Factors affecting drug absorption and distribution

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Abstract
The pharmacokinetic properties of a drug comprise the relationship between its absorption, distribution and inactivation. The passage of drugs across cell membranes is a key part of most pharmacokinetic processes. The most important means by which a drug crosses cell membranes is passive diffusion, the rate of which is determined by molecular size, the concentration gradient, lipid solubility, degree of ionization of the drug and protein binding. Pharmacokinetic processes can be summarized and the time course of drug action can be predicted using mathematical compartment models. In a single-compartment model, a drug is evenly distributed throughout the plasma and tissues and eliminated in an exponential manner. However, multicompartment models make allowance for the uptake of drugs from the plasma by different tissues and for different flow rates to these tissues. Drug distribution across the placenta is a special case and considered separately. The placental membrane is a lipid barrier that is less selective than the blood–brain barrier, allowing the passage of lipid-soluble drugs more easily than water-soluble drugs. The distribution and rate of equilibration across the placenta are determined by placental blood flow and the free drug concentration gradient.

Keywords Absorption; administration; drug distribution; pharmacokinetics

A drug is a chemical that affects physiological function in a specific way, generally by binding to particular target proteins such as receptors, ion channels, enzymes and carriers. The action of a drug requires the presence of an adequate concentration of the drug in the fluid bathing the target tissue, and this, in turn, is determined by the dynamic relationship between absorption into the plasma following administration, the extent and rate of its distribution and the rate of inactivation by the body. Within pharmacology, these relationships are termed pharmacokinetics.

Passage of drugs across cell membranes
The passage of drugs across cell membranes is necessary for most pharmacokinetic processes. Drugs are transported around the body in two ways: by bulk flow (i.e. in the bloodstream) and by diffusional transfer, predominantly across cell membranes. The composition of a drug does not affect bulk flow transfer, but, in general, the diffusional characteristics of the drug distinguish its pharmacokinetics.

All cell membranes are phospholipid bilayers, spanned partially or completely by glycoproteins, and are thus readily crossed by lipid-soluble substances. Adjacent epithelial or endothelial cells are joined by tight junctions that may or may not be traversed by channels through which water-soluble substances can travel. Epithelia with many such channels are termed 'leaky' (e.g. proximal renal tubules or gut mucosa), and those with no such channels are termed 'tight' (e.g. the blood–brain barrier). Specialized protein molecules within the lipid bilayer may allow specific substances to enter or leave the cell preferentially (carrier proteins). The passage of drugs across membranes occurs by one of four methods: diffusion, filtration, carrier-mediated transport or pinocytosis.

Passive diffusion
This is the most important means by which a drug crosses cell membranes. Passive diffusion is the passive movement of a substance from an area of high concentration to an area of lower concentration. The rate of diffusion is determined by molecular size, the concentration gradient, lipid solubility, degree of ionization of the drug and protein binding.

Molecular size: the rate of passive diffusion is inversely proportional to the square root of molecular size (Graham’s Law); therefore, smaller molecules will diffuse more readily than larger ones.

Concentration gradient: the rate of diffusion across a membrane is proportional to the concentration gradient across the membrane (Fick’s Law); therefore, increasing the plasma concentration of the unbound fraction of drug will increase the rate of transfer across the membrane, increasing its speed of onset.

Lipid solubility: non-polar substances dissolve freely in lipids and therefore easily diffuse through cell membranes. Greater solubility in the membrane generates a greater transmembrane concentration gradient, even if the aqueous concentration gradient between two compartments separated by the membrane remains the same. The solubility in the membrane can be expressed as a partition coefficient for the substance distributed between the lipid phase (membrane) and the aqueous phase.

After reading this article, you should be able to:
- list the factors affecting the passage of drugs across cell membranes
- list the main routes of drug administration
- describe how compartment models are used to predict the time course of drug action

Learning objectives

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Therefore, for an acid XH the relationship is:

$$\text{pH} = pK_a + \log_{10} \left( \frac{\text{proton acceptor}}{\text{proton donor}} \right)$$

Therefore, for an acid XH the relationship is:

$$\text{pH} = pK_a + \log_{10} \left( \frac{X^-}{XH} \right)$$

and for a base X, the corresponding equation is:

$$\text{pH} = pK_a + \log_{10} \left( \frac{X}{X^-} \right)$$

The $pK_a$ is a constant for each drug and is the pH at which 50% of the drug molecules are ionized. It can be seen from the above equations that at a pH below their $pK_a$, weak acids will be more un-ionized, and at a pH above their $pK_a$ they will be more ionized. The reverse is true for weak bases.

