Factors affecting drug absorption and distribution

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Abstract

Pharmacokinetics describes the processes that underpin how the human body handles a drug. There are four elements to pharmacokinetics: absorption, distribution, metabolism, and excretion. Drug absorption involves the movement of the drug across a cell membrane and is largely dependent on diffusion. The absorption rate is determined by the preparation of the drug, route of administration, size of the molecule, concentration gradient, degree of protein binding and lipid solubility of the drug. First pass metabolism can be responsible for reducing the bioavailability of drugs via certain routes like oral administration.

Different compartment models can be used to predict the pharmacokinetic process of drug distribution. Multicompartmental models are used to understand how the drug is distributed to model the uptake of the drug into different tissues at varying rates. These models are utilized for targeted controlled infusions in practice to maintain anaesthesia at an effect site concentration that is specified by the user.

Keywords Absorption; active transport; bioavailability; cell membrane; diffusion; distribution; half-life; metabolism

Royal College of Anaesthetists CPD Skills Framework: Scientific principles

Learning objectives

After reading this article, you should be able to:

- describe the factors affecting how different drugs are absorbed across various routes of administration
- understand the factors affecting drug distribution in the body and how this is modelled in clinical practice
- explain how targeted controlled infusions utilize mathematical models to maintain effect site concentration of drugs

The manner in which the human body handles drugs is described by four pharmacokinetic processes: absorption, distribution, metabolism, and excretion. This article will review the physiology behind absorption and distribution and summarize the important practical considerations behind the processes in anaesthesia and intensive care.

Drug absorption

The process of absorption is defined as the "transportation of unmetabolized drug from the site of administration to the circulatory system".[4] The key step of this process is the movement of the drug across cell membranes, which can occur in several different ways, depending on the structure and characteristics of the drug.

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The human cell membrane separates the intracellular and extracellular environment and therefore controls the passage of substances into the cell. The cell membrane is structured as a phospholipid bilayer with the hydrophobic head groups of the phospholipids facing externally and the hydrophobic lipophilic chains/tails facing internally to create a hydrophobic core, as shown in Figure 1. Throughout the bilayer, there are multiple ion channels, receptors, G proteins and enzymes which move fluidly within the membrane.

The membrane structure is designed to maintain an equilibrium. For substances to cross this layer, different processes are utilized depending on the characteristics of the substance. Generally, lipophilic substances (e.g. oxygen, carbon dioxide and steroids) are able to move through the hydrophobic core of the bilayer and cross the cell membrane using their concentration or pressure gradients. The hydrophobic core within the bilayer prevents the passage of water and hydrophilic substances (e.g. glucose and electrolytes) by diffusion, which are instead transported through channels or carriers.[3] Table 1 describes the different methods by which drugs can move through or be transported across the cellular membrane.

Bioavailability

Bioavailability is defined as the "fraction of administered drug that reaches the systemic circulation intact".[7] It therefore determines the dosage required for each drug via each route of administration. An intravenous dose of a drug has 100% bioavailability. Absolute bioavailability is measured by comparing the plasma concentrations of the test dose with the plasma concentration following intravenous administration. This can be calculated using a concentration time curve; dividing the area under the curve for the extravascular route of administration by the area under the curve for the intravenous dose will determine the bioavailability of the drug, as shown in Figure 2.[7]

First pass metabolism

First pass metabolism describes the metabolism of a drug prior to it reaching the systemic circulation. With oral administration, this can occur in the bowel wall and its lumen, or via hepatocytes. For drugs with a high first pass metabolism, there is a larger difference between the doses required via extravascular administration routes and the intravenous dose. There is also larger variation in plasma levels between individuals when administered. Drugs with a high first pass metabolism include propranolol, morphine, and amitriptyline.

