Part 1

Principles of clinical pharmacology

Chapter 1

Pharmacodynamics and pharmacokinetics

Prior to the twentieth century, medical practice depended largely on the administration of mixtures of natural plant or animal substances. These preparations contained a number of pharmacologically active agents in variable amounts. Their actions and indications were empirical and based on historical or traditional experience. Their use was rarely based on an understanding of the mechanism of disease or careful measurement of effect.

During the last 100 years an increased understanding has developed of biochemical and pathophysiological factors that influence disease. The chemical synthesis of agents with well-characterised, specific actions on cellular mechanisms has led to the introduction of many powerful and effective drugs. Additionally, advances in the detection of these compounds in body fluids have facilitated investigation into the relationships between the dosage regimen, the profile of drug concentration against time in body fluids, notably the plasma, and corresponding profiles of clinical effect. Knowledge of this concentration–effect relationship and the factors that influence drug concentrations are used to determine how much drug an individual patient will require, and how often it should be given.

More recently the elucidation of the human genome with the development of genomics and proteomics has provided new insights and opportunities for drug development, understanding adverse reactions and potentially individualising drug therapy.

Principles of drug action (pharmacodynamics)

Pharmacological agents are used in therapeutics to:

1 Cure disease:
- Chemotherapy in cancer or leukaemia
- Antibiotics in specific bacterial infections

2 Alleviate symptoms:
- Antacids in dyspepsia
- Non-steroidal anti-inflammatory drugs in rheumatoid arthritis

3 Replace deficiencies:
- Thyroxine in hypothyroidism
- Insulin in diabetes mellitus

4 Prevent or delay end-stage consequences of degenerative diseases, ageing, etc.

A drug is a single chemical entity that may be one of the constituents of a medicine.

A medicine may contain one or more active constituents (drugs) together with additives to facilitate administration.

Mechanism of drug action

Action on a receptor

A receptor is a specific macromolecule, usually a protein, to which a specific group of drugs or

naturally occurring substances (such as neurotransmitters or hormones) can bind.

An agonist is a substance that stimulates or activates the receptor to produce an effect.

e.g. salbutamol at the β_2-receptor

An antagonist prevents the action of an agonist but does not have any effect itself.

e.g. losartan at the angiotensin II receptor

A partial agonist stimulates the receptor to a limited extent, while preventing any further stimulation by naturally occurring agonists.

e.g. pindolol at the β_1-receptor

The biochemical events that result from an agonist–receptor interaction and which produce an effect, are complex. There are many types of receptors and in several cases subtypes have been identified which are also of therapeutic importance (Table 1.1).

Action on an enzyme

Enzymes, like receptors, are protein macromolecules with which substrates interact to produce activation or inhibition. Drugs in common clinical use which exert their effect through enzyme action generally do so by inhibition.

Table 1.1 Some receptors involved in the action of commonly used drugs.

Receptor	Subtype	Main actions of natural agonist	Drug agonist	Drug antagonist
Adrenoceptor	α_1	Vasoconstriction		Prazosin
	α_2	Hypotension, sedation		Moxonidine
	β_1	Heart rate	Dopamine	Atenolol
			Dobutamine	Metoprolol
	β_2	Bronchodilation	Salbutamol	
		Vasodilation	Terbutaline	
		Uterine relaxation	Ritodrine	
Cholinergic	Muscarinic	Heart rate		Atropine
		Secretion		Benzatropine (benztropine)
		Gut motility		Orphenadrine
		Bronchoconstriction		Ipratropium
	Nicotinic	Contraction of striated muscle	Suxamethonium	
			Tubocurarine	
Histamine	H_1	Bronchoconstriction		Chlorphenamine (chlorpheniramine)
		Capillary dilation		Terfenadine
	H_2	↑Gastric acid		Cimetidine
				Ranitidine
				Famotidine
5-Hydroxy-tryptamine			Fluoxetine	Ondansetron
			Fluvoxamine	Granisetron
	Dopamine	CNS neurotransmitter	Bromocriptine	Chlorpromazine
				Haloperidol
				Thioridazine
Opioid		CNS neurotransmitter	Morphine, pethidine, etc.	Naloxone

1 Digoxin inhibits the membrane bound Na^+/K^+ ATPase.
2 Aspirin inhibits platelet cyclo-oxygenase.
3 Enalapril inhibits angiotensin-converting enzyme.
4 Selegiline inhibits monoamine oxidase B.
5 Carbidopa inhibits dopa decarboxylase.
6 Allopurinol inhibits xanthine oxidase.

Drug receptor antagonists and enzyme inhibitors can act as competitive, reversible antagonists or as non-competitive, irreversible antagonists. The duration of the effect of drugs of the latter type is much longer than that of the former. Effects of competitive antagonists can be overcome by increasing the dose of endogenous or exogenous agonists, while effects of irreversible antagonists cannot usually be overcome.

Atenolol is a competitive β-adrenoceptor antagonist used in hypertension and angina. Its effects last for hours and can be overcome by administering an appropriate dose of a β-receptor agonist like isoprenaline.

Vigabatrin is an irreversible inhibitor of gamma aminobutyric acid (GABA) aminotransferase and is used in epilepsy. Its action and adverse effects may persist for days as a result of irreversible binding to the target enzyme.

Action on membrane ionic channels

The conduction of impulses in nerve tissues and electromechanical coupling in muscle depend on the movement of ions, particularly sodium, calcium and potassium, through membrane channels. Several groups of drugs interfere with these processes:
1 Anti-arrhythmic drugs
2 Calcium slow channel antagonists
3 General and local anaesthetics
4 Anticonvulsants.

