PHARMACOLOGY 2 - PHARMACOKINETICS

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Pharmacokinetics is the study of the way the body deals with any drugs that are given to it. Simply put "what the body does to a drug". In pharmacokinetics we study the processes of absorption, distribution, and elimination, either by metabolism or excretion, of drugs. Detailed pharmacokinetic studies quantify these events and their time course. The principles underlying pharmacokinetics help in the understanding of the methods of drug delivery used in anaesthesia, and the use of such techniques as total intravenous anaesthesia.

In this article we shall deal with the processes of pharmacokinetics in the three major areas:-

1. Absorption
2. Distribution
3. Elimination - Metabolism
   - Excretion

ABSORPTION

Most drugs do not have their site of action in the GI tract, or the plasma. They therefore need to cross cell membranes to reach their site of action. There are 3 ways in which drugs can cross lipid membranes:-

a) Simple diffusion.

Drug molecules move from a high to a low concentration. This is a passive process and no energy is required for it.

b) Non-ionic diffusion.

Most drugs are chemically weak acids or weak bases. This means that when dissolved in water they will either give us a hydrogen ion and become ionised (acids) or accept a hydrogen ion from the water and become ionised (bases). The ionised form has an electric charge, and in this form it cannot cross a lipid membrane.

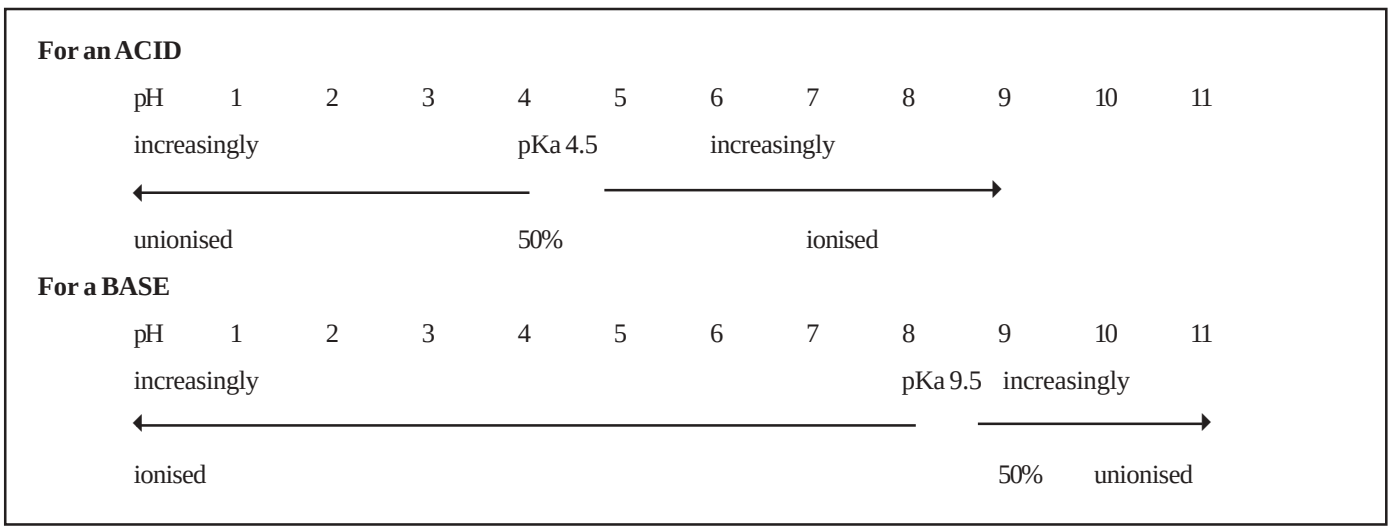
When in solution, the ionised form of the drug is present in equilibrium with the unionised form. How much of the drug changes to the ionised form will depend on two factors. The first is a characteristic of the drug and is called the pKa. It is a constant. The second is the pH of the solution. (See also Acid Base Balance, *Update in Anaesthesia* 2001:13;52). This is obvious if thought about for a moment. The pH of the solution indicates the hydrogen ion concentration, and so it will influence the rate of dissociation of both weak acids and weak bases. Weak **acids** dissociate, becoming **ionised**, in an **alkaline** environment (i.e. give up their hydrogen ions where there are relatively few, and weak **bases** become **ionised** in an **acid** environment (ie gain hydrogen ions where they are relatively plentiful).