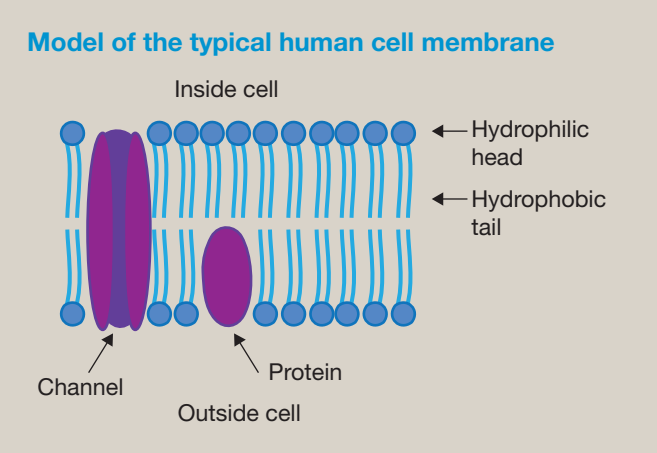

Figure 1

Within the bowel lumen, drugs can be metabolized by digestive enzymes which can destroy molecular bonds. Bacteria perform 'phase 1' reactions, including oxidation, reduction, and hydrolysis. The intestinal wall also has numerous enzymes and transporters responsible for first pass metabolism, for example, the enzymes monoamine oxidase and CYP3A4 are found here. Cells of the intestinal wall also contain a transporter called p-glycoprotein, which transports drugs back into the intestinal lumen after entering the enterocyte which can result in further metabolism within the gut.[10]

The liver has a rich blood supply from the gut via the portal vein and is responsible for the majority of the first pass drug metabolism in the body. Before reaching the systemic circulation, drugs can be metabolized by enzymes in the liver. This process can be accelerated by substances which induce the CYP450 system (e.g. rifampicin) increasing synthesis of the haemoprotein. Metabolism within the liver can conversely be slowed by CYP450 enzyme inhibitors (e.g. amiodarone).

First pass metabolism in the liver is directly proportional to the hepatic extraction ratio of a drug. Hepatic extraction ratio (HER) is defined as "the fraction of drug entering the liver in the blood that is irreversibly removed during one pass of blood through the liver".[5] If hepatic enzymes metabolize the drug efficiently, then first pass metabolism will be high. Glyceryl trinitrate (GTN), propofol, propranolol, and lidocaine all have high hepatic extraction ratios. The amount of free drug in the circulation, and the intrinsic clearance of the substance within the liver. The liver is only able to act on the free drug fraction, so

How substances move through the cell membrane[10]

Passive diffusion	• The molecules move down a concentration gradient. This process requires no energy
	• To pass through the cell phospholipid bilayer the drug needs to be lipid soluble
	• There are several factors that determine how quickly drugs diffuse across membranes when administered by various routes across the body
	  ○ Fick's law describes how the rate of diffusion is directly proportional to the concentration gradient
	  ○ Graham's law defines that diffusion of a drug is inversely related to the square root of its molecular weight
	  ○ The larger the surface area the drug encounters, the greater the rate of diffusion
	  ○ The thicker the membrane, the slower the rate of diffusion
	  ○ The higher the solubility of the substance, the faster the drug diffuses across a membrane

Carrier-mediated processes	The drug must resemble the natural ligand adequately enough to bind to the carrier protein. Once this has occurred, it can move through the membrane passively or actively **Facilitated diffusion** • This process is passive and does not consume energy • The rate of transfer is faster than diffusion alone but remains linked to the concentration gradient; however, the rate of transfer of the substance is limited by the amount of carrier protein • Membrane-bound carrier proteins combine with substances allowing them to cross the membrane • An example of a drug using this process is the transport of levodopa across the blood-brain barrier by an amino acid transporter **Active transport** • This is an energy consuming process: ATP is hydrolysed by the carrier protein to activate a pump • Movement of the drug occurs against a concentration gradient • For example, the cytotoxic medication 5-fluorouracil is actively transported into cells
Ion channel passage	• Within the membrane are pores which are highly specific for molecules. These channels include leak channels, voltage-gated, ligand-gated and mechanically gated • Movement of a drug through an ion channel requires a concentration gradient and a small molecular size (<100 Da) • For example, lithium and radioactive iodide move via ion channels between cells
Pinocytosis	• The cell membrane folds inwards to engulf the molecule and surrounding extracellular fluid in a vesicle before internalization • Usually for larger molecules • For example, doxorubicin is combined into a lipid vesicle to aid its transfer via this mechanism