Cytotoxic actions

Drugs used in cancer or in the treatment of infections may kill malignant cells or micro-organisms. Often the mechanisms have been defined in terms of effects on specific receptors or enzymes. In other cases chemical action (alkylation) damages DNA or other macromolecules and results in cell death or failure of cell division.

Dose–response relationship

In clinical practice dose–response relationships rarely follow the classical sigmoid pattern of experimental studies. It is uncommon for the upper plateau or maximum effect to be reached in humans or to be relevant therapeutically. Additionally, variability in the relationship between dose and concentration means that it is often difficult to detect a dose–response relationship. Consequently, concentration–response relationships are often more clinically relevant.

Dose– (or concentration–) response relationships may be steep or flat. A steep relationship implies that small changes in dose will produce large changes in clinical response or adverse effects, while flat relationships imply that increasing the dose will offer little clinical advantage (Fig. 1.1).

The potency of a drug is relatively unimportant; what matters is its efficacy or the maximum effect that can be obtained. In clinical practice the maximum therapeutic effect may often be unobtainable because of the appearance of adverse or unwanted effects: few, if any, drugs cause a single pharmacological response. The concentration–adverse response relationship is often different in shape and position to that of the concentration–therapeutic response relationship. The difference between the concentration that produces the desired effect and the concentration that causes adverse effects is called the therapeutic index and is a measure of the selectivity of a drug (Fig. 1.2).

The shape and position of dose–response curves for a group of patients is variable because of genetic, environmental and disease factors. However, this variability is not solely an expression of differences in response to drugs. It has two important

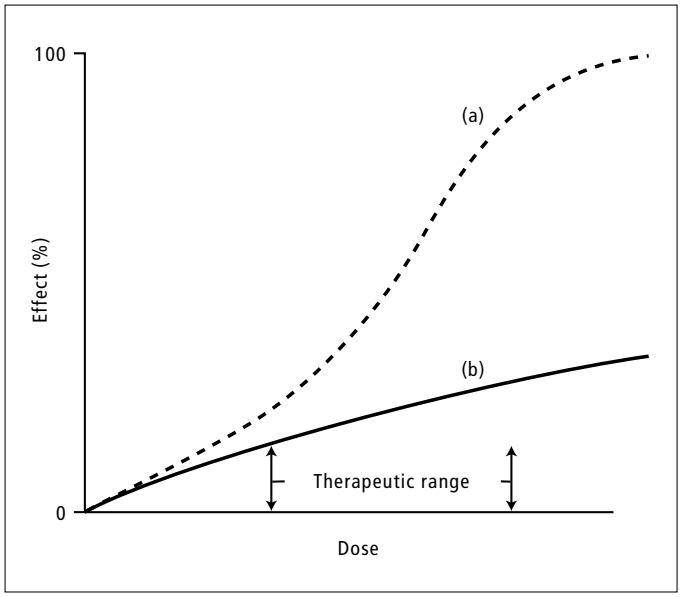


Figure 1.1 Schematic examples of a drug (a) with a steep dose– (or concentration–) response relationship in the therapeutic range, e.g. warfarin as an oral anticoagulant; and (b) a flat dose– (or concentration–) response relationship within the therapeutic range, e.g. thiazide diuretics in hypertension.

components: the dose–plasma concentration relationship and the plasma concentration–effect relationship.

$$\text{Dose} \rightarrow \text{Concentration} \rightarrow \text{Effect}$$

With the development of specific and sensitive chemical assays for drugs in body fluids, it has been possible to characterise dose–plasma concentration relationships so that this component of the variability in response can be taken into account when drugs are prescribed for patients with various disease states. For drugs with a narrow therapeutic index it may be necessary to measure plasma concentrations to assess the relationship between dose and concentration in individual patients.

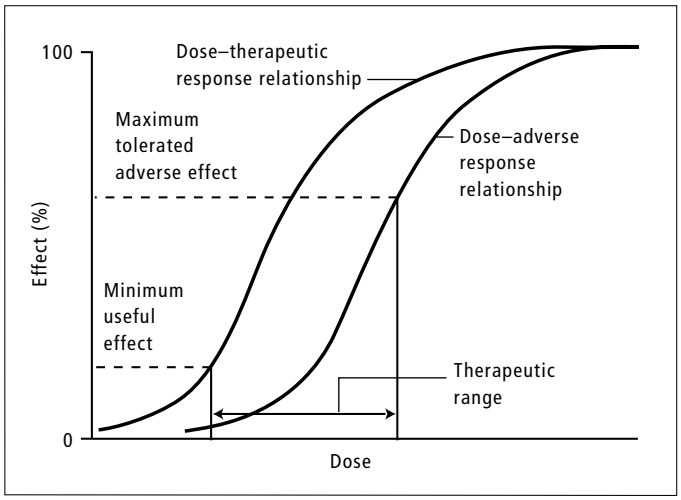


Figure 1.2 Schematic diagram of the dose–response relationship for the desired effect (dose–therapeutic response) and for an undesired adverse effect. The therapeutic index is the extent of displacement of the two curves within the normal dose range.

Clinical pharmacology: What are kinetics and dynamics?

The description of a drug concentration profile against time is known as pharmacokinetics and its application in clinical practice is clinical pharmacokinetics (Chapter 2). The residual variability in the relationship between dose and response is the concentration–effect component—a true expression of drug response, and a measure of the sensitivity of a patient to a drug. This is known as pharmacodynamics. Clinical pharmacology seeks to explore the factors that underlie variability in pharmacokinetics and pharmacodynamics and to use this information to optimise drug therapy for individual patients.

Principles of pharmacokinetics

Absorption

Drug absorption after oral administration has two major components: absorption rate and bioavailability. Absorption rate is controlled partially by the physicochemical characteristics of the drug but in many cases is modified by the formulation. A reduction in absorption rate can lead to a smoother concentration–time profile with a lower potential for concentration-dependent adverse effects and may allow less frequent dosing.

