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Drug Distribution and Drug Elimination

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<http://dx.doi.org/10.5772/59929>

1. Introduction

Pharmacokinetics is a branch of pharmacology that examines how drug concentrations change with respect to time as a function of absorption, distribution, metabolism and excretion [1]. These are disparate but interrelated processes that occur between drug administration and its irreversible elimination from the body. Another way to consider pharmacokinetic processes is to group them into two components:

1. intake, which describes the time course of drug movement from the site of administration, e.g. mouth, to the site of measurement, e.g. blood.
2. disposition, which describes the time course of drug distribution and elimination from the site of measurement e.g. blood.

Once absorbed into the body, drug compounds are distributed reversibly to various tissues of the body including the eliminating organs, such as liver and kidney, which results in a decrease in blood or plasma drug concentration. The decrease in the blood concentration could be due to reversible loss of drug from the blood to the tissues, defined as distribution, or the irreversible loss of drug from blood, defined as elimination. Disposition is therefore a combination distribution and elimination.

2. Distribution

Once in the systemic circulation, the blood or plasma concentrations of a drug will depend on how extensively it is distributed to extravascular sites [2]. Drug concentration in whole blood represents the total concentrations of drug in the circulatory system. Plasma concentration do not account for drug molecules that are sequestered into red or white blood cells. In general,

the blood and the plasma concentrations are assumed to be equal unless the drug is preferentially sequestered by red blood cells. Drug distribution will be influenced by tissue/organ blood flow, whether the drug is able to passively diffuse across cell membranes or is a substrate for active uptake or efflux transporters, and its extent of binding to plasma protein and tissue sites.

2.1. Tissue/organ blood flow

The transfer of many drug compounds from the systemic circulation to various tissues/organs follows the perfusion-rate diffusion process. Here, we assume that cell membranes do not present any barrier to drug transfer. This typically applies to drug compounds that are lipid soluble. Under perfusion-rate diffusion, the rate of delivery from the systemic circulation to a specific tissue/organ is primarily dependent on the blood flow within an organ or tissue. Organs like the liver and the heart are highly perfused with blood. By contrast, the bone and the adipose tissues experience less blood perfusion. Therefore, drugs are likely to distribute more rapidly to tissues/organs that are more richly perfused with blood.

2.2. Passive diffusion across cell membranes

A major factor affecting drug distribution is the physicochemical properties of the drug [3] since these would influence the permeability of the drug to various tissues. A drug that is highly lipophilic, such as chloroquine, may readily cross the lipidic bilayer of endothelial cells and most cell membranes to reach into the intracellular space via passive transcellular diffusion. Lipid-soluble drugs, because of their high partition coefficient, can also accumulate in organs or sites with fat deposits. On the other hand, drugs that are more water soluble and polar, such as aminoglycosides, do not distribute well into most tissues/organs. For such drug molecules, entry into the tissue spaces may rely on either paracellular diffusion via gaps in-between cells [4] or carrier-mediated uptake transport processes.

2.3. Influx or efflux transporters

Influx and efflux transporter are found in many tissues/organs and play a role in the distribution of drugs in the body [5]. The efflux transporter, P-glycoprotein (P-gp), which is expressed in the liver and the kidney, functions to keep drugs out of tissues [6]. By contrast, the influx transporter OATP1B1, an organic anion transporter expressed in the liver and the brain, acts on drug substrates to move them from the extracellular matrix into the tissue spaces. Since these transporters are subject to genetic polymorphisms, their underexpression or overexpression will result in differences in the extent of drug distribution between patients.

2.4. Plasma protein and tissue binding

Another factor influencing drug distribution is the preferential binding to plasma proteins and tissues [7]. It is the unbound or free portion of the drug that diffuses out of the plasma into the tissues/organs. Albumin and α_1 -acid glycoprotein are the two major proteins in plasma that are responsible for the binding of most drug compounds in the systemic circulation. The extent of plasma protein binding of a drug can be drug- or protein-concentration dependent, based

on the affinity and capacity of the plasma protein. A drug's protein-binding characteristics also depend on its physicochemical properties, with lipophilic drugs more likely to bind to plasma proteins and consequently, less available to the intracellular spaces [8]. Table 1 lists the extent of plasma protein binding of selected drugs. Binding to tissues also affects drug concentrations in the blood/plasma and the tissues/organs. However, compared to plasma protein binding, much less is known about tissue binding or the sequestration of drugs, since reliable methods for estimating binding to tissue components *in vivo* are experimentally more challenging.

Drug	Binding
Gentamicin	3
Digoxin	25
Vancomycin	30
Lidocaine	51
Phenytoin	89
Warfarin	99

Table 1. Extent of plasma protein binding of selected drugs.

