will show nonlinear handling if they are administered in high enough doses. However, only a small number of drugs show nonlinear handling at the doses used clinically.

Whether a drug will show linear or nonlinear drug handling in therapeutic doses depends on the drug's Michaelis constant K_m. For example, consider a drug that has a K_m that is much greater then C_p^{ss}, i.e. the plasma levels seen with normal therapeutic doses of the drug. The rate of elimination can be described as

$$\frac{-dX}{dt} = \frac{V_m \times C_p^{ss}}{K_m + C_p^{ss}}$$

Since K_m is much more than C_p^{ss}, the equation simplifies to

$$\frac{-dX}{dt} = \frac{V_m \times C_p^{ss}}{K_m}$$

Since V_m and K_m are constants, this now represents a first-order process.

In another simulation a drug has a K_m that is much less than C_p^{ss}, i.e. the plasma levels seen with normal therapeutic doses of the drug.

$$\frac{-dX}{dt} = \frac{V_m \times C_p^{ss}}{K_m + C_p^{ss}}$$

Since K_m is much less than C_p^{ss}, the equation simplifies to

$$\frac{-dX}{dt} = V_m$$

Since V_m is a constant, this now represents a zero-order process.

Hence, the relationship between the Michaelis constant (K_m) of the drug and the plasma levels of the drug normally achieved with therapeutic dosages will determine whether the drug will show linear first-order or zero-order saturation pharmacokinetics.

Practical clinical use of nonlinear equations

$$R \times F \times S = \frac{V_m \times C_p^{ss}}{K_m + C_p^{ss}}$$

The above equation can be used

- To calculate predicted C_p^{ss} from a given dosage regimen, to estimate the patient's V_m using population K_m values.
- To describe the relationship between the total daily dose R (mg/day) and the steady-state serum concentration.

$$C_p^{ss} = \frac{K_m \times (R \times F \times S)}{V_m - (R \times F \times S)}$$

$$R \times F \times S = \frac{(V_m - K_m) \times R}{C_p^{ss}}$$

$$C_p^{ss} = \frac{(V_m \times C_p^{ss}) - K_m}{R \times F \times S}$$

or

$$C_p^{ss} = \frac{(D_{max} \times C_p^{ss}) - K_m}{D}$$

N.B. The last three equations are linear relationships.

Clearance (CL) is the parameter that relates the rate of elimination to the plasma concentration. Since $CL = R/C_p^{ss}$,

$$CL = \frac{V_m}{K_m + C_p^{ss}}$$

And since apparent $t_{1/2} = (0.693 \times V_d)/\text{CL}$,

$$t_{1/2} = \frac{0.693 \times V_d(K_m + C_p^{ss})}{V_m}$$

From the above equations, it can be noted that the clearance and half-life will alter depending on the steady-state concentration. Thus V_m and K_m should be used to describe the kinetics of phenytoin and not clearance and half-life.

Toxic drug levels

For the decay of a toxic plasma concentration (C'_p) to a desired plasma concentration (C_p):

$$C'_{p\,t\ \text{decay}} = \frac{(K_m \times \ln(C'_p/C_p)) + (C'_p - C_p)}{V_m/V_d}$$

where t decay = time (days) to allow C'_p to fall to C_p.

Phenytoin serum levels in the presence of altered plasma protein binding

To calculate a 'corrected' C_p^{ss} for a patient with a low serum albumin:

$$C_{p\ \text{adjusted}} = \frac{C_p^*}{(1 - \alpha)(P'/P) + \alpha}$$

where $C_{p\ \text{adjusted}}$ = plasma concentration that would be expected if the patient had a normal serum albumin; C_p^* = steady-state serum level observed; P' = serum albumin concentration observed; P = 'normal' serum albumin concentration (40 g/L); α = phenytoin free fraction (0.1).

To calculate a 'corrected' C_p^{ss} for a patient with both uraemia and hypoalbuminaemia:

$$C_{p\ \text{adjusted}} = \frac{C_p^*}{(1 - \alpha)(0.44\,P'/P) + \alpha}$$

where 0.44 is an empirical adjustment factor and $\alpha = 0.2$.

Chapter 10 on antiepileptics describes the clinical use of the above equations.

