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Chapter 3

Pharmacokinetics of Drugs Following IV Bolus, IV Infusion, and Oral Administration

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Additional information is available at the end of the chapter

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1. Introduction

Pharmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (i.e., metabolism and excretion). Kinetics is the study of the rate of a process and the factors affecting on it. The rate of a process is the change in velocity or speed with (in relation to) time.

Usually, pharmacokinetics study involves considering both experimental and theoretical approaches. The former involves development of biologic sampling techniques, analytical methods for drugs and their metabolites measurement, and procedures that help in data collection and handling, while the latter approach of pharmacokinetics involves development of pharmacokinetic models that facilitate prediction of drug disposition after drug administration [1].

For the processes of drug absorption, distribution, and elimination, there is a rate that governs each process. The rate is the change in concentration with time and is given by ± dC/dt.

According to the law of mass action, the rate of a chemical reaction (or a kinetic process) is proportional to the products of the molar concentration of the reactants each raised to a power equal to the number of molecules of substances undergoing reaction (process).

- The rate expression for zero order reaction:
  \[ \frac{dC}{dt} = k_o \text{ and hence, } C_t = C_o - k_o t \text{ and } t_{1/2} = \frac{C_o}{2 k_o} \]

- For first-order reaction:
  \[ \frac{dC}{dt} = -k \text{ and hence, } \log C = \log C_o - k t / 2.303 \text{ and } t_{1/2} = 0.693 / k \]
• For second-order reaction:

\[
\frac{dC}{dt} = K(A)^2 \text{ or } \frac{dC}{dt} = K(A)(B) \text{ or } \frac{dC}{dt} = K(B)^2
\]

and hence, \(1/C = 1/C_a + kt\) and \(t_{1/2} = 1/kC_a\).

Mostly, the pharmacokinetic processes (absorption, distribution, and elimination) are first-order, although zero-order also accounts for some processes such as the process of absorption, which is first-order for the passive transport mechanism and zero-order for the carrier-mediated transport (1).

It must be mentioned that drug kinetics after distribution is characterized by the first-order rate constant.

A compartment in pharmacokinetics is an entity that can be described by a definite volume and a concentration of a drug contained in that volume, which may be:

1. Central Compartment
   
The central compartment includes blood and the highly perfused organs and tissues such as heart, brain, lungs, liver, and kidney. In these organs, the administered drug usually equilibrates rapidly.

2. Peripheral Compartment(s)
   
   This compartment(s) include(s) those organs that are less well-perfused such as adipose and skeletal muscle, and therefore the administered drug will equilibrate more slowly in these organs. The duration of the drug effect at the target tissue will often be affected by the redistribution from one compartment to another. For example, the general anesthetic drug, thiopental, which is a highly lipid-soluble agent, induces anesthesia within seconds owing to drug rapid equilibration between blood and brain. The duration of anesthesia is short due to drug redistribution into adipose tissue, which can act as a storage site, or drug reservoir, although thiopental is slowly metabolized.

3. Special Compartments
   
   Drug access to some body parts such as the cerebrospinal fluid (CSF) and central nervous system (CNS) is controlled by the structure of the CNS blood capillaries and the outermost layer of the neural tissue, i.e., pericapillary glial cells (the choroid plexus is an exception). Also, some drugs have relatively poor access to pericardial fluid, bronchial secretions, and fluid in the middle ear, thus making the treatment of infections in these regions difficult. These special compartments deserve mention as a separate category.

   A pharmacokinetic model is a model devised to simulate the rate process of drug absorption, distribution, metabolism, and elimination with little physiological detail.
During development and formulation of pharmaceutical dosage forms and drug delivery systems, an interrelationship between these dosage forms/drug delivery systems and biopharmaceutical principals must be established to ensure clinical application of these dosage forms in patient care [2]. Drugs may be introduced into the body via some routes that involve an absorption phase such as oral, topical, intramuscular, subcutaneous, nasal, pulmonary and rectal. For intramuscular, and subcutaneous routes of administration, the absorption is uncomplicated and there is less variability in the absorption process and hence the bioavailability is often considered close to 100%. Drugs that are administered by intravascular route (Intravenous and intrarterial) do not involve an absorption step [3]. Assessment of bioavailability could be achieved from plasma data, urine data, acute clinical response and clinical trials [3].

When a drug is administered into the body, it will distribute into the different organs and body compartments. Analysis of the drug kinetic in the body may be compartmental or non-compartmental. The former is used to describe the drug disposition (distribution and elimination) and the drug concentration in plasma and highly perfused organs assuming that changes in drug plasma concentration are equivalent with that in tissue concentration and the elimination process is achieved from central compartment. The latter is used to identify certain pharmacokinetic parameters without deciding on a particular compartmental model. The basic calculations are based on the area under the plasma concentration versus times curve (zero moment) and the first moment curve (AUMC).

2. One-Compartment Open Model: Intravenous Bolus Administration

This model represents the simplest way to describe the process of drug distribution as well as elimination in the body. In this model, the body acts like a single, uniform unit in which the drug can enter or leave the body easily (i.e., the model is “open” for the drug movement).

For IV bolus administered drugs, the entire dose enters the bloodstream directly. This is followed by distribution of the drug through the circulatory system to all the tissues in the body. Concentration of the drug in various tissue organs or the process of drug distribution in the body will occur depending on the blood flow to the tissue, the molecular weight of the drug, the drug lipophilicity, plasma protein binding, and the binding affinity of the drug toward certain tissue.

Mostly, drugs are eliminated from the body either through the kidney and/or the liver following drug metabolism.

The first pharmacokinetic parameter that arises in this model is the apparent volume of distribution, $V_D$, which is the volume in which the drug is distributed on it within the body, while the elimination rate constant, $k$, is the second pharmacokinetic parameter in this model, which governs the rate at which the drug concentration in the body declines over time.

A representative diagram that describes this model is illustrated below:
This model does not give information about the actual drug levels in the body tissues. However, the model assumes that any changes in the plasma drug levels will always result in a relative change in tissue drug levels.

The general equation that describes this model is:

\[ \frac{dC_p}{dt} = -k \cdot C_p \quad \text{and} \quad C_p = C_p^0 \cdot e^{kt} \quad \text{and} \quad \log C_p = \log C_p^0 - k \cdot t / 2.303 \]

Or

\[ \frac{dD_B}{dt} = -k \cdot D_B \quad \text{and} \quad D_B = D_B^0 \cdot e^{kt} \quad \text{So,} \quad \log D_B = \log D_B^0 - k \cdot t / 2.303 \]

### 2.1. Elimination Rate Constant

For most drugs, the process of drug elimination is a first-order rate process, i.e., the process is dependent on the amount or concentration of drug present, and the unit of the elimination rate constant \( k \) is time\(^{-1} \) (e.g., hr\(^{-1} \) or 1/hr).

Total removal or elimination of the parent drug from this compartment is effected by metabolism (biotransformation) and excretion. So, this constant represents the sum of these two processes:

\[ k = k_m + k_e \]

A rate expression for the first-order elimination is:

\[ \frac{dD_B}{dt} = -k \cdot D_B \]

Integration of the above equation gives the following expression:

\[ D_B = D_B^0 \cdot e^{kt} \]

The last equation can also be expressed in the logarithmic form as:

\[ \log D_B = \log D_B^0 - k \cdot t / 2.303 \]
The volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment is referred to as volume of distribution. This volume does not represent a physical space in the body but it is a dilution space. In other words, it is a theoretical volume that represents the distribution of the administered drug between the plasma and the rest of the body following administration of the medicament.

To predict the volume of distribution we must assume that the amount of the drug in the body ($D_B$) is the function of both the concentration of the drug in the plasma ($C_P$) and the volume of fluid the drug is distributed in.