Table 1

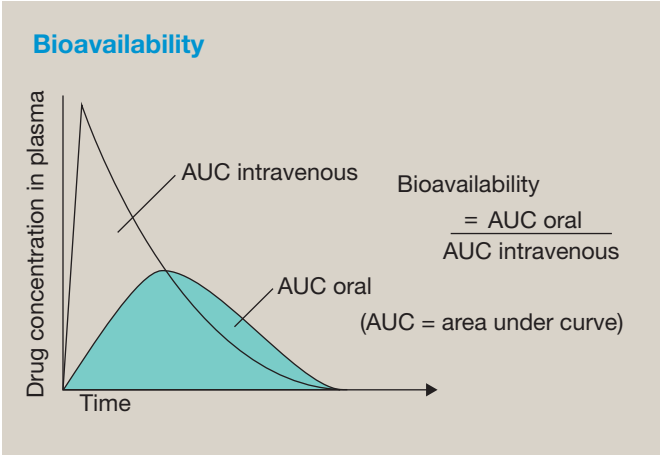

Figure 2 Drug concentration compared to time of intravenous and oral routes, and how this is used to establish the bioavailability of a drug.

therefore if there is a high proportion of unbound drug in the plasma, the HER is likely to be higher. The intrinsic clearance is the ability of the liver to remove the drug by metabolism. High hepatic blood flow will increase the clearance of the drug if the intrinsic clearance is high. However, hepatic blood flow will have minimal effect on metabolism if the intrinsic clearance is low.[5]

To avoid first pass metabolism, sublingual, nasal, rectal, and transdermal routes can be utilized. Sublingual administration bypasses first pass metabolism by draining into the venous blood of the tongue into the superior vena cava but is only useful for strongly lipophilic drugs like GTN when small amounts can produce the therapeutic effects desired.[7]

Absorption from the gut

Oral administration is the cheapest and most convenient method of administering medications. Once administered, the drug is absorbed through the mucosa; however, various factors influence the quantity and rate of the drug reaching the systemic circulation. Oral administration has the lowest bioavailability of any route due to having the highest first pass metabolism.

Firstly, the properties of the drug are crucial in determining how easily it can be absorbed from the gut once ingested. A higher administered dose will generate a bigger gradient for diffusion and a faster rate of absorption. Lipophilic drugs and small molecules are also absorbed more efficiently compared with larger hydrophobic drugs. Drug formulation can be adapted to change the absorption profile. Modified-release preparations are used to sustain serum levels of the drug to maintain therapeutic levels. They are designed to slowly dissolve by using a polymer of varying thickness to limit the amount of drug absorbed per unit time. Enteric-release tablets have a coating layer that is insoluble to acid, but freely soluble under basic conditions and are therefore designed to allow drugs to reach the duodenum if they are ordinarily inactivated by stomach acid or have undesirable gastric effects.

The stomach produces 2 litres of gastric fluid a day, which includes hydrochloric acid at a pH of 0.8 secreted by the parietal cells.[3] Therefore, the pH of the stomach is highly acidic. As discussed later in this article, a higher proportion of an acidic drug is unionized in acidic conditions, and unionized drug moves more freely across the cell membrane. Therefore, acidic drugs should be more rapidly absorbed in the lower pH of the stomach. However, the stomach also has a thick layer of mucus and a reduced surface area compared with the small intestine which slows the rate of absorption. For gastric absorption to contribute, the drug should be a small molecule, weakly acidic and highly concentrated, with examples including aspirin, furosemide, phenytoin and theophylline.[10]

Basic drugs are ionized in the stomach and therefore poorly absorbed; however, the increased pH in the small intestine results in a greater proportion of unionized drug and increases absorption. To be effectively absorbed in the small intestine, drugs are often small molecules, lipophilic in character, and if they use transporters, they must be similar enough to the substance which is actively transported into enterocytes normally. Smaller particles mean a greater surface area for drug dissolution and absorption.[9]

Properties of the gastrointestinal system can also determine how effectively the drug is absorbed into the systemic circulation and therefore influence drug bioavailability. Gastric stasis is common in the critically ill and can contribute to an increase in the time taken to reach adequate systemic concentrations due to delays in the drug reaching the main site of absorption, the small intestine. Enteral feeding, drugs such as nicotine and levodopa, ileus, and hyperglycaemia can slow the rate of gastric emptying. A slower intestinal transit time will also lead to a slower rate of absorption because the delivery of the drug to the surface of the small intestine is reduced. However, the longer duration of being exposed to the gut surface can increase overall absorption. Many factors influence intestinal motility including pain, diabetes, metabolic disease, and drugs. Generally, transit time in the small intestine is 5–10 hours, but most drug absorption tends to occur within the first hour in the small intestine. Therefore, motility would need to be very rapid to prevent absorption of a proportion of most drugs.