3. Volume of distribution

A quantitative analysis of distribution is needed to understand pharmacokinetics of a drug. A drug can be characterised by the volume of fluids into which it distributes [9]. Since the volume of body fluids cannot be easily measured, it is assumed that the body simplifies into a tank of fluid into which the drug is placed. This volume is known as the volume of distribution (V_d). The V_d of a drug is an important pharmacokinetic parameter and is defined as the ratio of the amount of drug in the body to the concentration in a biological matrix that is readily accessible, such as the plasma. The V_d has units of volume, such as litre.

The V_d of a drug given as an intravenous (i.v.) dose can be calculated by:

$$V_d = \frac{A}{C_p} \quad (1)$$

where A and C_p are the i.v. dose of the drug (units: mass) and the drug concentration (units, e.g.: g/L) in plasma at time zero, respectively. If direct measurement is impractical, this initial drug concentration is derived from the y-axis intercept of the extrapolated logarithmic concentration versus time line. In general, it is assumed that C_p is the total drug concentration of the drug (free and bound to plasma proteins).

The V_d of a drug is regarded as a hypothetical term as it has no direct correlation to anatomical spaces in the body. It denotes the apparent volume of space into which a drug can distribute after dosing, and is indicative of its relative storage in the plasma and in the tissue/organ spaces. For this reason, V_d has also been commonly called the apparent volume of distribution. The V_d provides an important guide when accessing the tissue penetration of a drug. Table 2 lists the V_d of selected drugs.

Drug	V_d (L)
Warfarin	8
Gentamicin	18
Digoxin	440
Diazepam	80
Nortriptyline	1700
Chloroquine	> 15000

Table 2. The V_d of selected drugs.

The concept of V_d is illustrated in Figure 1.

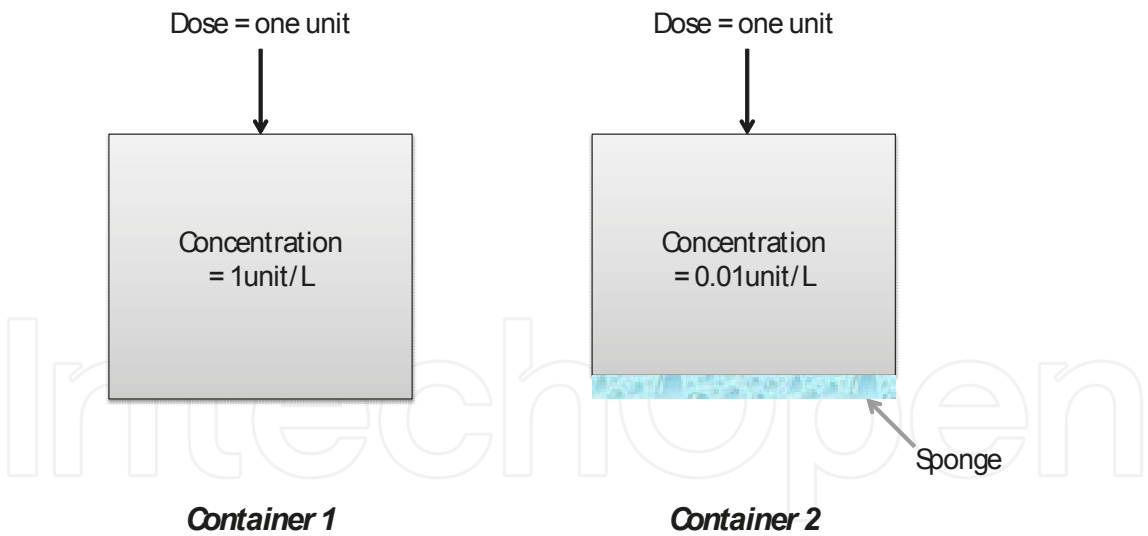


Figure 1. A clarification of the concept of V_d of a drug dissolved in two containers containing water. The V_d is an apparent volume term that is determined from the amount of drug added and the resulting concentration. Given the same dose amount and the 100-fold reduction in drug concentration in Container 2, the V_d of the drug in Container 2 is 100 times larger than that of the same drug present in Container 1.

Let us imagine there are two containers of the same size filled with 1L of water: Container 1 and Container 2. Container 2 also contains a small quantity of sponge that adds no significant volume to the overall container volume. A one unit dose of the same drug is then added to

each container. After complete dissolution of the drug in the volume of water within each container, the drug concentrations are measured. The concentrations in Container 1 and Container 2 are found to be 1unit/L and 0.01unit/L, respectively. Here, it is assumed that each container is a closed system after drug intake: no drug elimination occurs during the time for complete drug dissolution. By dividing the dose (one unit) by the measured concentration in each container (Eq. (1)), the volumes derived are 1L and 100L for Container 1 and Container 2, respectively. The explanation for this observation is that some of the drug in Container 2 is bound to the sponge, which renders it unavailable for measurement of the drug concentration in water. Consequently, the measured drug concentration in Container 2 is low and the calculated volume is high. However, each container still contains one unit of drug since none is eliminated. Put in another way, the V_d is an apparent or hypothetical quantity that relates the total drug amount in the system (dose) to its concentration in a matrix of measurement (water).