Since: $D_B = V_D C_P$

Assuming $D_B$ is the IV dose

$$V_D = \frac{IV \text{ dose } (D_B)}{C_P}$$

The amount of drug in the body is estimated by taking a blood sample at periodic intervals and analyzing for the concentration of drug present. So, it is not determined directly.
Similar expression based on drug concentration in plasma is obtained for the first-order decline of drug plasma levels:

\[ \log C_p = \log C_{p0} - k t / 2.303 \]

### 2.2.1. Calculation of Volume of Distribution

This pharmacokinetic parameter, volume of distribution \( (V_D) \), is calculated in the one-compartment model (IV administration) using the following equation:

\[ V_D = \frac{\text{IV dose}}{C_{p0}} = \frac{D_B}{C_{p0}} \]

Since the rate of drug elimination is: \( \frac{dD_B}{dt} = -k D_B \)

substitution of \( D_B = V_D C_p \); so, \( \frac{dD_B}{dt} = -k V_D C_p \)

Rearrangement of the equation: \( D_B = -k V_D C_p dt \)

Integration of the last equation and assuming AUC is the summation of the area under the curve from \( t=0 \) to \( t=\alpha \):

\[ D_B = k V_D \left[ \text{AUC} \right]_0^\alpha \]

Thus, the apparent \( V_D \) may also be obtained from knowledge of the dose, elimination rate constant, and the area under the curve (AUC) from \( t = 0 \) to \( t = \infty \):

\[ V_D = \frac{D_0}{k \left[ \text{AUC} \right]_0^\alpha} \]

N.B: The AUC\(_{\infty}^0\) is usually estimated by the trapezoidal rule.

### 2.2.2. Significance of the Apparent Volume of Distribution

Assuming the following equation:

\[ V_D = \frac{\text{IV dose}}{C_{p0}} = \frac{D_B}{C_{p0}} \]

The apparent \( V_D \) is dependent on \( C_{p0} \). Drugs characterized by a large apparent \( V_D \) are mainly concentrated in extravascular tissues and are less concentrated in the intravascular capillaries. In case of drugs that are highly bound to plasma proteins or remain in the vascular capillaries, as for highly hydrophilic drugs, the \( C_{p0} \) will be high and this is resulting in a smaller \( V_D \).
It must be mentioned that the apparent volume of distribution is not a true physiologic volume. This pharmacokinetic parameter is useful in considering distribution and the relative amounts of drug in both vascular and extravascular tissues.

### 2.3. Clearance

**Clearance** or drug clearance is a pharmacokinetic term describing the process of drug elimination from the body without identifying the mechanism of the process. It refers to the volume of plasma fluid that is cleared of drug per unit time (volume approach, L/hr or mL/hr) or the amount of the drug eliminated from the body per unit time (mass approach, mg/min or mg/hr). It may also be considered as the fraction of the drug $V_D$ that is excreted by the kidney per unit time (fraction approach). It must be mentioned that a constant volume of plasma (about 120 mL/min in humans) is filtered through the glomeruli of the kidneys. For drugs that exhibit significant plasma protein binding, clearance is related to the total drug concentration in the plasma (free + protein-bound) and not the free concentration [5].

For drugs that are eliminated by first-order elimination process, the elimination rate is not constant and changes with respect to the drug concentration in the body, and hence, the drug clearance is expressed as volume per unit time (e.g., L/hr or mL/min). This is convenient because the volume per unit time is a constant, whereas for drugs that are eliminated from the body by a zero-order elimination process, expressing the rate of drug elimination as mass per unit time is convenient because the clearance rate is constant and does not depend on the drug plasma concentration.

Mathematically, since the rate of drug change (elimination) in the body is dependent on the drug plasma concentration $C_P$,

$$\frac{dD_B}{dt} = -kD_B$$

and since

$$D_B = V_DC_P$$

so,

$$\frac{dD_B}{dt} = -kV_DC_P$$

Dividing the above equation by $C_P$,

$$\frac{[dD_B/dt]}{C_P} = -k \frac{V_DC_P}{C_P}$$

or

$$\frac{dD_B}{dt}/C_P = -k V_D = -\text{clearance}$$

The term $[dD_B/dt]/C_P$ in the above equation is considered clearance according to the fraction approach.

The term fraction of total drug eliminated is applicable and convenient during expressing drug elimination whether one is dealing with an amount or a volume because of its dimensionless nature.

### 2.4. Calculation of ‘k’ from Urinary Excretion Data

Assuming the excretion rate of the drug is first-order, the elimination rate constant $k$ may be calculated from urinary excretion data. The term $k_e$ is the renal excretion rate constant, and $D_a$ is the amount of drug excreted in the urine.

$$\frac{dD_a}{dt} = k_e D_B, \text{ } D_B \text{ can be substituted for } D_B \text{ } e^{-kt}$$
So, \( \frac{dD_u}{dt} = k_e D_B \cdot e^{-kt} \)

and \( \log \frac{dD_u}{dt} = \log k_e D_B - kt / 2.303 \)

Plotting \( \log \frac{dD_u}{dt} \) versus time on regular paper or on semilog paper \( dD_u/dt \) against time results in a straight line in which the slope of this curve is equal to \(-k/2.3\) and the y intercept is equal to \(k_e D_B\). If \( D_B \) is known, the renal excretion rate constant \((k_e)\) can be obtained.

For nonrenal rate constant \((k_{nr})\), i.e., for any route of elimination other than renal excretion, it could be estimated from: \( k - k_e = k_{nr} \).

N.B: Experimentally, it is difficult to determine the drug urinary excretion rate \((dD_u/dt)\) and it is more convenient to plot the average rate of urinary drug excretion \((D_u/t)\) against the average time \(t^*\) for the collected urine samples. \(Du/t\) is the amount of drug excreted divided by the time interval.

**Practice Example**

A single intravenous dose of an antibiotic was administered to a 50-kg woman at a dose level of 20 mg/kg. Samples of urine and blood were removed periodically and assayed for parent drug. The following data were obtained:

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Cp (µg / ml)</th>
<th>Du (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>4.2</td>
<td>160</td>
</tr>
<tr>
<td>0.50</td>
<td>3.5</td>
<td>140</td>
</tr>
<tr>
<td>1.0</td>
<td>2.5</td>
<td>200</td>
</tr>
<tr>
<td>2.0</td>
<td>1.25</td>
<td>250</td>
</tr>
<tr>
<td>4.0</td>
<td>0.31</td>
<td>188</td>
</tr>
<tr>
<td>6.0</td>
<td>0.08</td>
<td>46</td>
</tr>
</tbody>
</table>

**Solution**

Here \(t^*\) = midpoint of collection period; and \( t \) = time interval for collection of urine sample.

To solve this problem, first plot on a semilogarithmic scale the relation between \(D_u/t\) versus \(t^*\). A straight line is obtained; the slope of this line should equal \(-k/2.3\). Then, determine the elimination \(t_1/2\) directly from the curve and calculate \(k\) from the first-order equation \(k = 0.693/t_{1/2}\).

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>D_u (mg)</th>
<th>Time Interval</th>
<th>D_u/t (mg / hr)</th>
<th>t^*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>160</td>
<td>0-0.25 = 0.25</td>
<td>160/0.25 = 640</td>
<td>(0+ 0.25)/2 = 0.125</td>
</tr>
<tr>
<td>0.50</td>
<td>140</td>
<td>0.5-0.25 = 0.25</td>
<td>140/0.25 = 560</td>
<td>(0.25 + 0.5)/2 = 0.375</td>
</tr>
<tr>
<td>1.0</td>
<td>200</td>
<td>1-0.5 = 0.5</td>
<td>200/0.5 = 400</td>
<td>(0.5 + 1)/2 = 0.750</td>
</tr>
<tr>
<td>2.0</td>
<td>250</td>
<td>2-1 = 1</td>
<td>250/1 = 250</td>
<td>(1+2)/2 = 1.5</td>
</tr>
<tr>
<td>4.0</td>
<td>188</td>
<td>4-2 = 2</td>
<td>188/2 = 94</td>
<td>(2+4)/2= 3</td>
</tr>
<tr>
<td>6.0</td>
<td>46</td>
<td>6-4 = 2</td>
<td>46/2 = 23</td>
<td>(4+6)/2= 5</td>
</tr>
</tbody>
</table>

In this example, \(t_{1/2} = 1.0\) hr and \(k = 0.693\) hr\(^{-1}\).
The sigma-minus method, or the amount of drug remaining to be excreted method, is an alternative method for calculation of the elimination rate constant \(k\) from urinary excretion data is. This method is sometimes preferred over the previous method since minimum fluctuations in the rate of elimination is obtained by this method.

