Instant Clinical Pharmacology

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Introduction

This book is written mainly for medical students and doctors undergoing postgraduate training. Students of allied health professionals, such as pharmacy, nursing, dentistry and physiotherapy may also find it useful.

The aim is to provide essential information about the core topics in clinical pharmacology. There is general agreement across the world about what constitutes this core curriculum. These topics are covered, the emphasis reflecting my own biases.

The book assumes a knowledge of basic pharmacology and does not embrace specific therapeutics. It aims to bridge the gap between basic pharmacology and the therapeutic use of drugs in humans.

Some readers may be put off by the slightly mathematical nature of the initial section on clinical pharmacokinetics. I apologize for this, but unfortunately this is the basis of clinical pharmacology. The book gets easier after this.

Any feedback would be appreciated, particularly in terms of improving the user-friendliness of the book.

I acknowledge with warm gratitude the input and inspiration of all the members of my department, both past and present. The book is dedicated to my students, whose humour and wide-eyed enthusiasm makes teaching so worthwhile.

How to use the book

Mindful of the fickle nature of the learning process, I have tried to keep things simple and to encapsulate each topic within two facing pages. Hopefully, this will enable the reader to complete a topic in a short learning session before the inevitable build-up of boredom!

Happy learning!

Evan J. Begg

What is Clinical Pharmacology?

Clinical pharmacology is concerned with the rational, safe and effective use of medicines.

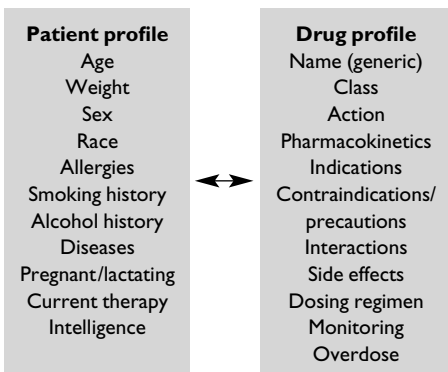
Clinical pharmacology
The principles behind the prescribing process

as opposed to

Therapeutics
The process of medical treatment

Clinical pharmacology involves the complex interaction between the **patient** and the **drug**. The patient is a unique individual, with many distinguishing features that need to be taken into account during prescribing. The patient can be described in terms of the **patient profile**. The drug, likewise, is unique, with its own distinguishing features. It may be described in terms of the **drug profile**.

Good prescribing involves tailoring the drug and dosing regimen to the unique patient. Clinical pharmacology provides the basis of this.



For example, once a diagnosis has been made and drug therapy is considered appropriate, a particular drug must be chosen. The ideal drug is chosen, based on the best evidence. This drug is then examined to see if it is appropriate for *this* patient.

- Is the patient allergic to this drug or class?
- Are there any potential interactions with the patient's other drugs?
- Does the patient have other diseases that might be made worse (or better) by the addition of the new drug?
- Is compliance likely to be a problem?

If the drug passes this first test, then a dosage regimen must be chosen. The starting point is the 'normal' dose regimen that would be appropriate for the 'average' patient. This dosage regimen is then adjusted to tailor it to *this* patient.

- Is the patient old? (may need a lower dose)
- Is there any renal impairment/liver impairment? (may need a lower dose or a longer dose interval)
- Are there any drug interactions that might require dose alteration?

Problems with these 'ideals'

It is easy to preach a 'holier than thou' approach to therapeutics, but harder to achieve this in practice. Individualizing drugs to the patient may be different in different settings. Prescribing in outback Australia is likely to be very different from prescribing in central Sydney. Access to laboratories and medical follow-up will be different. The ideal drug, based on evidence, may be totally impractical for your particular patient.

The 'rational, safe and effective use of medicines' must be tolerant of all this. Prescribers should not be expected to achieve perfection, but to pursue the greatest possible effectiveness, with minimal risks, and to respect the patient's choice. The word 'rational' is relevant here, denoting not only scientific rationality, but also situational rationality.

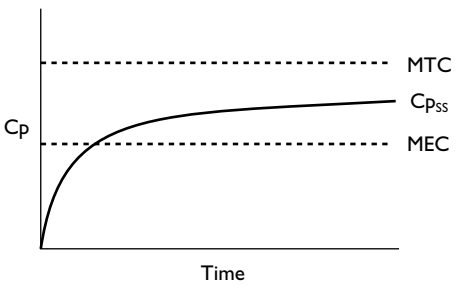
1 Clinical pharmacokinetics

General Overview of Pharmacokinetics

The aim of drug therapy is to achieve efficacy without toxicity. This involves achieving a plasma concentration (Cp) that is above the *minimal effective concentration* (MEC), but below the *minimal toxic concentration* (MTC).

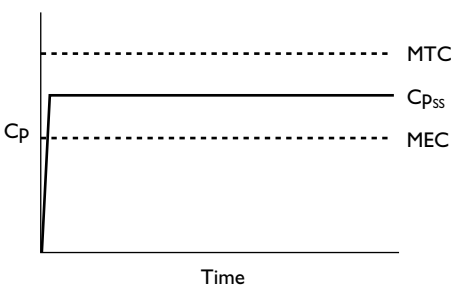
Clinical pharmacokinetics is about all the factors that determine the Cp and its time-course, i.e. it is about variability. The various factors are dealt with in subsequent chapters.