Bioavailability is the term used to describe the fraction of the dose that is absorbed into the systemic circulation and is usually designated F. It can range from 0 to 1 (0–100%) and depends on a number of physicochemical and clinical factors. Low bioavailability may occur if the drug has low solubility or is destroyed by the acid in the stomach. Changing the formulation can affect the bioavailability of a drug and it can also be altered by food or the co-administration of other drugs. For example, antacids can reduce the absorption of quinolone antibiotics by binding them in the gut. Other factors influencing bioavailability include metabolism by gut flora, the intestinal wall or the liver.

First-pass metabolism refers to metabolism of a drug that occurs en route from the gut lumen to the systemic circulation. For the majority of drugs given orally, absorption occurs across the portion of gastrointestinal epithelium that is drained by veins forming part of the hepatoportal system. Consequently, even if they are well absorbed, drugs must pass through the liver before reaching the systemic circulation. For drugs that are susceptible to extensive hepatic metabolism, a substantial proportion of an orally administered dose can be metabolised before it ever reaches its site of pharmacological action. Drugs with a high first-pass metabolism are listed in Table 1.2.

Table 1.2 Several drugs that undergo extensive first-pass metabolism.

Analgesics	*Drugs acting on CNS*
Aspirin	Clomethiazole (chlormethiazole)
Morphine	Chlorpromazine
Paracetamol	Imipramine
Pethidine	Levodopa
	Nortriptyline
Cardiovascular drugs	
Glyceryl trinitrate	*Respiratory drugs*
Isoprenaline	Salbutamol
Isosorbide dinitrate	Terbutaline
Labetalol	
Lidocaine (lignocaine)	*Oral contraceptives*
Metoprolol	
Nifedipine	
Prazosin	
Propranolol	
Verapamil	

The importance of first-pass metabolism is twofold:

1 It is one of the reasons for apparent differences in drug absorption between individuals. Even healthy people show considerable variation in liver metabolising capacity.

2 In patients with severe liver disease first-pass metabolism may be dramatically reduced, leading to the appearance of greater amounts of parent drug in the systemic circulation.

Distribution

Once a drug has gained access to the bloodstream it begins to distribute to the tissues. The extent

of this distribution depends on a number of factors including plasma protein binding, the pK_a of the drug, its partition coefficient in fatty tissue and regional blood flow. The volume of distribution V_D is the *apparent volume* of fluid into which a drug distributes based on the *amount* of drug in the body and the *measured concentration* in the plasma or serum. If a drug was wholly confined to the plasma, V_D would equal the plasma volume—approximately 3 l in an adult. If, on the other hand, the drug was distributed throughout the body water, V_D would be approximately 42 l. In reality, drugs are rarely distributed into physiologically relevant volumes. If most of the drug is bound to tissues, the plasma concentration will be low and the apparent V_D will be high, while high plasma protein binding will tend to maintain high concentrations in the blood and a low V_D will result. For the majority of drugs, V_D depends on the balance between plasma binding and sequestration or binding by various body tissues, for example, muscle and fat. Volume of distribution can vary therefore from relatively small values (e.g. an average of 0.14 l/kg body weight for aspirin) to large values (e.g. an average of 200 l/kg body weight for chloroquine) (Table 1.3).

Table 1.3 Average volumes of distribution of some commonly used drugs.

Drug	Volume of distribution (l/kg)
Chloroquine	200
Nortriptyline	20
Digoxin	7
Propranolol	4
Phenytoin	0.65
Theophylline	0.50
Gentamicin	0.25
Aspirin	0.14
Warfarin	0.10

In general, a small V_D occurs when:
1 Lipid solubility is low.
2 There is a high degree of plasma protein binding.
3 There is a low level of tissue binding.
A high V_D occurs when:
1 Lipid solubility is high.
2 There is a low degree of plasma protein binding.
3 There is a high level of tissue binding.

Plasma protein binding

In the blood, a proportion of a drug is bound to plasma proteins—mainly albumin (acidic drugs) and α_1-acid glycoprotein (basic drugs). Only the unbound, or free, fraction distributes because the protein-bound complex is too large to pass through membranes. Movement of the drug between the blood and other tissues proceeds until equilibrium is established between the unbound drug in plasma and the drug in tissues. It is the unbound portion that is generally responsible for clinical effects—both the target response and the unwanted adverse effects. Changes in protein binding (e.g. resulting from displacement interactions) generally lead to a transient increase in free concentration and are rarely clinically relevant because the equilibrium becomes re-established with the same unbound concentration. However, a lower total concentration will be present and the measurement might be misinterpreted if the higher free fraction is not taken into account. This is a common problem with the interpretation of phenytoin concentrations, where free fraction can range from 10% in a normal patient to 40% in a patient with hypoalbuminaemia and renal impairment.

Clinical relevance of volume of distribution

Knowledge of volume of distribution (V_D) can be used to determine the size of a *loading dose* if an immediate response to treatment is required. This assumes that therapeutic success is closely related to the plasma concentration and that there are no adverse effects if a relatively large dose is suddenly administered. It is sometimes employed when drug response would take many hours or days to develop if the regular maintenance dose was given from the outset, e.g. digoxin.

A loading dose can be calculated as follows:

$$\text{Loading dose} = V \times \text{Desired concentration} \qquad \text{(Eqn. 1.1)}$$

In practice, because most values for V_D are related to weight, this calculation is often simplified to a mg/kg dose.

Clearance

Clearance is the sum of all drug-eliminating processes, principally determined by hepatic metabolism and renal excretion. It can be defined as the theoretical volume of fluid from which a drug is completely removed in a given period of time.