If the amount of unchanged drug that is ultimately excreted in the urine is \(D_\infty\) and, \(D_u\) is the cumulative amount of unchanged drug excreted in the urine at a specific time. The amount of the drug remaining to be excreted is \(D_\infty - D_u\), in which the rate of excretion of this amount is dependent on or proportional to \(D_\infty\) as the process is a first-order and so,

\[
D_\infty - D_u = D_\infty e^{-kt}
\]

The last equation can be written in the logarithmic form as:

\[
\log (D_\infty - D_u) = \log D_\infty - kt / 2.303
\]

This equation describes the relationship for the amount of drug remaining to be excreted \((D_\infty - D_u)\) versus time.

A linear curve is obtained by plotting on a semilog paper the amount of the drug unchanged yet to be eliminated, \(\log (D_\infty - D_u)\) versus time, the slope of this curve is \(-k/2.3\), and the \(y\) intercept is \(D_\infty\).

**Practice Example**

Using the data in the preceding problem, determine the elimination rate constant.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Cp (µg / ml)</th>
<th>(D_u) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>4.2</td>
<td>160</td>
</tr>
<tr>
<td>0.50</td>
<td>3.5</td>
<td>140</td>
</tr>
<tr>
<td>1.0</td>
<td>2.5</td>
<td>200</td>
</tr>
<tr>
<td>2.0</td>
<td>1.25</td>
<td>250</td>
</tr>
<tr>
<td>4.0</td>
<td>0.31</td>
<td>188</td>
</tr>
<tr>
<td>6.0</td>
<td>0.08</td>
<td>46</td>
</tr>
</tbody>
</table>

**Solution**

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>(D_u) (mg)</th>
<th>Cumulative Du</th>
<th>(D_\infty - D_u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>160</td>
<td>160</td>
<td>984 - 160 = 824</td>
</tr>
<tr>
<td>0.50</td>
<td>140</td>
<td>160 + 140 = 300</td>
<td>984 - 300 = 684</td>
</tr>
<tr>
<td>1.0</td>
<td>200</td>
<td>300 + 200 = 500</td>
<td>984 - 500 = 484</td>
</tr>
<tr>
<td>2.0</td>
<td>250</td>
<td>500 + 250 = 750</td>
<td>984 - 750 = 234</td>
</tr>
<tr>
<td>4.0</td>
<td>188</td>
<td>750 + 188 = 938</td>
<td>984 - 938 = 46</td>
</tr>
<tr>
<td>6.0</td>
<td>46</td>
<td>938 + 46 = 984</td>
<td>984 - 984 = 0</td>
</tr>
</tbody>
</table>
Plot log \((D_{\infty} - D_u)\) versus time. Use a semilogarithmic scale for \((D_{\infty} - D_u)\). Evaluate \(k\) and \(t_{1/2}\) from the slope.

3. Multicompartment Models: Intravenous Bolus Administration

3.1. Introduction

It was observed that the plasma-level time curve for some drugs following its rapid IV injection does not decline linearly as a single, first-order rate process. This nonlinear plasma-level time curve is attributed to distribution of these drugs at various rates into different tissue groups. So, these multicompartment models were developed to explain and also to predict the plasma and tissue concentrations of these drugs. Again, drug distribution in the body depends mainly on plasma protein binding, tissue affinity, and drug lipo- or hydrophilicity.

It must be mentioned that the kinetic description of the multicompartment process assumes that the rate of drug transfer between central and tissue compartments is first-order.

It is noteworthy to mention that the body can be divided into organs with high blood perfusion and those with slow blood perfusion. The heart, brain, liver, lungs, kidney, endocrine glands, skin and muscle, adipose tissue, and marrow, which account for 78% of the body weight, are highly blood-perfused organs, while bones, ligaments, tendons, cartilage, teeth and hair which comprise the remaining 22% of the body weight are slowly blood-perfused.

The central compartment consists of the plasma, extracellular fluids and highly perfused tissues in which drug equilibrate rapidly. The kidney and liver, which are the tissues for drug elimination, are considered integral parts of the central compartment.

3.2. Two-Compartment Open Model

The plasma-level time curve for a drug that follows a two-compartment model shows that the plasma drug concentration declines biexponentially as the sum of two first-order processes—distribution and elimination. This is attributed to distribution of the administered drug between the central compartment and tissue (peripheral compartment).

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Figure shows distribution of the administered drug between central and peripheral compartment

Construction of the plasma-level time curve for a drug that follows a two-compartment model indicates that the curve may be divided into two phases: a distribution phase and an elimination phase. At \(t = 0\), no drug is in the tissue compartment and hence, the *distribution phase* of
the curve begins and represents the initial, more rapid decline of drug from the central compartment into the tissue compartment. Later, the drug starts to enter the tissue (peripheral compartment) and when the drug reaches the maximum tissue concentrations, an equilibrium is established and the rate of drug entry into the tissue equals the rate of drug exit from the tissue. At this stage, the drug concentrations in the central and tissue compartments will decline in a parallel and slower manner when compared to the distribution phase. This phase is the elimination phase and the decline is a first-order process.

For most two-compartment models the elimination occurs from the central compartment model unless other information about the drug is known since the major sites of drug elimination (renal excretion and hepatic metabolism) occur from organs such as the kidney and liver, which are highly perfused with blood [6, 7].

If \( k_{12} \) and \( k_{21} \) are first-order rate constants that govern the rate of drug change in and out of the tissues, then the change in drug concentration in the tissue with time could be calculated from the following equation:

\[
dC_t / dt = k_{12}C_p - k_{21}C_t
\]

And since \( C_p = D_p / V_p \) and \( C_t = D_t / V_t \) then

\[
dC_t / dt = k_{12}D_p / V_p - k_{21}D_t / V_t
\]

where \( D_p \) represents the amount of drug in the central compartment, \( D_t \) is the amount of drug in the tissue compartment, \( V_p \) represents the volume of drug in the central compartment, and \( V_t \) is the volume of drug in the tissue compartment.

The mathematical expression that best describes the two-compartment IV bolus is:

\[
C_p = A e^{-at} + B e^{-bt}
\]

The constants \( a \) and \( b \) represent the rate constants for the two phases, distribution phase and elimination phase, respectively. The constants \( A \) and \( B \) are intercepts on the \( y \) axis obtained from the plasma-level time curve after IV bolus, which exhibit two compartments. These values may be obtained graphically by the method of residuals or by computer.

---

**Figure 4.** Semilog plot of plasma-level versus time for a two-compartment IV bolus model
### 3.2.1. Method of Residuals

This method is used for fitting curve into the experimental data when the drug does not follow a one-compartment model. The method is sometimes called **Feathering or Peeling method**.

#### Practice Example

A 70-kg patient was administered a drug by rapid IV injection in a dose of 100 mg. Blood samples were taken periodically after the administration of drug, and the plasma samples were assayed for the drug concentration. The following data were obtained:

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Plasma Concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>43</td>
</tr>
<tr>
<td>0.5</td>
<td>32</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>1.5</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>6.5</td>
</tr>
<tr>
<td>8</td>
<td>2.8</td>
</tr>
<tr>
<td>12</td>
<td>1.2</td>
</tr>
<tr>
<td>16</td>
<td>0.52</td>
</tr>
</tbody>
</table>

If you plotted the provided data on semilogarithmic graph paper, a curved line is observed which indicates that the drug is distributed in more than one compartment.