Constant IV infusion



The Cp rises to reach the desired steady state concentration (Cp_{SS}). The main determinant of the Cp_{SS} is the dose and the clearance (Cl).

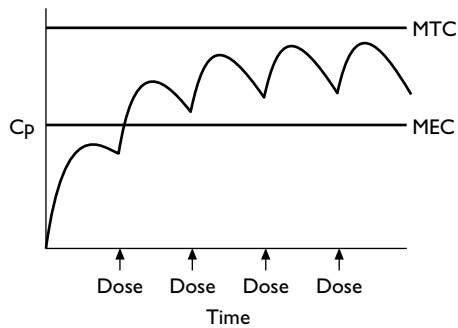
Loading dose (IV injection followed by a constant infusion)



In order to achieve early effect (e.g. treating status epilepticus with phenytoin) it is important to get the Cp up to the effect zone as soon as possible. This is achieved with a loading dose.

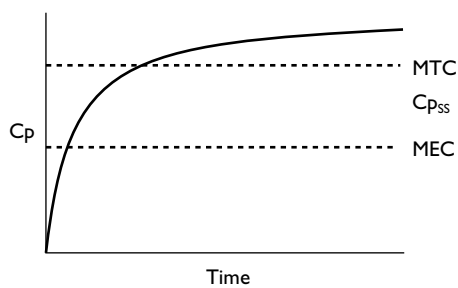
The factor determining the loading dose is the volume of distribution (Vd).

Oral dosing



The curve reflects assimilation and elimination, and intermittent administration.

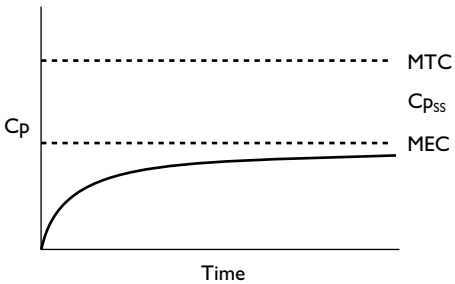
Cp higher than desired



The two factors involved are excessive dosage and/or decreased Cl.

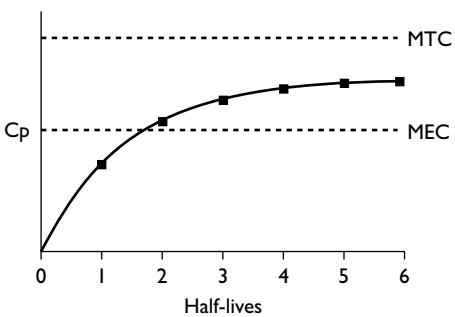
Factors causing decreased Cl are:
- normal variation
- saturable metabolism
- genetic enzyme deficiency
- renal failure
- liver failure
- old age
- very young age (neonate)
- enzyme inhibition.

Cp lower than desired



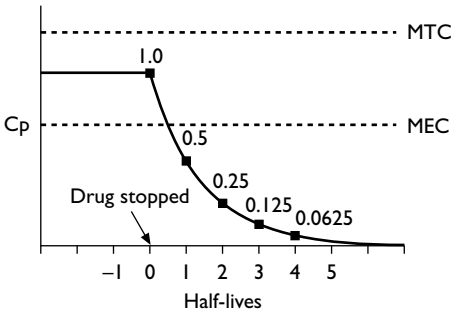
Dose may be too low, or Cl too high. Factors causing increased Cl are:
- normal variation
- poor absorption
- high first-pass metabolism
- genetic hypermetabolism
- enzyme induction
- non-compliance.

Time to steady state



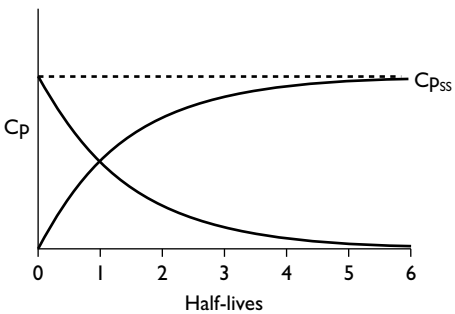
This is determined by the $t_{1/2}$ of the drug. It takes $4 \times t_{1/2}$ to achieve >90% of the steady-state concentration.

Time for drug elimination



This is determined by the $t_{1/2}$ of the drug. It takes $4 \times t_{1/2}$ for concentrations to reduce to <10% of the starting value.

Components of the line of steady state



The line of steady state is effectively made up of the sum of the line of accumulation and the line of elimination. i.e. the net effect of input and output.

