

I: CLINICAL PHARMACOKINETICS

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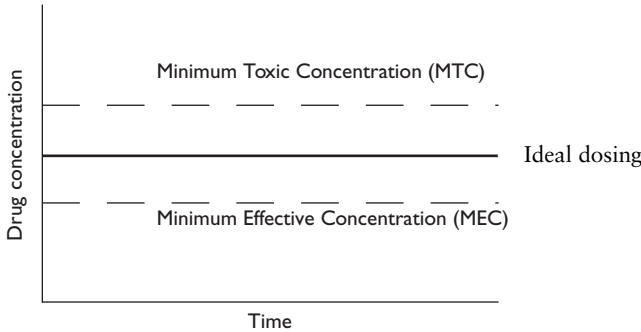
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General overview: clinical pharmacokinetics

The ultimate aim of drug therapy is to achieve efficacy without toxicity. This involves achieving a plasma concentration (C_p) within the ‘therapeutic window’, i.e. above the *minimal effective concentration* (MEC), but below the *minimal toxic concentration* (MTC).

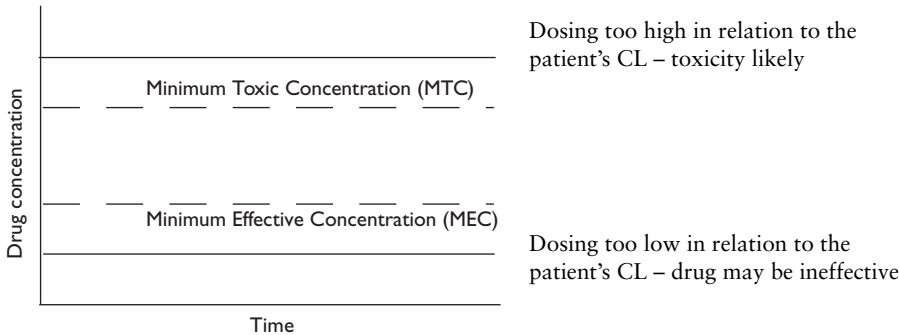
Clinical pharmacokinetics is about all the factors that determine variability in the C_p and its time-course. The various factors are dealt with in subsequent chapters.

Ideal therapeutics: efficacy without toxicity



The graph shows a continuous IV infusion at steady state, where the dose-rate is exactly appropriate for the patient’s clearance (CL).

Inappropriate dosing

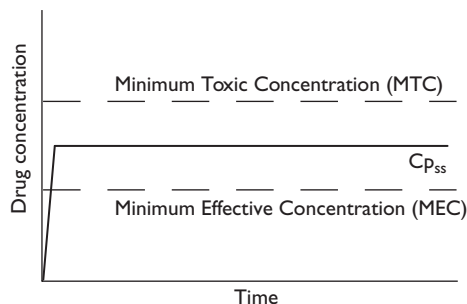


Some reasons for variation in CL

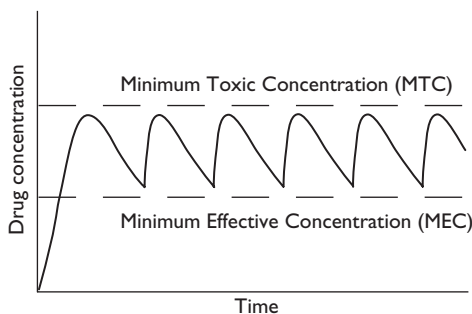
Low CL	High CL
Normal variation	Normal variation
Renal impairment	Increased renal blood flow
Genetic poor metabolism	Genetic hypermetabolism
Liver impairment	Enzyme induction
Enzyme inhibition	
Old age/neonate	

Pharmacokinetic factors determining ideal therapeutics

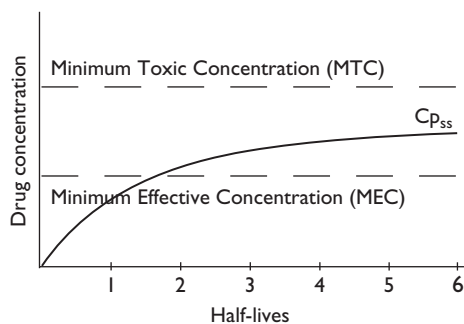
If immediate effect is needed, a loading dose (LD) must be given to achieve a desired concentration. The LD is determined by the volume of distribution (V_d). To maintain the concentration requires a maintenance dose regimen. The maintenance dose-rate is determined by the CL. The fluctuations within a dosing interval are determined by the half-life ($t_{1/2}$).