From the data, the constants may be obtained either by the computer or by the method of residuals, in which the equation that describes the process is:

\[
C_p = A e^{-at} + B e^{-bt}
\]

Plotting of the data indicates that the curve is biexponential: the first segment for the distribution phase (rapid phase), while the second for the elimination phase. The rapid distribution phase is confirmed when comparing the values for \(a\) and \(b\), the constant \(a\) being larger than the rate constant \(b\). Therefore, at some later time, the term \(Ae^{-at}\) will approach zero, while \(Be^{-bt}\) will still have a value. At this later time, the two-compartment IV bolus equation will reduce to:

\[
C_{p_{late}} = Be^{-bt}
\]

And the logarithmic form is:

\[
C_{p_{late}} = B e^{(-bt)}
\]
\[
\log C_p = \log B - \frac{b \cdot t}{2.303}.
\]

It is possible to calculate the rate constant \( b \) from the slope \((-b/2.3)\) of a straight line representing the terminal exponential phase in which \( b \) was found to be 0.21 hr\(^{-1}\). The \( t_{\text{1/2}} \) for the elimination phase (beta half-life) can be derived from:

\[
t_{\text{1/2}} = \frac{0.693}{b}
\]

The regression line for the terminal phase could be extrapolated to the \( y \) axis, in which the \( y \) intercept is equal to \( B \), or 15 µg/mL.

**Figure 5.** Semilog Plot of \( C_p \) versus Time Showing \( C_{p}^{\text{late}} \)

To obtain the constant \( a \), the values for the drug plasma concentrations at the extrapolated line are subtracted from the original experimental data point to get the residual plasma concentration. Plotting the values of the residual plasma concentrations versus time will yield a straight line that represents the rapid distribution (\( a \)) phase. The slope of the line \((-a /2.3)\) and the value of \( a \) is 1.8 hr\(^{-1}\), and the \( y \) intercept is 45 µg/mL.
A number of pharmacokinetic parameters may be derived by proper substitution of rate constants $a$, $b$, and $y$ intercepts ($A$ and $B$) into the following equations:

$$ k = ab \left( \frac{A+B}{A} \right) / (Ab + Ba), \quad k_{12} = \frac{AB \left( b-a \right)^2}{(A+B)(Ab + Ba)} $$

$$ k_{21} = \frac{Ab + Ba}{A + B} $$

### 3.2.2. Apparent Volumes of Distribution

As mentioned previously, drugs with extravascular distribution such as those with high peripheral tissue binding contribute to a large apparent volume of distribution, while drugs that are polar with low lipid solubility or which highly bound to plasma protein account for small apparent $V_D$.

In multiple-compartment kinetics, such as the two-compartment model, several volumes of distribution can be calculated.

### 3.2.3. Volume of the Central Compartment (At Zero Time)

It is important to mention that the adult person has around 5L blood; 45% of this volume is cellular part and 55% noncellular part, of which 90% of the noncellular part is plasma, and so the volume of plasma in the central compartment is approximately greater than 3 L.

For many polar drugs, an initial volume of 7–10 L may be interpreted as rapid distribution of the administered drug within the plasma and some body extracellular fluids. For example, the $V_p$ of the antibiotic moxalactam ranges from 0.12 to 0.15 L/kg, corresponding to about 8.4 to 10.5 L for a typical 70-kg patient.

In the two-compartment model, if we multiply the drug concentration by the volume of the fluid, it must equal to the dose at time zero since $D_0 = V_p C_p$. If this is true, then the volume of distribution will equal 3 L and if not, then distribution of drug may also occur outside the vascular pool.

The apparent volume of the central compartment is:
\[ V_p = \frac{D_o}{C_{p_o}} \]

\( D_o \) is the entire amount of the drug in the body which is equivalent to the IV dose while, \( C_{p_o} \) is the initial concentration of the drug in the central compartment or the concentration at time \( t = 0 \).

At zero time (\( t = 0 \)), the total drug in the body is in the central compartment. \( C_{p_o} \) will equal to \( A + B \) by the following equation:

\[ C_p = A \cdot e^{-at} + B \cdot e^{-bt} \]

At \( t = 0 \), \( e^0 = 1 \) and so, \( C_p = A + B \)

And so, \( V_p = \frac{D_o}{A + B} \)

Instead, the volume of the central compartment \( V_p \) may be calculated from the area under the curve \([AUC]_0^\alpha\) in a manner similar to the calculation of the apparent \( V_o \) in the one-compartment model.

\[ \left[ \text{AUC} \right]_0^\alpha = \frac{D_o}{kV_p} \]

In contrast, \([AUC]_0^\alpha\) for the two-compartment model is \( \frac{D_o}{kV_p} \)

And so,

\[ V_p = \frac{D_o}{k\left[ \text{AUC} \right]_0^\alpha} \]

### 3.2.4. Apparent Volume of Distribution at Steady-State

When the rate of drug entering the peripheral (tissue) compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment, this condition is achieved at steady-state and the rates of drug transfer between the two compartments are described by the following expressions:

\[ D_1k_{21} = D_{p}k_{12} \]

\[ D_1 = k_{12}D_{p} / k_{21} \]

Since the amount of drug in the central compartment, \( D_{p_o} \) is equal to \( V_p C_{p_o} \)

so, \( D_1 = k_{12}V_p C_{p_o} / k_{21} \)

Assuming a steady-state condition is reached, therefore the apparent volume of drug distribution at steady-state (\( V_{pss} \)) may be determined by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady-state:
3.2.5 Volume of Distribution by Area

The volume of distribution by area, also known as \((V_{D_{area}})\) or simply \((V_D)\), is obtained by a method similar to that used to find \(V_p\), except that the rate constant \(b\) is used instead of the overall elimination rate constant \(k\). This is achieved through dividing the total body clearance by \(b\) and is influenced by drug elimination in the beta, or \(b\), phase.

So, the reduction in drug clearance from the body may increase the area under the curve AUC, which is reflected on the value of \((V_D)\) that is either reduced or unchanged depending on the value of \(b\).

\[
(V_D)_\beta = (V_D)_\text{area} = \frac{D_o}{b} \cdot \frac{[\text{AUC}]}{b} = \frac{\text{clearance}}{b} = \frac{kV_p}{b}
\]

Here the volume of distribution is related to the body clearance, and the body clearance usually occurs during the elimination phase.

**Example**

The first two columns of the provided table represent the time and plasma concentration, which may be collected after IV bolus administration of 500 mg of drug.
If these data are plotted, the following figure 7 is obtained:

![Figure 7](image-url)

At $t = 0$ gives $B = 10 \text{ mg/L}$. From the slope of the line $\beta = 0.25 \text{ hr}^{-1}$. C extrapolated values at early times are shown in column 3 and the residual in column 4. The residual values are plotted again, giving a value of $A = 25 \text{ mg/L}$ and $\alpha = 1.51 \text{ hr}^{-1}$. Note that $\alpha/\beta = 6$; thus, these values should be fairly accurate.

\[
B = 10 \text{ mg/L}, \quad \beta = \left(\ln 10 - \ln 0.5\right)/12 = 2.996/12 = 0.25 \text{ hr}^{-1}
\]

\[
A = 25 \text{ mg/L}, \quad \alpha = \left(\ln 25 - \ln 0.27\right)/3 = 4.528/3 = 1.51 \text{ hr}^{-1}
\]

Therefore $C_p = 25 \cdot e^{-1.51 \cdot t} + 10 \cdot e^{-0.25 \cdot t}$

\[
k_{21} = \frac{A \cdot \beta + B \cdot \alpha}{A + B} = \frac{25 \times 0.25 + 10 \times 1.51}{25 + 10} = 0.61 \text{ hr}^{-1}
\]

\[
k_{el} = \frac{\alpha \cdot \beta}{k_{21}} = \frac{1.51 \times 0.25}{0.61} = 0.62 \text{ hr}^{-1}
\]

\[
k_{12} = \alpha + \beta - k_{21} - k_{el} = 1.51 + 0.25 - 0.61 - 0.62 = 0.53 \text{ hr}^{-1}
\]

\[
V_1 = \frac{\text{Dose}}{A + B} = \frac{500}{35} = 14.3 \text{ L}
\]

\[
V_{aux} = \frac{\text{Dose}}{\beta \cdot \text{AUC}} = \frac{500}{0.25 \times 58.3} = 34.3 \text{ L}
\]
3.2.6. Drug Clearance

The concept for drug clearance that follows a two-compartment model is similar to that of the one-compartment. Clearance may be calculated without consideration of the compartment model. Clearance is calculated by dividing the IV bolus dose by the area under the plasma-level time curve from zero to infinity.

\[
C_t = \frac{D_i}{\text{AUC}}
\]

The last equation could also be expressed as a function of volume of distribution:

Since \((V_D)_b = D_i / \frac{b \cdot [AUC]}{0}\)

So, \(C_t = (V_D)_b\)

The last equation is simple and gives more accurate results than using the trapezoidal rule to obtain area.