Ionization affects both the rate at which drugs cross membranes and the steady state distribution of drug molecules between compartments of differing pH.

**Protein binding:** only free unbound drug is available to cross the cell membrane. In the plasma, both albumins and globulins bind drugs, and the number and characteristics of the binding sites are determined by the pH of plasma. In general, albumin binds neutral or acidic drugs while globulins bind basic drugs. For drugs that are highly protein-bound, small changes in the fraction of protein binding produce large changes in the total amount of unbound drug. Pathological conditions such as acute infective or inflammatory processes, or reduction in synthetic capacity due to liver impairment, will cause a reduction in albumin concentration and markedly affect the proportions of unbound drugs.

**Filtration**

Aqueous channels in the tight junctions between adjacent epithelial cells allow passage of some water-soluble substances. Non-polar molecules pass most readily as the channels are electrically charged. Such channels are plentiful in gut mucosa and renal tubules and absent in blood–brain barrier and placenta.

**Carrier-mediated transport**

This is the mechanism used by drugs to cross cell membranes against a concentration gradient. The processes involve endogenous carrier proteins and show a large degree of specificity for particular compounds. Therefore, the drugs that are subject to these processes are structurally similar to natural constituents of the body. Most of these processes expend cellular energy (active transport) but some do not (facilitated diffusion). The carriers involved are subject to saturation and can be inhibited.

**Pinocytosis**

Pinocytosis involves invagination of part of the cell membrane around a drug molecule, thus incorporating it into the cell within a small vacuole. The vacuole may then be released into the cell or extruded out of the other side of the cell. This mechanism is thought to be of importance in the transport of large molecules such as insulin.

**Drug absorption**

Many different routes may be used to administer drugs. The main routes of administration are:

- injection (intravenous, intramuscular, subcutaneous or intrathecal)
- oral
- rectal
- sublingual
- topical to epithelial surfaces
- inhalational.

Absorption is the passage of a drug from its site of administration into the plasma. Intravenous administration, therefore, requires no absorption. In some instances, administration is directly to the effect site, and therefore absorption into the plasma is not required for the therapeutic effect of the drug (e.g. inhalation of a bronchodilator aerosol to treat asthma or application of steroid creams to treat eczema). In such cases, absorption gives rise to the unwanted side effects of the drugs. However, in most cases the drug has first to be absorbed into the intravascular compartment to become available for distribution to its effect sites. The rate and extent of absorption after a particular route of administration are dependent on many drug and patient factors.

**Injection**

Intravenous injection is the most direct route of administration, providing a patient with drug that is immediately available for distribution to its effect sites. Intravenous injections may be given as a bolus, giving rise to peak and trough concentrations, or as a continuous infusion. The pharmacokinetic differences between these two methods will be considered later in relation to drug distribution.

The rate of absorption following subcutaneous or intramuscular injection depends on the site of injection and physiological factors such as local blood flow. Absorption from the site of injection can be increased by the application of heat or massage, both of which increase local blood flow. In patients who have a poor peripheral circulation (e.g. hypovolaemia or severe pain), absorption will be unpredictable. In some instances, it may be desirable to delay the absorption of subcutaneously-administered drugs (e.g. the addition of epinephrine to local anaesthetics increases duration of action and reduces systemic toxicity).

**Oral administration**

This is the commonest route of drug administration. The low pH of the stomach means that acidic drugs are largely un-ionized.
However, the small surface area and relatively rapid gastric emptying means that the stomach does not have a significant role in absorbing drugs. The principal site of absorption of orally administered drugs is the small intestine, due to its large surface area (250 m²) and its epithelium, through which fluid readily filters as a result of osmotic differences caused by the presence of food. The colon plays a small role in absorbing drugs and many slow-release preparations probably depend on absorption there. Absorption across the intestinal membrane is also affected by transporters for organic anions and cations on both luminal and basolateral membranes. Transporters may be influx or efflux, leading to a small proportion of drugs which have been absorbed into the systemic circulation to re-circulate back into the gastrointestinal tract. Basic drugs re-entering the stomach become ionized and are unable to be reabsorbed from there into the circulation, a phenomenon known as gastric base trapping.

Bioavailability is defined as the proportion of a drug that enters the systemic circulation compared with the same dose given intravenously. Although the definition applies to any route of administration, in practice the term is generally used for the oral route. Oral bioavailability can be found from the ratio of the areas under the concentration–time curves for the same dose given orally and intravenously (Figure 1).