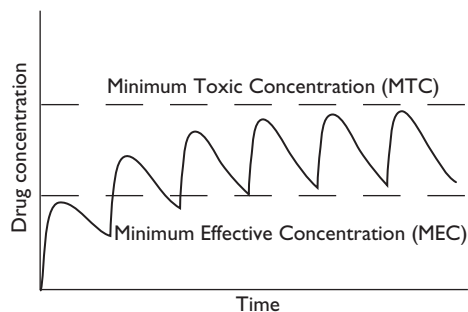
LD (IV) followed by maintenance dosing as continuous infusion



LD (oral) followed by oral maintenance dosing



If dosing is started by continuous infusion of the maintenance dose, it takes four half-lives to approach steady state



Similarly, if dosing is started with oral maintenance dosing, it takes four half-lives to approach steady state

Pharmacokinetics

The study of the movement of drugs into, within, and out of the body, and factors affecting this

or, more simply

What the body does to the drug

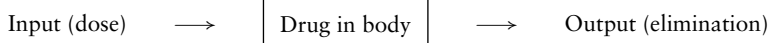
Pharmacokinetics should not be confused with pharmacodynamics. Pharmacodynamics is the study of drug effect, i.e. what the drug does to the body (see p. 60). Knowledge of pharmacokinetics enables drugs to be used rationally and doses tailored to the individual patient.

The most important pharmacokinetic parameters from a dosing point of view are:

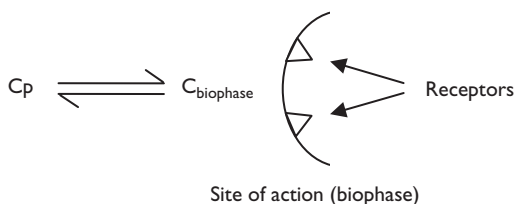
- The clearance (CL) – determines the maintenance dose-rate
- The volume of distribution (Vd) – determines the loading dose (LD)
- The half-life ($t_{1/2}$) – determines the time to steady state and the dosing interval

One-compartment model

In this simple model the body is considered as a single container (one compartment) in which the drug is instantaneously and uniformly distributed.



Pharmacokinetics describes the movement of the drug into, within, and out of the compartment (the body), and the time-course of this. From a drug effect point of view it is the concentration of drug at the site of action (the biophase) that is important. This is difficult to measure. Under steady-state conditions the C_p is in equilibrium with concentrations at sites of action. In practice it is usually the C_p that is measured.

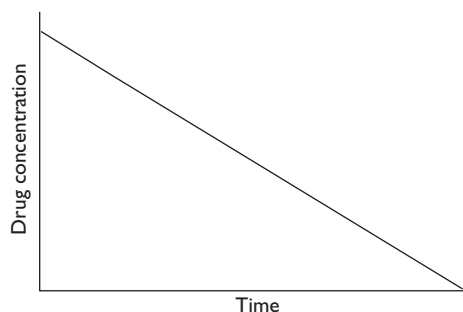


The pharmacokinetics of a drug are usually studied using an IV injection or infusion, as the dose can then be considered to be 100% assimilated into the body. The values of CL, Vd and $t_{1/2}$ for a drug are derived from the curve of concentration versus time.

Concentration versus time curves

Zero-order elimination

It would be very simple if the C_p declined linearly with time. This situation, called *zero-order* elimination, does occur but only rarely. A familiar example is ethanol, concentrations of which decline at a constant rate of approximately 15 mg/100 mL/h.

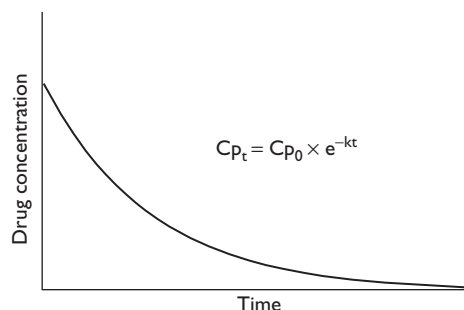


Rate of elimination constant with time

Note: linear y-axis

First-order elimination

The more common situation is *first-order* elimination, in which the decline in C_p is not constant with time, but varies with the concentration, i.e. rate of elimination $\propto C_p$. The term 'first order' reflects the fact that the rate of elimination is dependent on concentration (C_p to power of 1, or C_p^1 , which is the same as C_p).



