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PHARMACOLOGY PART 2: INTRODUCTION TO PHARMACOKINETICS.

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Foot line: Introduction to Pharmacokinetics

Abstract

Pharmacology principles provide key understanding that underpins the clinical and research roles of nuclear medicine practitioners. This article is the second in a series of articles that aims to enhance the understanding of pharmacological principles relevant to nuclear medicine. This article will build on the introductory concepts, terminology and principles of pharmacodynamics explored in the first article in the series. Specifically, this article will focus on the basic principles associated with pharmacokinetics. Article 3 will outline pharmacology relevant to pharmaceutical interventions and adjunctive medications employed in general nuclear medicine, the fourth pharmacology relevant to pharmaceutical interventions and adjunctive medications employed in nuclear cardiology, the fifth the pharmacology related to contrast media associated with computed tomography (CT) and magnetic resonance imaging (MRI), and the final article will address drugs in the emergency trolley.

Introduction

As previously outlined (*1*), *pharmacology* is the scientific study of the action and effects of drugs on living systems and the interaction of drugs with living systems (*1-7*). For general purposes, pharmacology is divided into *pharmacodynamics* and *pharmacokinetics* (Figure 1). The principle of pharmacokinetics is captured by philosophy of Paracelsus (medieval alchemist); "only the dose makes a thing not a poison" (*1,8,9*). Therapeutic benefits are gained from a drug within a window; below which there is no therapeutic benefit and above which there are harmful effects (*toxicity*). The narrow *therapeutic range* of some drugs means that only small variations in blood concentration are necessary to result in toxicity (or no effect). Key to maintaining drug concentrations within the therapeutic range is *bioavailability* and factors that may influence bioavailability are an essential aspect of pharmacokinetics. Pharmacokinetics provides a valuable insight into the biological behavior of interventional and adjunctive medications for the nuclear medicine patient, and for the radiopharmaceuticals administered to them. This is especially important to consider in nuclear medicine because both age (the mean age of nuclear medicine patients tends to exceed 60 years) and disease can have a significant impact on drug (or radiopharmaceutical) *bioavailability*, pharmacological response, *drug sensitivity* and drug interactions (*9-12*).

For a drug to have an effect, excepting intravenous (IV) or intraarterial (IA) administration, it must navigate at least one membrane (Figure 2). In the first, instance to enter general circulation from the site of administration and in some cases to get to the at the site of action (*3*). A drug may need to overcome physical, chemical and biological barriers; for example, the blood brain barrier (*6*). There are different mechanisms for a drug to be transported across a biological membrane that need to be considered (*3*):

- Passive (simple) diffusion requires a degree of lipid solubility to cross the phospholipid bilayer and moves using the concentration gradient until equilibrium is reached.
- Facilitated diffusion requires no energy nor can it move against a concentration gradient, but the drug sufficiently resembles the natural ligand to bind to the carrier macromolecule and traverse the membrane.

- Active transport also capitalizes on the drugs resemblance to the natural ligand allowing it to bind to carrier macromolecules, however, this process uses energy to transport a drug against the concentration gradient.
- Other carrier mediated transport mechanisms exist that are non-specific drug transporters, for example P-glycoprotein.
- Pinocytosis incorporates the drug into a lipid vesicle for carrier-mediated transport into the cell cytoplasm.
- Transport through pores or ion channels can occur with the concentration gradient for small water-soluble drugs.

Pharmacokinetics is essentially the study of the absorption, distribution, metabolism and excretion (ADME) of drugs (*1-7*); how the body affects the drug (Figure 3). It is, however, also the study of associated toxicity (ADMET) (*1-6*). Pharmacokinetics does not limit its scope to healthy or normal subjects but rather it includes variations in *bioavailability*, physiological or pathological conditions, disease related dose adjustment, and drug interactions (*1-7*). Combined, these aspects of pharmacokinetics allow customisation of drug dosage regimes to enhance outcomes (*1-7*).

Absorption

Absorption is the transportation of the drug from the site of administration to the general circulation (*2-6*). Absorption and the factors that may impede absorption of the drug directly affect drug *bioavailability*. Bioavailability in the context of pharmacokinetics is the fraction of the administered drug that reaches the systemic circulation (*2-6*). Clearly IV and IA injection transfer the drug directly into the general circulation and provides 100% bioavailability. This assumes drugs reach the site of action directly from systemic circulation and drugs requiring metabolism prior to action, even with IV administration, may have bioavailability less than 100%. Orally (*enteral*) administered medications are the simplest and most common dose administration route but may have variable bioavailability depending on many factors that influence drug absorption, including:

- molecular size of the drug,
- lipid solubility of the drug,
- degree of ionization of the drug,

- dosage form (e.g. tablet, solution),
- chemical nature of the drug,
- whether there is complex formation,
- pharmacological effect of the drug
- dose and concentration of the drug,
- blood flow (at site of administration),
- site of absorption, and
- route of administration (Table 1).

Generally speaking, the common routes of administration of drugs can be categorized as (*2-6*):

- Oral (enteral) administration is simple, convenient and painless allowing self-administration of drugs in easily handled drug forms. Gastrointestinal absorption means that the drug is transported via the portal system to the liver and undergoes *first pass metabolism*. First pass metabolism may render some of the drug inactive, decreasing bioavailability.
- Mucous membranes are highly vascular which allows rapid entry of the drug to the systemic circulation. This route avoids first pass metabolism and the hostile gut environment. In some cases, the drug can be delivered directly to the site of action (e.g. lungs). The drug may be delivered in a dissolvable form (suppository/pessary), mist, aerosol or liquid to any number of sites including sublingual, ocular, lung, intranasal, rectal, vaginal and more.
- Injection (parenteral) of drugs directly into tissue (e.g. systemic circulation, cerebrospinal fluid, tissue) avoids first pass metabolism and provides rapid delivery to the site of action. The degree of vascularity impacts the rate of onset of action with slow onset from subcutaneous (SC) administration, intermediate onset from intramuscular (IM) and rapid onset from IV. Parenteral administration affords the greatest control over drug delivery and includes; IV, IA, IM, SC, intraperitoneal (IP) and intrathecal (IT).

- Transdermal and percutaneous administration require passive diffusion of highly lipophilic drugs across the skin. This approach provides slow onset of action and potential for slow, continuous drug delivery (e.g. nicotine patches).

Distribution

Distribution refers to the movement of the drug from the systemic circulation to tissues (*2-6*). The drug needs to be distributed to the site of action in sufficient concentration to generate the therapeutic action. Distribution essentially involves the circulatory system (including some minor lymphatic involvement) which distributes drugs to all tissues except brain and testes (due to membrane barriers). Consequently, relative blood flow to tissues will impact on the drug dose required. Using simple diffusion following IV injection as an example, the initial high plasma concentration reaches equilibrium following rapid entry into cells with high perfusion. Poorly perfused tissues will continue to concentrate the drug which will decrease plasma concentrations. In turn, the high concentrations of drug in well perfused tissues will decrease to reach equilibrium across the membranes (Figure 4). This is a principle exploited in 201-thallium based stress / redistribution myocardial perfusion studies. Given tissue concentration of a drug is difficult to measure, plasma concentration is used to estimate tissue concentration (*6*). Major factors that affect the distribution of drugs include:

- diffusion rate,
- affinity of the drug to the tissues,
- blood flow (perfusion), and
- binding to plasma proteins.