The large gastrointestinal surface area is crucial to being able to utilize oral medications successfully. The small intestine is only 7 m long but has a vast surface area of over 250 m^2 due to valvulae conniventes, villi and microvilli.[3] Disease processes such as coeliac disease and short gut syndrome can significantly reduce intestinal surface area and therefore absorption. In critically ill patients, blood flow is often shunted away from the gastrointestinal tract because of hypotension and shock, infusions of inotropes and vasopressors, and increased sympathetic tone diverting blood flow to more vital organs. This can contribute to reduced levels of absorption of almost all orally administered drugs. Ischaemia also leads to loss of microvilli on the brush border, affecting plasma concentrations of drugs.

Finally, within the gastrointestinal tract, drugs have the potential to react with other substances. They can potentially form a complex which cannot be absorbed; for example, activated charcoal can be used therapeutically with poisoning cases because of its large surface area to absorb a variety of substances. Additionally, tetracycline chelates the calcium within milk to form an insoluble complex which cannot be absorbed. Certain bacteria within the lumen can also inactivate drugs by metabolizing them, for example, it has been found that gut bacteria can restrict levels of levodopa in patients with Parkinson's disease.

Non-specific interruption with faeces can limit the absorption of drugs administered rectally. The rectum has a low surface area for absorption, and if the drug is placed more proximally within the rectum, it can be absorbed into the hepatic portal circulation and subject to first pass metabolism; however, around 50% of rectally administered drugs avoid first pass metabolism.

Absorption from inhalational administered drugs

The size of the drug particle is crucial in determining the effects of a drug administered by inhalation. To be absorbed into the systemic circulation, the drug must reach the alveoli, which requires a droplet size of under 1 micron in diameter. To produce droplets of these dimensions, the drug can be administered via a nebulizer. Once the drug reaches the alveoli it is rapidly absorbed by diffusion due to the high surface area (70 m^2) and avoids first pass metabolism. Larger particles have a more localized effect within the respiratory system.[7]

Intramuscular administration

Administering a drug intramuscularly results in a bioavailability close to that achieved with intravenous administration; however, the speed of onset is heavily dependent on regional blood flow. For example, muscles with good perfusion such as the deltoid need to be used to avoid a delay in absorption and inadequate plasma concentrations. Erroneously performed intramuscular injections can lead to unintentional intravenous injections, abscesses and haematomas and careful patient selection is therefore necessary.[7]

Transdermal administration

Transdermal absorption is a non-invasive method of drug delivery via the skin surface. The skin has several layers: the epidermis, the dermis, and hypodermis. The epidermis is the uppermost layer which contains the stratum corneum. The lipid bilayers of the stratum corneum allow only lipid-soluble substances to be absorbed; however, damage to the epidermis, including burns or abrasions, can allow faster and less selective absorption.

The advantages of transdermal delivery of medications include avoidance of first pass metabolism, and ease of delivery for the patient which can improve patient compliance. Patches are commonly used to facilitate slow absorption over several days to maintain steady blood concentrations over that time.

In terms of ensuring effective delivery and absorption, a good blood supply is crucial to faster absorption; a patient who is in shock, cold, or dehydrated will not absorb medications effectively through the skin. High concentrations of drug are also required to maintain the concentration gradient to facilitate effective delivery. Other properties which improve passage of the drug include a larger patch, a drug with a lower molecular weight, a low melting point improving drug release, a high potency (meaning the drug is effective at lower doses) and a drug being unionized and lipophilic.[1]

Drug distribution

Volume of distribution

The volume of distribution (Vd) is a theoretical concept that describes the apparent volume that a drug disperses into to produce the observed plasma concentration. It assumes that a drug is distributed evenly among one compartment. Vd is equal to the dose of the drug divided by its plasma concentration, so if 1 g of a drug is administered and the plasma concentration is 1 mg/litre, then the Vd is 1000 litres (Vd = 1/0.001). The volume of distribution allows you to calculate the loading dose to obtain the plasma concentration required.[2]

$$\text{Volume of distribution} = \frac{\text{Dose of drug}}{\text{Concentration in plasma}}$$

Drug properties and patient factors influence the Vd of different drugs. Larger ionized molecules are less readily able to leave the central compartment, and therefore have a smaller Vd. Conversely, lipid-soluble drugs have the highest Vd as they penetrate lipid bilayers more easily. Women, and older dehydrated patients tend to have a smaller Vd, while pregnancy causes an increase in total body water and increase in Vd.