The pKa of a drug is related to the equilibrium that the drug has with its ionised form, it also happens to be the pH of the solution at which 50% of the drug will be ionised and 50% will be unionised. When the pH is the same as pKa the ratio of ionised to unionised drug will be 50:50. i.e. the pKa is the pH at which the drug is 50% ionised.

This is important for absorption because, as we have said, only the unionised form of the drug is lipid soluble and can cross cell membranes. The ionised form cannot cross the membrane easily.

Examples of acidic drugs include phenytoin, thiopentone, aspirin (salicylate), and penicillins. Basic drugs include diazepam, local anaesthetic drugs, non-depolarising neuromuscular blocking drugs, morphine and pethidine.

An example where this is relevant is the increased dissociation or ionisation of local anaesthetic agents (a basic drug) in infected tissues that tend to be acidic. There is less in the unionised form, required to cross the nerve cell membrane. This explains why lignocaine, when infiltrated into infected tissues has a poor effect. See Table one.



Some pKa's of common drugs

		pKa's	
STRONG		0	WEAK
		caffeine	
		1	
		2	
	benzypenicillin		
A		3	B
		diazepam	
C		4	A
	aspirin	chordiazepoxide	
I		5	S
	dicoumarol		
D		6 codeine	E
	sulphadiazine		
S		7	
	phenobarbitone		
		8 lignocaine	
	phenytoin	9 chlorpromazine	
		atropine	
		10	
		11	
WEAK			STRONG

Table 1

c) Carrier transport

Proteins within the cell membrane may act as carriers for the drug. These carriers are usually specific for the drug; they usually carry the drug in one direction only across the membrane and may be inhibited or affected by other drugs. Ionised forms of the drug may be able to cross the cell by carrier transport. For example the penicillins are actively excreted in the kidney by this type of transport mechanism. Probenecid is another drug, which uses the same transport mechanism but is preferentially excreted over penicillin. It has been used to prolong the duration of action of penicillins, by slowing excretion.

There are 2 types of carrier transport:

- facilitated diffusion in which drug molecules move passively across the membrane from a high to a low concentration, attached to a carrier. No energy is required for this process.

- active transport in which, on the other hand, drug molecules can be transferred against a concentration gradient (from a high to a low concentration). This process requires energy (ATP).

Routes of Absorption

Oral. The oral route is pleasant and convenient and is therefore widely used. Where and how the drug will be absorbed from the gastro-intestinal tract depends on a number of factors. The formulation, tablet or capsule form, its sensitivity to enzymatic attack, gut motility and how fat-soluble the drug is will all influence absorption. Gut pH plays an important role as it will affect how much of the drug is in the unionised form and therefore how much of the drug is fat-soluble, and will be absorbed. The stomach contents are very acidic with a low pH. Therefore, acidic drugs are more unionised and tend to be absorbed there. In contrast the small bowel is more alkaline (a higher pH) which will favour the absorption of basic drugs. The example most frequently quoted to illustrate this is aspirin, which has a pKa of 4.4 and is therefore relatively unionised in the gastric fluid that has a pH of approximately 1. This favours absorption of aspirin in the stomach. When aspirin passes into the small intestine, the equilibrium moves towards more ionised aspirin molecules, theoretically favouring less absorption. In actual fact the majority of aspirin is absorbed in the small intestine, because there is a very much greater surface area available for the absorption to take place. This shows how many factors contribute to the final process of absorption.

All drugs that cross the intestinal mucosa, enter the portal circulation, and pass through the liver before entering the systemic circulation. Most drugs will only reach their site of action from the systemic circulation. Some drugs, however, will be significantly broken down (metabolised) by the gut wall or by the liver before they reach the systemic circulation. This means that they will have a much lower concentration in the systemic circulation and at their site of action than might be expected from the dose given. This is called the first pass effect. It only affects drugs given orally and can be avoided by giving drugs by intravenous, intramuscular, subcutaneous or sublingual (under the tongue) routes. This is because the blood supply from these areas does not pass though the liver via the portal circulation, but drains directly into the systemic circulation. Examples of drugs with high first pass metabolism are propranolol and lignocaine which undergo liver metabolism, and morphine which is metabolised both in the gut mucosa and in the liver. When the oral dose of a drug is much larger than the intravenous dose it indicates that the drug has a high first pass metabolism.