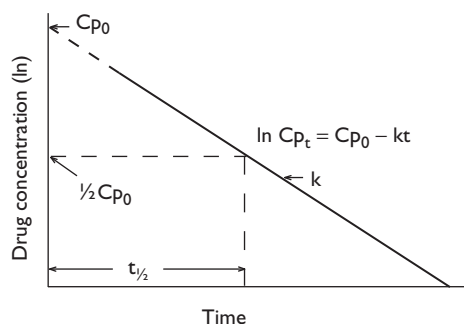
C_{p_t} is the concentration at any time t

C_{p_0} is the concentration at time 0

k is the elimination rate constant

The concentrations declines 'exponentially' with time.

Note: linear y-axis



This is the same curve as the one above but the y-axis is the natural logarithm of C_p ($\ln$). This enables the slope of the 'curve' to be estimated, which in turn allows the calculation of $t_{1/2}$ and V_d

Note: log y-axis

Drug clearance (CL)

CL is the single most important pharmacokinetic parameter. It is:

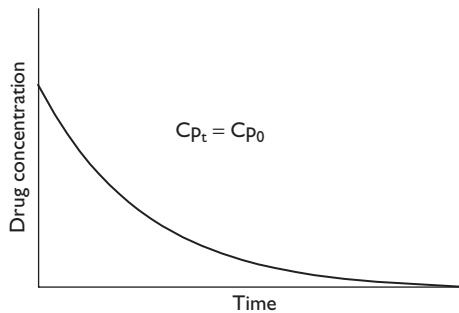
‘The volume of plasma cleared of drug per unit time’

or

‘A constant relating the rate of elimination to the C_p ,
i.e. rate of elimination = $CL \times C_p$ ’

CL is an index of how well a drug is removed irreversibly from the circulation. As a result it determines the dose-rate (dose per unit time) required to *maintain* a C_p .

CL only applies to drugs with first-order (exponential) kinetics, i.e. the majority of drugs.



Rate of elimination $\propto C_p$
 $\therefore$ Rate of elimination = a constant $\times C_p$
 i.e. Rate of elimination = $CL \times C_p$

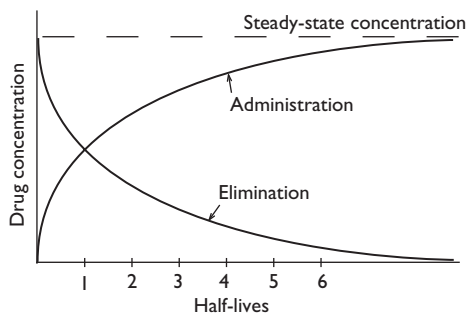
or

$$\therefore CL(L/h) = \frac{\text{Rate of elimination (mg/h)}}{C_p \text{ (mg/L)}}$$

Thus, CL is ‘a constant relating the rate of elimination to the C_p ’, and ‘the volume of plasma cleared of drug per unit time’. The units are vol/time (e.g. L/h)

Maintaining a constant steady-state concentration ($C_{p_{ss}}$)

To maintain a target steady state C_p , the drug must be administered at a rate equal to the rate of elimination at that concentration:



i.e. Rate of administration = rate of elimination

Since rate of elimination = $CL \times C_p$

Then rate of administration = $CL \times C_{p_{ss}}$

or

$$\text{Maintenance dose-rate} = CL \times C_{p_{ss}}$$

Physiological relevance of drug CL

The main organs responsible for drug CL are the liver (metabolism) and the kidneys (removal of unchanged drug). Total body CL is the sum of all CL processes, i.e.

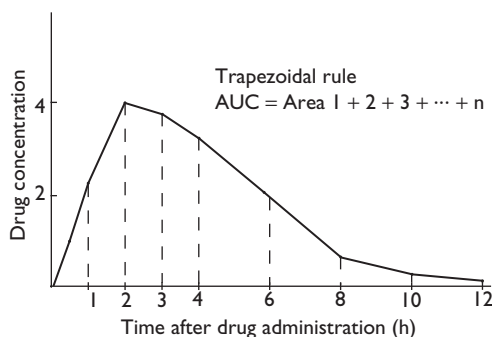
$$CL \text{ (total)} = CL \text{ (renal)} + CL \text{ (liver)} + CL \text{ (other)}$$

Comparison of drug CL values with glomerular filtration rate (GFR), renal blood flow or liver blood flow may give a clue to mechanisms of drug removal, e.g. a drug eliminated entirely by glomerular filtration will have a maximum CL of 120 mL/min (i.e. GFR). If there is tubular secretion the drug CL may be >120 mL/min, and if there is tubular reabsorption, it may be <120 mL/min. Similarly the maximum CL from blood by metabolism is equal to the liver blood flow (~1500 mL/min).