Pharmacokinetics

Pharmacokinetics:
The study of the **movement** of drugs into, within and out of the body
i.e. **what the body does to the drug**

as opposed to

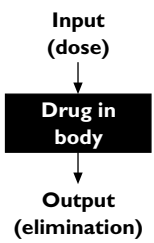
Pharmacodynamics:
The study of drug **effect**, and mechanisms of action
i.e. **what the drug does to the body**

It is important to know the pharmacokinetics of a drug so that the drug can be used in a rational and scientific manner, and the dose tailored to the patient.

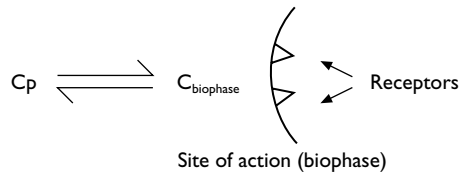
The most important pharmacokinetic parameters from a dosing point of view are the clearance (Cl), the volume of distribution (Vd) and the half-life of elimination ($t_{1/2}$). The Cl determines the maintenance dose, the Vd the loading dose, and the $t_{1/2}$ the dose interval.

One-compartment model

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



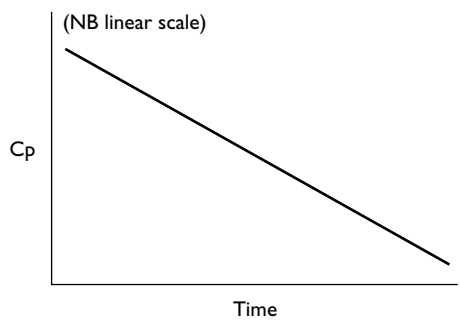
Pharmacokinetics involves the study of the movement of the drug into, within and out of the body. From a dosing point of view it is the concentration of drug at the site of action that is important. This is difficult to measure. Under steady-state conditions the plasma concentration (Cp) is in equilibrium with sites of action. In practice it is usually the Cp that is measured.



The pharmacokinetics of a drug are usually studied using an intravenous 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.

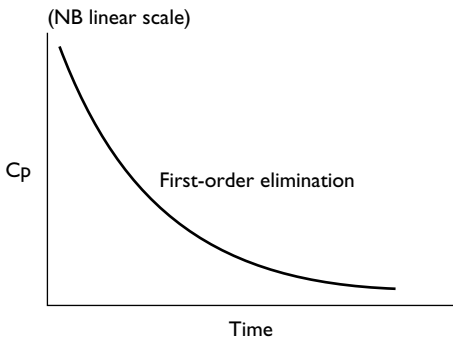
Zero-order elimination

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



First-order elimination

The more common situation is *first-order* elimination, in which the decline in plasma concentrations is not constant with time, but varies with the concentration. The higher the concentration, the greater the rate of elimination. The concentration declines 'exponentially' with time.



This curve can be described by:

$Cp_t = Cp_o * e^{-kt}$

where Cp_t is the concentration at any time t

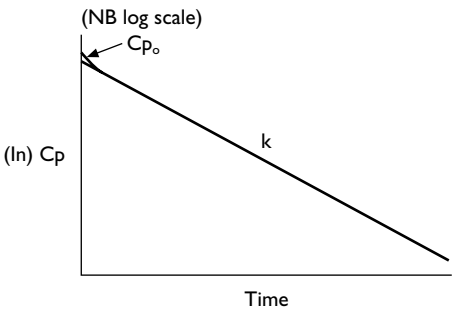
Cp_o is the concentration at time zero

and k is the elimination rate constant

This equation is difficult to use (for most of us!) and can be simplified by transforming it to a linear expression. This is done by taking the natural logarithm of each side:

$\ln Cp_t = \ln Cp_o - kt$

This now has the form of a linear equation $y = mx + c$, or in this case because the line is declining, $y = c - mx$, where m is the slope and c the intercept on the y-axis.



Important pharmacokinetic abbreviations

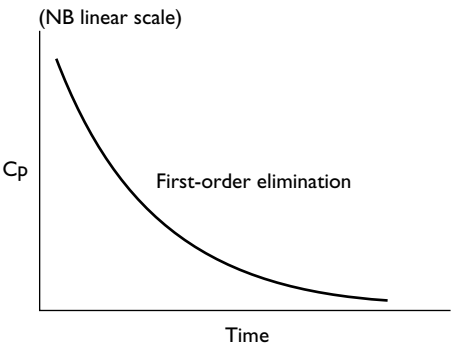
Abbreviation	Definition	Abbreviation	Definition
$t_{1/2}$	the half-life of elimination	ss	**S**teady **s**tate
Vd	**V**olume of **d**istribution	Cp	**P**lasma **c**oncentration
Cl	**Cl**earance	Cp_t	**P**lasma **c**oncentration at **t**ime = **t**
AUC	**A**rea **u**nder the **c**urve	Cp_o	**P**lasma **c**oncentration at time = **o**
F	**F**ractional oral availability	Cp_{ss}	**P**lasma **c**oncentration at **s**teady **s**tate
fu	**f**raction excreted **u**nchanged	Ab	**A**mount in **b**ody
PB	**P**rotein **B**inding	e	The natural logarithm
T_{max}	**T**ime to **max**imum concentration		(value = 2.7183)
C_{max}	Peak concentration	ln	log to the base e
	(**C**oncentration **max**imum)	k	the rate constant of elimination

Drug Clearance

Drug clearance (from plasma) is defined as:
'The volume of plasma cleared of drug per unit time';
or
'A constant relating the rate of elimination to the plasma concentration (Cp)'
i.e. rate of elimination = Cl * Cp
Units: vol/time (e.g. L/h)

Clearance (Cl) is the single most important pharmacokinetic parameter. Cl determines the **maintenance dose-rate**, i.e. dose per unit time, required to *maintain* a plasma concentration.