An important concept to understand when discussing pharmacokinetics, and one which surfaces in radiopharmacy, is *protein binding*. Within the blood a drug may have an affinity to plasma proteins; typically, intracellular proteins, albumin and glycoproteins (*3.6*). The protein binding of drugs in plasma (mostly albumin) has low specificity and has no action (no potency) but forms drug-protein complexes in a similar fashion to drug-receptor complexes previously discussed (*1*). Most drug-protein binding in plasma is reversible and can act as a reservoir; releasing free drug when unbound concentrations of

free drug decline (Figure 3) (*3*). For drugs with a large amount of plasma protein binding (e.g. ibuprofen), equilibrium may occur between tissues and plasma with a small fraction of the actual drug (free drug) in the body. The vast reserves of plasma protein bound drug can provide prolonged effects through sustained release of the drug. There is, however, competition for plasma binding that can have significant implications for drug effects. Ibuprofen, for example, if displaced through competition would result in significantly higher free drug in tissue and blood. Co-administration of aspirin and warfarin compete for the same plasma protein binding sites and, thus, potentiate the effects of each other (*3,6*). A small number of drugs may bind irreversibly to plasma proteins via covalent bonding. As a result, bound drug is not released in response to decreasing plasma / tissue concentrations. The radiopharmaceutical 99m-technetium (99mTc) diethylenetriaminepentaacetic acid (DTPA) has about 10% plasma protein binding and this will have a minor influence on half clearance and glomeruli filtration rate (GFR) calculations. Conversely, 99m-technetium gluconate has high protein binding (greater than 50%) which truncates pharmacokinetics. 99mTc mercaptoacetyltriglycine (MAG3) has as much as 90% plasma protein binding and so relies on tubular secretion and effective plasma renal flow (rather than GFR). When a drug is highly plasma protein bound it typically has a lower *volume of distribution* (*6*).

The *volume of distribution* (V) is an important concept for pharmacokinetic principles and calculations. The volume of distribution is the amount of drug administered divided by the plasma concentration of the drug. This (V) represents the distribution of the drug between plasma and tissue compartments (*2,3,6*). Most of the time the volume of distribution does not actually equal the real volume of the compartments; it is simply a model to help understand drug behavior. For example, a 70kg person might be expected to have less than 70L of volume throughout their body yet, a volume of distribution for a given drug might exceed several hundred liters. A volume of several hundred liters is clearly not possible in a 70kg person but allows a theoretical understanding of drug behavior. When the volume of distribution is high, it reflects a relatively low drug concentration in plasma (minimal plasma protein binding) and extensive distribution through body tissues. It really represents an *apparent* volume of distribution or the fluid

volume that would be required at *steady state* (equilibrium) to contain the plasma concentration equivalent total drug amount in the body (*6*). The volume of distribution is used as a principle for *compartment modeling* and in pharmacokinetic calculations but it should be kept in mind that it is not an actual physical volume.

Compartment modeling is used in pharmacokinetics and radiopharmacy to more simply understand the relationship between drugs (or radiopharmaceuticals) and their distribution within the body. The body might be considered to be comprised of four liquid compartments; plasma water (5%), interstitial water (16%), intracellular water (35%) and fat (20%) (*2*). A smaller fifth compartment transcellular water (2%) is sometimes used and represents compartments partitioned by a barrier like the blood brain barrier and testes (*2*). In each compartment, a drug may be present in either bound or free forms and it is the free form that can move from one compartment to another (*2*). Movement between compartments can be measured and expressed as a rate constant (k). For simplicity and depending on what is being modelled, compartment modeling may use single, two or multiple compartment models (figure 5).

Metabolism

Drug *metabolism* largely occurs in the liver but can also occur in the kidneys, lungs, skin and gastrointestinal tract (*6*). Metabolism involves enzymes that modify the drug in various cells; for the liver, in hepatocytes (*6*). Most drugs are lipid soluble to allow them to cross the phospholipid bilayer membranes and be suitable for oral absorption. Lipid soluble drugs would also be reabsorbed from urine after elimination and, therefore, this requires metabolism of lipid soluble drugs to water soluble structures for effective renal elimination (*3*). The concept of a *prodrug* was previously introduced. A prodrug is an inactive drug that is metabolized into an active form. Most angiotenisin converting enzyme (ACE) inhibitors are prodrugs (e.g. inactive enalapril biotransforms to enalaprilate) but captopril is already in its active form.

Conversely, metabolism of active drugs relates to enzymic modification of the drug structure to render it less active (e.g. aspirin becomes salicylic acid), inactive (e.g.

morphine becomes inactive morphine-3-glucuronide although a second metabolite morphine-6-glucuronide is more active) or for most drugs (e.g. paracetamol or acetaminophen in Figure 6), more susceptible to elimination (*3,6*). Some drug metabolites, however, can have their own activity and, in some cases, be more active (e.g. nitroglycerin becomes the more active nitric oxide).

Modifications to drugs / prodrugs are referred to as *biotransformations* and can be categorized as (*3,6*):

- *Phase I* or oxidative / reduction / hydrolysis reactions and may be referred to as pre-conjugation. Oxidation generally adds a polar group to the chemical structure of a drug by adding an oxygen. Reduction tends to add a hydrogen while hydrolysis adds water to the drug structure.
- *Phase II* or conjugation / hydrolysis reactions generally facilitate attachment of the drug to a polar molecule. Either the drug or the metabolite from phase I metabolism is covalently bonded to a substrate. Some examples include glucuronidation, methylation, acetylation and sulphation.

Most drugs undergo both phase I and phase II metabolism, however, some drugs will only undergo either phase I or phase II metabolism (*3*). While a detailed discussion of the mechanisms of metabolism are beyond the scope of this discussion, figure 6 provides a summary insight into the process.

Elimination

Drugs and their metabolites can be eliminated from the body through a number of mechanism and in several forms that will be familiar in nuclear medicine due to similar pathways for radiopharmaceuticals (*3,6*). Some drugs can have fractional elimination via several routes. Liquid elimination includes renal and biliary (urine and bile) excretion primarily but also in sweat, tears, saliva and breast milk. Paracetamol (acetaminophen) excreted via the kidneys, while salicylic acid (metabolite of aspirin) can be excreted via sweat. Lignocaine (xylocaine/lidocaine) is excreted via the biliary system. Caffeine and theophylline (metabolite of prodrug aminophylline) are excreted in saliva. People can be tested for drug use using urine and saliva samples. Solid excretion occurs via the

gastrointestinal tract (feces) and in hair. Differentiating fecally eliminated drugs can be confounded by biliary excretion that transits the colon and for drug administered orally, that which remains unabsorbed. Nonetheless, digoxin is an example of excretion in feces via colonic lumen secretion. Drugs eliminated via the hair can be incorporated into the hair structure (e.g. codeine / morphine) or secreted onto the hair by sebum or sweat. Volatile drugs may be eliminated via gases in the lungs with alcohol being the most common example.

There are two important mechanisms to briefly discuss. Renal excretion via glomeruli filtration may be followed by tubular reabsorption (*3,6*). This is to retain key nutrients and other substances (e.g. amino acids and vitamins). Some drugs may also pass back into circulation via reabsorption. Similarly, drugs eliminated via the biliary system may be reabsorbed back from the intestines and returned via the hepatic portal vein (enterohepatic cycle) (*3,6*). In both circumstances, the effective duration of effect of drugs is prolonged.

Elimination of drugs from the plasma introduces four important quantitative concepts (*2-6*):

- *Clearance* (CL) is the rate of elimination of the drug from the body and is the product of the elimination rate constant (k) and the volume of distribution (V).
- *Half-life* ($T_{0.5}$) is the time required for the amount of drug present to be reduced by 50%. This can be a measure of plasma half-life or total body half-life.
- *First order kinetics* is when a constant fraction (exponential) of drug is eliminated per unit of time and is similar in concept to radioactive decay (Figure 7). In theory, the amount of drug present never reaches zero.
- *Zero order kinetics* is when there is a constant rate (linear) of drug elimination and this means the rate of elimination is independent of drug concentration. Unlike first order kinetics, a constant amount of drug is eliminated per unit of time and drug present will reach zero (Figure 7).