When a drug is administered continuously by intravenous infusion or repetitively by mouth, a balance is eventually achieved between its input (dosing rate) and its output (the amount eliminated over a given period of time). This balance gives rise to a constant amount of drug in the body which depends on the dosing rate and clearance. This amount is reflected in the plasma or serum as a steady-state concentration (*C*ss). A constant rate intravenous infusion will clearly yield a constant *C*ss, while a drug administered orally at regular intervals will result in fluctuation between peak and trough concentrations (Fig. 1.3).

The average *C*ss in any dosage interval may be *approximated* by the concentration one-third of the way between the trough and the peak.

The relationship between the average *C*ss, drug input and drug output for a constant rate infusion can be written as

$$C\text{ss}_{\text{average}} = \frac{\text{Input rate}}{\text{Output rate}} = \frac{\text{Infusion rate}}{\text{Clearance}} \qquad \text{(Eqn. 1.2)}$$

or for oral therapy,

$$C\text{ss}_{\text{average}} = \frac{F \times \text{Dose}}{\text{Clearance} \times \text{Dosage interval}} \qquad \text{(Eqn. 1.3)}$$

Equations 1.2 and 1.3 highlight the important fact that if an estimate of clearance is available, it can be used to determine the *maintenance dose* for any desired *C*ss, thus

$$\text{Infusion rate} = \text{Clearance} \times \text{Desired}\, C\text{ss}_{\text{average}} \qquad \text{(Eqn. 1.4a)}$$

or for oral therapy,

$$\text{maintenance dose} = \text{Clearance} \times \text{Desired}\, C\text{ss}_{\text{average}} \times \text{Dosage interval}/F \qquad \text{(Eqn. 1.4b)}$$

Clearance depends critically on the efficiency with which the liver and/or kidneys can eliminate a drug; it will vary in disease states that affect these organs *per se*, or that affect the blood flow to these organs. In stable clinical conditions, clearance remains constant and Eqns. 1.2 and 1.3 show that the $C\text{ss}_{\text{average}}$ is directly proportional to dose rate. The important implication is that if the dose rate is doubled, the $C\text{ss}_{\text{average}}$ doubles: if the dose rate is halved, the $C\text{ss}_{\text{average}}$ is halved. This is illustrated in Fig. 1.4. If each $C\text{ss}_{\text{average}}$ is plotted against its corresponding dose rate, the direct proportionality becomes obvious (Fig. 1.5). In pharmacokinetic terms this is referred to as a first-order or linear process, and results from the fact that the rate of elimination is proportional to the amount of drug present in the body.

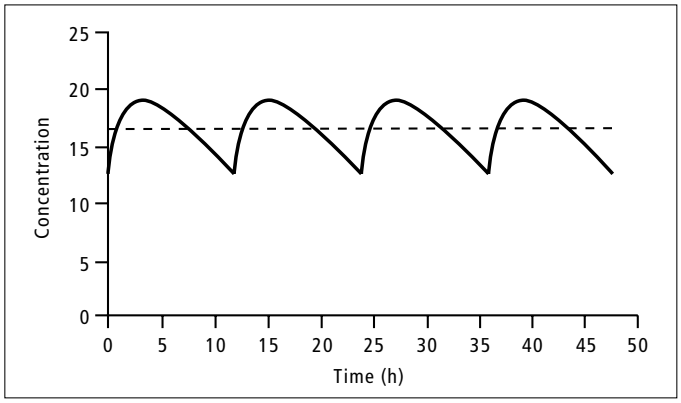


Figure 1.3 Steady-state concentration–time profile for an oral dose (——) and a constant rate intravenous infusion (- - - - -).

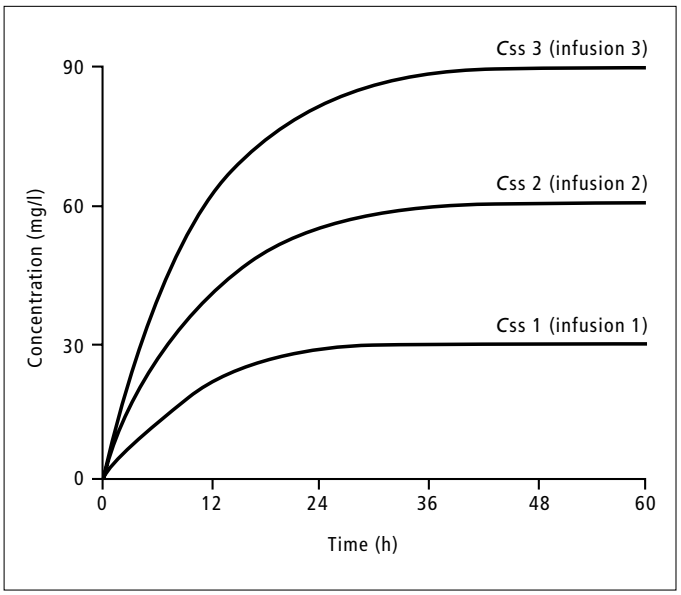


Figure 1.4 Plots of concentration vs. time for three infusions allowed to reach steady state. Infusion 2 is at a rate twice that of infusion 1; infusion 3 is at a rate three times that of infusion 1. The three steady-state concentrations (*C*ss 1, 2 and 3) are directly proportional to the corresponding infusion rates.