Drugs bind to proteins within the blood (e.g. albumin, α-1 acid glycoprotein, lipoproteins and globulins) which affects their action and distribution. Only the free fraction of drug is involved in binding to tissue sites and can be metabolized and eliminated from the body. When drugs interact with circulating protein, they form a reversible complex connected by hydrogen bonds and van der Waal forces.[3] This means that there is a dynamic equilibrium between the free fraction of drug and the protein bound fraction of drug. Higher protein and drug concentrations, more lipid-soluble drugs and drugs similar to endogenous ligands are more highly bound within the circulation to plasma proteins. pH influences lipid solubility and therefore protein binding.[5]

Protein binding to plasma proteins is a large factor in determining a drug's Vd. Warfarin is over 99% bound to albumin, with only 1% that remains unbound, and therefore has a Vd of just 0.14 litres/kg and a half-life of around 40 hours.[9]

Pka and ionization

Ionization and polarity determine drug distribution, effect, and elimination. Weak acids and bases will be present in both an ionized and unionized form in solution as they only partially dissociate. These two forms exist in an equilibrium and are determined by the strength of the ionizable group and the pH of the solution. The ratio of the dissociated state (A^-) and undissociated state (HA) determines the acid dissociation constant, which can be log transformed into the pKa of the drug.

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

$$pK_a = -\text{Log}K_a$$

The pKa is the pH at which the solution contains equal amounts of unionized and ionized drug. The ionized form is water soluble, and the unionized form is lipid soluble. Acids are more ionized at a pH above their pKa as acidic groups will donate a proton in an alkaline environment. Bases are more ionized at a pH below their pKa. Proportion of unionized drug, and therefore lipid solubility, is the most important factor in the drug penetrating to the site of action, crossing cell membranes and being distributed widely.[9]

For example, local anaesthetics are weak bases, with the pKa of lidocaine and bupivacaine 7.9 and 8.1, respectively. The plasma pH of 7.4 is below both of their pKa values, meaning that

a higher proportion of lidocaine will be unionized in the plasma compared with bupivacaine.[7]

Half-life and time constant

The elimination half-life describes how plasma concentration of a drug changes over time. It is defined as the time taken for the plasma concentration of a drug to reduce to half of the initial concentration, if the drug is eliminated in an exponential manner (first order kinetics). A higher Vd and lower clearance rate will result in a higher half-life. Two half-lives will lead to 75% of the drug being eliminated, while five half-lives result in a reduction in plasma levels by 96.86%. The half-life allows estimation of the duration for which a drug should elicit its clinical effects.

The time constant is the time taken for the plasma concentration to reach nil if the initial rate of decline in plasma concentration continued. Most drugs are eliminated in an exponential manner and therefore this initial rate of decline does not continue and slows. It is known that after one time constant the plasma concentration has dropped by 36.8% of the initial concentration in first order kinetics. Therefore, the half-life is calculated as 0.693 multiplied by the time constant.[7]

Models of drug distribution

To understand the distribution of drugs within the human body, compartment models have been created. These are mathematical constructs predicting the way that the drug is handled by the body following administration. The models allow us to understand how the drug will behave within a patient over time and forms the basis of the target-controlled infusion models.

One-compartment model

This simple model, as demonstrated in Figure 3, views the entire body as one single homogeneous compartment. Therefore, the drug enters the compartment (V), instantly being uniformly distributed, before being eliminated (K) in an exponential manner. This model does not consider distribution; therefore, it is too simplistic to use as a model of anaesthetic infusions. However, hydrophilic drugs which remain almost solely within the central compartment could be modelled by the single-compartment model.

Two-compartment model

This model differs by having an additional compartment representing peripheral tissues (V2), alongside the central compartment (V1) which represents the plasma. This is also shown in Figure 3. The drug is administered into the central compartment (V1) and the concentration here gradually declines due to elimination (K) from the body, and distribution (K12) to V2 (both these processes explain phase 1 on a concentration–time graph in Figure 4).

The drug cannot be eliminated from the peripheral compartment and needs to be redistributed to V1 (K21) to be removed from the body (K). This redistribution back into V1 means that the elimination phase (phase 2) on the concentration–time graph (Figure 4) is slower to decline and has a flatter gradient compared with the initial distribution phase (phase 1).