The bioavailability of a drug by any route is the ratio of the amount of drug reaching the circulation, to the amount present if the drug had been given intravenously. So a drug might have an oral bioavailability, and an intramuscular bioavailability which is different. It is expressed a percentage so a drug given intravenously have a bioavailability of 100%. We can express this in a mathematical way:

$$\textbf{Oral bioavailability} = \frac{\text{Amount of drug in the circulation after an oral dose} \times 100}{\text{Amount of drug in the circulation after an IV dose}}$$

Considering some other routes:

Intravenous. The drug enters the systemic circulation directly and bypasses the absorption barriers. Most drugs used in anaesthesia are given by this route, it provides a reliable and rapid way of giving drugs. The speed of onset is the most rapid of any route, but is still dependent on the drug leaving the circulation to enter its site of action. Other factors can affect speed of action of iv drugs, particularly cardiac output. If intravenous induction agents such as thiopentone are given rapidly to a patient with a low cardiac output it is possible to give too much thiopentone inadvertently. This is because the drug does not reach and enter the brain as quickly as in a patient with a normal cardiac output and the onset of effect is delayed. It is tempting to continue

to give the drug until a response is achieved, by which time too larger a dose has been given.

Intramuscular/subcutaneous. Drugs may be given by injection into muscle or tissues. Absorption via this route does not occur at a constant rate and depends on the local blood supply. First pass metabolism is avoided. These routes are particularly unreliable in the shocked patient. In hypovolaemia the blood flow to the muscles and skin is reduced to preserve flow to essential organs. As a result little of the drug will be absorbed, when the circulation is restored drug may be absorbed rapidly. It is often safer and more reliable to give small doses intravenously in a shocked patient rather than risk the effects of intramuscular or subcutaneous routes. A good example of this effect is the use of morphine in a shocked patient, if given intramuscularly the patient may not experience any analgesic effect, as absorption is poor, later when the circulation is restored, there may be rapid absorption and respiratory depression. Small doses of morphine iv are a better and safer alternative.

Inhalational. This is useful in anaesthesia for volatile agents both for induction and maintenance of anaesthesia. Plasma levels rise rapidly, and this route is also used for drugs that have their site of action in the lungs such as salbutamol. It can be used as an alternative route to intravenous when no intravenous access is available for example at a cardiac arrest.

Topical, sublingual, rectal. These routes avoid the problems of first pass metabolism as the venous drainage does not pass through the liver. Topical application has become popular for local anaesthetic creams such as EMLA, and for patches such as fentanyl. These patches have complicated pharmacokinetics and their formulation is difficult and complex to provide a consistent uptake of drug.

DISTRIBUTION

Once the drug is present in the bloodstream, it will be distributed to all the tissues. The drug leaves the blood and enters the extracellular fluid and from there enters the cells. The drug moves down the concentration gradient. After an intravenous injection the amount of drug present in the blood peaks very rapidly; faster than we can detect with sampling. The plasma concentration then falls due to two continuing processes, distribution to other tissues and elimination by metabolism and excretion. These processes go on together, but distribution tends to cause the initial rapid fall in levels. It is logical that drugs will distribute to tissues with a high blood flow (heart, lungs, brain) most rapidly, then to those with a moderate blood flow (muscle) and finally to those with a poor blood flow (fat, tendons, cartilage) (Figure 1). The rate of fall slows, as distribution contributes less and elimination becomes the predominant process. If plasma concentrations are measured at regular times after an intravenous injection and plotted graphically the decline produced is exponential. (Figure 2). Exponential means that the rate of the fall of concentration depends on the amount of drug present. The process is known as **first order kinetics**. Most drugs behave in this way.

However, there are exceptions to the rule. If a drug is reliant on an enzyme system for its metabolism/elimination, then the enzyme system may be overwhelmed by the amount of drug and become "blocked" or saturated. Once the enzyme system is working as fast as it can to eliminate the drug, it cannot increase its rate even if the amount of drug delivered to it is increased. This means that the drug will be metabolised at a constant rate in spite of the amount of drug present. This is known as **zero order kinetics**. Graphically this appears as a straight line. Examples of drugs with zero order kinetics are ethanol, and high doses of phenytoin. The exponential process has certain characteristics, and these are used to characterise the pharmacokinetics of each drug. Each of these values can be measured, or calculated from the plasma concentration verses time curve.