A physiology-driven formula has been proposed that accounts for the influence of blood or plasma volume, tissue volume (difference between total body water volume and plasma volume), drug binding to plasma proteins and drug binding to tissue sites on the V_d of a specific drug [10]. This formula is given by the following equation:

$$V_d = V_p + V_t \times \frac{f_{u,p}}{f_{u,t}} \quad (2)$$

where V_p , V_t , f_u and f_t denote the plasma volume, tissue volume, fraction of the drug unbound in plasma, and fraction of the drug unbound in tissue, respectively. Drugs such as nortriptyline and chloroquine have a large distribution volume, which indicates significant uptake and binding to tissue binding sites. By contrast, large-sized drug compounds (e.g. heparin), drugs that preferentially bind to plasma proteins (e.g. warfarin) and monoclonal antibodies, have a small V_d indicating that these remain mainly in the vascular space.

4. Elimination

Effective drug therapy involves achieving optimal efficacy without causing toxicity [11]. To this end, drug intake into and distribution within the body must be balanced with elimination so that appropriate concentrations at the receptor sites can be achieved. Elimination refers to the irreversible removal of a drug or its metabolite(s) from the body. For the majority of drugs, metabolism is the major pathway of elimination [12, 13]. The primary organ involved is the liver, although the gastrointestinal (GI) tract, kidney, lung and skin may also contain drug metabolising enzymes and may contribute to regional concentrations of the drug and the metabolites. Excretion of drugs and their metabolites mainly occur in the kidneys, but may also involve the GI tract and lung. This section describes the key aspects of liver metabolism and factors that may govern it, and the components of renal and biliary excretion.

4.1. Liver metabolism

In the liver, a wide array of enzymes exists to biotransform drugs, producing less active (or in some cases more active) metabolites [14]. Drug metabolism is defined as the biotransformation of lipid-soluble chemicals into water-soluble forms, so that these can be excreted in the urine. Metabolism is divided into two phases (Figure 2). Drugs may undergo one phase only, or be metabolised through both phases sequentially.

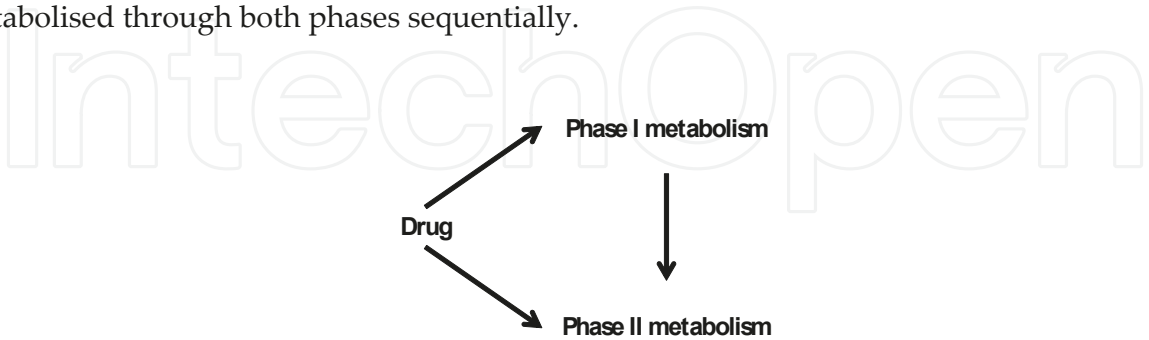


Figure 2. The phases of drug metabolism. Phase I reaction functionalises the drug with a ‘reactive’ group. Phase II metabolism typically results from the conjugation of an endogenous molecule to the ‘reactive’ group.

4.1.1. Phase I metabolism

Phase I reactions involve the introduction into or unveiling of a polar functional group (e.g. –OH, –SH) on the drug molecule, rendering it a suitable substrate for conjugation with another molecule during phase II metabolism. Such reactions typically involve oxidation, reduction or hydrolysis processes. Often, the by-product of phase I metabolism, called a derivative, is pharmacologically inactive but more chemically reactive than the parent drug, and may be toxic or even carcinogenic.

The major liver enzyme system involved in phase I metabolism (oxidation) is the cytochrome P450 (CYP) enzyme system [15]. Thus far, 18 CYP families have been identified in mammals, although only CYP1, CYP2, CYP3 and CYP4 are involved in drug metabolism, with CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 being responsible for the biotransformation of greater than 90% of drugs undergoing phase I metabolism (Table 3).

CYP enzyme	Examples of substrate drugs	Induced by	Inhibited by
CYP1A2	Acetaminophen, caffeine, theophylline	Smoking	Ciprofloxacin, fluvoxamine
CYP2C9	Warfarin, phenytoin	Phenytoin, carbamazepine	Fluoxetine
CYP2C19	Omeprazole, phenytoin	Phenytoin, carbamazepine	Fluvoxamine
CYP2D6	Codeine, risperidone	Glutethimide	Fluoxetine
CYP2E1	Acetaminophen, ethanol	Ethanol	Disulfiram
CYP3A4	Midazolam, simvastatin	Rifampicin	Ritonavir, ketoconazole

Table 3. Selected CYP enzyme-substrate drugs and their respective inducers and inhibitors.