Clearance does not apply to drugs with zero-order kinetics, but only to those with first-order (exponential) kinetics. This applies to the majority of drugs.



The graph shows that the rate of elimination (RE) is different at different concentrations, i.e. it is *driven* by concentration.

rate of elimination $\propto$ Cp
$\therefore$ rate of elimination (mg/h) = constant (L/h) * Cp (mg/L)

This 'constant' is the **clearance** (Cl) and by deduction has units of volume/time (e.g. L/h), since the units for rate of elimination are mg/h, and for concentration mg/L.

i.e. rate of elimination = Cl * Cp

Thus, Cl is 'A constant relating the rate of elimination to the plasma concentration'; and

'The volume of plasma cleared of drug per unit time'.

The equation can be rearranged as follows:

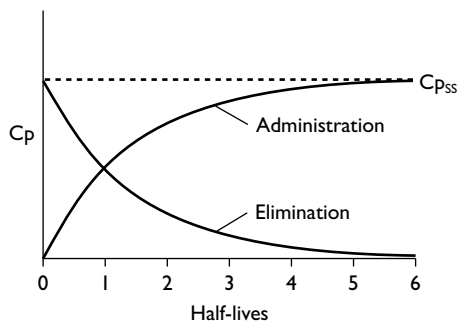
$$\text{Cl (L/h)} = \frac{\text{rate of elimination (mg/h)}}{\text{Cp (mg/l)}}$$

Achievement of a constant steady-state plasma drug concentration (Cp_{SS})

In order to maintain a target Cp, 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 * Cp, then
rate of administration = Cl * Cp_{SS}, or

Maintenance dose-rate = Cl * Cp_{SS}



Physiological relevance of drug clearance

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

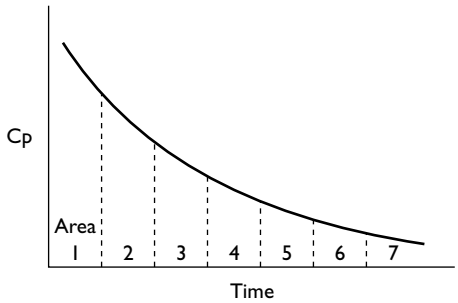
Cl (total) = Cl (renal) + Cl (liver) + Cl (other)

Determination of Cl

Plasma Cl is usually determined from the area under the plasma concentration vs time curve (AUC) after IV administration.

The AUC is determined using the 'trapezoidal rule'.

AUC = Area 1 + Area 2 + Area 3 + . . . Area n, where each area is approximated by a trapezium.



Area under the curve (AUC)

The bigger the AUC, the smaller the Cl.

$$Cl = \frac{Dose}{AUC}$$

After oral administration:

$$Cl = \frac{F * Dose}{AUC}$$

where F = oral availability.

Volume of Distribution

The **volume of distribution** 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 plasma concentration (Cp) to the amount of drug in the body (Ab).'
i.e. Ab = Vd * Cp
Units: Volume or vol/kg

The volume of distribution (Vd) is the second most important pharmacokinetic parameter (after Cl). It determines the **loading dose**, i.e. the dose required to achieve a target plasma concentration (Cp) as soon as possible.

In order to achieve a target Cp, the tissues into which the drug distributes (i.e. the volume of distribution) must be 'filled up'.

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 plasma concentration (Cp).

i.e. $Ab \propto Cp$
or $Ab = \text{constant} * Cp$

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 plasma concentration to the amount of drug in the body.'

i.e. $Ab = Vd * cp$

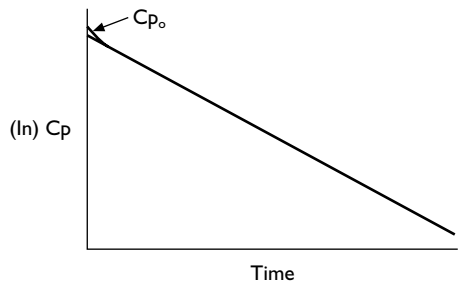
or $$Vd = \frac{Ab}{Cp}$$

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 (50–100 L) is compared with Vds of drugs, e.g. heparin (5 L); gentamicin (15 L); digoxin (500 L); and quinacrine (20 000 L).

Highly lipid soluble drugs such as quinacrine have much larger Vds than very polar, water soluble drugs such as heparin.