Single intravenous bolus dose

A number of other important pharmacokinetic principles can be appreciated by considering the concentrations that result following a single intravenous bolus dose (see Fig. 1.6a). If we assume that the drug distributes instantaneously into its volume of distribution V_D, then its initial concentration C_0 depends only on the dose (D) and V_D; thus

$$C_0 = \frac{D}{V_D} \qquad \text{(Eqn. 1.5)}$$

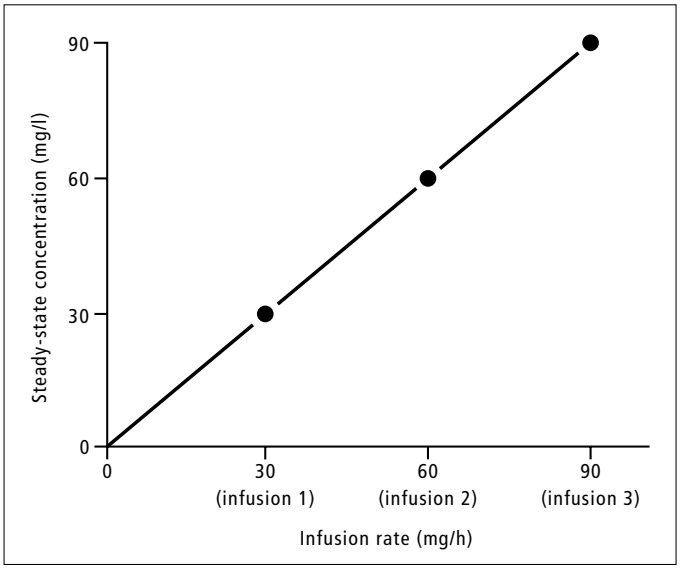
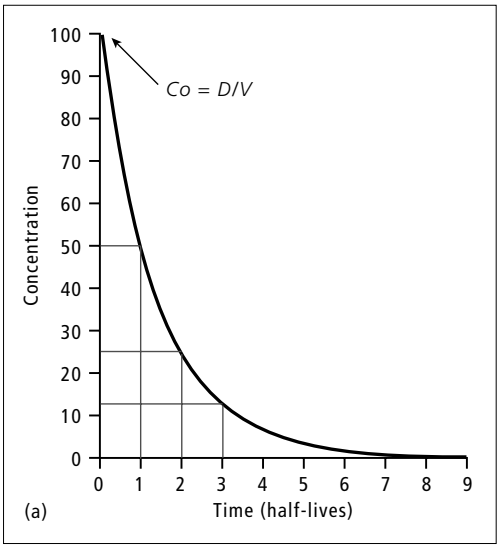


Figure 1.5 Three steady-state concentrations plotted against corresponding infusion rates showing the linear relationship between dose and $C\text{ss}_{\text{average}}$.



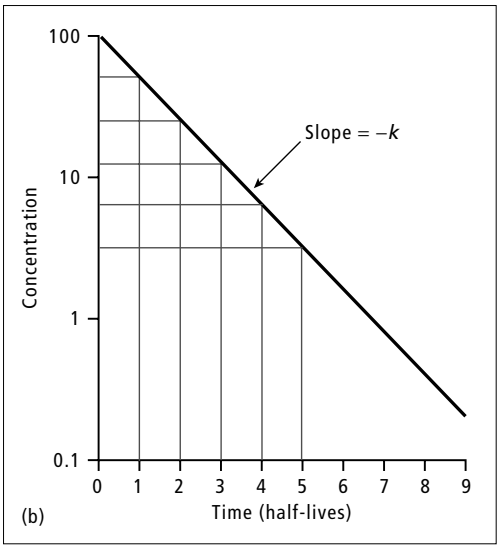


Figure 1.6 (a) Plot of concentration vs. time after a bolus intravenous injection. The intercept on the *y*-(concentration) axis, C_0, is the concentration resulting from the instantaneous injection of the bolus dose. (b) Semi-logarithmic plot of concentration vs. time after a bolus intravenous injection. The slope of this line is $-k$; the elimination rate constant (Eqns. 1.6 and 1.7) and the elimination half-life of the drug can be easily determined from such a plot by noting the time at which the concentration has fallen to half its original value.

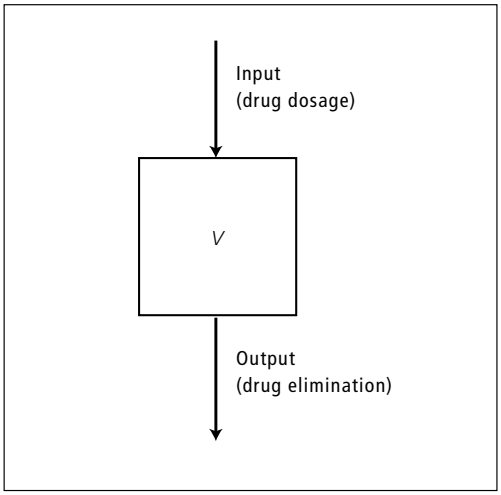


Figure 1.7 The body depicted as a single compartment of volume V.

This is based on the concept that the body can be depicted as a single homogeneous compartment of volume V, as shown in Fig. 1.7. The concentration will then decline by a constant proportion per unit time, giving rise to an exponential decline. The concentration at any time t after the dose can therefore be determined from the exponential expression

$$C(t) = \frac{D}{V}e^{-kt} \qquad \text{(Eqn. 1.6)}$$

where k is the elimination rate constant of the drug, t is any time after drug administration and e^{-kt} is the fraction of drug remaining at time t. If the concentrations are plotted on a logarithmic scale, a linear decline will be obtained with slope-k and intercept ln D/V; thus

$$\text{In } C(t) = \text{In}\frac{D}{V} - kt \qquad \text{(Eqn. 1.7)}$$

Semi-logarithmic graph paper allows $C_0(D/V)$ to be determined directly (Fig. 1.6b). k represents the constant fraction of the volume of distribution from which a drug is eliminated in a given period of time and therefore depends on both clearance and volume of distribution; thus