Kinetics

Perhaps the best way to demonstrate an understanding of pharmacokinetics is mathematically. These are simple calculations for those in nuclear medicine as there are parallels with a number of other equations used. A number of scenarios are presented below that are designed to highlight application of pharmacokinetic calculations (Table 2). Of course, these applications are examples and the methods of calculation can be readily adapted for other scenarios.

Consider a patient weighing 70kg who is given an IV bolus injection of 25mg of a drug. If plasma concentrations after injection are as per Table 3, the elimination rate constant and half-life can be readily calculated. The first step would be to plot the data on semi-logarithmic scales to demonstrate a straight line (confirming first order kinetics). Rather than use the slope of the line (Figure 8) for subjective calculations (or estimates), it is easier to use the following equation where C is the drug concentration at a given time, C_0 is the drug concentration at the reference time, k is the elimination rate constant and t is time between C and C_0:

$$\mathbf{C = C_0\, e^{-kt}}$$

$$14.6 = 139\, e^{-k.6}$$

$$14.6 / 139 = e^{-k.6}$$

$$\ln 0.1057 = -k.6$$

$$\mathbf{k = 0.3745\ h^{-1}}$$

With the elimination rate constant now determined, the half clearance time can also be calculated:

$$\mathbf{k = \ln 2 / T_{0.5}}$$

$$T_{0.5} = \ln 2 / k$$

$$T_{0.5} = 0.693 / 0.3745$$

$$\mathbf{T_{0.5} = 1.85\ h}$$

The volume of distribution (V) in litres can be calculated as:

V = amount of drug in body (ug) / actual C_0

Convert mg to ug

While the origin (actual C_0) can be estimated to determine the theoretical blood concentration at the point of drug administration by reading off the plot, it will be more accurate, given k has been determined, to simply calculate it:

$$\mathbf{C = C_0\, e^{-kt}}$$

$$139 = C_0\, e^{-0.3745 \times 2}$$

$$139 = C_0 \times 0.4728$$

$$C_0 = 139 / 0.4728$$

$$\mathbf{C_0 = 294}$$

Thus

$$V = 25000 / 294$$

$$\mathbf{V = 85\ L}$$

The area under the curve (AUC) from the time of administration to infinity ($AUC_{0-\infty}$) can be used to calculate total drug burden where F is the fraction of the drug absorbed (100% for IV) and D is the dose (ug):

$$\mathbf{AUC_{0-\infty} = FD / Vk}$$

$$AUC_{0-\infty} = 25000ug / (85 \times 0.3745)$$

$$AUC_{0-\infty} = 25000 / 31.8325$$

$$\mathbf{AUC_{0-\infty} = 785.36ug\ or\ 0.785\ mghrs / L}$$

Clearance (CL) can be readily calculated as:

$$\mathbf{CL = k \times V}$$

$$CL = 0.3745 \times 85$$

$$\mathbf{CL = 31.83\ L / h}$$

Scenario two considers a more complex problem. Drug concentrations of interest may include other tissues (other than plasma compartment) or plasma concentrations but without advantage of immediate absorption associated with an IV administration (eg. oral). In these cases, both absorption and the absorption rate constant need to be considered rather than just elimination. Consider the plasma concentrations in arbitrary units (U) of an orally administered drug in table 4. Graphing this data does not yield the mono-exponential curve expected of first order kinetics and this represents the overlapping influence of absorption and elimination (Figure 9). The logarithmic plot does, however, demonstrates a late section with a straight line from 7 hours onwards. This section has minimal impact from absorption so can be used to determine the elimination rate constant and half clearance time.

$$\mathbf{C = C_0\, e^{-kt}}$$

$$25.3 = 58.1\, e^{-k \times 17}$$

$$25.3 / 58.1 = e^{-k \times 17}$$

$$\ln 0.4355 = -k \times 17$$

$$\mathbf{k = 0.0489\ m^{-1}}$$

$$\mathbf{k = \ln 2 / T_{0.5}}$$

$$T_{0.5} = \ln 2 / k$$

$$T_{0.5} = 0.693 / 0.0489$$

$$\mathbf{T_{0.5} = 14.17\ m}$$

To determine the absorption rate constant, a process known as *curve stripping* is required. Using the elimination rate constant determined above and the data from 7 hours onward (Table 5), the equation can be used to determine the value for each time interval projected back along the elimination line (bold figures in Table 5); in effect stripping away the influence of absorption. For example, times 1, 3 and 5 hours can be calculated respectively as:

$$\mathbf{C = C_t\, e^{-kt}}$$

$$25.3 = C_1\, e^{-0.0489 \times 23}$$

$$25.3 = C_1 \times 0.3247$$

$$\mathbf{C_1 = 77.92}$$

$$\mathbf{C = C_t\, e^{-kt}}$$

$$25.3 = C_3\, e^{-0.0489 \times 21}$$

$$25.3 = C_3 \times 0.3581$$

$$\mathbf{C_3 = 70.65}$$

$$\mathbf{C = C_t\, e^{-kt}}$$

$$25.3 = C_5\, e^{-0.0489 \times 19}$$

$$25.3 = C_5 \times 0.3949$$

$$\mathbf{C_5 = 64.06}$$

Subtraction of the plasma values from the elimination curve values generates a value, R, which can be added to the table of data (Table 5). Graphing R on a logarithmic / linear

plot (Figure 10) generates an absorption rate. It is worth noting that the absorption line may not be a straight line representing a second compartment associated with distribution (e.g. vascular and extra vascular). While one should not assume a straight line for absorption in calculations, it offers a practical approach. In this particular case, there is a straight line relationship between time zero and 3 hours that can be used for accurate calculations. Thus, the absorption rate constant (k_a) can be determined as:

$$\mathbf{C = C_0\, e^{-ka \times t}}$$

$$12.1 = 46.6\, e^{-ka \times 2}$$

$$12.1 / 46.6 = e^{-ka \times 2}$$

$$\ln 0.2596 = -k_a \times 2$$

$$\mathbf{k_a = 0.6742\ m^{-1}}$$

With both the elimination and absorption rate constants now calculated, the time to peak concentration (T_{max}) can be calculated as:

$$\mathbf{T_{max} = (1/[k_a - k])\ \ln\ (k_a/k)}$$

$$T_{max} = (1/[0.6742 - 0.0489])\ \ln\ (0.6742/0.0489)$$

$$T_{max} = (1/[0.6742 - 0.0489])\ \ln\ (13.8)$$

$$T_{max} = 1.6 \times 2.6$$

$$\mathbf{T_{max} = 4.2\ m}$$

A third scenario provides an opportunity to incorporate AUC calculations in a more complex scenario. Consider the data in Table 6. After SC injection of a drug with a dose of 7.5mg/kg, plasma concentrations in blood were monitored (in ug/ml). The data can be plotted (Figure 11) and the straight line portion of the logarithmic curve used to determine both the elimination rate constant and subsequently the backprojected values for the elimination curve as per scenario two above (Table 7). The elimination rate constant (k) is calculated as:

$$\mathbf{C = C_0\, e^{-kt}} \qquad \mathbf{T_{0.5} = \ln 2 / k}$$

$$3.2 = 11\, e^{-k \times 4} \qquad T_{0.5} = \ln 2 / 0.3087$$

$$\mathbf{k = 0.3087\ h^{-1}} \qquad \mathbf{T_{0.5} = 2.25\ h}$$

Subtraction of the plasma values from the elimination curve values generates the previously introduced value, R, which can be added to the table of data (Table 7). Graphing R on a logarithmic / linear plot (Figure 12) generates an absorption curve. Thus, the absorption rate constant (k_a) can be determined as:

$$\mathbf{C = C_0\, e^{-k}a \cdot t}$$

$$5.8 = 37.8\, e^{-k}a^{\,x\,1}$$

$$\mathbf{k_a = 1.8744\ h^{-1}}$$

As previously discussed, AUC is a valuable metric in pharmacokinetics. There are a number of methods employed to determine the total AUC when absorption and elimination phases need to be accommodated; most tend to be unnecessarily complex or inaccurate due to estimation errors. The total AUC represents the total drug dose or drug burden. An understanding of mathematics provides both greater accuracy and simplification. This method relies on an accurate determination of k_a. It also assumes accurate calculation of k and then C_0 (plasma). The mathematics above indicate that the AUC is simply the area prescribed by k_a subtracted from the area prescribed by k. Thus, AUC can be calculated as:

$$\mathbf{AUC = [\ C_0 / k\ ] - [\ C_0 / k_a\ ]}$$

$$AUC = [\ 37.8 / 0.3087\ ] - [\ 37.8 / 1.8744\ ]$$

$$AUC = 122.45 - 20.17$$

$$\mathbf{AUC = 102.28\ ug}$$

These tools have a raft of applications to problem solve or to better understand drug (or radiopharmaceutical) behaviour. To avoid duplication, not all parameters were calculated in each scenario, however, they could if appropriate. One may also note parallels between these calculations and those used to problem solve in radiopharmacy.

Effects of Aging and Disease

Changes in physiology occur with disease and aging and can affect drug pharmacokinetics (*10,11*). Older people can also have altered responses to the drugs due to changes in mechanical responses, receptor mechanisms, homeostatic changes and CNS

function (*12*). It is worth considering that older patients are disproportionately represented in the nuclear medicine patient cohort and that older patients also have a higher use of medications; in particular, the use of multiple and concurrent medications (*polypharmacy*). Older patients and those with disease (or older patients with disease) have a less homogenous response to medications that make responses difficult to predict. With aging and disease comes (*9-12*):

- Altered absorption (e.g. slower gut absorption of captopril).
- Changed biodistribution (e.g. diazepam volume of distribution doubles).
- Altered metabolism especially with liver function changes or disease (e.g. decreased for ibuprofen).
- Altered elimination (e.g. diazepam half clearance almost triples).
- Changed bioavailability (e.g. increased digoxin toxicity) is influenced by all of these factors to either reduce bioavailability or increase it.

Conclusion

Pharmacokinetics is the study of how the body affects drug and these concepts translate from drugs to principles in radiopharmaceuticals. Pharmacokinetics provides essential insights into the behavior of interventional and adjunctive medications on the nuclear medicine patient. These principles provide the tools to problem solve both practically and quantitatively. This article completes the foundation understanding of pharmacology that will be detailed with respect to specific applications in subsequent articles in this series.

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Table 1: Characteristics of various routes of administration of drugs (*2-6*).

ROUTE	ADVANTAGE	DISADVANTAGE
Intranasal (e.g. antihistamine)	Rapid delivery and immediate effect. High bioavailability. No first pass metabolism. Avoids gastric environment.	Local irritation. Limited to small doses and small range of drugs.
Sublingual (e.g. nitroglycerin)	Easy and convenient delivery. Rapid delivery and immediate effect. High bioavailability. No first pass metabolism. Avoids gastric environment. Self-administration.	Changes in absorption if swallowed, chewed or following emesis.
Oral / enteral (e.g. captopril)	Easy, reliable, economic, convenient, painless, no infection risk. Self-administration.	First-pass metabolism / elimination decreases bioavailability. Slow delivery and onset of action. Dose form needs to accommodate gastric environment (e.g. transit stomach intact for small bowel absorption). Bioavailability can be influenced by changes in gut status (e.g. emesis, diarrhea or constipation.
Rectal (e.g. laxatives)	Rapid delivery and immediate effect. High bioavailability. No first pass metabolism. Avoids gastric environment. Suitable for patients with emesis or otherwise inappropriate oral route.	Unpleasant form of administration with bacteremia risk for the immunocompromised. Altered absorption in diarrhea and constipation.
Inhalation (e.g. ventolin**)**	Rapid delivery and immediate effect. High bioavailability. No first pass metabolism. Avoids gastric environment. Direct delivery to affected tissues. Self-administration.	Local irritation. Limited to small doses and small range of drugs. May require special equipment and decreased efficacy with incorrect use.
Intramuscular (e.g. morphine)	Intermediate onset of action. Suitable for oil based drugs. Easier (less skill) administration than intravenous.	Local edema, irritation or pain. Slower onset of action. Infection risk.
Intravenous (e.g. lasix / furosemide)	Rapid delivery and immediate effect. 100% bioavailability. No first pass metabolism. Avoids gastric environment. Controlled drug delivery.	Irritation or pain. Risk of infection. Solution must be dissolved well. Risk of embolism. Action not easily reversed. Rapid onset of toxicity.
Subcutaneous (e.g. insulin)	Slower absorption and onset of action. Suitable for oil based drugs.	Local edema, irritation or pain. Small volumes. Slow onset of action. Infection risk.
Transdermal (e.g. fentanyl)	Easy, reliable, economic, convenient, painless. Enables slow and prolonged drug delivery. No first pass metabolism. Avoids gastric environment. Self-administration.	Slow onset of action. Local skin reactions can occur. Needs highly lipophilic drugs.
Percutaneous (e.g. diclofenac / voltaren gel)	Easy, reliable, economic, convenient, painless. Suitable for local effect.	Slow onset of action. Local skin reactions can occur.

Table 2: Summary of useful formulae and definitions.

Use	Equation	Definitions
Drug concentration	$C = C_0 e^{-kt}$	C = drug concentration at time t after C_0 C_0 = drug concentration at reference time k = elimination rate constant t = time between C and C_0
Elimination rate constant	$k = \ln 2 / T_{0.5}$	k = elimination rate constant ln2 = 0.693 $T_{0.5}$ = half clearance time
Volume of distribution	V = amount in body (ug) / actual C_0	V = volume of distribution actual C_0 = concentration at the time of administration
Area under the curve	$AUC_{0-\infty} = FD / Vk$	$AUC_{0-\infty}$ = area under the curve (total drug dose) from time zero to infinity F = fraction of drug absorbed D = dose V = volume of distribition k = rate constant
Clearance	CL = k x V	CL = clearance k = rate constant V = volume of distribution
Time to maximum concentration	$T_{max} = (1/[k_a-k]) \ln (k_a/k)$	T_{max} = time to maximum concentration k_a = absorption rate constant k = elimination rate constant

Table 3: Data for the first scenario.

Time (hours)	Plasma concentration (micrograms / L)
2	139
4	65.6
6	31.1
8	14.6

Table 4: Data for the second scenario.

Time (min)	Plasma concentration (U / L)
0	0
1	31.3
2	49.3
3	58.6
4	62.5
5	62.8
7	58.1
10	50.6
16	36.1
24	25.3

Table 5: Data for the stable elimination period (7-24 hours) are used to calculate the elimination rate constant (k) and backproject the elimination curve by calculating the earlier values for the elimination confounded by absorption (bold). Simple subtraction of the plasma concentration from the elimination values generates R which can be plotted to determine absorption.

Time (hours)	Plasma concentration (U / L)	Elimination curve concentration	R (elimination – plasma)
0	0	**81.8**	**81.8**
1	31.3	**77.9**	**46.6**
2	49.3	**74.0**	**24.7**
3	58.6	**70.7**	**12.1**
4	62.5	**67.1**	**4.6**
5	62.8	**64.1**	**1.3**
7	58.1	58.1	
10	50.6	50.6	
16	36.1	36.1	
24	25.3	25.3	

Table 6: Data for third scenario.