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 intravenously (prior to elimination), i.e. the dose. If the Cp at time zero (Cp_o) is known, then the Vd can be calculated. The Cp_o can be determined from the lnCp vs time curve after intravenous (IV) administration. After initial distribution, there is a 'log-linear' decline in plasma concentration. The Cp_o can be determined by back-extrapolating the linear portion of the curve to its intercept on the y-axis. Vd can then be calculated.



i.e. At time zero, $Ab = \text{dose}$
then $\text{dose} = Vd * Cp_o$
or $Vd = \text{dose}/Cp_o$

Calculation of loading dose (LD)

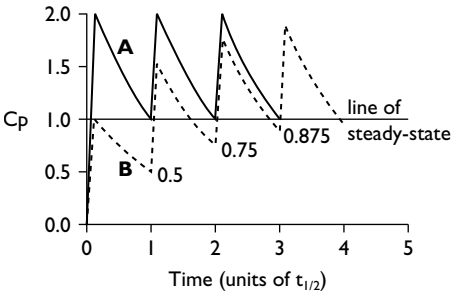
It follows from the above that to achieve a target Cp, the Vd of the drug must be known

LD = Vd * target Cp

e.g. to achieve a target Cp of digoxin (Vd ~ 500 L) of 1.5 µg/L, a loading dose (LD) of 750 µg, or 0.75 mg is needed, i.e.

LD (µg) = 500 (L) * 1.5 (µg/L)
= 750 µg

With a loading dose, steady-state concentrations can be achieved quickly.



Curve A — loading dose followed by maintenance dosing.
Curve B — maintenance dosing every half-life.

In summary, the most important thing about Vd is that it enables the calculation of a loading dose to achieve any desired Cp.

LD = Vd * Cp

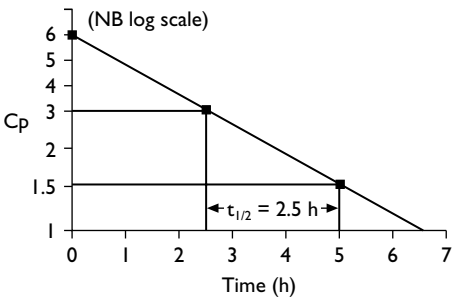
The Half-Life

The **half-life of elimination** ($t_{1/2}$) is:
'The time for the concentration of the drug in plasma (or the amount of drug in the body) to halve.'
Units: Time (usually h)

The $t_{1/2}$ provides an index of:
1 the time-course of drug elimination;
2 the time-course of drug accumulation; and
3 choice of dose interval.

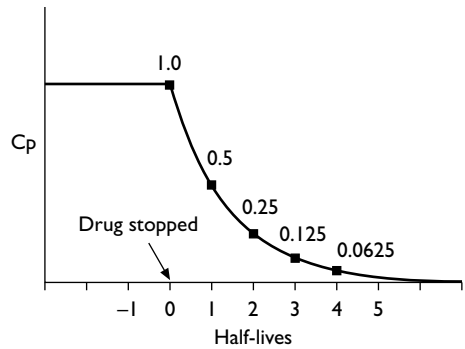
Derivation of $t_{1/2}$

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



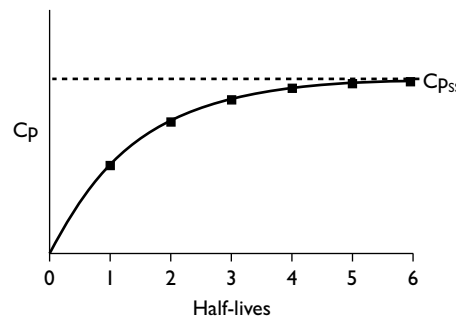
Time-course of drug elimination

If a drug is discontinued after an infusion, the Cp will decline exponentially to <10% of its starting value after four half-lives.



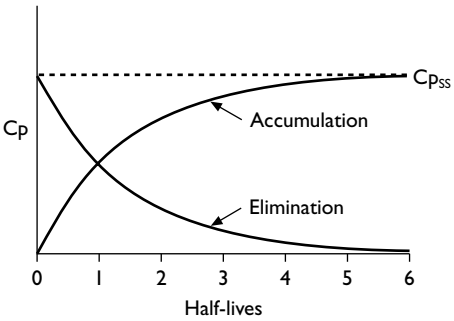
Time-course of drug accumulation

If a drug is started as a constant infusion, the Cp will accumulate to approach steady-state (>90% of steady state concentration) after four half-lives.



Components of the line of steady state

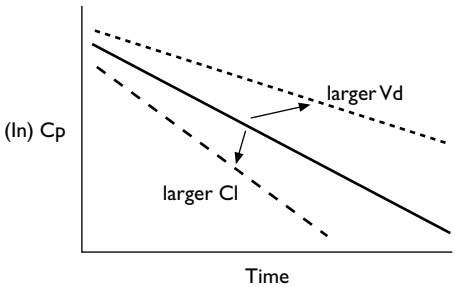
The line of steady state is effectively the combination of accumulation and elimination. i.e. it is the sum of the effect of dose and elimination at any time point.



