PHARMACOKINETICS AND TOXICOKINETICS – A REVIEW

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ABSTRACT
Pharmacokinetics describes how the body affects a specific drug after administration. Pharmacokinetic properties of drugs may be affected by elements such as the site of administration and the dose of administered drug. These may affect the absorption rate. A fifth process, Liberation has been highlighted as playing an important role in pharmacokinetics. The process of release of drug from the formulation. Hence LADME may sometimes be used in place of ADME in reference to the core aspects of pharmacokinetics.

KEY WORDS: Pharmacokinetics, Toxicokinetics, Biological Half Life.

INTRODUCTION
Pharmacokinetics, sometimes abbreviated as PK, (from Ancient Greek pharmakon "drug" and kinetikos "to do with motion"; see chemical kinetics) is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism. The substances of interest include pharmaceutical agents, hormones, nutrients, and toxins. Pharmacokinetics is often studied in conjunction with pharmacodynamics. Pharmacokinetics includes the study of the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body (e.g. by metabolic enzymes such as CYP or UGT enzymes) and the effects and routes of excretion of the metabolites of the drug [1].

ADME
Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as the ADME scheme: Absorption - the process of a substance entering the blood circulation.

Plasma concentration curves
Drugs injected intravenously are removed from the plasma through two primary mechanisms: (1) Distribution to body tissues and (2) metabolism + excretion of the drugs. The resulting decrease of the drug's plasma concentration follows a biphasic pattern (Figure 1).

α Phase: An initial phase of rapid decrease in plasma concentration. The decrease is primarily attributed to drug distribution from the central compartment (circulation) into the peripheral compartments (body tissues). This phase ends when pseudo-equilibrium of drug concentration is established between the central and peripheral compartments.

β Phase: A phase of gradual decrease in plasma concentration.
concentration after the alpha phase. The decrease is primarily attributed to drug metabolism and excretion [5]. Additional phases (gamma, delta, etc.) are sometimes seen [6].

Fig 1. Plasma drug concentration vs time after an IV dose

In pharmacokinetics, steady state refers to the situation where the overall intake of a drug is fairly in dynamic equilibrium with its elimination. In practice, it is generally considered that steady state is reached when a time of 4 to 5 times the half-life for a drug after regular dosing is started.

The following graph depicts a typical time course of drug plasma concentration and illustrates main pharmacokinetic metrics: The time course of drug plasma concentrations over 96 hours following oral administrations every 24 hours. Note that the AUC in steady state equals AUC∞ after the first dose.

Analysis
Pharmacokinetic analysis is performed by noncompartmental or compartmental methods. Noncompartmental methods estimate the exposure to a drug by estimating the area under the curve of a concentration-time graph. Compartmental methods estimate the concentration-time graph using kinetic models. Noncompartmental methods are often more versatile in that they do not assume any specific compartmental model and produce accurate results also acceptable for bioequivalence studies.

Noncompartmental analysis
Noncompartmental PK analysis is highly dependent on estimation of total drug exposure. Total drug exposure is most often estimated by area under the curve (AUC) methods, with the trapezoidal rule (numerical integration) the most common method. Due to the dependence on the length of ‘x’ in the trapezoidal rule, the area estimation is highly dependent on the blood/plasma sampling schedule. That is, the closer time points are, the closer the trapezoids reflect the actual shape of the concentration-time curve.

Compartmental analysis
Compartmental PK analysis uses kinetic models to describe and predict the concentration-time curve. PK compartmental models are often similar to kinetic models used in other scientific disciplines such as chemical kinetics and thermodynamics. The advantage of compartmental over some noncompartmental analyses is the ability to predict the concentration at any time. The disadvantage is the difficulty in developing and validating the proper model. Compartment-free modeling based on curve stripping does not suffer this limitation. The simplest PK compartmental model is the one-compartmental PK model with IV bolus administration and first-order elimination. The most complex PK models (called PBPK models) rely on the use of physiological information to ease development and validation.