Determination of CL

- From the Area Under the Curve (AUC)

Plasma CL is usually determined from the area under the C_p versus time curve (AUC) after IV administration. The AUC is determined using the 'trapezoidal rule'.



Each area is approximated by a trapezium, except for Area 1 (a triangle). The area from the last point to infinity is $C_{last/k}$, where k is determined from the $\ln C_p$ versus time curve

$$\text{After IV dosing: } CL = \frac{\text{Dose}}{AUC}$$

$$\text{After oral dosing: } CL = \frac{F \cdot \text{Dose}}{AUC}$$

where F = oral availability

- From the V_d and $t_{1/2}$

The V_d and $t_{1/2}$ can be calculated from the $\ln C_p$ versus time curve as described in the following two chapters, and the CL calculated using:

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

Volume of distribution (Vd)

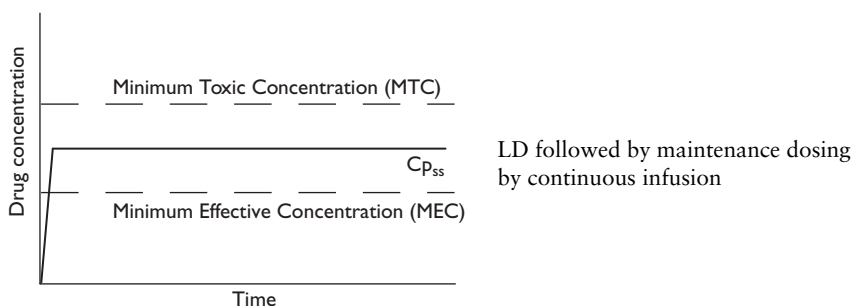
The Vd is the second most important pharmacokinetic parameter (after CL). It is:

‘The volume into which a drug appears to be distributed with a concentration equal to that of plasma’

or

‘A proportionality constant relating the Cp to the amount of drug in the body (Ab),’ i.e. $Ab = Vd \times Cp$ Units: Volume or vol/kg

The Vd determines the LD, to achieve a target Cp as quickly as possible.



In order to achieve a target Cp, the tissues into which the drug distributes must be ‘filled up’ with drug. The Vd is therefore ‘the volume into which a drug appears to be distributed with a concentration equal to that of plasma.’

After distribution is complete, the amount of drug in the body (Ab) is proportional to the Cp.

$$\text{i.e. } Ab \propto Cp \quad \text{or} \quad Ab = a \text{ constant} \times Cp$$

This constant has units of volume (e.g. L) since the Ab is in mass units (e.g. mg) and Cp is in concentration units (e.g. mg/L). Hence the Vd is ‘a proportionality constant relating the Cp to the amount of drug in the body.’

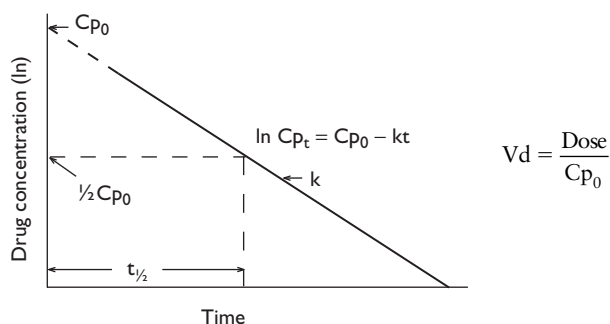
$$\text{i.e. } Ab = Vd \times Cp \quad \text{or} \quad Vd = \frac{Ab}{Cp}$$

The Vd is often called the ‘apparent’ Vd since the volume has no real anatomical meaning. This can be appreciated when the volume of the body (50–100L) is compared with Vds of drugs, e.g. heparin (5L); gentamicin (15L); digoxin (500L); and quinacrine (20000L). Drugs with small Vds tend to be polar and water soluble, while drugs with large Vds tend to be highly lipid soluble.

Unless otherwise specified, the Vd is based on total drug concentration (protein bound + unbound).

Determination of Vd

To calculate Vd, the Ab and Cp need to be known. The only time Ab is known accurately is immediately after the drug has been given IV (i.e. prior to elimination), because this is the dose. If the Cp at time 0 (Cp₀) is known, then the Vd can be calculated. The Cp₀ is determined by back extrapolation of the ln Cp versus time curve to the intercept on the y-axis.