Choice of dose interval

The dose interval is usually chosen based on:
1 the $t_{1/2}$
2 the therapeutic index of the drug
3 compliance — it is best, if possible, to have dosing once or twice a day.
If drug Cl decreases (say in renal dysfunction), 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 $t_{1/2}$, Vd and Cl



It is logical that the larger the Vd, the longer the $t_{1/2}$, i.e. it takes longer to remove drug from deep within the tissues. Similarly, it is logical that the larger the Cl, the shorter the $t_{1/2}$. In other words:

$$t_{1/2} \propto \frac{Vd}{Cl}$$

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.

$$t_{1/2} = \frac{0.693Vd}{Cl}$$

This is one of the most important equations in clinical pharmacokinetics.
- It indicates that the $t_{1/2}$ is *dependent* on Vd and Cl.
- Vd and Cl are the *independent* variables.

Oral Availability

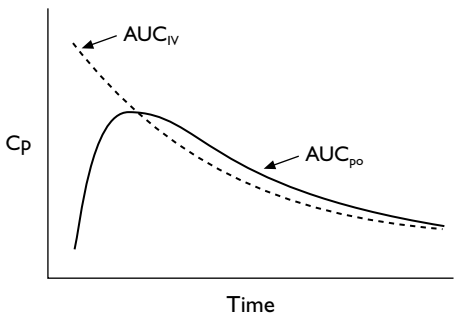
Oral availability is:
The fraction of drug that reaches the systemic circulation after oral ingestion

Oral availability defines how much drug gets 'on board' after oral ingestion. 'Absorption' and 'first-pass' metabolism are the main determinants of oral availability.

Oral availability is usually defined by comparison with the total availability of drug in the systemic circulation after IV dosing, i.e. the fraction (F) of drug that gets into the body after oral (po) versus IV administration:

$$\text{i.e.} \quad F = \frac{AUC_{po}}{AUC_{IV}}$$

The total amount of drug in the systemic circulation is defined by the **a**rea **u**nder the **c**oncentration–time curve (AUC). The AUC may be different after oral compared with IV administration. The oral availability may have a value of one, or less than one.



Determinants of oral availability

1 Absorption.
2 First-pass metabolism.

Absorption

This refers to the ability of the drug to cross a biological barrier into the blood. In the case of oral absorption, it refers to crossing the gut wall into the portal circulation. Absorption is usually a passive process governed by the principles of diffusion (i.e. flows down a concentration gradient). Sometimes, active transport is involved (e.g. L-dopa). Factors favouring absorption include high lipid solubility and low ionization. pH may also influence absorption, but probably affects the rate more than the extent.

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 oral availability

Interestingly, food affects absorption and first-pass metabolism in opposite ways. Food usually *decreases* the oral availability of sparingly lipid-soluble drugs that are subject to absorptive problems, e.g. food decreases the oral availability of atenolol by 50%.

However, food usually increases the oral availability of drugs that are subject to high first-pass metabolism. This is because food increases portal venous blood flow, thereby increasing the presentation of absorbed drug to the liver, partially saturating metabolizing

pathways and opening up shunts that bypass metabolizing pathways. The net result is *greater* oral availability, e.g. food increases the oral availability of metoprolol by 50%.

Some foods, e.g. grapefruit juice, compete with drugs for presystemic elimination, thereby causing increased oral availability of the drug (e.g. calcium antagonists, some statins).

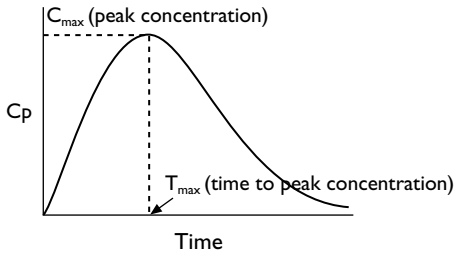
Confusing terminology

There is sometimes confusion between the terms 'oral *availability*', 'bioavailability' and 'absorption'. Oral availability 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. oral availability defines the *extent*, and another term, T_{max}, defines the *rate*.

Time to peak concentration (T_{max})

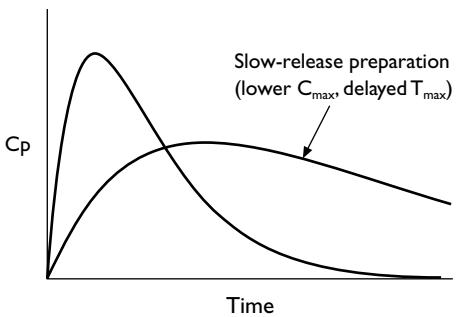
T_{max} defines the time to **max**imum (or peak) concentration



T_{max} is less important than the total oral availability. A short T_{max} may be useful where an immediate effect is desired, e.g. analgesia for a headache. A short T_{max} 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. This flattens the concentration–time profile, giving a more even drug response.



Protein Binding

The major message about protein binding (PB) is that it is usually not important.