Bioanalytical methods
Bioanalytical methods are necessary to construct a concentration-time profile. Chemical techniques are employed to measure the concentration of drugs in biological matrix, most often plasma. Proper bioanalytical methods should be selective and sensitive. For example microscale thermophoresis can be used to quantify how the biological matrix/liquid affects the affinity of a drug to its target [8,9].

Mass spectrometry
Pharmacokinetics is often studied using mass spectrometry because of the complex nature of the matrix (often plasma or urine) and the need for high sensitivity to observe concentrations after a low dose and a long time period. The most common instrumentation used in this application is LC-MS with a triple quadrupole mass spectrometer. Tandem mass spectrometry is usually employed for added specificity. Standard curves and internal standards are used for quantitation of usually a single pharmaceutical in the samples. The samples represent different time points as a pharmaceutical is administered and then metabolized or cleared from the body. Blank samples taken before administration are important in determining background and insuring data integrity with such complex sample matrices. Much attention is paid to the linearity of the standard curve; however it is not uncommon to use curve fitting with more complex functions such as quadratics since the response of most mass spectrometers is less than linear across large concentration ranges [10-12].

There is currently considerable interest in the use of very high sensitivity mass spectrometry for microdosing studies, which are seen as a promising alternative to animal experimentation [13].
Population pharmacokinetics

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest [14-16]. Certain patient demographic, pathophysiological, and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships. For example, steady-state concentrations of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function receiving the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiological factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified. An advantage of population pharmacokinetic modelling is its ability to analyze sparse data sets (sometimes only one concentration measurement per patient is available).

In pharmacology, bioavailability (BA) is a subcategory of absorption and is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100% [17]. However, when a medication is administered via other routes (such as orally), its bioavailability generally decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient. Bioavailability is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

For dietary supplements, herbs and other nutrients in which the route of administration is nearly always oral, bioavailability generally designates simply the quantity or fraction of the ingested dose that is absorbed [18].

Bioavailability is defined slightly differently for drugs as opposed to dietary supplements primarily due to the method of administration and Food and Drug Administration regulations. Bioaccessibility is a concept related to bioavailability in the context of biodegradation and environmental pollution. A molecule (often a persistent organic pollutant) is said to be bioavailable when "[i]t is available to cross an organism’s cellular membrane from the environment, if the organism has access to the chemical" [19].

In pharmacology, bioavailability is a measurement of the rate and extent to which a drug reaches the systemic circulation [20]. It is denoted by the letter f (or, if expressed in percent, by F).

In nutritional sciences

In nutritional sciences, which covers the intake of nutrients and non-drug dietary ingredients, the concept of bioavailability lacks the well-defined standards associated with the pharmaceutical industry. The pharmacological definition cannot apply to these substances because utilization and absorption is a function of the nutritional status and physiological state of the subject [21], resulting in even greater differences from individual to individual (inter-individual variation). Therefore, bioavailability for dietary supplements can be defined as the proportion of the administered substance capable of being absorbed and available for use or storage [22].

In both pharmacology and nutrition sciences, bioavailability is measured by calculating the area under curve (AUC) of the drug concentration time profile.

In environmental sciences

Bioavailability is commonly a limiting factor in the production of crops (due to solubility limitation or adsorption of plant nutrients to soil colloids) and in the removal of toxic substances from the food chain by microorganisms (due to sorption to or partitioning of otherwise degradable substances into inaccessible phases in the environment). A noteworthy example for agriculture is plant phosphorus deficiency induced by precipitation with iron and aluminum phosphates at low soil pH and precipitation with calcium phosphates at high soil pH [23]. Toxic materials in soil, such as lead from paint may be rendered unavailable to animals ingesting contaminated soil by supplying phosphorus fertilizers in excess [24]. Organic pollutants such as solvents or pesticides may be rendered unavailable to microorganisms and thus persist in the environment when they are adsorbed to soil minerals [25] or partition into hydrophobic organic matter [26].