Glossary of pharmacokinetic equations and their application in clinical practice

$$C_{\mathrm{p}}^{0} = \frac{S \times F \times D}{V_{\mathrm{d}}} \tag{1}$$

$$t_{1/2} = \frac{0.693}{k} \tag{2}$$

$$\mathrm{CL} = k \times V_{\mathrm{d}} \tag{3}$$

Single IV bolus injection

$$C_{\mathrm{p}t} = C_{\mathrm{p}}^{0} \exp(-kt) \tag{4}$$

Single oral dose

Equation to describe plasma concentration at any time (t) after a single oral dose:

$$C_{\mathrm{p}t} = C_{\mathrm{p}}^{0} \frac{k_{\mathrm{a}}}{k_{\mathrm{a}} - k} [\exp(-kt) - \exp(-k_{\mathrm{a}}t)] \tag{5}$$

Multiple IV bolus injections

Equations to describe the concentration at any time within a dosing interval:

$$C_{\mathrm{p}t}^{\mathrm{ss}} = C_{\mathrm{p}}^{0} \left[\frac{\exp(-kt)}{1 - \exp(-k\tau)} \right] \tag{6a}$$

$$C_{\mathrm{p\,max}}^{\mathrm{ss}} = C_{\mathrm{p}}^{0} \left[\frac{1}{1 - \exp(-k\tau)} \right] \tag{6b}$$

$$C_{\mathrm{p\,min}}^{\mathrm{ss}} = C_{\mathrm{p}}^{0} \left[\frac{\exp(-k\tau)}{1 - \exp(-k\tau)} \right] \tag{6c}$$

IV infusion prior to steady state

$$C_{\mathrm{p}t} = \frac{D \times S}{\tau \times \mathrm{CL}} [1 - \exp(-kt)] \tag{7}$$

IV infusion at steady state

$$C_p^{ss} = \frac{D \times S}{\tau \times CL} \tag{8}$$

Multiple oral dosing at steady state

Equation to describe the concentration at any time (t) within a dosing interval, at steady state:

$$C_p^{ss} = C_p^0 \frac{k_a}{k_a - k}\left[\frac{\exp(-kt)}{1 - \exp(-k\tau)} - \frac{\exp(-k_a t)}{1 - \exp(-k_a \tau)}\right] \tag{9}$$

The maximum concentration is given by:

$$C_{p\,max}^{ss} = C_p^0 \frac{k_a}{k_a - k}\left[\frac{\exp(-kt_{max}^{ss})}{1 - \exp(-k\tau)} - \frac{\exp(-k_a t_{max}^{ss})}{1 - \exp(-k_a \tau)}\right] \tag{10}$$

The time at which the maximum concentration occurs is given by:

$$t_{max}^{ss} = \frac{1}{k_a - k} \ln\left\{\frac{k_a[1 - \exp(-k\tau)]}{k[1 - \exp(-k_a \tau)]}\right\} \tag{11}$$

The minimum concentration is given by:

$$C_{p\,min}^{ss} = C_p^0 \frac{k_a}{k_a - k}\left[\frac{\exp(-k\tau)}{1 - \exp(-k\tau)} - \frac{\exp(-k_a \tau)}{1 - \exp(-k_a \tau)}\right] \tag{12}$$

Loading doses

$$LD = \frac{V_d \times C_p}{S \times F} \tag{13}$$

$$LD = \frac{V_d(C_{p\,desired} - C_{p\,observed})}{S \times F} \tag{14}$$

The average steady state concentration (C_p^{ss}) can be described by:

$$C_p^{ss} = \frac{S \times F \times D}{CL \times \tau} \tag{15}$$

Toxic level decay for drugs that show first-order elimination

$$\text{Time for decay} = \frac{\ln C_{p1} - \ln C_{p2}}{k} \tag{16}$$

Where C_{p1} = toxic plasma level and C_{p2} = desired plasma level.

Nonlinear pharmacokinetic equations

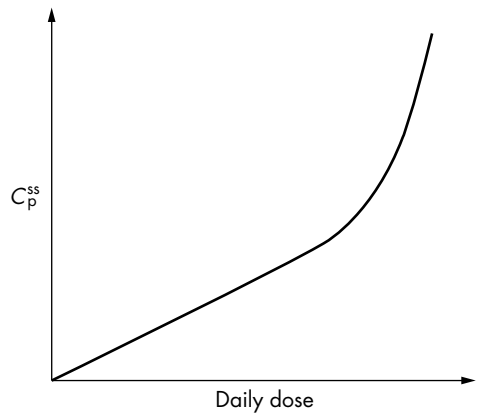

Figure 1.19 C_p^{ss} profile following different doses of phenytoin.