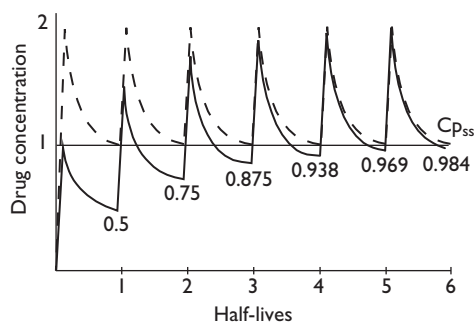
Calculation of LD

It follows from the above, that to achieve a target Cp, the Vd of the drug must be known.

$$LD = V_d \times \text{target } C_p$$

e.g. to achieve a target Cp of 1.5 µg/L for digoxin (Vd ~ 500L)

$$LD (\mu\text{g}) = 500 (\text{L}) \times 1.5 (\mu\text{g/L}) = 750 \mu\text{g}$$



LD enables steady-state concentrations to be achieved quickly

Top curve – LD followed by maintenance dosing every $t_{1/2}$

Bottom curve – maintenance dosing every $t_{1/2}$ (i.e. no LD)

Changing doses to achieve higher concentrations

The concepts described above also apply if a patient is already on a drug but needs higher concentrations. If the maintenance dose is increased, it will take four half-lives to achieve >90% of the new Cp_{ss}. To get there more quickly, a 'LD' is given, as follows:

$LD = V_d \times (C_{pss2} - C_{pss1})$ where Cp_{ss1} and Cp_{ss2} are the starting and new steady-state concentrations. An increased maintenance dose will keep concentrations at the new level.

The half-life ($t_{1/2}$)

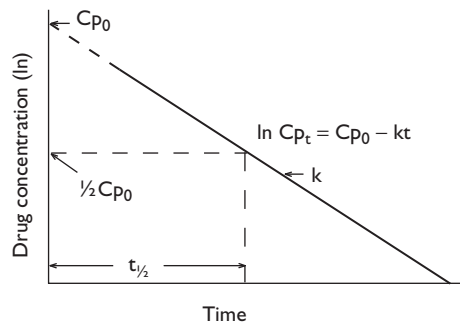
‘The time for the concentration of the drug to halve’

The $t_{1/2}$ provides an index of:

- the time-course of drug elimination;
- the time-course of drug accumulation;
- choice of dose interval.

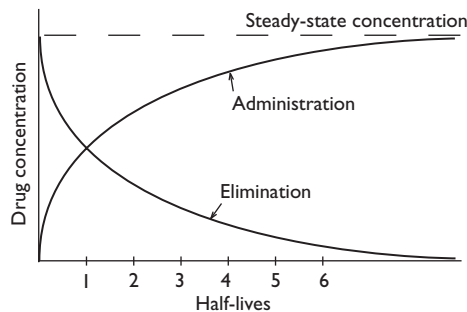
Derivation of $t_{1/2}$

The half-life of elimination ($t_{1/2}$) can be derived by plotting actual concentrations on semi-log graph paper, or the log of the concentrations on linear graph paper. The $t_{1/2}$ is the time taken for any concentration to halve, e.g. from 3 to 1.5 mg/L, or from C_{p0} to $\frac{1}{2}C_{p0}$.



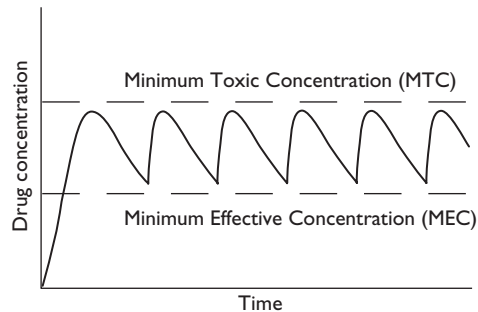
Time-course of drug elimination and accumulation

If a drug is discontinued after an infusion, the C_p will decline exponentially to <10% of its starting value after four half-lives. Similarly, if a drug is started as a constant infusion it will take four half-lives to accumulate to >90% of the final steady-state concentrations.



Choice of dose interval

The dose interval is usually chosen so that concentrations stay above the MEC but below the MTC.



Other considerations in the choice of dose interval are the therapeutic index of the drug and compliance. A drug with a high therapeutic index may be dosed less frequently. Compliance is best with dosing once or twice daily.