Time (hours)	Plasma concentration (micrograms / ml)
0	0
0.5	16
1	22
1.5	22
2	19
4	11
6	5.6
8	3.2

Table 7: Data for the stable elimination period (2-8 hours) are used to calculate the elimination rate constant (k) and backproject the elimination curve by calculating the earlier values for the elimination confounded by absorption (bold). Simple subtraction of the plasma concentration from the elimination values generates R which can be plotted to determine absorption.

Time (hours)	Plasma concentration (micrograms / ml)	Elimination	R
0	0	**37.8**	**37.8**
0.5	16	**32.4**	**16.4**
1	22	**27.8**	**5.8**
1.5	22		
2	19	19	
4	11	11	
6	5.6	5.6	
8	3.2	3.2	

List of figures

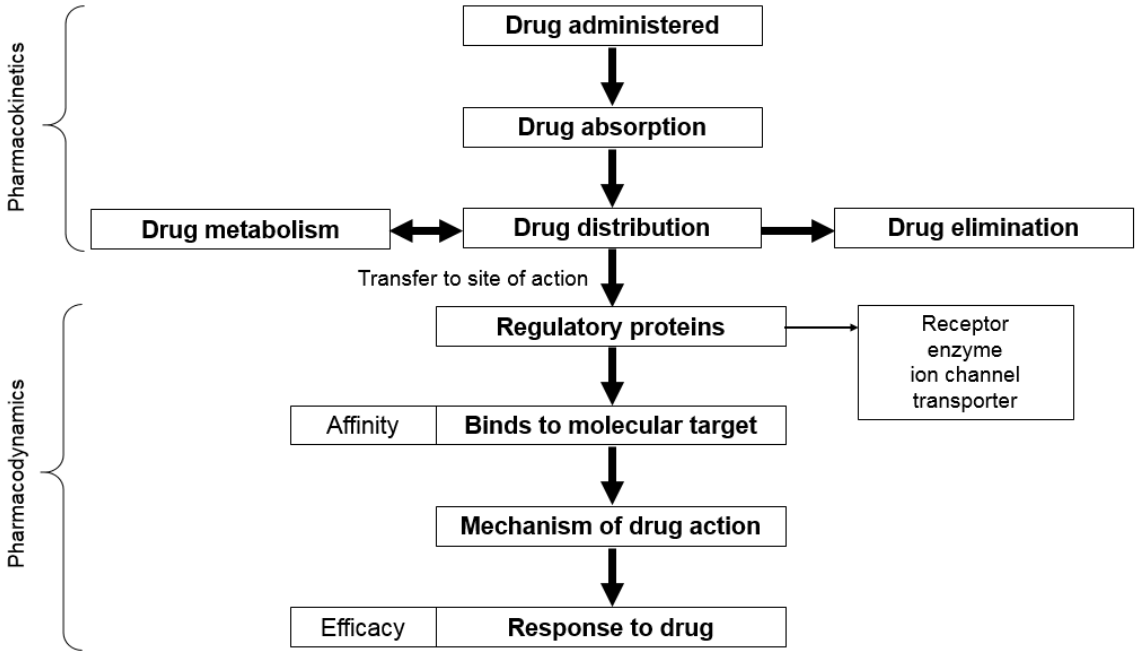

Figure 2: Schematic representation of pharmacokinetics and the ADME concept.

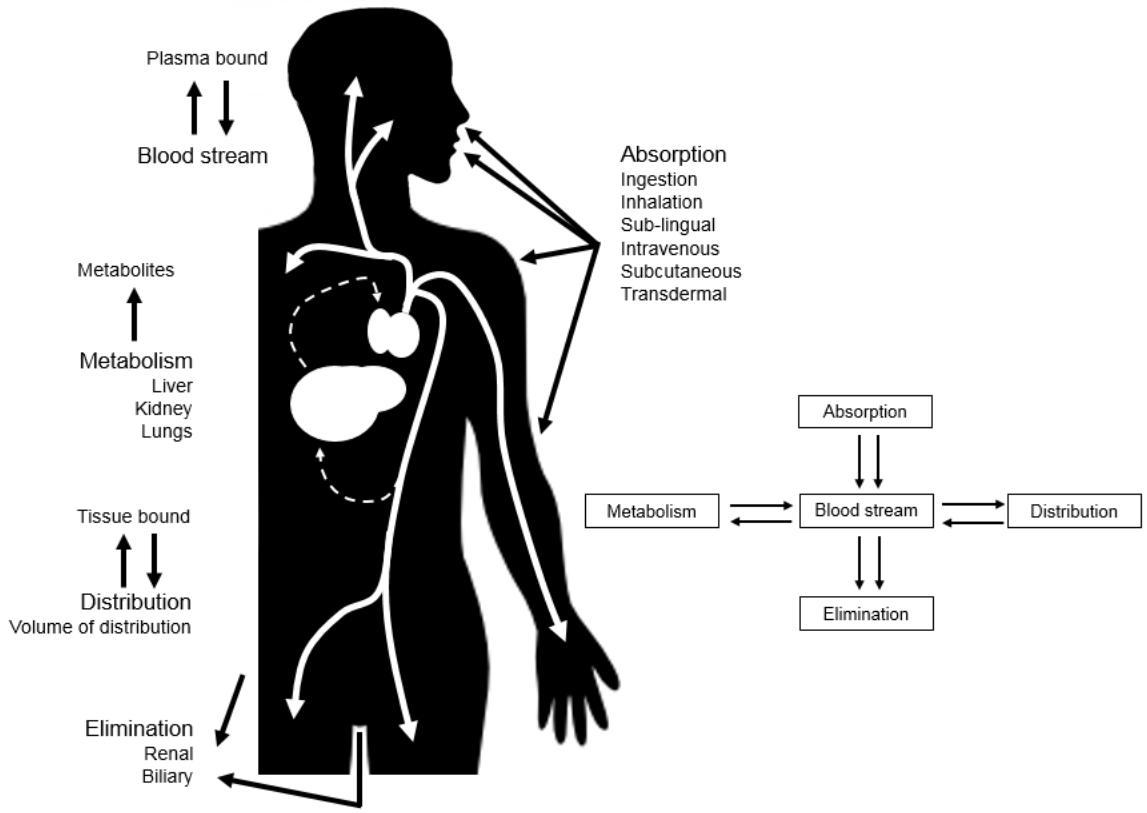

Figure 3: Schematic representation of pharmacokinetics and the ADME concept highlighting the interplay between free and bound drug, and the pathway from site of administration to site of action.