4. Intravenous Infusion

4.1. Introduction

Drugs administered by IV route may either be given at once (as a bolus dose) or by slower IV infusion over a definite time such as Phenytoin which must be given slowly, no greater than 50 mg/min (and preferably 25 mg/min or less) in adults. Such drugs are infused slowly through a vein into the blood at a constant rate (zero order input) which allows precise control of plasma drug concentrations.

The following figure represents the plasma-level time curve for a drug given by constant IV infusion. At time zero, no drug was present in the body after which the drug level gradually increases until it becomes constant (plateau or steady-state). Once the drug has reached the steady-state, the rate of drug leaving the body is equal to the rate of drug entering the body.

The mathematical expression or the pharmacokinetic equation for drug administered by infusion will depend on whether the drug follows the one- or two-compartment model.

4.2. One-Compartment IV Infusion

Drugs administered by constant IV infusion show a zero-order input process, during which the drug is introduced into the bloodstream while the elimination process for most drugs is
first-order. The rate of input minus the rate of output represents the change in the amount of drug in the body at any given time \( \frac{dD_B}{dt} \) [1].

If \( D_B \) is the amount of the drug in the body, \( R \) is the rate of drug input (infusion rate) and \( k \) is the elimination rate constant. The expression that best describes the process is:

\[
\frac{dD_B}{dt} = R - k D_B
\]

\[
\frac{dD_k}{dt} = R - k C_k V_d
\]

Integration of the last equation will give:
At infinite time, \( t = \alpha \) and \( e^{-kt} \) will approach zero (at steady-state) and the last equation will be:

\[
C_p = \left[ \frac{R}{V_D k} \right] \left( 1 - e^{-\alpha} \right)
\]

\[
C_{ss} = \frac{R}{V_D k} = \frac{R}{\text{Clearance}}
\]

**N.B:**

1. At steady-state, the rate of drug input (\( R \)) is equal to the rate of drug output (\( k D_p \)), so, \( R = k D_p \) and \( R = k_c \cdot V_D C_p = R / V_D k \)

At steady-state, \( C_p = C_{ss} \)

So, \( R = k_c \cdot V_D C_{ss} = \frac{R}{k_c} \cdot V_D \cdot C_{ss} = R / C_I \)

2. Once the infusion stops either this achieved or before steady-state is reached, the drug concentration will decline according to first-order rate kinetics with the slope of the elimination curve that is equal to \(-k/2.3\).

**Example**

A desired steady-state plasma concentration of theophylline may be 15 mg/L. The average half-life of theophylline is about 4 hr and the apparent volume of distribution is about 25 liter. What is the necessary infusion rate?

From the \( t_{1/2} \) or \( k \) = 0.693/4 = 0.17 hr

\[
R = C_{ss} k D_p = 15 \times 0.17 \times 25 = 63.75 \text{ mg/hr}
\]

4.2.1. **Steady-State Drug Concentration (\( C_{ss} \)) and Time to Reach Steady-State**

During administration of a drug by IV infusion, the plasma drug concentration starts to increase and the rate of drug elimination will also increase since the latter is concentration-dependent. \( C_p \) keeps increasing until a steady-state condition is reached at which the rate of drug input (IV infusion rate) equals the rate of drug output (elimination rate). At this stage, a steady-state (\( C_{ss} \)) is reached and the resulting plasma drug concentration is directly related to the rate of infusion and inversely related to the body clearance of the drug.

For drug administered by IV infusion, the therapeutic activity is observed when the concentration of the drug is close to the desired plasma concentration, which is usually the required steady-state drug concentration.

The time to reach steady-state could be determined by knowing the time to reach half the steady-state which can be derived:
Since $C_{ss} = R/V_D k = R/Clearance$

At ($t_{1/2}$); time to reach half the steady-state $C_P = C_{ss}/2$

$C_P = \left( \frac{R}{V_D \cdot k} \right) \left( 1 - e^{-k \frac{t_{1/2}}{half}} \right) = \frac{C_{ss}}{2}$

$C_{ss} \left( 1 - e^{-k \frac{t_{1/2}}{half}} \right) = \frac{C_{ss}}{2}$

$1 - e^{-k \frac{t_{1/2}}{half}} = \frac{1}{2}$

$- e^{-k \frac{t_{1/2}}{half}} = \frac{1}{2} - 1$

$e^{-k \frac{t_{1/2}}{half}} = 0.5$

Taking the ln to both sides, $t_{1/2} = 0.693/k$

It must be noticed that the time to reach half the steady-state has the same value for the elimination half-life and is dependent on the elimination process not the infusion rate while the value of $C_{ss}$ is controlled by the infusion rate. An increase in the infusion rate will not shorten the time to reach the steady-state drug concentration.

From the pharmacokinetic point of view, for drugs administered by IV infusion, the clinical effect of the drug (activity) is observed when the drug concentration in the plasma is close to the desired plasma drug concentration, which is the desired steady-state drug concentration.

Examples

1. A drug belonging to the cephalosporins antibiotics has a volume of distribution of 10 L and an elimination rate constant (k) value of 0.2 hr$^{-1}$. A steady-state plasma concentration of 10 µg/mL is desired. What is the infusion rate required to maintain this concentration.

$R = C_{ss} \cdot V_D \cdot k \quad R = 10 \times (10 \times 1000) \times 0.2 = 20 \text{ mg/hr}$

2. A septicemia patient was administered by constant IV infusion an antibiotic that has an elimination half-life ($t_{1/2}$) of 6 hr. The rate of infusion was 2 mg/hr. At the end of second day of treatment, the serum drug concentration was 10 mg/L. Calculate the total body clearance $Cl_t$ for this drug.
3. An infinitely long period of time is needed to reach a steady-state level of a certain drug. However, in clinical practice it is quite acceptable to reach 99% of the steady-state level (99% \( C_{ss} \)). Calculate a time required to reach steady-state relative to the half-life of this drug.

\[
C_p = \left[ \frac{R}{V_D k} \right] \left( 1 - e^{-kt} \right)
\]

At 99% steady-state, \( C_p = 99\% \) \( C_{ss} = 99\% \) \( R/V_D k \)

So, \( \left[ \frac{R}{V_D k} \right] \left( 1 - e^{-kt} \right) = 99\% \) \( R/V_D k \)

\[
1 - e^{-kt} = 99\%
\]

Taking the natural logarithm, \( \ln 0.01 = -kt \)

\[
t_{99\%ss} = \ln 0.01 / -k = 4.69 / k
\]

Substitution for \( k = 0.693 / t_{\frac{1}{2}} \)

\[
t_{99\%ss} = 4.61 / \left( 0.693 / t_{\frac{1}{2}} \right) = 6.65 \, t_{\frac{1}{2}}
\]

Accordingly, as a general example, if the \( t_{\frac{1}{2}} \) for a drug is 6 hr, the time needed to reach 90%, 95%, and 99% of the steady-state is to be calculated. So, at those concentrations, 10%, 5%, and 1% respectively dropped from the total will take 3.32, 4.32, and 6.65 half-lives. Thus, the time for a drug whose \( t_{\frac{1}{2}} \) is 6 hr to reach at least 95% of the steady-state plasma drug concentration will be 5 \( t_{\frac{1}{2}} \) or 5 x 6 hr = 30 hr. Also, for theophylline with a \( t_{\frac{1}{2}} \) equal to 4 h, the time to reach 94% of steady-state will be 16 hr.