In addition to genetic polymorphism, liver CYP enzymes are subject to induction and inhibition by certain drugs. As a consequence, elimination of such CYP enzyme–substrate drugs administered concomitantly may increase or decrease. Additionally, where metabolic pathways involve the production of pharmacologically active or toxic metabolites, induction or inhibition of CYP enzymes could result in unanticipated changes in plasma drug concentrations, with potential clinical relevance to its therapeutic or toxicity profile. Some examples of inducers or inhibitors of CYP enzymes are provided in Table 3.

4.1.2. Phase II metabolism

The derivative from phase I metabolism may be excreted via the urine immediately if high aqueous solubility is achieved. If not, the derivative undergoes a phase II reaction that brings about the conjugation of its functional group(s) to various hydrophilic endogenous compounds [16]. Examples of phase II reactions include sulfation, glucuronidation and glutathione conjugation. Sufficient water solubility is normally achieved in conjugates, which facilitate renal excretion. In addition, the insertion of a large polar substrate to the parent drug or derivative would make it more amenable for active secretion into the bile for subsequent excretion into the GI tract.

4.1.3. Prodrugs

After a phase I metabolism reaction, a drug may become “activated” or pharmacologically active. This biotransformation process is the basis for the development and usage of prodrugs [17]. The prodrug is typically a structural derivative of the active drug and synthesised by adding or changing a functional group(s) on the active drug structure. The ester is a common prodrug form of drug with hydroxyl or carboxylic groups. Esters can be synthesised with desired degrees of lipophilicity or hydrophilicity, and with controlled rates of the activating hydrolytic reaction. Once the prodrug gets inside the body, enzymes work to metabolically cleave the prodrug in order to form the active drug. Examples of prodrugs include levodopa, which is an amino acid derivative form of dopamine, and codeine, which is metabolised in the body to form morphine for analgesic effect.

There are many reasons to administer a prodrug in lieu of the active drug. The active drug may be too polar or hydrophilic for sufficient absorption and oral bioavailability to be attained, or for transfer across into the lipidic cell membranes to reach receptor sites, such as in neurons. Under such conditions, a functional group, such as carboxylic or hydroxyl group, may be attached to the active drug in order to enhance membrane transport. After absorption and distribution to the site of action, the functional group is cleaved via metabolism to release the active drug. In this regard, esterases found in almost all tissues make conversion of prodrugs into active drugs relatively straightforward. Other reasons for synthesising prodrugs are poor stability or poor patient acceptability (odour, pain on injection, gastric irritation) of the active drug, or a need to prolong the stay of the drug in the body.

4.2. Drug excretion

Excretion is the principal mode of termination of drug and metabolite effects. Drugs and their metabolite(s) are most commonly removed from the body via two main routes: renal and biliary excretion.

4.2.1. Renal excretion

About 25% of cardiac output goes to the kidney at which a significant portion of foreign compounds are filtered out. Renal excretion incorporates the processes of glomerular filtration, reabsorption from the renal tubular lumen, and tubular secretion as the drug passes through the nephron, the functional excretory unit of the kidney [18].

As blood passes through the glomerulus, entities within it are filtered to form the renal filtrate in the tubular lumen. The process of filtration is passive in nature and is driven by a combination of the large hydrostatic and concentration gradients present across the glomerulus-Bowman's capsule junction. Nevertheless, large-sized components cannot be filtered through the glomerular membrane, which implies that large drugs (e.g. heparin), plasma proteins and plasma protein-bound drugs (e.g. warfarin) cannot cross into the tubular filtrate.

Water is reabsorbed along the nephron tubule so that only 1% of the original filtrate is passed out of the body as urine. Approximately 99% of substances filtered at the glomerulus are reabsorbed along the renal tubules. The majority of filtered, unmetabolised drug molecules are also reabsorbed, especially if these are lipophilic. This is because such drugs are more likely to cross the membranes of the cells lining the tubules. By contrast, polar drugs e.g. gentamicin and digoxin, are unable to do this. Such drugs will therefore be excreted unchanged in the urine because they do not need to undergo biotransformation to increase their water solubility.

Active secretion into the renal tubules occurs for some drugs that are not readily filtered in the glomerulus. This pathway occurs via a carrier mechanism and is sufficiently efficient as to not depend on binding between plasma proteins and drugs, ensuring almost complete clearance of drugs such as penicillin [19]. Other drugs excreted by this process include anti-inflammatory drugs and methotrexate.

There may be competition for the active transport sites amongst drug compounds [20]. This may be exploited for therapeutic care, such as probenecid inhibiting the active secretion of penicillin from the kidney, increasing the latter's elimination half-life and prolonging its effect on the body. Conversely, competition for transport sites may lead to increased morbidity, e.g. aspirin can inhibit the secretion of uric acid, leading to gout aggravation.