If drug CL decreases (say in renal impairment), it may be possible for a drug that is normally given three or four times a day to be given twice or once daily, with greater chance of compliance. This is good therapeutics.

Relationship between $t_{1/2}$, V_d and CL

The $t_{1/2}$ is dependent on V_d and CL. This is logical since the larger the V_d , the longer the $t_{1/2}$, i.e. it takes longer to remove drug from deep within the tissues. By contrast, the greater the CL, the shorter the $t_{1/2}$.

$$\text{i.e. } t_{1/2} \propto \frac{V_d}{CL}$$

This relationship can be turned into an equation by multiplying the right side by 0.693. This strange number is the natural logarithm of 2 (i.e. $\ln 2$) and gets into the equation because the $t_{1/2}$ involves a halving, i.e. the inverse of 2.

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

This is one of the most important equations in clinical pharmacokinetics.

- It indicates that the $t_{1/2}$ is *dependent* on V_d and CL.
- V_d and CL are the *independent* variables.

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

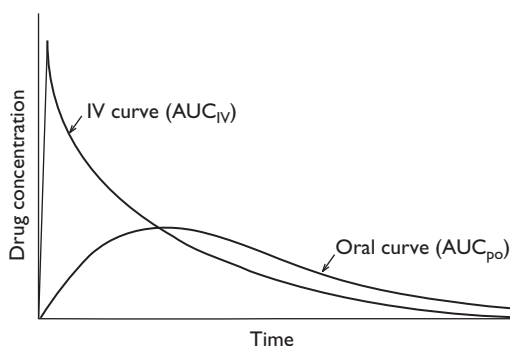
Oral availability (F)

F is the fraction of the dose of drug given orally that reaches the systemic circulation

The F defines how much drug gets into the systemic circulation after oral ingestion. It is usually defined by comparison of the area under the concentration–time curve (AUC) in the systemic circulation after oral ingestion with the AUC after IV dosing, i.e. the fraction (F) of drug that gets into the body after oral (po) versus IV administration:

$$F = \frac{AUC_{po}}{AUC_{IV}}$$

The total amount of drug in the systemic circulation is defined by the AUC. The AUC is often less after oral compared with IV administration. The F may have any value up to one. A value of one indicates complete assimilation.



Determinants of F: absorption and first-pass metabolism

Absorption

This refers to the ability of the drug to cross the gut wall (a biological barrier) into the blood. Absorption is usually a passive process governed by the principles of diffusion (i.e. flows down a concentration gradient). Factors favouring absorption include high lipid solubility and low ionization. The pH of the gastric secretions may also influence absorption, but probably affects the rate more than the extent. Sometimes active transport is involved (e.g. l-dopa), and is subject to saturability, competition, and the ability to move against a concentration gradient.

First-pass metabolism

This refers to metabolism of the drug prior to reaching the systemic circulation, i.e. *presystemic elimination*. Some drugs, such as highly lipid-soluble drugs, are so highly metabolized that on 'first-pass' through the liver there is substantial 'presystemic' elimination. Presystemic elimination can occur in the gut wall (e.g. oestrogens), in the portal circulation (e.g. aspirin → salicylic acid) or in the liver (the majority).

Effect of food on F

Interestingly, food affects absorption and first-pass metabolism in opposite ways. Food usually *decreases* the F of drugs that are poorly absorbed (e.g. F of atenolol decreases by 50%), but *increases* the F of drugs that are subject to high first-pass metabolism (e.g. F of metoprolol increases by 50%).

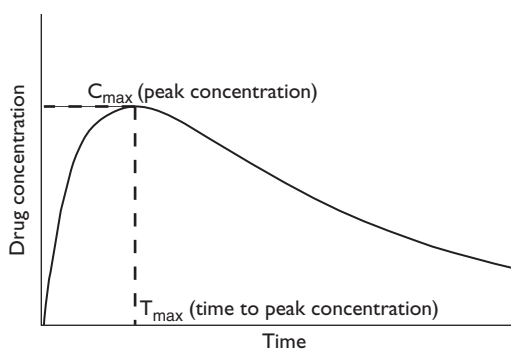
Some foods, e.g. grapefruit juice, have constituents that compete with drugs for presystemic elimination, thereby causing increased F of some drugs (e.g. calcium antagonists, some statins).

Confusing terminology

There is sometimes confusion between the terms 'F', 'bioavailability' and 'absorption'. The F is the preferred term because it is unambiguous.