$$k = \frac{\text{Clearance}}{\text{Volume of distribution}} \qquad \text{(Eqn. 1.8)}$$

k can also be expressed in terms of the half-life of a

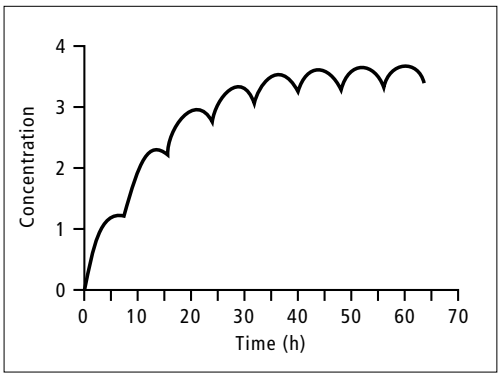


Figure 1.8 Plot of concentration vs. time illustrating the accumulation to steady state when a drug is administered by regular oral doses.

drug. The half-life $t_{1/2}$ is the time required for the plasma concentration to fall to half of its original value and can be derived either graphically (Fig. 1.6) or from the expression

$$t_{1/2} = \frac{\text{In2}}{k} \qquad \text{(Eqn. 1.9)}$$

where ln 2 is the natural logarithm of 2, or 0.693. It can be used to predict the time at which steady state will be achieved after starting a regular treatment schedule or after any change in dose. As a rule, in the absence of a loading dose, steady state is attained after four to five half-lives (Fig. 1.8). Furthermore, when toxic drug levels have been inadvertently produced, it is very useful to estimate how long it will take for such levels to reach the therapeutic range, or how long it will take for all the drug to be eliminated once the drug has been stopped. Usually, elimination is effectively complete after four to five half-lives (Fig. 1.6).

The elimination half-life can also be used to determine dosage intervals to achieve a target concentration–time profile. For example, in order to obtain a gentamicin peak of 8 mg/l and a trough of 0.5 mg/l in a patient with an elimination half-life of 3 h, the dosage interval should be 12 h. (The concentration will fall from 8 mg/l to 4 mg/l in 3 h, to 2 mg/l in 6 h, to 1 mg/l in 9 h and to 0.5 mg/l in 12 h.) However, for many drugs, dosage regimens should be designed to maintain concentrations within a range that avoids high (potentially toxic) peaks or low, ineffective troughs. Excessive fluctuations in the concentration–time profile can be prevented by giving the drug at intervals of less than one half-life or by using a slow-release formulation.

Linear vs. non-linear kinetics

In the discussion on clearance, it was pointed out that the hallmark of linear pharmacokinetics is the proportionality between dose rate and steady-state concentration. This arises because the rate of elimination is proportional to the amount of drug in the body, while the clearance remains constant. This is not, however, always the case as is exemplified by the anticonvulsant drug phenytoin. When the enzymes responsible for metabolism reach a point of saturation, the rate of elimination, in terms of amount of drug eliminated in a given period of time, does not increase in response to an increase in concentration (or an increase in the amount of drug in the body) but becomes constant. This gives rise to non-linear or zero-order kinetics.

The general relationship between drug concentration (C) and rate of metabolism is shown in Fig. 1.9. The maximum rate at which the enzymes can function, V_{max}, corresponds to the plateau attained by the curve.

The equation relating the rate of metabolism to C is the Michaelis–Menten equation

$$\text{Rate of metabolism} = \frac{V_{max} \times C}{K_m \times C} \qquad \text{(Eqn. 1.10)}$$

and the fundamental difference between linear and non-linear kinetics can be appreciated by considering two extreme cases.

1 The serum concentration is considerably less than K_m. In this case, the Michaelis–Menten equation can be approximated to

$$\text{Rate of metabolism} = \frac{V_{max} \times C}{K_m} \qquad \text{(Eqn. 1.11)}$$

where V_{max}/K_m is a constant. This means that the rate of change of concentration is then proportional to the concentration (linear kinetics).

2 The serum concentration is considerably greater than K_m.

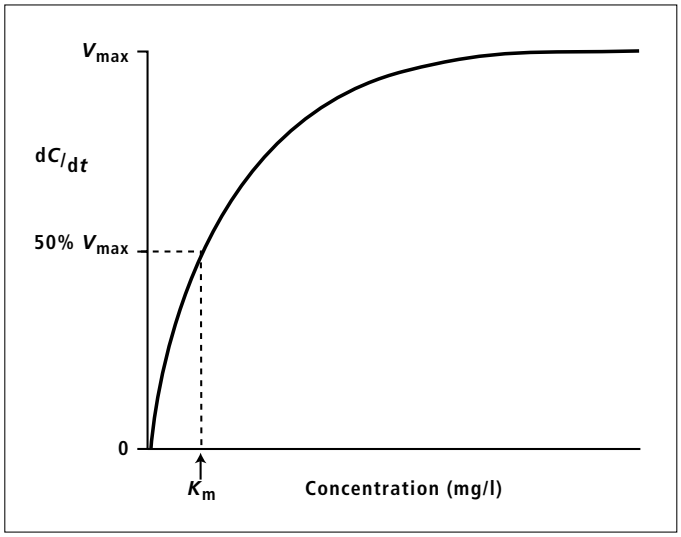


Figure 1.9 Diagrammatic representation of the general relationship between drug concentration C and the rate of metabolism. V_{max} is the maximum velocity at which the drug-metabolising enzyme can function and is a constant (with units of mass/time). K_m is the concentration at which V_{max} is 50%. The K_m is usually much higher than therapeutic concentrations and the rate of metabolism vs. C is essentially linear (Eqn. 1.11). With a few drugs, notably phenytoin, therapeutic plasma concentrations are in the region of K_m so that rate of metabolism vs. C is non-linear and governed by the relationship shown in Eqn. 1.10.