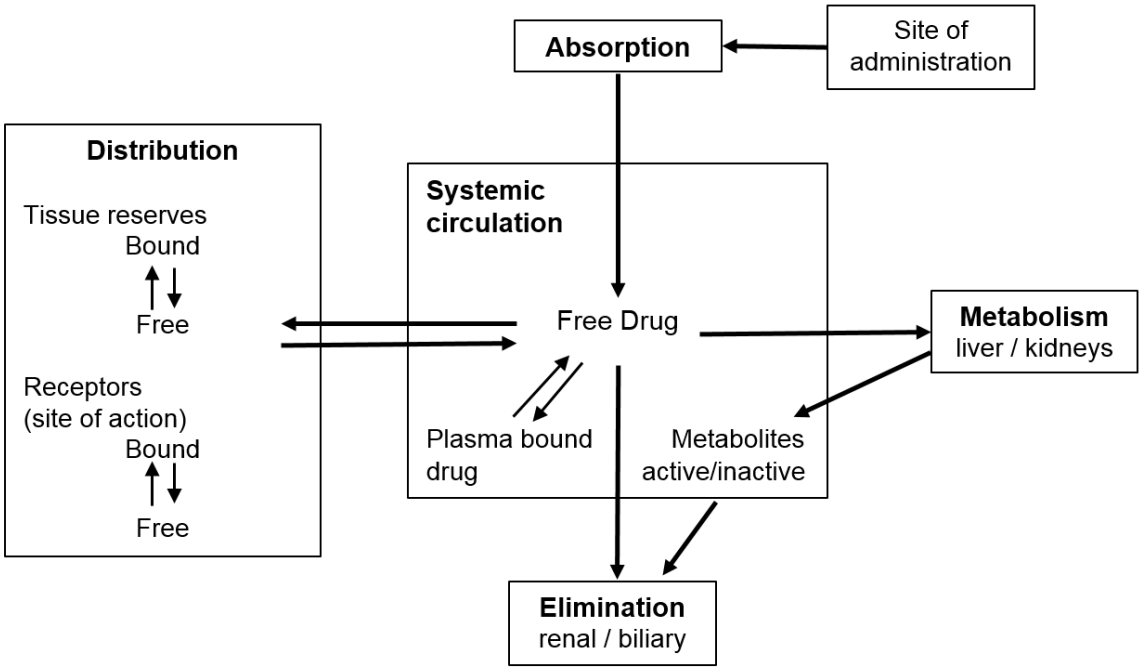

Figure 4: Schematic representation of equilibrium between drug concentration and plasma, well perfused tissue, poorly perfused tissue. The set of three on the top do not incorporate the effects of metabolism or elimination but illustrate early equilibrium in well perfused tissue (A) followed by a period of concentration in poorly perfused tissues (A to B) before reaching equilibrium in all tissues and plasma (B). The set of three schematics on the bottom provide the phases as discrete intervals (straight line) and illustrate the impact of elimination (adapted from *3*).

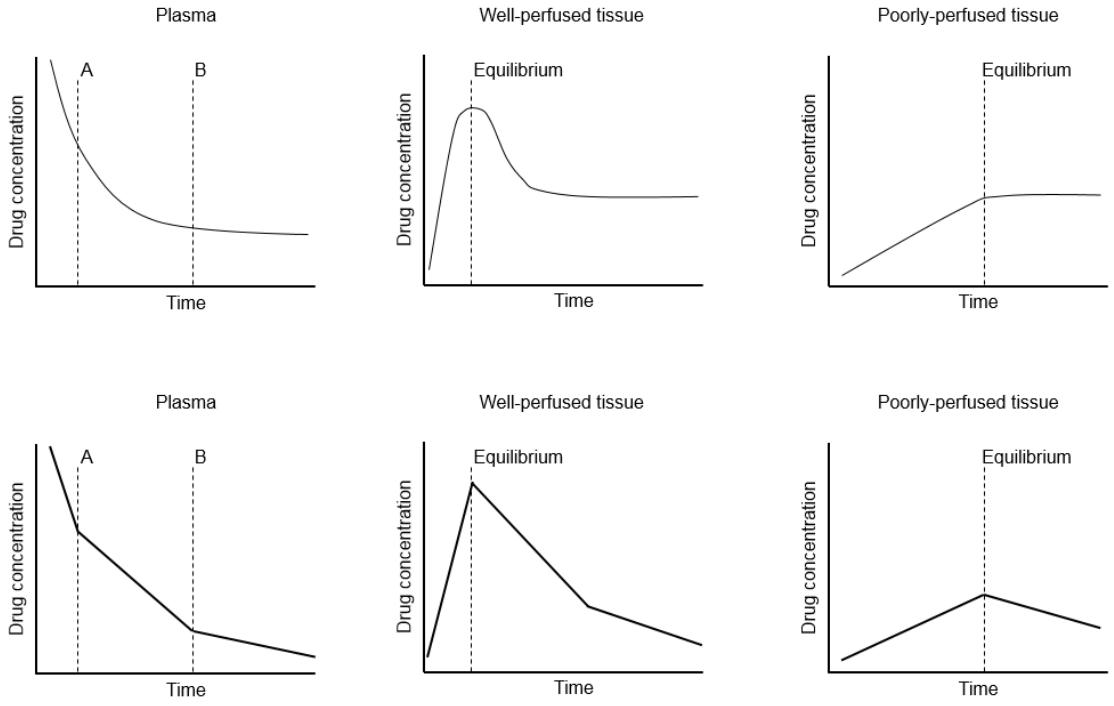

Figure 5: Schematic representation of single compartment model, two compartment model and multi-compartment model. The rate constant (k) reflects the movement from one compartment or volume of distribution (V) to the other and can be calculated numerically. Schematically the rate constant may be represented in several ways. On the multiple compartment model, k_5 and k_6 have arrows with different sizes and this indicates greater movement of drug to the tissue compartment than from it. Likewise, for k_7 and k_8, a single arrow might be used with a different size arrow head representing the relative k values. When drug transport between compartments is not reversible, a single arrow is used (k_9). Note that multiple methods would not be used on a single schematic as is done here.

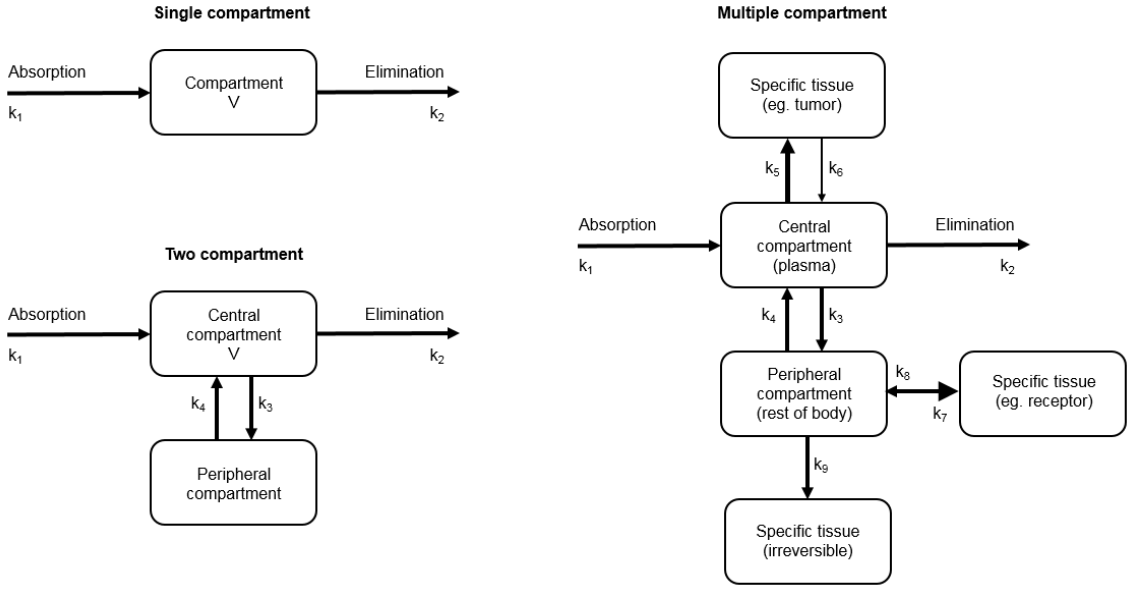

Figure 6: Phase I and phase II metabolism of paracetamol (acetaminophen). Phase I hydroxylation results in a toxic metabolite with three forms of phase II metabolism converting the metabolite to a form for urine excretion. Toxic interaction can occur leading to liver necrosis and potentially renal failure; especially with deleted hepatic glutathione (adapted from *13*).