Oral bioavailability depends not only upon the ability of a drug to penetrate the gut mucosa, but also upon the extent to which the drug is metabolized either by enzymes in the gut wall or in the liver. This metabolism, which occurs before oral drugs are able to reach the systemic circulation, is known as first-pass metabolism. First-pass metabolism for certain drugs may be increased or decreased by induction or inhibition of hepatic enzymes (e.g. erythromycin inhibits a cytochrome P450 enzyme and thus increases the bioavailability of warfarin).

Other factors affect oral bioavailability: drug formulation (particle size, tablet size, enteric coating and pressure used in the tableting machine can affect drug dispersion); physicochemical interactions with other drugs or food leading to binding of the drug and reduced absorption; and various patient factors such as malabsorption syndromes or altered intestinal mobility. In addition, concentration of drug entering the intestine and gastrointestinal transit times affects the degree of saturation of intestinal enzymes and hence the extent of first-pass metabolism.

**Rectal administration**

Blood that supplies the lower rectum drains via the inferior rectal vein to the internal pudendal vessels, thus bypassing the portal circulation. Therefore, the rectal route may avoid first-pass metabolism and is useful for drugs such as progesterone that would otherwise be inactivated rapidly in the liver. However, drugs absorbed in the upper rectum enter the portal system, and so the extent of first-pass metabolism depends upon distribution within the rectum and is unpredictable.

**Sublingual administration**

The oral mucosa has a rich blood supply that bypasses the portal circulation. Therefore, the sublingual and buccal routes are useful when a rapid effect is required, particularly for drugs that are unstable at gastric pH or rapidly metabolized by the liver. Drugs that are often given sublingually include glyceryl trinitrate for angina and nifedipine for rapid control of blood pressure. Large molecular weight substances are not well absorbed by this route.

**Topical administration**

Although topical drugs are often given for their local effects (e.g. steroid creams for eczema, eye drops, EMLA), certain highly lipid-soluble drugs may be given transdermally for systemic effects. This route avoids first-pass metabolism and can provide a steady rate of drug delivery over a few days. Absorption is improved if there is a good regional blood supply to the site of application and so transdermal patches are usually applied to the thorax or abdomen rather than limbs. Drugs administered by this route include fentanyl and glyceryl trinitrate.

**Inhalation**

Inhaled drugs can be given for either local or systemic effects. Drugs given for their effect on the respiratory tree (e.g. bronchodilators) are given by aerosol or nebulizer. Systemic absorption occurs when particles reach the alveoli, and this is dependent on particle size. Droplets of 2–4 μm diameter tend to deposit in the pharynx and upper airways, with a small amount reaching the bronchioles, whereas droplets of 1 μm or less are deposited in alveoli and lower airways. Systemic absorption of these drugs may give rise to unwanted side effects.

Inhalation is the route used for volatile anaesthetics. The lung serves as the route for both administration and elimination of these drugs. The large surface area and blood flow allow for rapid adjustments of plasma concentrations. The lower the solubility of the volatile agent in blood, the more rapidly the alveolar concentration rises, equilibrating with brain concentration and therefore the quicker the onset of effect. Nitrous oxide is more soluble in blood than either oxygen or nitrogen. Therefore, when a volatile agent is inhaled in a mixture of gases containing nitrous oxide, the alveolar concentration of the volatile agent will rise more rapidly (as the nitrous oxide is absorbed into the blood) than when inhaled in a mixture of just oxygen or air. This is

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**Figure 1**

*Concentration–time curves for a drug given orally and intravenously*

Plasma concentration

Intravenous

Oral

Oral bioavailability can be found from the ratio of the areas underneath each curve.
known as the second gas effect and is important when considering the uptake of anaesthetic agents.

**Distribution of drugs in the body**

Once drugs have been absorbed into the circulation, they need to be distributed to their effect sites to exert their clinical effects. Distribution to individual tissues depends on blood flow to the tissues, and solubility and uptake into those tissues.

**Body fluid compartments**

Total body water for a man is between 50% and 70% of body weight, being less in elderly people and less in women because of smaller proportions of lean body mass. Body water is distributed into four compartments as follows: intracellular fluid 40%, plasma 5%, interstitial fluid 15% and transcellular fluid 1% (expressed as percentages of body weight). Transcellular fluid includes cerebrospinal, intraocular, peritoneal, pleural and synovial fluids and digestive tract secretions. To enter other fluid compartments and tissues from the plasma, drugs must cross epithelial barriers, moving out of the plasma or back into the plasma towards equilibrium. Within the different body water compartments drug molecules will exist in both free solution and bound form and in an equilibrium mixture of charged and uncharged forms. The pattern of distribution between the compartments therefore depends on the ability to cross cell membranes, the ratio of bound to free drug within the compartments, the pH partition and the fat-to-water partition.