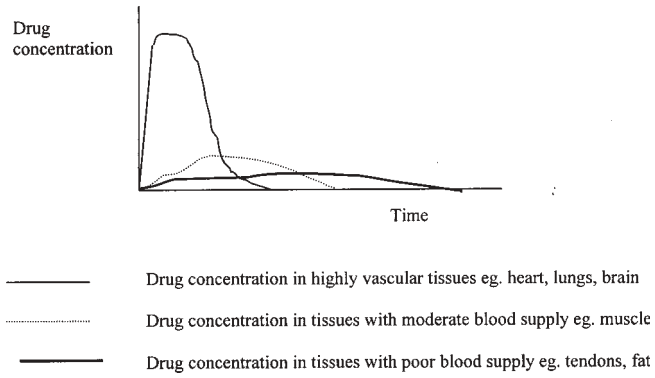


Figure 1. Drug distribution to different tissues

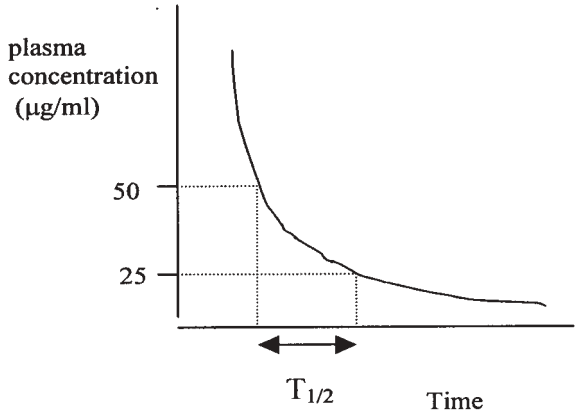


Figure 2. Plasma concentration/time curve. Showing the derivation of the half life

Half life (t1/2) is the time it takes for the concentration of the drug in the bloodstream to fall to half of its original value. The half-life is an important characteristic of the drug, as it defines the time interval between doses, and is very important in the design of infusion systems. Drugs given by infusion need to have, among other characteristics, a short half life.

Volume of distribution (Vd) is derived from the curve. It is not a real anatomical volume, but is the theoretical volume that the drug would be in if all the body had the same concentration as the plasma. It is calculated as follows:

$$Vd = \frac{\text{dose of drug given}}{\text{concentration of drug in blood at time zero on the graph.}}$$

In order to find the concentration at time zero accurately we employ a mathematical trick. The curve is an exponential, as we have said, and if we were to take logs of the concentration values (remember you cannot log time!) and plot them against time, the curve will become a straight line. The straight line allows us to accurately extrapolate back to the time zero position and read off the concentration. It is this Log plasma concentration verses time curve that is used to measure and derive the functions we use.

The Vd gives some idea of how fat soluble the drug is and how well it binds to proteins. In order to understand this, you need to think back to total body water (TBW) and the way it is distributed between different compartments (intracellular fluid, extracellular fluid, interstitial fluid). Extracellular fluid consists of interstitial fluid and plasma (15L), TBW = 60% of body weight, which is approximately 45 litres in an "average" man.

This is distributed as follows:

Intracellular fluid (30L)	Interstitial fluid (11.5L)	Plasma (3.5L)

The value for Vd varies from 5-1000 litres! Remember it is a theoretical and not an actual volume.

Vd = blood volume (5L) for drugs that are protein bound. These proteins are found in the blood and therefore the drug is limited to this compartment. eg. Warfarin, heparin.

- Vd approximates extracellular fluid volume (5-30L) for drugs that are ionised (have a charge). This is because these drugs are not very soluble in fat and cannot easily cross cell membranes to enter the intracellular fluid, but can easily diffuse out of the vascular space into the interstitial space thereby occupying the whole extracellular space. eg. Curare, gentamicin

- Vd is close to total body water (30-45L) for drugs that are highly fat soluble. These drugs are able to cross cell membranes to enter the intracellular fluid. eg. Phenytoin, ethanol, diazepam.