Renal clearance of a drug can be measured with timed collection of urine and analysis of the drug concentration in the urine using the following equation [21]:

$$CL_R = \frac{C_u \times Q_u}{C_p} \quad (3)$$

where CL_R is renal clearance, C_u is the concentration of the drug in urine, Q_u is the volume of urine formation per unit time, and C_p is the concentration of the drug in plasma. Here, $C_u \times Q_u$ represents the excretion rate of drug in urine.

4.2.2. Biliary excretion

While in the liver, drugs or metabolites can also be secreted into the bile in much the same manner as the kidney secretes drugs into the nephron tubular filtrate [22, 23]. Biliary excretion is facilitated by active transport systems located in the canalicular membrane of the hepatocyte, and can be an important hepatic elimination pathway for many compounds. Since bile is an aqueous solution, it is suitable for dissolving hydrophilic drugs. In addition, bile acids allow solubilisation of lipid-soluble drugs. Thus, all types of species (anionic, cationic and un-ionised drugs), polar and lipophilic, can be secreted into the bile. These include drug metabolites that have undergone conjugation with glucuronate during phase II metabolism. The main criterion for significant biliary excretion seems to be molecular weight > 500.

Once bile and its constituents enter into the intestines, many organic biliary constituents, including bile salts and cholesterol, are reabsorbed from intestines back into the blood with high efficiency. These components then return to the liver via the hepatic portal vein. Drugs or metabolites excreted in the bile may recirculate in the same manner. If the drug has favourable physicochemical properties, it can be partially reabsorbed from the intestines back into the blood stream just like an orally ingested drug. Metabolites with glucuronate or sulfate groups may be removed by enzymes produced by the resident bacteria of the lower small intestine and colon, and the now-active drug is able to be reabsorbed. One example is mycophenolic acid. This immunosuppressant drug undergoes conjugation to glucuronate in the liver. The glucuronide metabolite of mycophenolic acid is secreted into the bile, cleaved in the small intestines, and reabsorbed back into the systemic circulation as the parent drug compound. Thus, a reservoir of the drug is established in the enterohepatic circulation, with an ongoing cycle of absorption, metabolism, secretion into the bile and reabsorption. Enterohepatic circulation hence increases the persistence of drugs in the body, and reduces overall clearance in the bile.

The clearance of a drug from various eliminating tissues occurs in parallel so the total body clearance of the drug (CL_T) is equal to the sum of the clearances of the individual tissues:

$$CL_T = CL_R + CL_H + CL_L + CL_{other} \quad (4)$$

where CL_H is hepatic clearance of the drug, CL_L is clearance of the drug from the lung, and CL_{other} denotes the respective clearance values from the other eliminating tissues.

Clearance is a constant that describes the relationship between drug concentration ($C(t)$) in the body and the rate of elimination of the drug from the body and has units of volume per time.

Figure 3 shows a way of schematically visualising CL .

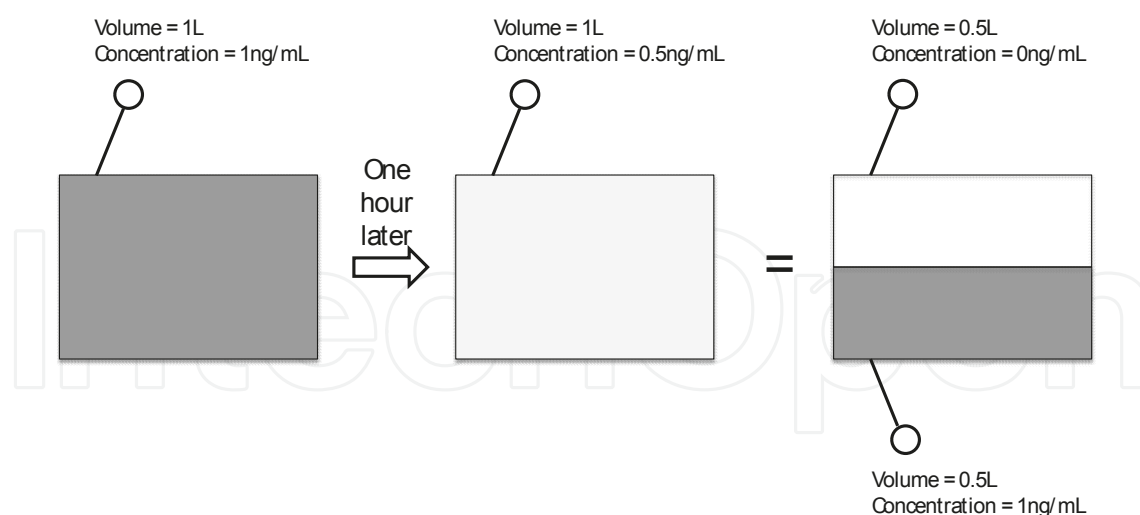


Figure 3. Clearance may be viewed as the volume of plasma from which the drug is totally removed over a specified time period.