In this case, the Michaelis–Menten equation can be approximated to

$$\text{Rate of metabolism} = V_{max} \qquad \text{(Eqn. 1.12)}$$

which indicates that the rate of elimination is a constant.

At steady state, dose rate can be substituted for rate of metabolism, i.e.

$$\text{Steady-state dose rate} = \frac{V_{max} \times Css}{K_m + Css} \qquad \text{(Eqn. 1.13)}$$

For phenytoin, V_{max} has a typical value of 7.2 mg/kg per day and K_m has a typical value of 4.4 mg/l (17.6 μmol/l). In the case of phenytoin, the range of concentrations used clinically encompasses and exceeds K_m. Consequently, the relationship between the steady-state concentration and dose rate will alter as the concentration changes. At low concentrations, the increase in concentration will be proportional to the dose rate (linear pharmacokinetics). At higher concentrations, the increase will be much greater than would have been anticipated (non-linear pharmacokinetics). Steady state will not be achieved if the dose rate exceeds V_{max}. This can be seen in Fig. 1.10.

Comment. The clinical relevance of non-linear kinetics is that a small increase in dose can lead to a large increase in concentration. This is particularly important when toxic side effects are closely related to concentration, as with phenytoin.

Principles of drug elimination

Drug metabolism

Drugs are eliminated from the body by two principal mechanisms: (i) liver metabolism and (ii) renal excretion. Drugs that are already water-soluble are generally excreted unchanged by the kidney. Lipid-soluble drugs are not easily excreted by the kidney because, following glomerular filtration, they are largely reabsorbed from the proximal tubule. The first step in the elimination of such lipid-soluble drugs is metabolism to more polar (water-soluble) compounds. This is achieved mainly in the liver, but can also occur in the gut and may contribute to first-pass elimination. Metabolism generally occurs in two phases:

Phase 1 Mainly oxidation (sometimes reduction or hydrolysis) to a more polar compound.

Phase 2 Conjugation, usually with glucuronic acid or sulphate, to make the compound substantially more polar.

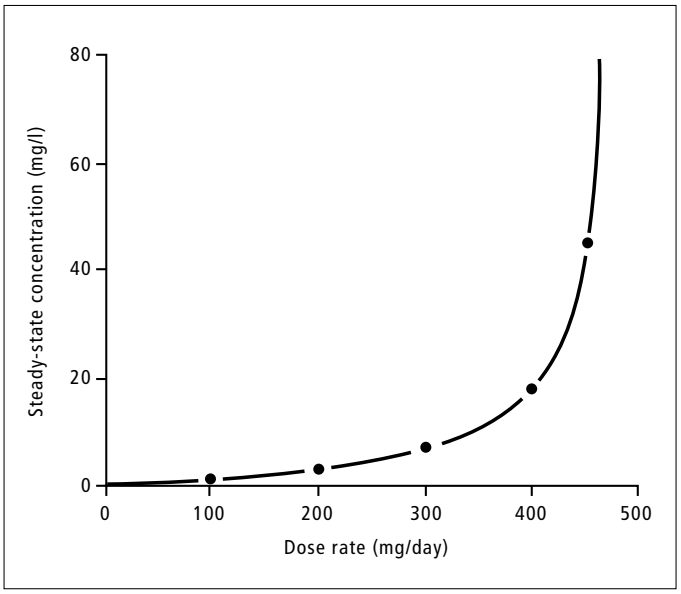


Figure 1.10 The *C*ss vs. dose rate relationship for phenytoin. This is governed by Michaelis–Menten kinetics (Eqn. 1.13).

Phase 1 metabolism

Oxidation can occur in various ways, including aromatic or aliphatic hydroxylation, oxygenation at carbon, nitrogen or sulphur atoms and N- and O-dealkylation. These reactions are catalysed by the cytochrome P-450-dependent system of the endoplasmic reticulum. Knowledge of P-450, which exists as a superfamily of similar enzymes (isoforms), has increased greatly recently. The P-450 superfamily is divided into a number of families and subfamilies, where genes encoding for proteins within a family have at least 40% nucleotide sequence homology and subfamilies have over 65% homology. Although numerous P-450 isoforms are present in human tissue, only a few of these have a major role in the metabolism of drugs. These enzymes, which display a distinct but overlapping substrate specificity, are listed in Table 1.4.

Phase 1 metabolites usually have only minor structural differences from the parent drug, but may exhibit totally different pharmacological actions. For example, the metabolism of azathioprine produces the powerful antimetabolite 6-mercaptopurine.

Phase 2 reactions

These involve the addition of small endogenous molecules to the parent drug, or to its phase 1 metabolite, and almost always lead to abolition of pharmacological activity. Multiple forms of conjugating enzymes are also known to exist, although these have not been investigated to the same extent as the P-450 system.

Metabolic drug interactions

The wide range of drugs metabolised by the P-450 system provides the opportunity for interactions of two types, namely enzyme induction and inhibition.

Induction

Enzyme induction, which may be defined as the increase in amount and activity of drug-metabolising enzymes, is a consequence of new protein synthesis resulting from prolonged exposure to the inducing drug. While a drug may induce its own metabolism, it can also accelerate the metabolism and clearance of unrelated compounds. Many

Table 1.4 Major human P-450 enzymes involved in drug metabolism.