4.2.2. Calculating Patient Elimination Half-Life Following Drug Infusion

The half-life for drug administered by IV infusion could be calculated from \( (0.693/k) \). So, a mathematical expression that describes the elimination rate constant should first be determined.

\[
C_p = \left[ \frac{R}{V_D k} \right] \left( 1 - e^{-kt} \right)
\]
And since $C_{ss} = \frac{R}{kVD}$

$$C_p = \left[ C_{ss} \right] \left( 1 - e^{-\frac{kt}{V}} \right)$$

$$C_p = C_{ss} + C_{ss} \cdot e^{\frac{kt}{V}}$$

$$C_{ss} \cdot e^{\frac{kt}{V}} = C_{ss} - C_p$$

$$e^{\frac{kt}{V}} = \frac{C_{ss} - C_p}{C_{ss}}$$

$$kt / 2.303 = \log \left( \frac{C_{ss} - C_p}{C_{ss}} \right)$$

$$k = \frac{-2.303}{t} \log \left( \frac{C_{ss} - C_p}{C_{ss}} \right)$$

It is noteworthy to mention that knowing the half-life for the administered drug in the general population helps to determine if the sample is taken at steady-state in the patient, and after administration of the drug by the IV infusion, one or two plasma samples must be taken at a known time to compare.

Examples

A patient was administered an IV infusion of a certain antibiotic at an infusion rate of 15 mg/hr. Blood samples were taken from this patient at 8 and at 24 hr and the plasma concentrations for this drug were found to be 5.5 and 6.5 mg/L, respectively. Calculate approximately the elimination half-life of this drug.

N.B: The antibiotic has an elimination half-life of 3–6 hr in general population.

Answer

Assuming the extreme case of $t_{\frac{1}{2}}$ (6 hr), the second plasma sample was taken at 24 hr, or $24/6 = 4$ half-lives after infusion, which is supposed to be near the theoretical time for steady-state.

$$k = \left[ -\frac{2.303}{t} \right] \log \left( \frac{C_{ss} - C_p}{C_{ss}} \right)$$

$$k = \left[ -\frac{2.303}{8} \right] \log \left( \frac{6.5 - 5.5}{6.5} \right)$$

$$k = 0.234 \text{ hr}^{-1}$$

$t_{\frac{1}{2}} = 0.693 / 0.234 = 2.96 \text{ hr}$

In the previous example, if we desire to let the steady-state plasma concentration equal 8 mg/L, what is the suitable infusion rate?
Answer

First from the old data, we should calculate the clearance rate:

\[ \text{Css} = \frac{R}{C_l} \quad C_l = \frac{15}{6.5} = 2.31 \text{ L/hr} \]

Then, for the new infusion rate \( R = \text{Css} \times Cl = 8 \times 2.31 = 18.48 \text{ mg/hr} \)

4.2.3. Loading Dose plus IV Infusion (Combined Infusion and Bolus Administration)

If we desire to achieve a quick therapeutic concentration, a loading dose by rapid intravenous injection (bolus injection) is first administered and then starts the slower maintenance infusion. At this condition, the total drug concentration in the plasma is the function of both; the IV bolus and the infusion doses.

The concentration following IV bolus (\( C_l \)) is described by:

\[ C_l = C_0 e^{-\frac{t}{k}} = \text{Loading Dose} \times \left( \frac{D_L}{V_D} \right) e^{-\frac{t}{k}} \]

The concentration following IV infusion at rate \( R \) is:

\[ C_2 = \frac{R}{V_D k} \left( 1 - e^{-\frac{t}{k}} \right) \]

The total concentration \( C_p \) will be the sum of bolus and infusion:

\[ C_p = C_1 + C_2 \]

\[ C_p = \frac{D_L}{V_D} e^{-\frac{t}{k}} + \frac{R}{V_D k} \left( 1 - e^{-\frac{t}{k}} \right) \]

Or, \( C_p = \frac{R}{V_D k} + \left( \frac{D_L}{V_D} e^{-\frac{t}{k}} - \frac{R}{V_D k} e^{-\frac{t}{k}} \right) \)

If the loading dose (\( D_L \)) represents or equals the amount of drug in the body at steady-state,

so, \( D_L = C_{ss} \cdot V_D \) and since \( C_{ss} = \frac{R}{V_D k} \), so, \( C_{ss} \cdot V_D = \frac{R}{k} \)

Therefore, \( D_L = \frac{R}{k} \)

Examples
An anesthetic agent was administered by IV infusion at a rate of 2 mg/hr. The drug has an elimination rate constant of 0.1 hr$^{-1}$, and a volume of distribution (one compartment) equals to 10 L. What loading dose is recommended if the physician wants the drug level to reach 2 µg/mL immediately?

**Solution**

\[
D_L = C_{ss} \cdot V_D = 2 \mu g / mL \times 10 \times 1000 = 20000 \mu g = 20 mg
\]

Or, \( D_L = \frac{R}{k} \Rightarrow D_L = 2 / 0.1 = 20 mg \)

A drug was given to a patient by simultaneous administration of a loading dose of 10 mg and an infusion rate of 2 mg/hr (the drug has a \( t_{1/2} \) of 3 hr and a volume of distribution of 10 L)? What is the concentration of a drug following 6 hr of administration?

**Solution**

\[
k = 0.693 / 3 = 0.231
\]

The concentration of the drug \( (C_P) \) after 6 hrs = Loading dose \( (C_1) \) + Concentration by infusion \( (C_2) \)

\[
C_P = \frac{D_L}{V_D} \cdot e^{-kt} + \frac{R}{V_D} \cdot k \cdot \left(1 - e^{-kt}\right)
\]

\[
C_P = \frac{10 \times 1000}{10 \times 1000} \cdot e^{-\left(0.231 \times 6\right)} + \left[\frac{2 \times 1000}{(10 \times 1000) \cdot (0.231)}\right] \left(1 - e^{-\left(0.231 \times 6\right)}\right)
\]

\[
C_P = 0.9 \mu g / ml
\]

N.B: To determine the concentration of the drug in the body after infusion has been stopped, first the final concentration of drug at the end of the infusion is to be calculated and considered as \( C_D \). Then, use the IV bolus dose equation \( (C = C_0 \cdot e^{kt}) \) for calculations for any further point in time.

A patient was infused for 6 hr with a drug \((k = 0.01 \text{ hr}^{-1} ; V_D = 10 \text{ L})\) at a rate of 2 mg/hr. What is the concentration of the drug in the body 2 hr after cessation of the infusion?

**Solution**

\[
C_P = \frac{R}{V_D} \cdot k \cdot \left(1 - e^{-kt}\right) = \frac{2 \times 1000}{10 \times 1000 \times 0.01} \cdot \left(1 - e^{-0.01 \times 6}\right)
\]
The obtained value for \( C_P \) is to be considered the initial concentration of the drug in the plasma after cessation of the infusion in which the IV bolus equation could be applied:

\[
C_P = 1.14 \text{ mg/ml}
\]

1. A 35-year-old male patient of 80 kg was given a chemotherapeutic agent by IV infusion. The administered drug has been reported to have an elimination half-life \( (t_{1/2}) \) of 2 hr, an apparent volume of distribution of 1.25 L/kg. If the effective plasma concentration of this drug is 14 mg/l and the drug is commercially supplied in ampoules of 5-mL each containing 150 mg/mL:

2. What is the recommended starting infusion rate in milligrams per hour and liters per hour?

3. After the start of the infusion, blood samples were taken from the patient at 12, 16, and 24 hr and the plasma drug concentrations were found to be 16.1, 16.3, and 16.5 mg/L. Calculate the drug total body clearance \( C_l \) in this patient.

4. Considering the data provided above, calculate approximately the elimination half-life for this antibiotic.

**Solution**

\[
k = 0.693 / 2 = 0.3465
\]

Assume the effective plasma drug concentration is the target drug concentration or \( C_{SS} \):

\[
R = C_{SS} k V_D = 14 \times 0.3465 \times 1.5 \times 80 = 582.1 \text{ mg/hr},
\]

which is equivalent to 582.1/150 = 3.88 ml, since each ampoule contains 150 mg/ml.