Three-compartment model

The three-compartment model has two peripheral compartments: a well-perfused peripheral compartment (e.g. muscle)

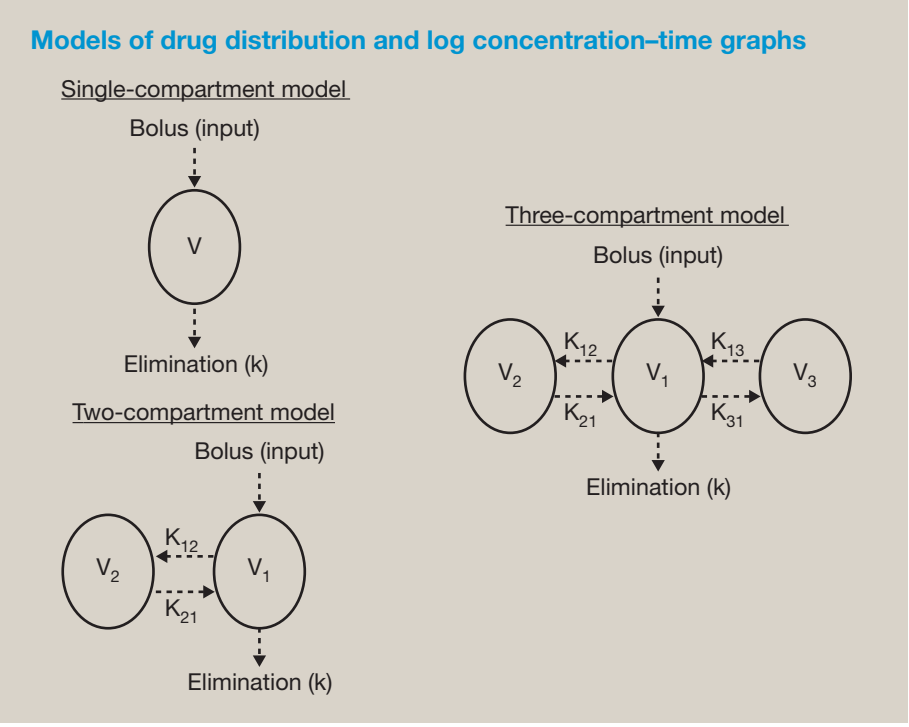

Figure 3 Models of drug distribution and log concentration–time graphs, comparing how drugs are modelled in practice using the one-, two- and three-compartment models.