Absolute bioavailability

Absolute Bioavailability is a ratio of areas under the curves. Absolute bioavailability compares the bioavailability of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration. It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. The comparison must be dose normalized (e.g. account for different doses or varying weights of the subjects); consequently, the amount absorbed is corrected by dividing the corresponding dose administered.

In pharmacology, in order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs time plot for the drug after both intravenous (iv) and extravascular (non-intravenous, i.e., oral) administration. The absolute
bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous.

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 100% (f=1), whereas drugs given by other routes usually have an absolute bioavailability of less than one. If we compare the two different dosage forms having same active ingredients and compare the two drug bioavailability is called comparative bioavailability. Although knowing the true extent of systemic absorption (referred to as absolute bioavailability) is clearly useful, in practice it is not determined as frequently as one may think. The reason for this is that its assessment requires an intravenous reference, that is, a route of administration that guarantees that all of the administered drug reaches the systemic circulation. Such studies come at considerable cost, not least of which is the necessity to conduct preclinical toxicity tests to ensure adequate safety, as well as there being potential problems due to solubility limitations. These limitations may be overcome, however, by administering a very low dose (typically a few micrograms) of an isotopically labelled drug concomitantly with a therapeutic non-labelled oral dose.

Providing the isotopically-labelled intravenous dose is sufficiently low so as not to perturb the systemic drug concentrations achieved from the absorbed oral dose, then the intravenous and oral pharmacokinetics can be deconvoluted by virtue of the their different isotopic constitution and thereby determine the oral and intravenous pharmacokinetics from the same dose administration. This technique eliminates pharmacokinetic issues on non-equivalent clearance as well as enabling the intravenous dose to be administered with a minimum of toxicology and formulation. The technique was first applied using stable-isotopes such as C-13 and mass-spectrometry to distinguish the isotopes by mass difference. More recently, C-14 labelled drugs are administered intravenously and accelerator mass spectrometry (AMS) used to measure the isotopically labelled drug along with mass spectrometry for the unlabelled drug [27].

There is no regulatory requirement to define the intravenous pharmacokinetics or absolute bioavailability however regulatory authorities do sometimes ask for absolute bioavailability information of the extravascular route in cases in which the bioavailability is apparently low or variable and there is a proven relationship between the pharmacodynamics and the pharmacokinetics at therapeutic doses. In all such cases, to conduct an absolute bioavailability study requires that the drug be given intravenously [28].

Intravenous administration of a developmental drug can provide valuable information on the fundamental pharmacokinetic parameters of volume of distribution (V) and clearance (CL) [28].

Relative bioavailability and bioequivalence

In pharmacology, relative bioavailability measures the bioavailability (estimated as the AUC) of a formulation (A) of a certain drug when compared with another formulation (B) of the same drug, usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug, this is known as absolute bioavailability.

Relative bioavailability is one of the measures used to assess bioequivalence (BE) between two drug products. For FDA approval, a generic manufacturer must demonstrate that the 90% confidence interval for the ratio of the mean responses (usually of AUC and the maximum concentration, Cmax) of its product to that of the "Brand Name drug" is within the limits of 80% to 125%. While AUC refers to the extent of bioavailability, Cmax refers to the rate of bioavailability. When Tmax is given, it refers to the time it takes for a drug to reach Cmax.

While the mechanisms by which a formulation affects bioavailability and bioequivalence have been extensively studied in drugs, formulation factors that influence bioavailability and bioequivalence in nutritional supplements are largely unknown [29]. As a result, in nutritional sciences, relative bioavailability or bioequivalence is the most common measure of bioavailability, comparing the bioavailability of one formulation of the same dietary ingredient to another.

Factors influencing bioavailability

The absolute bioavailability of a drug, when administered by an extravascular route, is usually less than one (i.e., F <100%). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation. Whether a drug is taken with or without food will also affect absorption, other drugs taken concurrently may alter absorption and first-pass metabolism, intestinal motility alters the dissolution of the drug and may affect the degree of chemical degradation of the drug by intestinal microflora. Disease states affecting liver metabolism or gastrointestinal function will also have an effect.