It is obvious that the drug has reached a steady plasma level of approximately 16.3 (average value).

So, \( C_l = R / C_{SS} = 582.1 / 16.3 = 35.7 \text{ L/hr} \)

\[
C_l = k V_D = k = CL / V_D = 35.7 / 1.25 \times 80 = 0.357 \text{ hr}^{-1}
\]
### 4.3. Intravenous Infusion of Two-Compartment Model Drugs

Some drugs such as lidocaine and theophylline when administered by IV infusion do not follow the one- but rather the two-compartment model. As has been discussed in the IV bolus, during a constant IV infusion, the drug in the tissue compartment is in distribution equilibrium with that in the plasma and a steady state concentration is reached during equilibrium.

The mathematical expression that describes the drug plasma concentration is:

\[
C_p = \frac{R}{V_p k} \left[ 1 - \left( \frac{k - b}{a - b} \right) e^{-\alpha t} - \left( a - k / a - b \right) e^{-\beta t} \right]
\]

At steady-state \((t=\alpha)\), the last equation could be reduced into:

\[
C_{ss} = \frac{R}{V_p k}
\]

**N.B:** It is not possible to maintain a steady-state stable blood level for a drug that exhibits a two-compartment model drug following a zero-order rate of infusion. Therefore, a loading dose is administered to produce an initial plasma level either slightly higher or lower than that of the desired steady-state level. Several IV bolus injections may be given as short intermittent IV infusions as a method for administering a loading dose to the patient.

### 4.3.1. Apparent Volume of Distribution at Steady State, Two-Compartment Model

The amount of the drug in the body at steady-state is the product of the plasma concentration and the steady-state volume of distribution \((V_{D,ss})\). Assuming equilibrium has been attained between the central and peripheral compartments:

\[
D_2k_{21} = D_1k_{12}Dt = k_{12}D_p / k_{21}Dt = k_{12}C_p V_p / k_{21}
\]

At the steady-state, the total amount of drug in the body is equal to the sum of the amount of drug in tissue \((D_t)\) and central compartment \((D_p)\). Consequently, \((V_{D,ss})\) could be determined by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady-state:

\[
\begin{align*}
(V_D)_{ss} &= D_p + D_t / C_p \\
(V_D)_{ss} &= \left[ C_p V_p + k_{12} V_p C_p / k_{21} \right] / C_p \\
(V_D)_{ss} &= V_p + k_{12} / k_{23} V_p
\end{align*}
\]
5. Pharmacokinetics of Drugs Following Oral Absorption

Unlike the process of IV administration, when a drug is introduced into the body by extravascular route such as oral, intramuscular, subcutaneous, or transdermal administration, an absorption phase that transfers the drug from the absorption site into the systemic vascular system must take place. The oral route of drug administration represents the most popular of the extravascular routes and so, in this chapter, we will focus on its pharmacokinetics; although, the same principles could be applied for the other extravascular routes. The plasma-level time curve for drugs administered by intramuscular, subcutaneous, or transdermal showed the same profile for orally administered drugs. Also, it is important to mention that for the same route, different drug formulations such as oily, aqueous liquid, suspension, emulsion, semisolid, fast dissolving tablets, oral disintegrating tablets, or buccal tablets exhibit the same plasma time curve but with slight modification in the rate and extent of absorption and/or distribution phases [8]. This concept is common during relative bioavailability study that involves identification of a significant difference between different pharmaceutical products administered by the same or another non-intravenous route of administration.

As previously mentioned, the process of gastrointestinal (GIT) absorption is mainly dependent on physiology and anatomy of the GIT, physicochemical factors of the drug, and dosage-form-related factors [1, 3].

The process of oral drug absorption (drug input) is mainly first-order, unless it has been verified experimentally or through the pharmacokinetic models that it is zero-order.

The figure below represents the plasma-level time curve for a drug administered by oral route; unlike the IV bolus, there is an absorption phase and the overall rate of change in the amount of the drug in the body $dD/dt$ is the function of both the rate of drug absorption and elimination. The maximum plasma concentration is represented as $C_{\text{max}}$ and the time needed to reach maximum concentration is represented as $t_{\text{max}}$.

![Plasma-level time curve for a drug administered by oral route](image)

**Figure 10.** Plasma-level time curve for a drug administered by oral route
If $D_GI$ represents the amount of the drug in the GIT and $D_E$ represents the amount of the drug eliminated, the change in the amount of the drug in the body $dD_B/dt$ could be expressed as:

$$dD_B/dt = dD_GI/dt - dD_E/dt$$

The above curve could be classified into three segments (phases):

- **The absorption phase**, where the rate of drug absorption ($dD_GI/dt$) is greater than the rate of drug elimination ($dD_E/dt$)
- **The peak drug plasma concentration**, in which the rate of drug absorption ($dD_GI/dt$) is equal to the rate of drug elimination ($dD_E/dt$)
- **The elimination phase**, when the rate of drug elimination ($dD_E/dt$) is greater than the rate of drug absorption ($dD_GI/dt$)

It must be noted that, during the absorption phase and once the drug is available in the plasma, some of the absorbed drug may be eliminated, but absorption is major. Also, during the elimination phase, some drug may still remain at the absorption site; however, the rate of drug elimination is higher than the rate of drug absorption until the entire drug at the absorption site is depleted and hence, $dD_GI/dt = 0$ and at this stage $dD_B/dt = -dD_E/dt$.

### 5.1. Zero-Order Absorption Model

It is previously mentioned that the oral drug absorption process is mainly first-order. Zero-order absorption of drug is expected in two cases:

- Drugs absorbed through carrier-mediated transport
- The absorption of controlled release drug dosage forms

In this process, the drug is absorbed at a constant rate $k_0$ and is eliminated by first-order rate process in a model similar to that of the intravenous infusion.

The mathematical expression for this model is:

$$dD_B/dt = k_0 - k_B D_B$$

Integration of the above equation:

$$C_p = k_0 \int V_D \cdot k \left(1 - e^{-kt}\right)$$

### 5.2. First-Order Absorption Model

Drugs absorbed by passive diffusion transport mechanism exhibit first-order absorption. Such behavior is expected from:

- Drugs administered as solution and most suspension
• Immediate release tablets, capsules, and suppositories

• Intramuscular and subcutaneous aqueous injections

For any orally absorbed drug, if \( F \) is the fraction of drug absorbed, \( D_{GI} \) is the amount of drug in solution in the GIT at any time \( t \), \( k_a \) is the first-order absorption rate constant and \( k \) is the first-order elimination rate constant; therefore:

The rate of drug disappearance from GIT is: \( \frac{dD_{GI}}{dt} = -k_a \cdot D_{GI} \cdot F \)

The rate of first-order elimination process is: \( \frac{dD_B}{dt} = -k \cdot D_B \)

The rate of the amount of drug changed in the body is: \( \frac{dD_B}{dt} = F \cdot k_a \cdot D_{GI} - k \cdot D_B \)

Since drug absorption is first-order, the amount of drug in the GIT \( (D_{GI}) \) at any time \( t \) is equal to \( D_o \cdot e^{-k_a t} \), in which \( D_o \) is the dose of drug given.

So,

\[
\frac{dD_B}{dt} = F \cdot k_a \cdot D_o \cdot e^{-k_a t} - k \cdot D_B
\]

The last equation could be integrated to give the general oral absorption equation as follow:

\[
C_p = \left[ F \cdot k_a \cdot D_o / V_p \cdot (k_a - k) \right] \cdot (e^{-k t} - e^{-k_a t})
\]

It must be noted that the value of \( F \) may vary from 1 for completely absorbed drug to zero for drug that is fully unabsorbed.