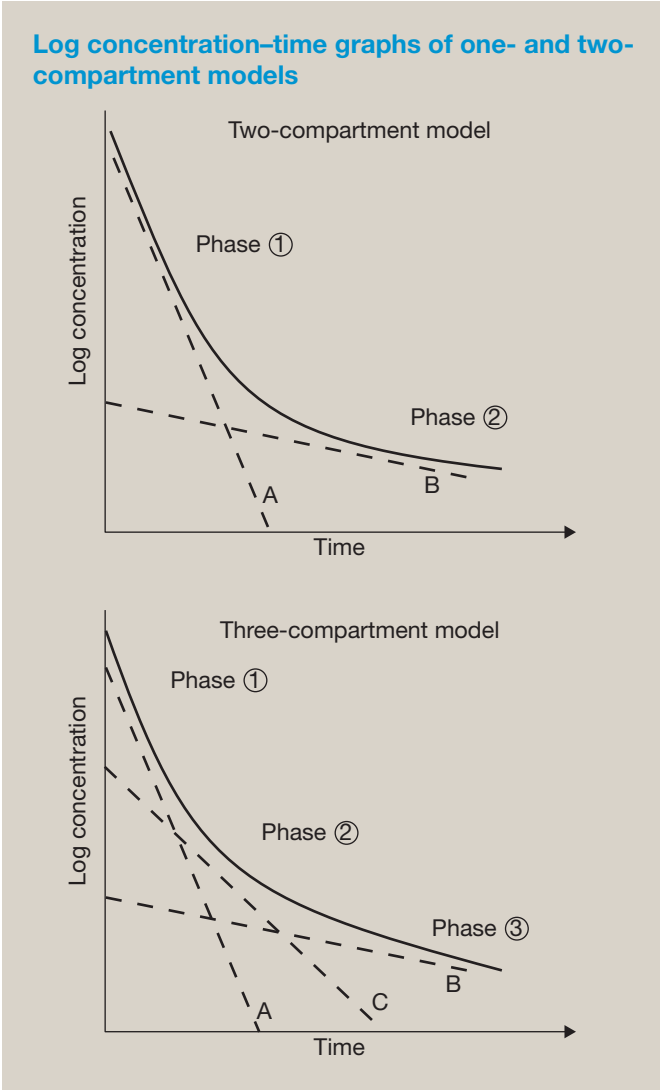

Figure 4

(V2), and a poorly perfused peripheral compartment (e.g. fat) (V3). This is the model most utilized for anaesthetic drugs. These peripheral compartments act as stores of drug, which allow redistribution to the central compartment even after the infusion has ceased (Figure 3). Therefore, the effect of the drug continues long after the infusion has stopped.[7]

In the three-compartment model, analysis of the time–log plasma concentration curve in Figure 4, shows three exponential processes. Two for distribution (phase 1 and 2) to each of the peripheral compartments and one for terminal elimination (phase 3) from the central compartment (V1). When a drug is administered into V1 there is a rapid decline in the concentration as it is eliminated from the body and distributed to the well-perfused V2 (phase 1). Phase 2 on the graph has a less steep gradient due to the continued elimination, but a slower distribution to the poorly perfused V3. This continues until equilibrium is established between the three zones.

Finally, there is a slower rate of decline as the drug is eliminated from the body (K) and redistributed (K21 and K31) from the peripheral compartments back into the central zone. This is demonstrated by phase 3 on the concentration–time graph in Figure 4.

Context sensitive half life

The context sensitive half-life is the time taken for a drug to reach 50% of the plasma concentration following termination of an infusion that was designed to reach steady state. The term context refers to the duration of infusion, and steady state occurs when the quantity of drug eliminated from the circulation is equal to that being introduced.

When an infusion is stopped, the drug in the central compartment continues to be metabolized, distributed to the second and third compartments and eliminated from the body. This continues until an equilibrium occurs between the three compartments. At this point, redistribution occurs from the second and third compartments to the central compartment because metabolism and elimination result in establishment of a reverse concentration gradient. This maintains the plasma concentration well beyond the end of the infusion.

The main considerations for the context sensitive half-life are the volume of the central compartment and the rate of clearance from the body. A small central compartment volume and rapid clearance will result in a small context sensitive half-life. The context sensitive half-life at 8 hours for fentanyl is 300 minutes, while remifentanil is only 8 minutes. The reason for this disparity is that fentanyl is distributed more quickly to the other compartments compared with its elimination from the body (five times faster), therefore with ongoing infusions the context specific half-life increases rapidly. Remifentanil also accumulates in peripheral tissues; however the clearance rate is greatly elevated, meaning that the context specific half-life is much lower.[9]

Continuous infusions of drugs using targeted controlled infusions

Pumps used for targeted controlled infusions (TCI) utilize a mathematical model that can predict the concentration of the drug within the blood. It uses a bolus followed by a prolonged infusion to achieve a user defined target concentration. The system has an infusion device, a user interface and microprocessor. It is an open loop system, which means that the effect of the drug is not measured like end-tidal gas monitoring with volatile anaesthesia.

Typically, propofol is used to maintain anaesthesia using a TCI model, and two different models are used in clinical practice in the UK, both of which were developed in healthy volunteers.

The Marsh model was developed in 1991. The compartments in the model are proportional to total body weight, while the rate constants between compartments are fixed. Therefore, after a bolus the estimated plasma concentration varies according to weight, but the decrease in concentration over time is identical between all patients.

The Schneider model was published in 1998 and is a three-compartment model which requires input of information on patient age, gender, height, and weight. This model uses a fixed volume for V1 and V3, and fixed rate constants (K13 and K31) between these compartments. However, V2 and the associated rate constants (K12 and K21) are influenced by age. Therefore, after a bolus, the initial peak plasma concentration will be identical for all patients, but the decrease in concentration over time

varies according to age. However, the elimination rate constant is determined by the lean body mass of the patient, which determines the speed of the infusion to maintain a steady state concentration. Lean body mass is calculated using the James formula, but in severely obese patients this can be inaccurate.[6]

The Schneider model uses a fixed volume central compartment of 4.27 litres, which is smaller than that used by the Marsh model (15.9 litres for a 70-kg man). Utilizing total body weight in the Marsh model increases the risk of overdosing propofol, especially in severely obese patients. ◆

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