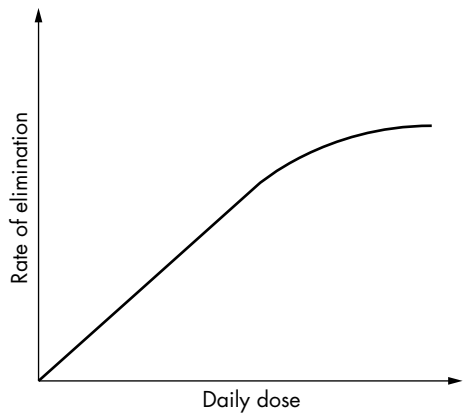

Figure 1.20 Profile of elimination following phenytoin administration.

Pharmacokinetic model

The model that appears to fit the pattern for the metabolic elimination of phenytoin is not linear and is the one proposed by Michaelis and

Menten. The velocity (V) or rate at which an enzyme can metabolise a substrate (C_p) can be described by the following equation:

$$V = \frac{V_m \times C_p}{K_m + C_p} \tag{17}$$

where V is the rate of metabolism and V_m (sometimes referred to as V_{max}) is the maximum rate of metabolism and K_m is the substrate concentration at which V will be half V_m, i.e. when half the total enzyme is complexed with the substrate.

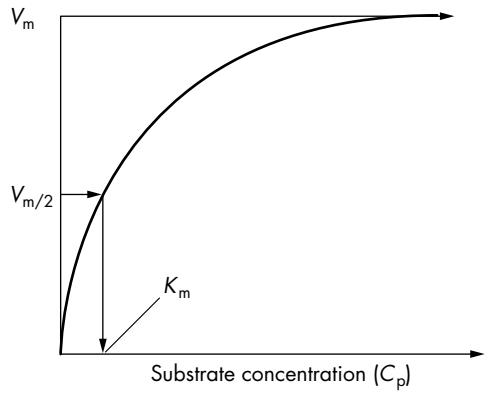

Figure 1.21 Relationship between rate of metabolism (V) versus substrate concentration (C_p) for a drug showing nonlinear pharmacokinetics.

When equation (18) is used in the clinical situation, the daily dose (R, or D) is substituted for velocity (V), and the steady-state phenytoin concentration (C_p^{ss}) is substituted for substrate concentration. Expressions can then be derived for steady state concentrations.

$$R \times F \times S = \frac{V_m \times C_p^{ss}}{K_m + C_p^{ss}} \tag{18}$$

$$C_p^{ss} = \frac{K_m \times (R \times F \times S)}{V_m - (R \times F \times S)} \tag{19}$$

$$R \times F \times S = \frac{(V_m - K_m) \times R}{C_p^{ss}} \tag{20}$$

$$C_p^{ss} = \frac{(V_m \times C_p^{ss}) - K_m}{R \times F \times S} \tag{21}$$

or

$$C_p^{ss} = \frac{(D_{max} \times C_p^{ss}) - K_m}{D} \tag{22}$$

Toxic drug levels

For the decay of a toxic plasma concentration (C'_p) to a desired plasma concentration (C_p):

$$C'_{p\,t\ \text{decay}} = \frac{(K_m \times \ln(C'_p/C_p)) + (C'_p - C_p)}{V_m/V_d} \tag{23}$$

where t decay = time (days) to allow C'_p to fall to C_p.

Phenytoin serum levels in the presence of altered plasma protein binding

To calculate a 'corrected' C_p^{ss} or a patient with a low serum albumin:

$$C_{p\ \text{adjusted}} = \frac{C_p^*}{(1-\alpha)(P'/P) + \alpha} \tag{24}$$

where $C_{p\ \text{adjusted}}$ = plasma concentration that would be expected if the patient had a normal serum albumin; C_p^* = steady-state serum level observed; P' = serum albumin concentration observed; P = 'normal' serum albumin concentration (40 g/L); α = phenytoin free fraction (0.1).

To calculate a 'corrected' C_p^{ss} for a patient with both uraemia and hypoalbuminaemia:

$$C_{p\ \text{adjusted}} = \frac{C_p^*}{(1-\alpha)(0.44P'/P) + \alpha} \tag{25}$$

where 0.44 is an empirical adjustment factor and $\alpha = 0.2$.
N.B. The last three equations are linear relationships.

Clearance (CL) is the parameter that relates the rate of elimination to the plasma concentration.
Since

$$\text{CL} = \frac{R}{C_p^{ss}} \tag{26}$$

$$\text{CL} = \frac{V_m}{K_m + C_p^{ss}} \tag{27}$$

And since

$$\text{Apparent } t_{1/2} = \frac{0.693 \times V_d}{\text{CL}} \tag{28}$$

$$t_{1/2} = \frac{0.693 \times V_d(K_m + C_p^{ss})}{V_m} \tag{29}$$

From the above equations, it can be noted that the clearance and half-life will alter depending on the steady-state concentration. Thus V_m and K_m should be used to describe the kinetics of phenytoin and not clearance and half-life.