Major human P-450s	Typical substrates
CYP1A2	Theophylline, caffeine, tacrine, fluvoxamine, oestradiol, phenacetin (*R*)-warfarin
CYP2C9	(*S*)-Warfarin, tolbutamide, glipizide, losartan, ibuprofen, diclofenac, phenytoin
CYP2C19	(*S*)-Mephenytoin, omeprazole, diazepam, citalopram, proguanil, moclobemide
CYP2D6	(*S*)-Metoprolol, bufuralol, dextromethorphan, fluoxetine, desipramine, nortryptiline
CYP2E1	Enflurane, halothane, chlorzoxazone, ethanol
CYP3A4	Astemizole, terfenadine, cisapride, pimozide, nisoldipine, midazolam, indinavir, lovastatin, St. John's wort

compounds are known to act as enzyme inducers in animals at toxicological dose levels, but relatively few drugs produce clinically significant induction in humans when used at therapeutic dose levels.

The compounds shown in Table 1.5 are the most potent enzyme inducers in clinical use and have produced numerous clinically significant drug interactions, related primarily to increases in the metabolism of CYP2C9, CYP2C19 and CYP3A4 substrates. For example, the anticonvulsants phenytoin and carbamazepine, as well as the herbal remedy St. John's wort, induce the enzymes that metabolise the constituents of oral contraceptives. If a woman receiving an oral contraceptive starts taking one of these drugs, the metabolism of the oestrogen and progestogen in the oral contraceptive increases, with the risk of contraceptive failure. Enzyme induction is not, however, limited to drug administration. Cigarette smoking, for example, results in enzyme induction with increased metabolism of CYP1A2 substrates, such as theophylline, and ethanol is an inducer of CYP2E1.

Table 1.5 Some of the most potent enzyme inducers in humans.

Carbamazepine
Phenytoin
Rifampicin

Inhibition

Concurrently administered drugs can also lead to inhibition of enzyme activity, with many P-450 inhibitors showing considerable isoform selectivity. Some of the most clinically relevant inhibitors are listed in Table 1.6, together with the isoform inhibited. For example, ketoconazole decreases the metabolism of the CYP3A4 substrate, terfenadine, leading to potentially dangerous adverse effects, e.g. QT interval prolongation and torsades de pointes.

Table 1.6 P-450 inhibitors involved in drug interactions.

Major human P-450s	Typical inhibitors
CYP1A2	Furafylline, fluvoxamine, ciprofloxacin
CYP2C9	Fluconazole, ketoconazole, sulfaphenazole
CYP2C19	Omeprazole, ketoconazole, cimetidine
CYP2D6	Quinidine, fluoxetine, ritonavir
CYP2E1	Disulfiram
CYP3A4	Ketoconazole, itraconazole, ritonavir, erythromycin, diltiazem

Table 1.7 Major enzymes displaying genetic polymorphism.

Enzyme	Typical substrates	Characteristics
CYP2C19	(*S*)-Mephenytoin, diazepam, omeprazole	About 2–5% of white people are poor metabolisers, but 18–23% of Japanese people have this phenotype
CYP2D6	Propafenone, flecainamide, desipramine	About 7% of white people are poor metabolisers, but this frequency is only about 2% in black Americans and <1% in Japanese/Chinese
N-Acetyl- transferase	Hydralazine, sulphonamides, isoniazid, procainamide	About 50% of white people are slow acetylators

As with induction, P-450 inhibition is not limited to drug administration. Grapefruit juice is a fairly potent inhibitor of CYP3A4 activity and produces clinically significant interactions with a number of drugs, including midazolam, simvastatin and terfenadine. This type of information, together with some knowledge of the enzymes involved in a particular drug's clearance, makes it much easier to understand and predict drug interactions.

Comment. Enzyme induction produces clinical changes over days or weeks, but the effects of enzyme inhibition are usually observed immediately. In most circumstances, these changes are manifest as decreases in efficacy resulting from induction, or as increases in adverse effects resulting from inhibition. Clinical relevance occurs when drug therapy needs to be altered to avoid the consequences of the drug interaction and this is most common and most serious in compounds that have a narrow therapeutic index. Clearly, pronounced enzyme inhibition, which may result in plasma concentrations of the inhibited drug being many times higher than intended, can be a major safety issue. For example, co-administration of ketoconazole or ritonavir with the hypnotic drug midazolam increases the midazolam plasma AUC by 15–20 times, a situation which should be avoided.

Genetic factors in metabolism

The rate at which healthy people metabolise drugs is variable. Although part of this variability is a consequence of environmental factors, including the influence of inducers and inhibitors, the main factor contributing to interindividual variability in metabolism is the underlying genetic basis of the drug-metabolising enzymes. Although there is probably a genetic component in the control of most P-450 enzymes, some enzymes (e.g. CYP2C19 and CYP2D6) actually show genetic polymorphism. This results in distinct subpopulations of poor and extensive metabolisers, where the poor metabolisers are deficient in that particular enzyme. There are a number of enzymes under polymorphic control and some clinically important examples are shown in Table 1.7. As with enzyme inhibition, genetic polymorphism is primarily a concern for drugs that have a narrow therapeutic index and that are metabolised largely by a single polymorphic enzyme. In such cases, the phenotype of the patient should be determined and lower doses of the drug used, or alternative therapy should be considered.

Renal excretion

Three processes are implicated in renal excretion of drugs:

1 *Glomerular filtration*. This is the most common route of renal elimination. The free drug is cleared by filtration and the protein-bound drug remains in the circulation where some of it dissociates to restore equilibrium.

2 *Active secretion in the proximal tubule*. Both weak acids and weak bases have specific secretory sites in proximal tubular cells. Penicillins are

eliminated by this route, as is about 60% of procainamide.

3 *Passive reabsorption in the distal tubule*. This occurs only with un-ionised, i.e. lipid-soluble, drugs. Urine pH determines whether or not weak acids and bases are reabsorbed, which in turn determines the degree of ionisation.

If renal function is impaired, for example by disease or old age, then the clearance of drugs that normally undergo renal excretion is decreased.