**Volume of distribution and compartment models**

**Volume of distribution:** the volume of distribution is a theoretical volume reflecting the distribution of a drug throughout the body. It is defined as the volume of fluid required to contain the total amount of drug in the body at the same concentration as that present in the plasma. Drugs that are mostly confined to the plasma have a small volume of distribution, while those that redistribute rapidly and bind to tissues will have a large volume of distribution.

**Single-compartment model:** compartment models are used to summarize pharmacokinetic processes mathematically and to predict the time course of drug action. In a single-compartment model, the plasma and all tissues are considered as one compartment, throughout which the drug is evenly distributed and from which it is eliminated in an exponential (washout) manner. However, the single-compartment model is too simple to describe drug behaviour and so multicompartment models are used to make allowance for the uptake of drugs from the plasma by different tissues within the body and for the different flow rates to these tissues.

**Multicompartment models** may include any number of theoretical compartments, but more than three become experimentally indistinguishable. The sum of the compartment volumes is referred to as the volume of distribution at steady state. Large drug molecules that are highly bound by plasma proteins have a small volume of distribution, as do polar drug molecules (e.g. nondepolarizing muscle relaxants), because they do not readily cross cell membranes.

In the two-compartment model, the tissues are considered together as the peripheral compartment that drug molecules can enter and leave only via the central compartment, which is generally considered to be the plasma. Adding a second compartment introduces a second exponential component into the predicted time course of the change in plasma concentration. The first ‘fast’ process represents distribution and the second ‘slow’ process represents terminal elimination, which comprises both elimination from the body and redistribution of drug to plasma from the second compartment (Figure 2).

The rate constants of the two processes are calculated from the gradients of the lines. The reciprocals of these rate constants give the time constants, which is the time taken for the plasma concentration to fall to 37% of its starting value.

In a three-compartment model, each compartment has an inflow and an outflow represented by an exponential process. There are two possible arrangements of the compartments: mamillary and catenary. The mamillary type is most commonly used to model the actual physiological situation, and is the type described here. The model consists of a central compartment, into which a drug is infused and from which excretion can occur, together with two peripheral compartments with which drugs can be exchanged. Again, the central compartment generally represents the plasma while the second and third compartments may represent well-perfused and poorly-perfused tissues, respectively. This model is represented by three exponential processes with, by convention, the kinetics of the second compartment being faster than those of the third compartment.

**Figure 2**

Drug distribution and terminal elimination in the two-compartment model

The curve is the sum of two straight lines representing the two exponential processes of distribution and terminal elimination. The rate constants (K) of the two processes are calculated from the gradients of the lines. The half-life = ln2/K for each process.
The application of compartment models is used in target-controlled infusions of intravenous agents of anaesthesia. Interindividual variability in drug pharmacokinetics arises from covariates such as age, gender and body mass index, which alter the relative proportions of body water, lean body mass and fat. The various commercial models available adjust for these covariates, giving greater accuracy of target drug concentrations and therefore greater predictability of drug response.

**Distribution of drugs to the fetus**

Chorionic villi of the placenta consist of a layer of trophoblastic cells enclosing fetal capillaries. The placental syncytiotrophoblast and fetal capillary membranes fuse to form a single membrane, forming the lipid barrier that separates fetal and maternal blood. This barrier allows the passage of lipid-soluble substances more easily than water-soluble substances, especially those with a molecular weight greater than 600. The placental membrane is much less selective than the blood–brain barrier and even moderately lipid-soluble molecules cross easily.

The rate of equilibration of drugs across the placenta is determined by placental blood flow and the free drug concentration gradient across the placenta. The pH of fetal blood is lower than that of the mother and this may affect drug transfer across the placenta in two ways. The degree of ionization of drugs is altered in fetal blood. Weak bases that have a pKa that is higher than physiological pH (e.g. local anaesthetics) will be more ionized at the lower pH of the fetus. This can lead to the phenomenon of ion trapping, whereby ionized drug in fetal capillary blood is unable to go back across the placenta. This situation is worsened if the fetus becomes even more acidotic, and can lead to toxic levels of drug in the fetus. Secondly, the pH differences in maternal and fetal blood alter the relative protein binding of drugs across the placenta, which in turn alters the free drug concentration gradient across the placenta. Higher protein binding in the fetus would increase drug transfer from mother to fetus, whereas higher protein binding in the mother would reduce drug transfer from mother to fetus. Ratios of albumin and globulin may also differ between mother and fetus, particularly in pre-eclampsia when maternal serum albumin levels are low. This increases the transfer of neutral and acidic drugs across the placenta from mother to fetus.

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**FURTHER READING**