- Vd is greater than total body water (>45L) for drugs which enter cells and which bind extensively to tissue proteins. eg. Morphine, digoxin

Clearance is the volume of blood or plasma that is cleared of the drug per unit time. It is usually measured in millilitres per minute (ml/min). Clearance gives an indication of the ability of the kidneys and the liver to dispose of the drug. Clearance, volume of distribution and half-life are related to one another as follows:

$$t^{1}/_{2} \quad \alpha \quad \frac{Vd}{clearance}$$

This means that the time it takes for the drug concentration to fall is directly proportional to its volume of distribution and indirectly proportional to its clearance. In simple terms, this means that the half-life will be short if the drug has a small volume of distribution and is cleared fast (high clearance); the half-life will be long if the drug is widely distributed in the body (large Vd) and is excreted slowly by the kidneys and liver (slow clearance).

For example alfentanil which is relatively insoluble, has a small volume of distribution and has a very short half life. In contrast

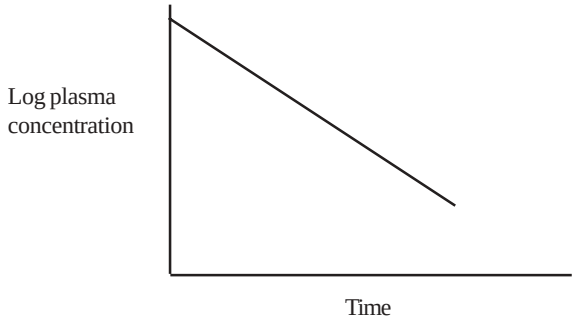
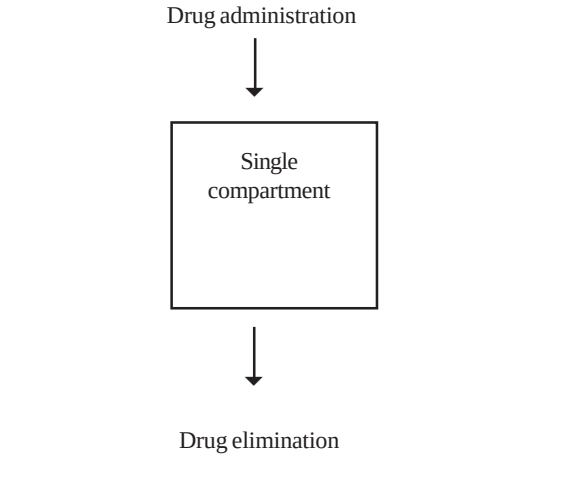


Figure 3: Log plasma concentration/time curve. Showing extrapolation to time zero, to obtain concentration at time zero.

remifentanil, a new potent opiate which has so short a half life that it can only be given by infusion, has a very brief effect due to rapid clearance of the plasma by metabolism by plasma esterases. A more traditional example would be suxamethonium, which is also brief in action due to metabolism by cholinesterase.

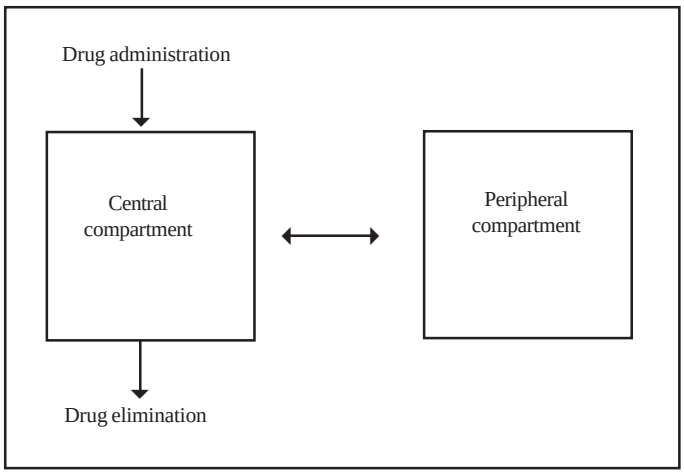
- **One compartment model** is a term mentioned frequently in books. This describes a theoretical situation in which the drug enters the plasma and is removed from it in a single, simple system. Drugs are administered into the single compartment and then eliminated from it by the kidneys and/or liver.