Other factors may include, but are not limited to:

- Physical properties of the drug (hydrophobicity, pKa, solubility)
- The drug formulation (immediate release, excipients used, manufacturing methods, modified release – delayed release, extended release, sustained release, etc.)
- Whether the formulation is administered in a fed or fasted state
- Gastric emptying rate
- Circadian differences
- Interactions with other drugs/foods:
  - Interactions with other drugs (e.g., antacids, alcohol, nicotine)
  - Interactions with other foods (e.g., grapefruit juice, pomello, cranberry juice, brassica vegetables)
- Transporters: Substrate of efflux transporters (e.g. P-glycoprotein)
- Health of the GI tract
Enzyme induction/inhibition by other drugs/foods:
- Enzyme induction (increased rate of metabolism), e.g., Phenytoin induces CYP1A2, CYP2C9, CYP2C19, and CYP3A4
- Enzyme inhibition (decreased rate of metabolism), e.g., grapefruit juice inhibits CYP3A → higher nifedipine concentrations
- Individual variation in metabolic differences
- Age: In general, drugs are metabolized more slowly in fetal, neonatal, and geriatric populations
- Phenotypic differences, enterohepatic circulation, diet, gender
- Disease state E.g., hepatic insufficiency, poor renal function

Each of these factors may vary from patient to patient (inter-individual variation), and instead in the same patient over time (intra-individual variation). In clinical trials, inter-individual variation is a critical measurement used to assess the bioavailability differences from patient to patient in order to ensure predictable dosing.

Bioavailability of drugs versus dietary supplements

In comparison to drugs, there are significant differences in dietary supplements that impact the evaluation of their bioavailability. These differences include the following: the fact that nutritional supplements provide benefits that are variable and often qualitative in nature; the measurement of nutrient absorption lacks the precision; nutritional supplements are consumed for prevention and well-being; nutritional supplements do not exhibit characteristic dose-response curves; and dosing intervals of nutritional supplements, therefore, are not critical in contrast to drug therapy.

In addition, the lack of defined methodology and regulations surrounding the consumption of dietary supplements hinders the application of bioavailability measures in comparison to drugs. In clinical trials with dietary supplements, bioavailability primarily focuses on statistical descriptions of mean or average AUC differences between treatment groups, while often failing to compare or discuss their standard deviations or inter-individual variation. This failure leaves open the question of whether or not an individual in a group is likely to experience the benefits described by the mean-difference comparisons. Further, even if this issue were discussed, it would be difficult to communicate meaning of these inter-subject variances to consumers and/or their physicians [29].

Nutritional science: reliable and universal bioavailability

One way to resolve this problem is to define "reliable bioavailability" as positive bioavailability results (an absorption meeting a predefined criteria) that include 84% of the trial subjects and "universal bioavailability" as those that include 98% of the trial subjects. This reliable-universal framework would improve communications with physicians and consumers such that, if it were included on products labels for example, make educated choices as to the benefits of a formulation for them directly. In addition, the reliable-universal framework is similar to the construction of confidence intervals, which statisticians have long offered as one potential solution for dealing with small samples, violations of statistical assumptions or large standard deviations [30].

The Biopharmaceutics Classification System is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration [31]. The fundamental basis for the BCS was established by Dr. Gordon Amidon who was presented with a Distinguished Science Award at the August 2006 International Pharmaceutical Federation (FIP) congress in Salvador, Brazil.

This system restricts the prediction using the parameters solubility and intestinal permeability. The solubility classification is based on a United States Pharmacopoeia (USP) aperture. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important, since 85% of the most sold drugs in the USA and Europe are orally administered.