Here, it is assumed that a container is present that contains 1L of water with a drug concentration of 1ng/mL immediately after drug intake (Figure 3, left container). The container is used to denote the human body (the system) and water is used to denote the plasma. After one hour, the drug concentration is measured in the 1L of water and found to decrease to 0.5ng/mL due to drug elimination (Figure 3, middle container). Another way of viewing this is that, after one hour, half of the water volume contains the original drug concentration (1ng/mL), whereas the other half of the water volume is completely voided of the drug (Figure 3, right container). This means that the clearance of the drug is 500mL/h.

Clearance can also be understood as the product of the perfusion of the eliminating organ (Q) and the intrinsic ability of the organ to eliminate the drug termed extraction (E):

$$CL = Q \times E \quad (5)$$

where E is calculated by $\frac{C_{in} - C_{out}}{C_{in}}$, and C_{in} and C_{out} are the drug concentrations in the blood entering and leaving the organ, respectively. Since E is unitless, CL has the same units as perfusion (volume per time). The CL of the drug is always constant and is considered a primary parameter. This is a physiologically appealing definition of CL in the sense that alterations in perfusion and extraction can be shown to change CL in a predictable manner.

5. Introduction to compartmental modelling

The body can be regarded as compartmental systems to describe the many processes involved in the absorption, distribution, metabolism and excretion of drugs. Three different approaches can be used to describe the pharmacokinetics of drugs in the body:

1. Non-compartmental (NCA) pharmacokinetic model
2. Compartmental pharmacokinetic model
3. Physiologically based pharmacokinetic (PBPK) model

The NCA approach (using statistical moment analysis) does not require the assumption of any compartments for the purpose of data analysis [24]. This method is based on the area under the drug concentration versus time curve (AUC) and the mean residence time (MRT). Although the NCA approach can be applied to most pharmacokinetic data, it lacks the ability to predict pharmacokinetic profiles when there are changes to the dosing regimen since it cannot estimate the concentration value at a specific time point.

The compartmental approach divides the body into a series of pharmacokinetically distinct compartments, each of which denotes a collection of tissues and organs that have similar rate of change of the drug concentration [25]. Drugs may exhibit single- or multi-compartment plasma concentration versus time profiles, with the number of compartments referring to the total number of disposition compartments. The compartment model assumes that each of the compartments is a well-stirred, kinetically homogenous unit. In addition, it is often assumed when constructing a compartmental model that the rate of elimination of the drug from the compartment and the transfer of the drug between the compartments (for a multi-compartment model) follows first-order (linear) kinetics. Under first-order kinetics, the rate of change of the drug amount or concentration is directly proportional to the remaining drug amount or concentration within the compartment.

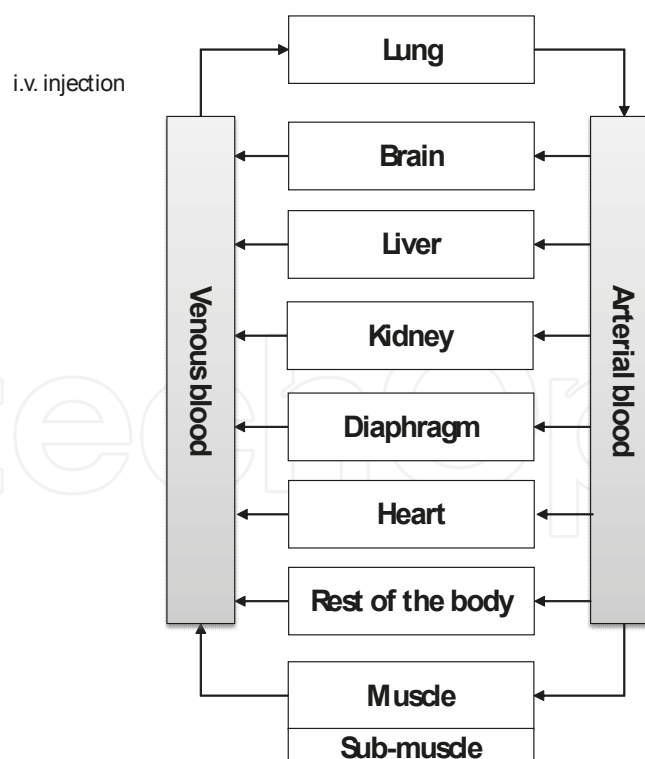


Figure 4. A physiologically based pharmacokinetic (PBPK) model for the description of drug pharmacokinetics in anatomically relevant tissues and organs. Here, the drug is administered as a bolus dose into the venous blood compartment.

Unlike the aforementioned compartment model, a PBPK model (Figure 4) comprises compartments that are defined based on anatomy, e.g. a compartment each for the liver and the brain. In addition, the PBPK model is also based on actual physiological and biochemical factors important in the input and disposition of the drug [26]. Such factors include cardiac output, organ blood flow rates, blood-to-plasma drug concentration ratio, partition coefficients in each organ, and transporter activities.