Selection of equations in clinical practice

In considering which equation to apply, use the algorithms shown in Figures 1.22a–c. The relevant questions are answered and the correct equation is selected from the summary of equations above.

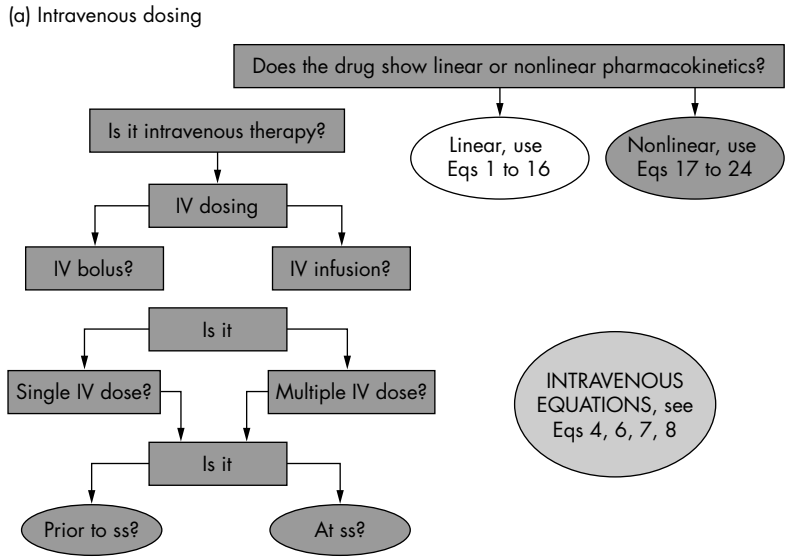

Figure 1.22 Getting the correct equation: the equation numbers link to the glossary of equations. (a) Intravenous dosing. (b) Oral dosing. (c) Loading doses and toxic level decay.

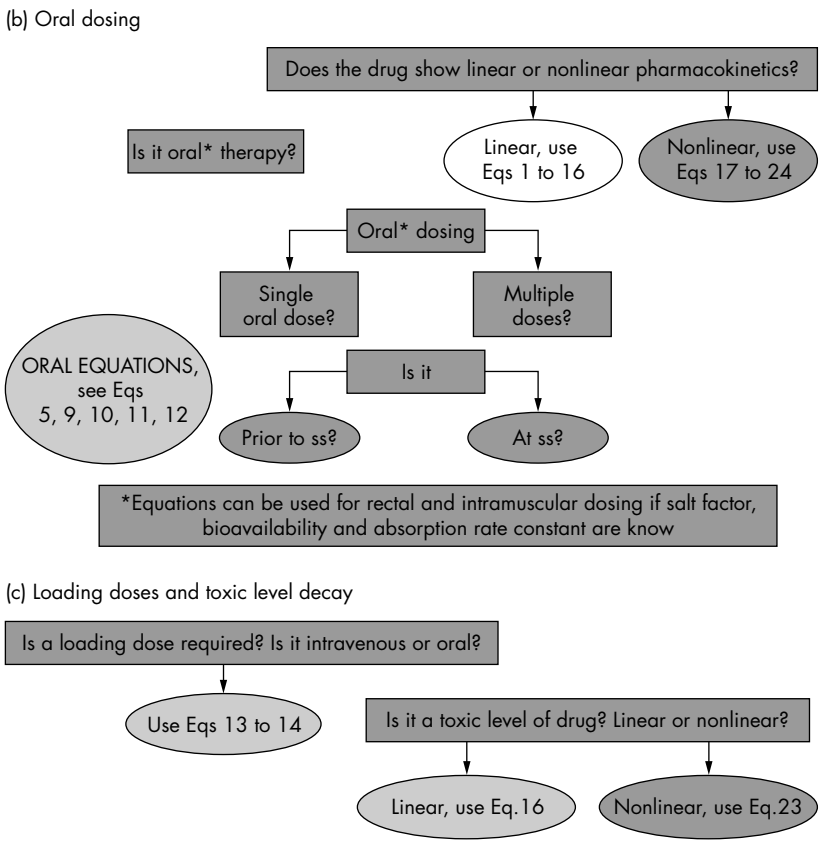

Figure 1.22 (continued).

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