According to the Biopharmaceutics Classification System, drug substances are classified as follows:
- Class I - high permeability, high solubility
  Example: metoprolol
  Those compounds are well absorbed and their absorption rate is usually higher than excretion.
- Class II - high permeability, low solubility
  Example: glibenclamide
  The bioavailability of those products is limited by their solvation rate. A correlation between the in vivo bioavailability and the in vitro solvation can be found.
- Class III - low permeability, high solubility
  Example: cimetidine
  The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.
- Class IV - low permeability, low solubility
  Example: hydrochlorothiazide
  Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

The drugs are classified in BCS on the basis of following parameters:
1. Solubility
2. Permeability
3. Dissolution

The class boundaries for these parameters are:
- 1. Solubility class boundaries- It is based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250ml is derived from

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**P1A2, CYP2C9, 3**

**Application of bioavailability -**

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**Nutritional science:** **reliable and universal bioavailability**

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typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.

2. Permeability class boundaries- It is based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Alternatively non-human systems capable of prediction the drug absorption systems capable of predicting the drug absorption in humans can be used (such as in-vitro culture methods). A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of the administered dose based on a mass-balance determination or in comparison to and intravenous dose.

3. Dissolution class boundaries- An immediate release products is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolve within 15 minutes using USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900ml or less in following media,) 0.1 N HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid.

Toxicokinetics

Toxicokinetics is the description of what rate a chemical will enter the body and what happens to it once it is in the body. It is an application of pharmacokinetics to determine the relationship between the systemic exposure of a compound in experimental animals and its toxicity. It is used primarily for establishing relationships between exposures in toxicology experiments in animals and the corresponding exposures in humans. However, it can also be used in environmental risk assessments in order to determine the potential effects of releasing chemicals into the environment. In order to quantify toxic effects toxicokinetics can be combined with toxicodynamics. Such toxicokinetic-toxicodynamic (TKTD) models are used in ecotoxicology (see ecotoxmodels a website on mathematical models in ecotoxicology).

Similarly, physiological toxicokinetic models are physiological pharmacokinetic models developed to describe and predict the behavior of a toxicant in an animal body; for example, what parts (compartments) of the body a chemical may tend to enter (e.g. fat, liver, spleen, etc.), and whether or not the chemical is expected to be metabolized or excreted and at what rate.

Four potential processes exist for a chemical interacting with an animal: absorption, distribution, biotransformation and excretion. Absorption describes the entrance of the chemical into the body, and can occur through the air, water, food, or soil. Once a chemical is inside a body, it can be distributed to other areas of the body through diffusion or other biological processes. At this point, the chemical may be biotransformed through metabolism into other chemicals (metabolites). These metabolites can be more toxic than the parent compound. After this potential biotransformation occurs, the metabolites may leave the body, be transformed into other compounds, or continue to be stored in the body compartments.

The biological half-life or elimination half-life of a substance is the time it takes for a substance (for example a metabolite, drug, signalling molecule, radioactive nuclide, or other substance) to lose half of its pharmacologic, physiologic, or radiologic activity, as per the MeSH definition. In a medical context, half-life may also describe the time it takes for the blood plasma concentration of a substance to halve ("plasma half-life") its steady-state. The relationship between the biological and plasma half-lives of a substance can be complex depending on the substance in question, due to factors including accumulation in tissues, active metabolites, and receptor interactions. Biological half-life is an important pharmacokinetic parameter and is usually denoted by the abbreviation t½ [32].

While a radioactive isotope decays perfectly according to first order kinetics where the rate constant is fixed, the elimination of a substance from a living organism, into the environment, follows more complex kinetics. See the article rate equation.

Examples of biological half-lives

Water

The biological half-life of water in a human is about 7 to 14 days. It can be altered by behavior. Drinking large amounts of alcohol will reduce the biological half-life of water in the body. This has been used to decontaminate humans who are internally contaminated with tritiated water (tritium). Drinking the same amount of water would have a similar effect, but many would find it difficult to drink a large volume of water. The basis of this decontamination method (used at Harwell) is to increase the rate at which the water in the body is replaced with new water.