5.1. One-compartment model

Although more complex pharmacokinetic models may be necessary, a one-compartment model with first-order input provides a reasonable description of the time course for many drugs given at therapeutic doses (Figure 5), for example [27-29].

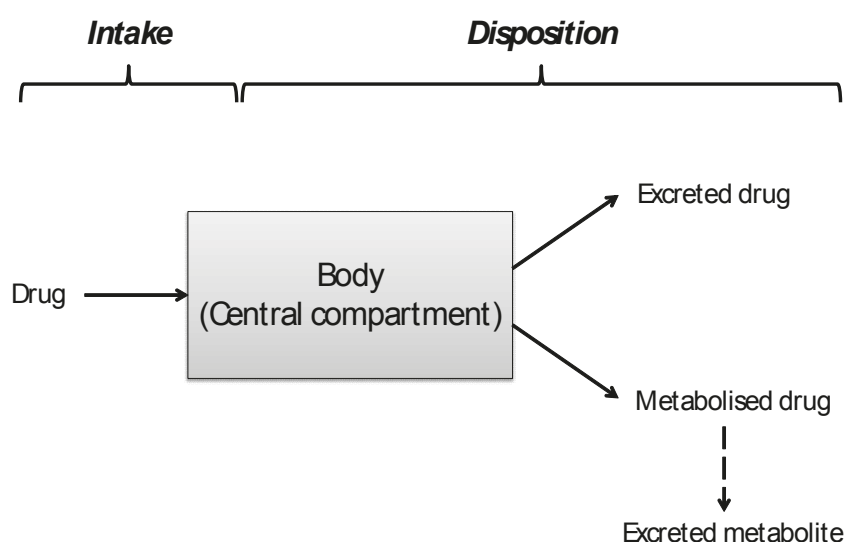


Figure 5. A one-compartment model with first-order input for describing the drug plasma concentration versus time profile. The arrows indicate the movement of the drug with respect to the body. Further, the diagram depicts that part of the drug may be excreted unchanged and some part may be metabolised by enzymes in the body.

In the one-compartment model, all the tissues of the body are lumped together as a single kinetically homogeneous compartment, commonly referred to as the central compartment. The one-compartment model is typically applied to drugs that distribute to only richly-perfused tissues and organs, such as liver, kidney and brain, in addition to the systemic circulation. The strongest indication that the body behaves as a single pharmacokinetically homogenous compartment for a drug is given by the presence of a mono-exponential decline in concentration values with respect to time when the concentrations are plotted on a logarithmic scale (Figure 6). For such a drug, it is assumed that all tissues and organs have a similar rate of change of the drug concentration as that of the systemic circulation, i.e. the source compartment.

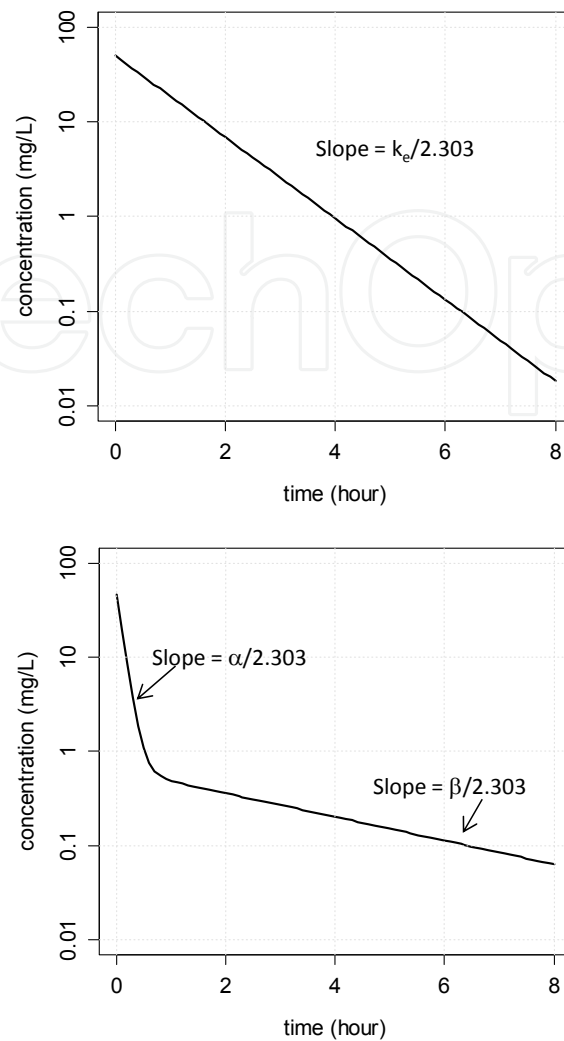


Figure 6. Plasma concentration versus time profiles following i.v. bolus administration on a semi-logarithmic graph for a drug exhibiting a one-compartment model (upper panel) and a two-compartment model (lower panel). For the two-compartment model, the slopes α and β denote the rates of combined distribution plus elimination, and elimination, respectively, of the drug from the central compartment.

