Factors affecting drug absorption and distribution

Shruti Chillistone

Jonathan G Hardman

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

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Learning objectives

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

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 (environment). The mobility of molecules within the lipid varies very little between different drugs and so the partition coefficient is the most important variable affecting the permeability of the cell membrane.

Shruti Chillistone *MRCS FRCAI is a Consultant Anaesthetist at the Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

Jonathan G Hardman *FANZCA FRCA is Professor of Anaesthesia, University of Nottingham and Honorary Consultant Anaesthetist, Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

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pH and ionization: only the un-ionized fraction of a drug is available to cross the cell membrane because of the lipid nature of the membrane. The degree of ionization of a drug in solution depends on the molecular structure of the drug and the pH of the solution. Most drugs are weak acids or weak bases and exist in an equilibrium of un-ionized and ionized forms. The variation in the ratio of the two forms with varying pH is given by the Henderson—Hasselbalch equation. This may be expressed as:

$$\mathrm{pH} = \mathrm{pK_a} + \mathbf{log}_{10}\left(\frac{\text{proton acceptor}}{\text{proton donor}}\right)$$

Therefore, for an acid XH the relationship is:

$$\mathrm{pH} = \mathrm{pK_a} + \mathbf{log}_{10}\frac{[\mathrm{X}^-]}{[\mathrm{XH}]}$$

and for a base X, the corresponding equation is:

$$\mathrm{pH} = \mathrm{pK_a} + \mathbf{log}_{10}\frac{[\mathrm{X}]}{[\mathrm{XH}^+]}$$

The $\mathrm{pK_a}$ 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 $\mathrm{pK_a}$, weak acids will be more un-ionized, and at a pH above their $\mathrm{pK_a}$ 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 produces 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 most common 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 m^2) and its epithelium, through which fluid readily

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