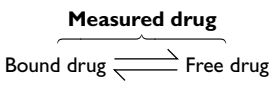
> Protein binding is only important in the interpretation of measured plasma concentrations

There is enormous confusion about the importance of protein binding and the drug effects attributed to it. While drugs may displace each other from protein-binding sites, this is almost always unimportant. Most alleged protein binding interactions of clinical importance have an additional mechanism operating, such as altered drug clearance, that is the reason underlying the observed clinical effects.

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

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

NB: When plasma concentrations of drugs are measured, it is *total drug*, i.e. bound + unbound, that is measured. It is possible, but not routine (except perhaps for phenytoin), to measure free or unbound drug.



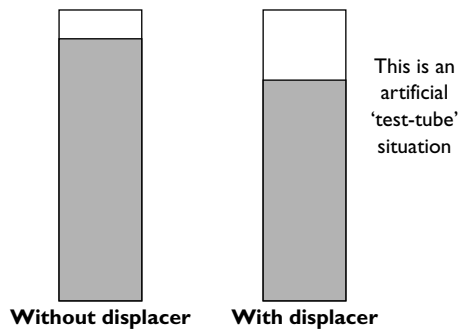
Altered albumin or α_1-acid glycoprotein concentrations will alter the measured (total) concentrations of drugs bound highly to these proteins.

However, it is free drug that acts on receptors to produce effect. Therefore, it is the concentration of free drug, not total drug, that is actually important in terms of desired effects and side effects.

Free drug concentration is dependent on free drug clearance (see Clearance, page 6), 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 protein binding.

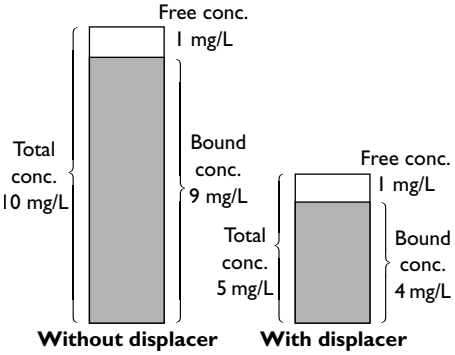
The fallacy of protein-binding drug interactions

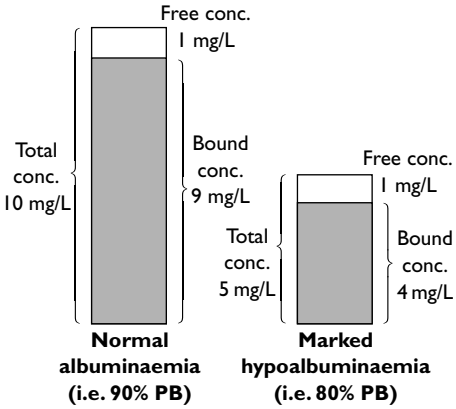
Many so-called protein-binding drug interactions have been reported. While drugs can compete for protein binding sites, especially on albumin, this does not affect the free concentration.



If a drug in the body was not subject to drug elimination, then introduction of a protein-binding displacer would increase the concentration of the free drug.

In reality drug elimination does occur. Since the steady-state free drug concentration is only dependent on maintenance dose and free drug clearance (remember, Maintenance dose = Cl * Cp), then free drug concentration returns to its predisplacement level. However, the total drug concentration is now lower than it was.





Interpretation of measured plasma concentrations during therapeutic drug monitoring

Protein binding 'problems' arise from the fact that the measured drug concentration is total drug (bound + unbound). In hypoalbuminaemia (e.g. in renal disease) an acidic drug such as phenytoin will have a lower total drug concentration because of lower protein binding. Free drug concentration will, however, be 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. *phenytoin* (therapeutic range 10–20 mg/L total concentration, 1–2 mg/L free concentration).

In hypoalbuminaemia free concentration (and effect) is identical but total measured concentration is half. If the dose was increased to give a total concentration of 10 mg/L, the free concentration would be 2 mg/L and may be toxic. Note that the situation for hypoalbuminaemia is identical to that involving drug displacement interactions (see above).

Drugs with saturable protein binding

Some drugs at clinical concentrations saturate the available protein-binding sites. In this situation total drug concentration (bound + unbound) does not increase linearly with dose. Interpretation of measured concentrations is difficult. If free concentrations were measured, these would be seen to rise linearly with dose.

Drugs with saturable protein binding 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 protein binding makes interpretation of valproate concentrations difficult. For the other drugs protein binding 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

In some situations drug disposition varies 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.

Background theory

Acids are ionized in basic media
Bases are ionized in acidic media

i.e. $H^+ + X^- \rightleftharpoons HX$

(ionized) (unionized)

If more H^+ ions are added (i.e. adding acidity), the equilibrium moves to the right. If base (e.g. OH^-) is added, H^+ ions are consumed, and the equilibrium moves to the left. Unionized drug crosses lipid biological barriers (e.g. membranes) better than ionized drug.