After intravenous (i.v.) bolus administration, the blood or plasma drug concentrations ($C(t)$) at

After intravenous (i.v.) bolus administration, the blood or plasma drug concentrations ($C(t)$) at time t may be represented as:

$$C(t) = \frac{Dose_{iv}}{V_d} \times e^{-k_e \times t} \quad (6)$$

where $Dose_{iv}$, V_d and k_e are the administered i.v. dose (units: mass), volume of distribution (units: volume), and first-order elimination rate constant (units: reciprocal time), respectively. This equation may be converted to the natural logarithm to yield:

$$\ln C(t) = \ln \left(\frac{Dose_{iv}}{V_d} \right) - k_e \times t \quad (7)$$

The total body clearance (CL_T) and elimination half-life, $t_{1/2}$ (units: time), can be calculated by:

$$CL_T = k_e \times V_d \quad (8)$$

$$t_{1/2} = \frac{0.693}{k_e} \quad (9)$$

For an i.v. administered drug displaying one-compartmental pharmacokinetic behaviour, drug concentrations of tissues will decay in parallel with plasma concentrations. However, it does not imply that the concentration in the plasma is equal to the concentration in these body tissues.

When a drug is administered extravascularly, such as oral ingestion, it has to be absorbed through biological barriers prior to reaching the central compartment (blood or plasma). Only when the drug enters the blood or plasma will it be regarded as systemically available. The process of absorption is complex and is governed by myriad factors including the administration route, formulation type, dose amount, and the physicochemical properties of the drug. Following extravascular administration, compartment models become more complicated because now the drug's absorption rate constant (k_a) needs to be considered in the model. Despite the complexity involved, drug absorption is generally regarded as a first-order input process. For this first-order input, one-compartment model, the drug concentration at any time t is given by:

$$C(t) = \frac{F \times k_a \times Dose_{ex}}{V_d \times (k_a - k_e)} \times (e^{-k_e \times t} - e^{-k_a \times t}) \quad (10)$$

where F and $Dose_{ex}$ are the bioavailability (no units) and extravascular dose (units: mass), respectively. F denotes the proportion of extravascularly-administered drug that reaches the system circulation after drug administration. The maximum concentration (C_{max}) after extravascular administration and the time at which C_{max} is attained (t_{max}) are calculated by:

$$C_{max} = \frac{F \times Dose_{ex}}{V_d} \times e^{-k_e \times t_{max}} \quad (11)$$

$$t_{max} = \frac{\ln(k_a / k_e)}{k_a - k_e} \quad (12)$$

5.2. Two-compartment model

Sometimes, drugs may display two or more phases during the declining portion of the concentration versus time profile [30]. This phenomenon may be encountered when multiple

blood samples are collected during the drug's distribution and elimination phases. When the plasma drug concentration exhibits a bi-exponential decay (Figure 6, lower panel) on a semi-logarithmic scale following an i.v. bolus injection, a two-compartment model is necessary to describe the underlying pharmacokinetics. The two-compartment model divides the body into the central compartment as per the one-compartment model, as well as a peripheral compartment that lumps together slowly-perfused tissues, such as fat and muscle. It is generally assumed that drug is eliminated still from the central compartment that comprises the liver and the kidney, since most compounds are metabolised by the liver and/or undergo renal excretion.

As portrayed by Figure 6 (lower panel), the concentration versus time profile after a single i.v. bolus dose on the semi-logarithmic scale has a rapidly declining phase followed by a shallower declining phase. The initial rapid decline in concentration is a consequence of simultaneous elimination (to the external environment) and distribution of the drug from the plasma to tissues lumped under the peripheral compartment. After the distribution process is completed and equilibrium is established between drug concentrations in the central compartment and the peripheral compartment, the drug concentration in the central compartment decreases at a rate dependent on the drug elimination rate. In general, the drug elimination rate is lower than the initial rate of decline in concentration due to the simultaneous distribution and elimination of the drug from the central compartment.

Without specifically describing the micro rate constants, the drug concentration at any time t after a single i.v. bolus administration of a two-compartment system is represented by:

$$C(t) = A \times e^{-\alpha \times t} + B \times e^{-\beta \times t} \quad (13)$$

where A , B , α and β are derived from the intercepts and slopes of the respective distribution plus elimination, and elimination phases of the drug concentration versus time profile by curve fitting, such as nonlinear regression analysis.

6. Conclusion

Drug disposition refers to the combination of distribution and elimination. Distribution is a reversible process of movement of drugs from and to the site of measurement, typically the plasma or blood. Elimination comprises metabolism and excretion, and represents the total irreversible loss of the drug from the body. Drug disposition and elimination contribute to overall efficacy or toxicity and hence, up-to-date understanding of these pharmacokinetic processes is essential to safe, professional practice around medications and drug treatment. Compartmental modelling is a useful method to understand distribution and excretion processes [27, 31].

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