Alcohol

The removal of ethanol (drinking alcohol) through oxidation by alcohol dehydrogenase in the liver from the human body is limited. Hence the removal of a large concentration of alcohol from blood may follow zero-order kinetics. Also the rate-limiting steps for one substance may be in common with other substances. For instance, the blood alcohol concentration can be used to modify the biochemistry of methanol and ethylene glycol. In this way the oxidation of methanol to the toxic formaldehyde and formic acid in the (human body) can be prevented by giving an appropriate amount of ethanol to a person who has ingested methanol. Note that methanol is very toxic and causes blindness and death. A person who has ingested ethylene glycol can be treated in the same way.
Fig 2. The time course of drug plasma concentrations over 96 hours following oral administrations every 24 hours. Note that the AUC in steady state equals $AUC_{\infty}$ after the first dose.

Table 1. Half-life of some important drugs

<table>
<thead>
<tr>
<th>Common prescription medications</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>&lt; 10 seconds</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2 minutes</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>14 minutes</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>1.6 hours</td>
</tr>
<tr>
<td>Morphine</td>
<td>2 to 3 hours</td>
</tr>
<tr>
<td>Methadone</td>
<td>15 hours to 3 days, in rare cases up to 8 days,</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>16-72 hours</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>18-50 hours</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20-100 hours (active metabolite, nordazepam 1.5-8.3 days)</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>0.8-4.2 days (active metabolite, desflurazepam 1.75-10.4 days)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4 to 6 days (active lipophilic metabolite 4-16 days)</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>5 weeks</td>
</tr>
</tbody>
</table>

Metals

The biological half-life of caesium in humans is between one and four months. This can be shortened by feeding the person prussian blue. The prussian blue in the digestive system acts as a solid ion exchanger which absorbs the caesium while releasing potassium ions. For some substances, it is important to think of the human or animal body as being made up of several parts, each with their own affinity for the substance, and each part with a different biological half-life (physiologically-based pharmacokinetic modelling). Attempts to remove a substance from the whole organism may have the effect of increasing the burden present in one part of the organism. For instance, if a person who is contaminated with lead is given EDTA in a chelation therapy, then while the rate at which lead is lost from the body will be increased, the lead within the body tends to relocate into the brain where it can do the most harm.
Polonium in the body has a biological half-life of about 30 to 50 days.
Caesium in the body has a biological half-life of about one to four months.
Mercury (as methylmercury) in the body has a half-life of about 65 days.
Lead in bone has a biological half-life of about ten years.
Cadmium in bone has a biological half-life of about 30 years.
Plutonium in bone has a biological half-life of about 100 years.
Plutonium in the liver has a biological half-life of about 40 years.

Rate equations
First-order elimination
There are circumstances where the half-life varies with the concentration of the drug. Thus the half-life, under these circumstances, is proportional to the initial concentration of the drug $A_0$ and inversely proportional to the zero-order rate constant $k_0$ where:

$$t_{1/2} = \frac{0.5A_0}{k_0}$$

This process is usually a logarithmic process - that is, a constant proportion of the agent is eliminated per unit time. Thus the fall in plasma concentration after the administration of a single dose is described by the following equation:

$$C_t = C_0e^{-kt}$$

$C_t$ is concentration after time $t$
$C_0$ is the initial concentration ($t=0$)
$k$ is the elimination rate constant

The relationship between the elimination rate constant and half-life is given by the following equation:

$$k = \frac{\ln 2}{t_{1/2}}$$

Half-life is determined by clearance (CL) and volume of distribution (VD) and the relationship is described by the following equation:

$$t_{1/2} = \frac{\ln 2 \cdot V_D}{CL}$$

In clinical practice, this means that it takes 4 to 5 times the half-life for a drug's serum concentration to reach steady state after regular dosing is started, stopped, or the dose changed. So, for example, digoxin has a half-life (or $t_{1/2}$) of 24–36 h; this means that a change in the dose will take the best part of a week to take full effect. For this reason, drugs with a long half-life (e.g. amiodarone, elimination $t_{1/2}$ of about 58 days) are usually started with a loading dose to achieve their desired clinical effect more quickly [33-35].

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