Henderson–Hasselbalch equation

For acids:

$$pH = pK_a + \log_{10} \times \left(\frac{[\text{ionized}]}{[\text{unionized}]} \right)$$

For bases:

$$pH = pK_a + \log_{10} \times \left(\frac{[\text{unionized}]}{[\text{ionized}]} \right)$$

NB 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 this important?

- Drug absorption from the stomach
- Drug elimination via the kidneys
- Drug distribution into milk
- Drug distribution across the placenta.

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, because of the far greater absorptive surface area in the small intestine, the bulk of absorption occurs there, even for acids.

Drug elimination in the kidney

The pH in the urine varies from 4.5 to 7.5. 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 will occur 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 acid urine. This principle is sometimes used in enhancing the elimination of drugs after overdoses (e.g. aspirin elimination can be enhanced by administration of bicarbonate).

Drugs with pH-dependent 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 '3rd spaces'

Milk, the fetus, and most '3rd 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. abscesses, synovial fluid.

2 Factors affecting dosing

Drug Metabolism

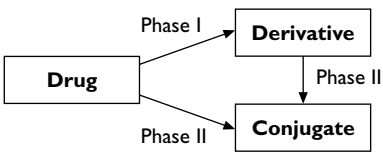
Variation in drug metabolism is a major cause of variation in drug clearance

Some drugs are excreted unchanged through the kidneys because they are polar and are not reabsorbed in the renal tubules. Other drugs, especially those that are lipid-soluble, are reabsorbed in the renal tubules and would circulate forever if they were not biotransformed to more readily excretable forms.

Metabolic biotransformation converts drugs to more polar and excretable forms. The resulting metabolite may be inactive, less active or occasionally more active (e.g. metabolite of a prodrug) than the parent molecule.

Where does biotransformation occur?

Metabolism occurs mainly in the liver, but also in the kidney, lung, GI mucosa, plasma, the CNS and probably most tissues. Some drugs undergo sequential biotransformation.

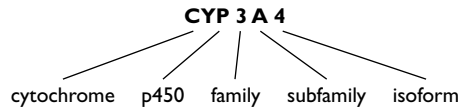


Phase I reactions include oxidation, reduction and hydrolysis. The most common are *oxidation* reactions (adding oxygen, or removing hydrogen). Oxidation reactions include dealkylation, hydroxylation, deamination and desulphuration. Most occur via the cytochrome p450 enzymes.

Phase II reactions involve conjugations, such as glucuronidation, acetylation, sulphation and methylation. Glucuronidation is quantitatively the most important.

Cytochrome R450 metabolism (CYP)

CYP reactions are catalysed by the cytochrome p450 mixed function oxidases, mostly in the liver. These are iron-containing enzymes, named p for pigment, and 450 for the wavelength, in nM, at which spectrophotometric absorption occurs. At least 13 CYP gene families exist in humans, with various subfamilies. Each CYP family is encoded by a separate gene. The nomenclature is:



Drug clearance by the liver

The fraction of drug removed from blood in one passage across the liver is the extraction ratio (ER).

$$ER = \frac{C_{in} - C_{out}}{C_{in}}$$

where C = drug concentration

Hepatic drug clearance depends on the extraction ratio, but also on the hepatic blood flow (HBF) since the greater the blood flow the greater the presentation of drug to the liver. Thus,

Hepatic Cl = HBF * ER

High Cl, flow-dependent elimination: If the extraction ratio approaches 1 (complete extraction), then hepatic Cl approaches hepatic blood flow. In this case the elimination

is said to be 'blood flow dependent', or 'high clearance'.

Low Cl, flow-independent elimination: If the extraction ratio is small, there is no blood flow dependence, since presentation of more drug to the liver will not result in greater elimination.

First-pass metabolism: Drugs entering the portal system after absorption have to pass through the liver prior to reaching the systemic circulation. If the extraction ratio approaches 1, little drug will reach the systemic circulation. In this case, 'first-pass' elimination approaches 100%, and oral availability (F) approaches zero. For example, lignocaine has an extraction ratio of 0.7, and therefore an F of 0.3.

There are three situations in which the extent of first-pass metabolism decreases, resulting in increased oral availability:

1 High oral doses — Drugs such as propranolol saturate the metabolizing enzymes, resulting in less first-pass metabolism, and greater oral availability.

2 High blood flow — Increased liver blood flow, such as after food, delivers more drug to the metabolizing enzymes, sometimes saturating them. This results in less first-pass metabolism for high clearance drugs such as propranolol.

3 Chronic liver disease — There is lower intrinsic clearance, as well as increased shunting.

Some examples of high and low clearance drugs.

High clearance	Low clearance
Antidepressants	NSAIDs
Antipsychotics	Anticonvulsants
Calcium antagonists	Most benzodiazepines
Narcotics	
Nitrates	
Most antiparkinson's	
Most statins	
Many β-blockers	

Clinical significance of high-clearance drugs

- Subject to first-pass metabolism
- Subject to flow-dependent elimination
- May require dose-reduction in situations of decreased blood flow, e.g. congestive heart failure (CHF)
- May be subject to pre-systemic drug interactions, e.g. with grapefruit juice.