'Bioavailability' has a strict historical definition – 'the rate and extent of *absorption*'. One problem with 'bioavailability' is its reference to absorption. As noted above, absorption is only one part of the process of drug attaining the systemic circulation. The other problem with 'bioavailability' is that it is a single term that defines two processes – the *rate* of absorption, and the *extent*. It is more instructive to think of each of these components independently, i.e. F defines the *extent*, and another term, $T_{\max}$, defines the *rate*.

Time to peak concentration ($T_{\max}$)



$T_{\max}$ is less important than F. A short $T_{\max}$ may be useful where an immediate effect is desired, e.g. analgesia for a headache, but may also be a problem, e.g. adverse effects related to the peak concentration.

Slow-release preparations

A delayed $T_{\max}$ and a longer drug action may be achieved using tablets or capsules designed to release their contents slowly in the gut. These are called slow release, sustained release, or controlled-release preparations. The concentration–time profile is much flatter after these, giving a more even drug response (see p. 64).

Protein binding (PB)

The major message about PB is that it is usually not important clinically

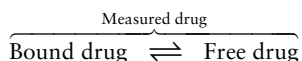
PB is only important in the interpretation of measured drug concentrations

There is enormous confusion about the importance of PB. While drugs may displace each other from PB sites, the free concentration (i.e. the active component) is governed by CL. Most PB interactions of alleged clinical importance have an additional mechanism operating, such as altered drug CL.

Many drugs bind to plasma proteins. Acidic drugs bind largely to albumin. Basic drugs bind mainly to α_1 -acid glycoprotein (i.e. orosomucoid), an acute phase reactant, as well as to albumin and β -lipoproteins.

The significance of PB lies in the interpretation of concentrations of drugs. If concentrations are not measured, PB can largely be ignored.

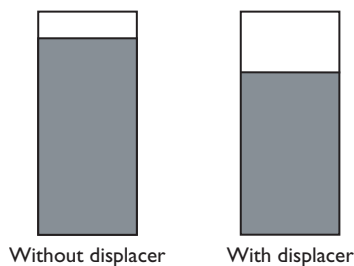
When drug concentrations of drugs are measured, it is almost invariably *total drug*, i.e. bound+unbound, that is measured. It is possible, but not routine (except occasionally for phenytoin), to measure free or unbound drug. Remember that it is free drug that acts on receptors and is important for drug activity.



Altered albumin or α_1 -acid glycoprotein concentrations will alter the measured (total) concentrations of drugs bound highly to these proteins, but will not alter the free concentrations. Free drug concentration is dependent on free drug CL, and does not vary in relation to changes in plasma proteins. Therefore, except for rare exceptions, no alteration in dosage is required in states of altered PB.

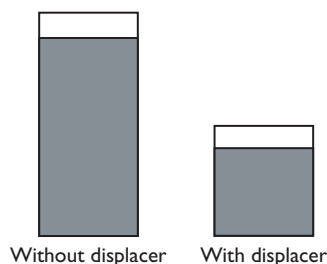
The fallacy of PB drug interactions

Effects of PB displacement *in vitro*.



In this 'test-tube' situation, free drug concentration increases as the percentage bound changes. However, this is not relevant to the *in vivo* situation, where elimination is also occurring.

Effects of PB displacement *in vivo*.

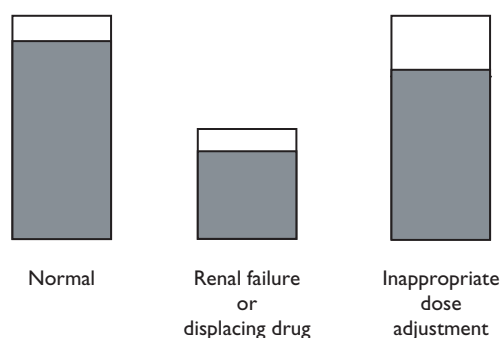


The percentage PB changes as *in vitro*, but free concentration returns to the pre-displacement level due to the increased drug elimination that follows the temporary increase in free drug concentrations.

Total drug concentration is now lower, but because free drug is now at pre-displacement levels, drug effect is unaltered.