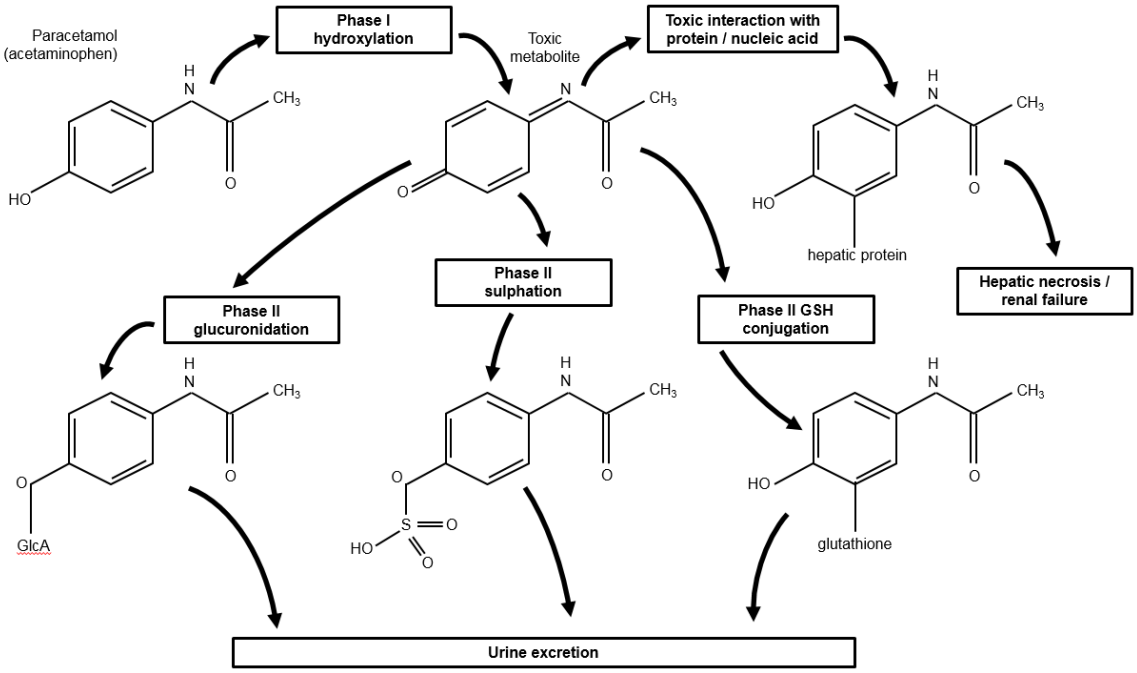

Figure 7: Schematic representation of first order and zero order elimination. First order elimination follows an exponential trend and can be displayed with a logarithmic Y-axis to generate a straight line (inset). Zero order elimination eliminates a constant amount of drug per unit time.

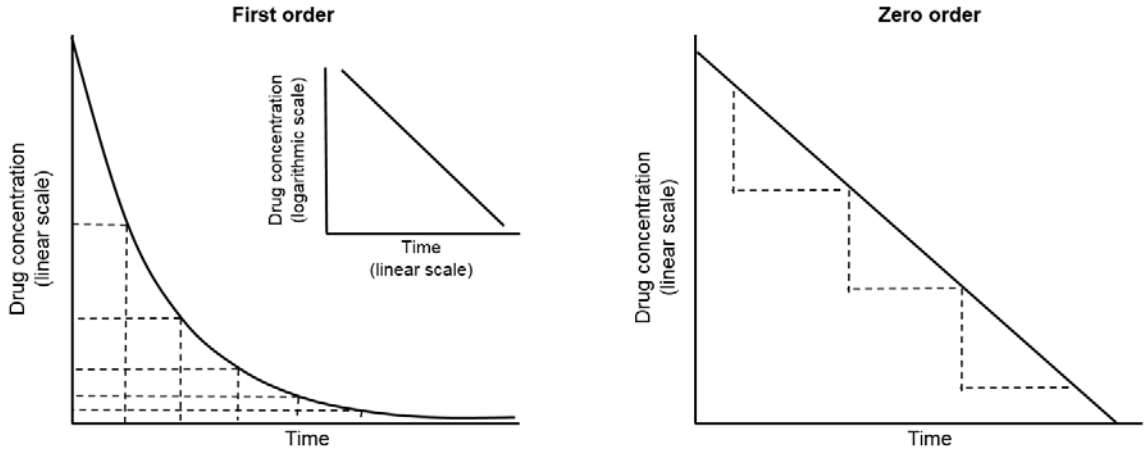

Figure 8: Logarithmic / linear plot confirming a single compartment mono-exponential curve.

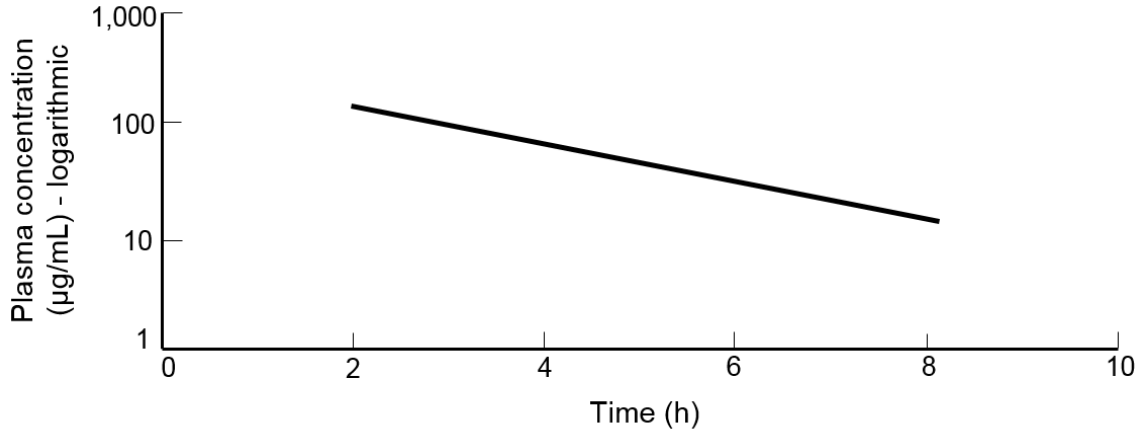

Figure 9: Linear / linear and logarithmic / linear plots demonstrating interplay between absorption and elimination for scenario two.