If we give an intravenous dose of a drug which is distributed only to the extracellular space, we could sample the plasma at intervals after administration and would see our exponential curve (figure 2). When we take logs of these concentrations we produce a straight line (figure 3), which indicates that one exponential process is involved the so called 'one compartment' model applies.

- **Two, or more compartment models**. In practice the models are more complicated, because the drug is not confined to the extracellular compartment and may enter other compartments

such as the brain, heart, muscles, these are well supplied with blood and may act as part of the central compartment. Other tissues, such as fat, bone, connective tissues may act as second, or even third and fourth compartments. The plasma concentration that we can measure then reflects movement of the drug in and out of all these compartments. Instead of a simple exponential, the process is made up of lots of exponentials! At this point the mathematics becomes very complex, and the log plasma concentration against time graph becomes a very complex connection of straight lines. It is important to remember that these processes, distribution out into the compartments, elimination via the kidneys and liver, and re-distribution back to the plasma from the compartments are going on all the time, it is no wonder the mathematics is complex.



ELIMINATION

For most drugs the kidneys or the liver achieves this process. However some drugs are excreted through the lungs, the skin or the breast milk, the latter being a route by which fat soluble drugs can be excreted. In order to be excreted through the kidney, the drug must be water soluble. Some drugs are excreted unchanged but the majority of drugs are metabolised in the liver to produce a water soluble and inactive form. The phase two process of metabolism, conjugation, usually renders the drug breakdown products soluble; glucuronide formation is an example. Drugs that cannot be rendered water soluble can be excreted in the bile, which contains sufficient cholesterol to dissolve the fat soluble products of drug breakdown. The bile passes into the jejunem, and there is the potential for re-absorption from the small intestine, and a prolongation of the half life. In anaesthetics, pancuronium and vecuronium are partly excreted in the bile.

The kidneys are responsible for the elimination of most drugs. Drugs are filtered by the glomerulus and excreted in the urine, and some drugs are actively secreted into the tubules. The rate of elimination will depend on the glomerular filtration rate, and like most biological processes it behaves in an exponential fashion.

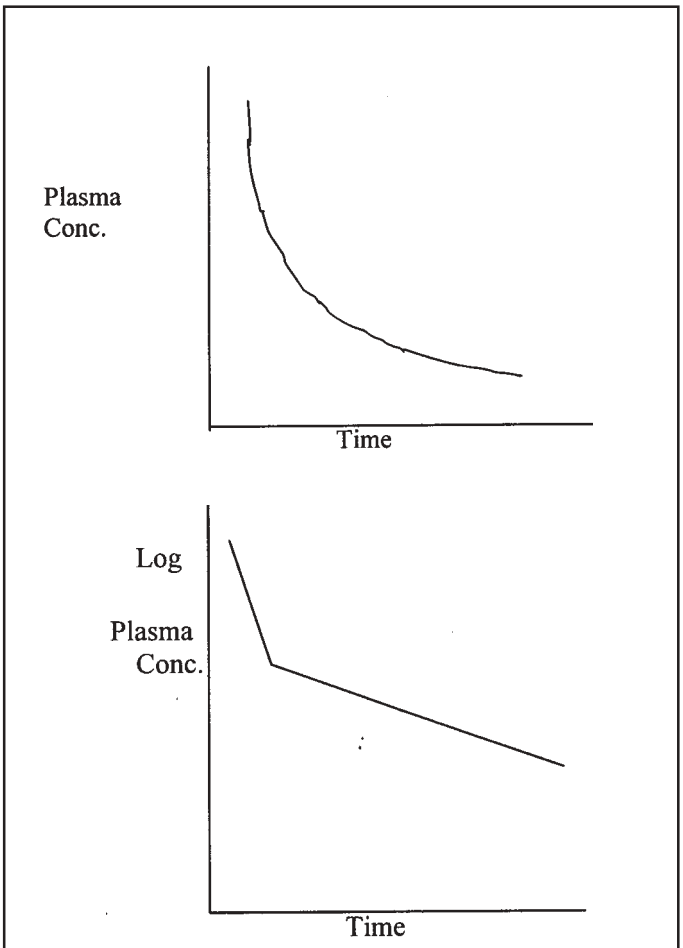


Figure 4: Pharmacokinetics of a two compartment model. The plasma concentration curve is a complex exponential, revealed in the log plasma concentration curve as two straight lines