Interpretation of measured C_p during therapeutic drug monitoring

PB 'problems' arise from the fact that drug concentrations are usually measured as total drug (bound + unbound). In hypoalbuminaemia (e.g. in renal disease), an acidic drug, such as phenytoin, has a lower total drug concentration because of lower PB. Free drug concentration is the same as in the non-hypoalbuminaemic state (assuming free drug CL is constant). The same principles apply with displacing drugs in normoalbuminaemia, e.g. for *phenytoin* (therapeutic range 10–20 mg/L total concentration, 1–2 mg/L free concentration), if the dose is increased to bring total concentration up into the therapeutic range, the free concentration may be toxic.



Drugs with saturable PB

A few drugs, at clinical concentrations, saturate the available PB sites. In this situation total drug concentration (bound + unbound) does not increase linearly as dose increases. If free concentrations were measured, these would be seen to rise linearly with dose. Drugs with saturable PB include ceftriaxone, hydrocortisone, prednisone, thioridazine and sodium valproate. Of these, the only one that has clinical importance is sodium valproate, because this is sometimes measured during therapeutic drug monitoring. Saturable PB makes interpretation of valproate concentrations difficult. For the other drugs PB does not need to be taken into account during dosing, because drug concentrations are not usually measured, and free concentrations behave predictably.

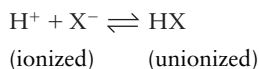
pH and pharmacokinetics

Drug disposition may vary in relation to pH differences across biological barriers. The disposition of some weak acids and bases is susceptible to small pH differences because of variation in the state of ionization and hence the ability to cross membranes. Unionized drugs cross lipid membranes better than ionized drugs.

Background theory

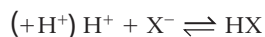
Acids are ionized in basic media.

Bases are ionized in acidic media.

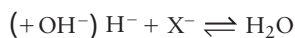


The equilibrium can be moved to the left or right if acid or alkali is added.

Adding acid (H^+): equilibrium shifts to the right since X^- is consumed.



Adding alkali (OH^-): equilibrium shifts to the left as H^+ is consumed, producing H_2O



Henderson-Hasselbalch equation:

$$\text{For acids: } \text{pH} = \text{pK}_a + \log_{10} \times \left(\frac{[\text{ionized}]}{[\text{unionized}]} \right)$$

$$\text{For bases: } \text{pH} = \text{pK}_a + \log_{10} \times \left(\frac{[\text{unionized}]}{[\text{ionized}]} \right)$$

Note: The pK_a is the pH at which a drug is 50% ionized and 50% unionized. Weak acids, with pK_a values between 3 and 7.5, may show variation in the ionized/unionized ratio at pHs encountered in physiology. Similarly, weak bases with pK_a values between 5 and 11, may show variation in the unionized/ionized ratio.

When is pH important in pharmacokinetics?

- Drug absorption from the stomach
- Drug elimination via the kidneys
- Drug distribution into milk, the placenta and 'third spaces'

Drug absorption from the stomach

Gastric pH is usually between 1 and 4. Acids are therefore largely unionized and may be absorbed in the stomach (e.g. aspirin). However, the bulk of absorption (even for acids) occurs in the small intestine, because of the far greater absorptive surface area.

Drug elimination in the kidney

The pH of the urine varies from 4.5 to 7.5 because the urine is largely unbuffered. Weak acids may vary from unionized at pH 4.5 to largely ionized at pH 7.5. Reabsorption from the renal tubular lumen into the blood occurs if the drug is in the unionized state. Therefore, reabsorption will occur in acid urine, while elimination will occur in alkaline urine. Conversely, weak bases will be reabsorbed in alkaline urine and eliminated in acidic urine.

These principles are sometimes used to enhance the elimination of drugs after overdose (e.g. aspirin elimination can be enhanced by administration of bicarbonate, and amphetamine elimination is enhanced by the administration of NH_4Cl).

Drugs with pH-dependent renal elimination

Acids (elimination enhanced by alkaline diuresis)

- Phenobarbitone
- Salicylates

Bases (elimination enhanced by acid diuresis)

- Amphetamines
- Methadone
- Mexiletine
- Phencyclidine
- Phenylpropanolamines, e.g. ephedrine, pseudoephedrine
- Quinidine

Drug distribution into milk, across the placenta, and into 'third spaces'

Milk, the fetus, and most 'third spaces' have pH values that are acidic (~ 7.0) in relation to plasma (~ 7.4). Therefore bases tend to concentrate in these 'compartments' because they are relatively ionized on the acidic side, and effectively 'trapped'. This is called 'ion trapping'. It applies to any situation where a pH gradient exists across a biological barrier, and where the principles of diffusion apply, e.g. breast milk, the fetus, abscesses and synovial fluid.