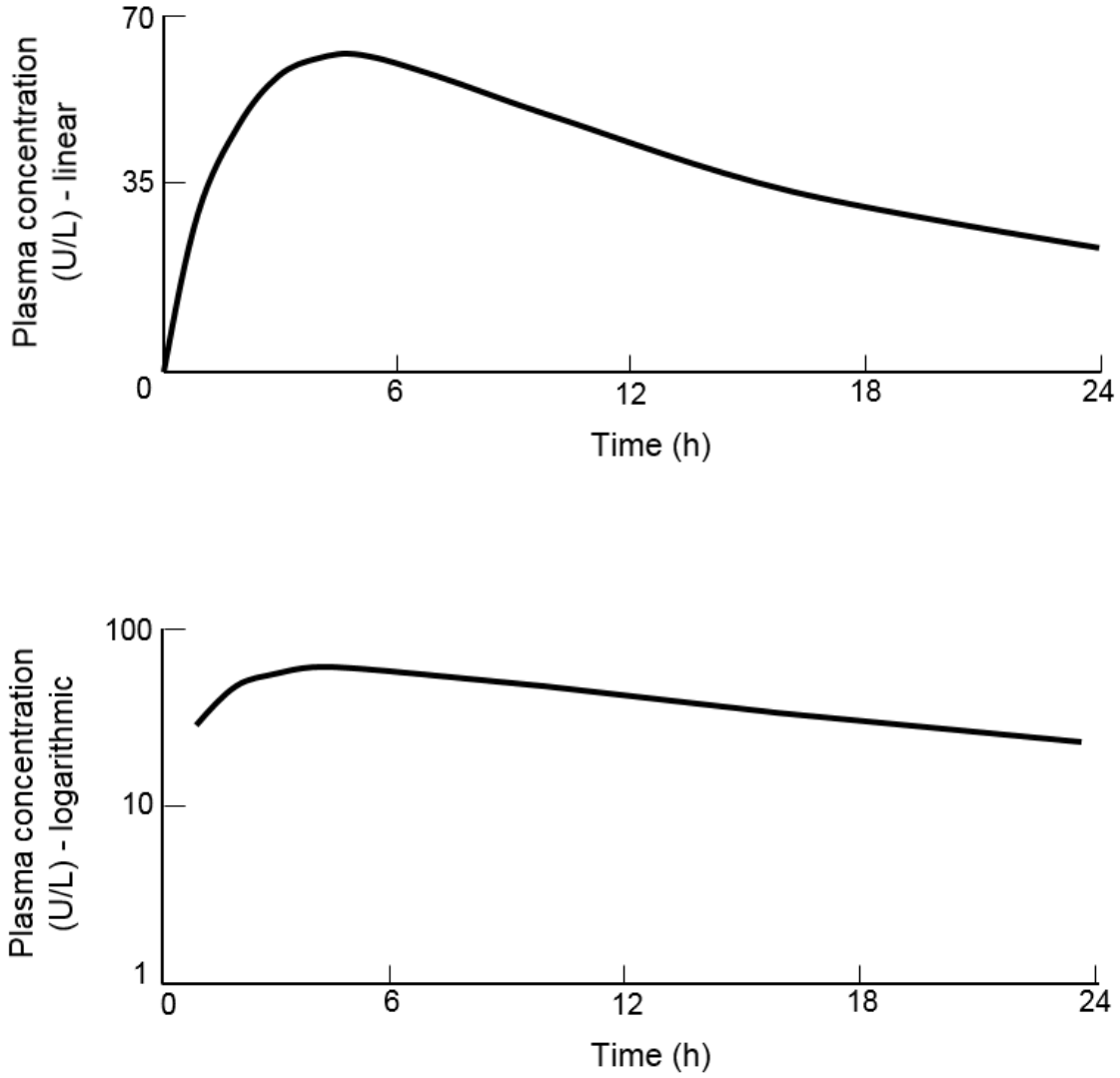

Figure 10: Logarithmic / linear plots for raw data (dashed) and for R.

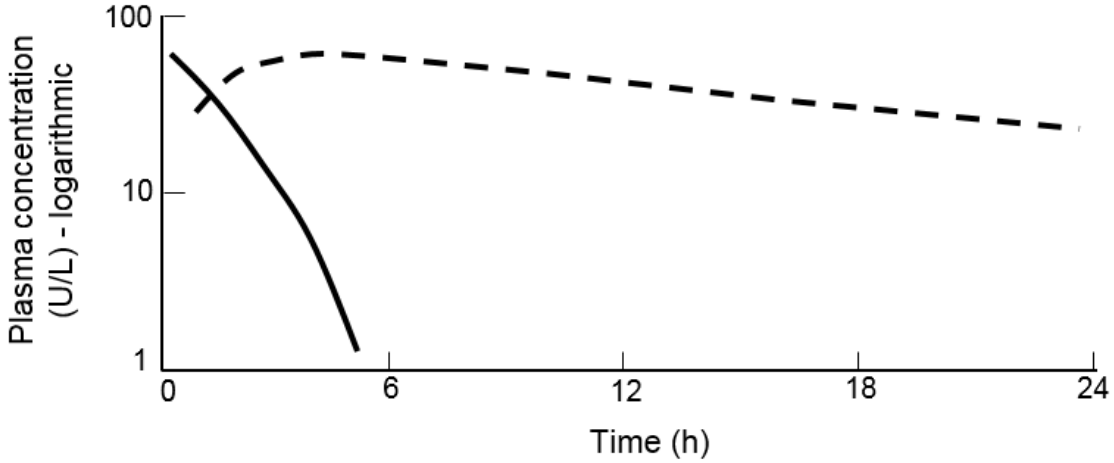

Figure 11: Linear / linear and logarithmic / linear plots demonstrating interplay between absorption and elimination for scenario three.

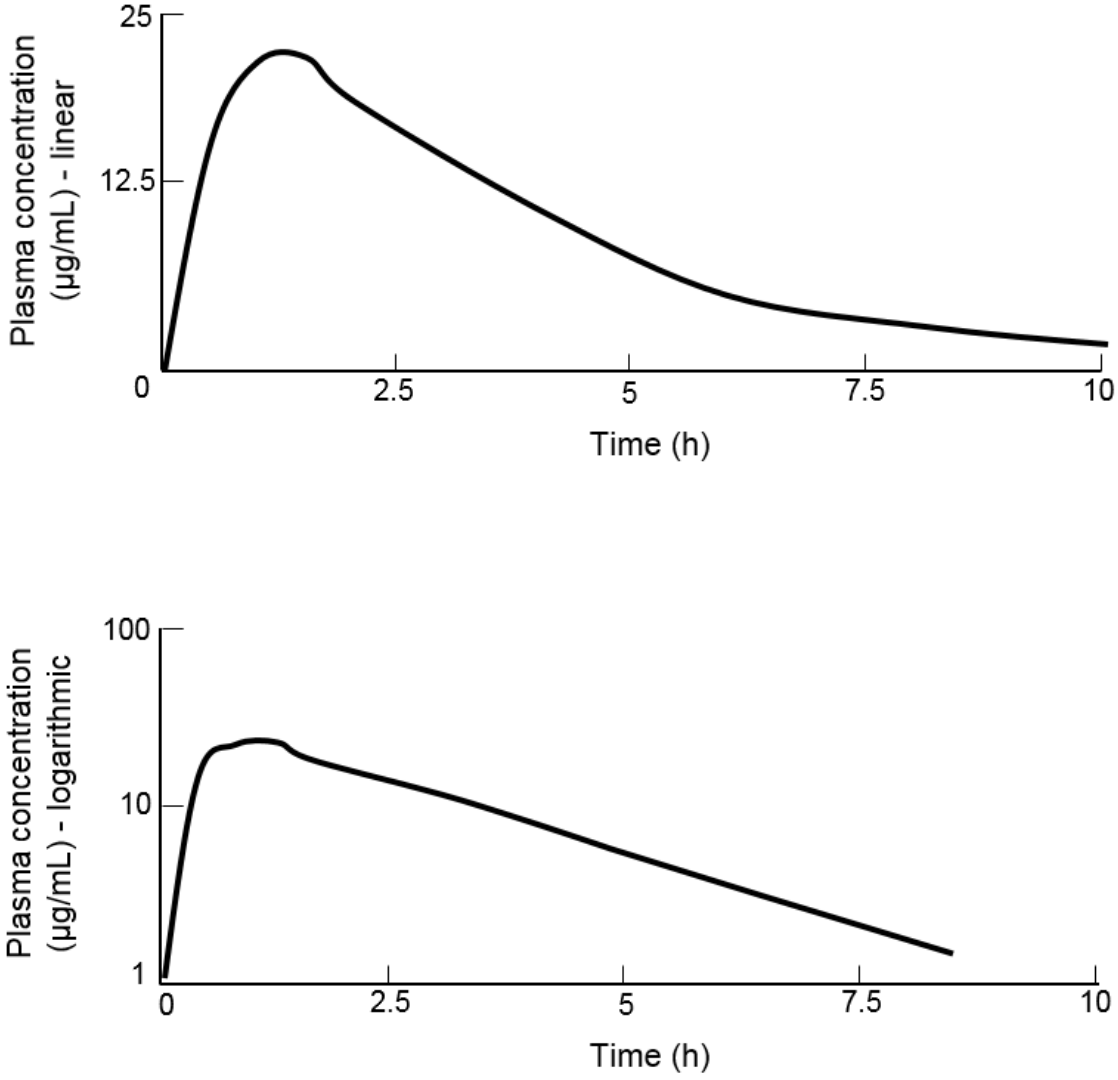

Figure 12: Logarithmic / linear plots for raw data (dashed) and for the elimination curve minus the plamsa curve (R) (solid line).