The time needed to reach the maximum plasma concentration \( t_{max} \) could be calculated by considering that at \( C_{max} \) (maximum plasma concentration), the rate of drug absorbed is equal to the rate of drug eliminated:

\[
\frac{dD_B}{dt} = F \cdot k_a \cdot D_{GI} - k \cdot D_B = 0
\]

\[
F \cdot k_a \cdot D_o = k \cdot D_B
\]

\[
F \cdot k_a \cdot D_o \cdot e^{-k_a t} = k \cdot D_B \cdot e^{-k t}
\]

\[
k_a e^{-k_a t} = k e^{-k t}
\]

\[
\ln k_a - k_a t = \ln k - k t
\]

\[
\ln k_a - \ln k = k_t - k t
\]

\[
\ln k_a - \ln k = t \cdot (k - k)
\]
From the above equation, \( t_{\text{max}} \) is independent of the dose and is dependent on the rate constants for absorption (\( k_a \)) and elimination (\( k \)).

The value of \( C_{\text{max}} \) is better to obtain mathematically (kinetically) since measurement of \( C_{\text{max}} \) may not be possible due to improper timing of the blood samples.

\( C_{\text{max}} \) is determined first; calculate \( t_{\text{max}} \) using the last equation:

\[
t_{\text{max}} = \left[ \frac{2.303 \log \left( \frac{k_a}{k} \right)}{k_a - k} \right]
\]

Then, use the obtained \( t_{\text{max}} \) value and substitute in the \( C_P \) equation to get \( C_{\text{max}} \), in which

\[
C_{\text{max}} = \frac{F \cdot k_a \cdot D_o / V_d (k_a - k)}{\left( e^{-kt} - e^{-ka t} \right)}
\]

The value for the first-order elimination rate constant (\( k \)) could be determined graphically from the plasma-level time curve after single oral administration, in which at later time, when the drug absorption has been completed, the value \( e^{ka t} \approx \) zero and plasma concentration equation will be:

\[
C_P = \left[ F \cdot k_a \cdot D_o / V_d (k_a - k) \right] e^{-kt}, \text{ which is analogue to } C_P = C_P e^{-kt}
\]

And so, \( \log C_P = \log \left[ F \cdot k_a \cdot D_o / V_d (k_a - k) \right] - kt / 2.303 \)

If the log drug plasma concentration is plotted against time, a straight line for the elimination phase is obtained, from which the slope of the line is \( -kt / 2.303 \)

Figure 11. Semi-log plot of plasma concentration against time curve following oral administration.
The urinary drug excretion data could be used also to determine the first-order elimination rate constant in the same manner in which the kinetic process could be expressed as:

\[
dD_u / dt = \left[ F \cdot k_a \cdot k_e \cdot D_d / (k_e - k) \right] \left( e^{-kt} - e^{-kt'} \right)
\]

A plot of \(dD_u/dt\) versus time will give a curve similar to the above curve, in which also after drug absorption has been completed, the value \(-e^{-ka t} = 0\) and a straight line for the terminal part is obtained, from which the slope of the line is \(-kt/2.303\).

5.3. Determination of Absorption Rate Constant \((k_a)\); Method of Residual

The value for \(k_a\) cannot be obtained directly from the plasma-level time curve for the drug administered by oral route as we calculated the elimination rate constant \((k)\), but it could be obtained using the method of residuals or a feathering technique, which is illustrated in the following graph:

1. On a semilog paper, plot the relation between plasma drug concentrations versus time.
2. Extrapolate the linear part of the terminal phase.
3. Identify a minimum of three points on the upper part of the extrapolated line \((X'1, X'2, \text{ and } X'3)\).
4. From each identified point, drop a vertical line on the curve to obtain their corresponding points on the curve \((X_1, X_2, \text{ and } X_3)\).
5. Plot again the values for the differences \((X'1 - X_1), (X'2 - X_2), \text{ and } (X'3 - X_3)\) versus time.
6. A straight line will be obtained in which the slope = \(-k_a/2.303\).

![Figure 12. The plasma-level time curve for a drug administered by oral route used to determine \(k_a\) by the method of residual](image)
5.4. Lag time

Some physiological factors such as gastric-emptying rate and motility of the intestine may cause delay in the oral absorption after single oral administration of some drugs in some candidates. In such case, there is a gap or a delayed period before the appearance of the first-order plasma-level time curve as shown in the following figure, where the two residual lines obtained by feathering the oral absorption plasma-level time curve intersect at a point greater than \( t = 0 \) on the x axis.

![Figure 13. First-order plasma level time curve showing lag time](image)

The drug plasma concentration can be described in this case as:

\[
C_p = \left[ F \cdot k_a \cdot D_o / V_d \left( k_a - k \right) \right] \left( e^{-k \left( t-t_0 \right)} - e^{-k_a \left( t-t_0 \right)} \right)
\]

5.5. Flip-Flop of \( k_a \) and \( k \)

According to the previous discussion for drugs administered by single oral dose, the absorption phase is much faster than the elimination phase and so, \( k_a > k \). It has been observed with some drugs such as isoproterenol and salicylic acid that the elimination rate of these drugs is much greater than their absorption rate, such drugs exhibit flip-flop phenomenon (reversal or interchange of the values of the rate constants). To make sure of this behavior, the drug is administered by oral and IV bolus routes and elimination rate \( k \) is calculated for both routes; then the absorption rate \( k_a \) is determined for oral route by the method of residual. It will be obvious that the values for \( k_a \) and \( k \) obtained by the method of residuals have been interchanged. Such behavior is expected from drugs that have a fast elimination rate in which \( k > k_a \) and from controlled release products.

5.6. Determination of \( k_a \) by Plotting Percent of Drug Unabsorbed versus Time (Wagner–Nelson Method)

For any drug administered as a single oral dose \( (D_o) \), after an elapsed time \( (t) \), there will be an amount unabsorbed or remains in the GIT \( (D_{GI}) \), amount will be excreted in the urine \( (Du) \) and an amount will be available in the body plasma \( (D_B) \); \( D_o = D_{GI} + Du + D_B \)

- The amount of the drug absorbed \( (Ab) = Du + D_B \)
• The fraction of the drug remaining (unabsorbed) in the GIT is $D_{CI}/D_o$

The amount of the drug remaining in the GIT (unabsorbed) at any time ($t$) could be expressed by:

$$\frac{dD_{CI}}{dt} \propto D_o \quad \frac{dD_{CI}}{dt} = k_a D_o$$

$$D_{CI} = D_o e^{-k_a t}$$

$$\frac{D_{CI}}{D_o} = e^{-k_a t} \quad \log \frac{D_{CI}}{D_o} = -k_a t / 2.303$$

Plotting the fraction of drug unabsorbed versus time in a semilog graph paper will yield a straight line, the slope of which is $k_a / 2.303$.

5.7. Effect of $k_a$ and $k$ on $C_{max}$, $t_{max}$ and AUC

It could be asked: Does the change in $k_a$ and $k$ affect the values of $t_{max}$, $C_{max}$, and AUC? The answer is illustrated in the following figures and it could be explained as follows:

1. If the value for $k_a$ increased (0.3 to 0.7/hr) while the elimination rate is kept constant, then $t_{max}$ becomes shorter, $C_{max}$ increases, and AUC remains constant.

2. If the absorption rate is kept constant and the elimination rate increases (0.1 to 0.5/hr), then $t_{max}$ decreases, $C_{max}$ decreases, and AUC decreases.

3. If the values for the absorption rate $k_a$ and the elimination rate $k$ are reversed, then the same $t_{max}$ is obtained while $C_{max}$ and AUC are different.

5.8. Drug Elimination

The process of drug elimination from the body involves two major ways: metabolism/biotransformation (by the liver) and/or excretion (mostly by the kidney). The rate process for drug elimination is an overall first-order.
The high blood supply to the liver, 20% arterial blood directly from the heart and 80% venous blood from the gastro-intestinal tract through the hepatic-portal vein (first-pass effect), and the liver microsomal enzymes make the liver the main site for drug metabolism. Oxidation, reduction, hydrolysis, and conjugation are the four metabolic processes.

Drug excretion is the removal of the drug from the body, which is mainly renal for nonvolatile, water-soluble, and low molecular weight drugs. Some other routes of drug excretion involve removal of the drug through bile, sweat, saliva, milk, or other body fluids.

Anatomically, the kidneys are paired retroperitoneal structures with the left kidney located somewhat more superior in position than the right. The outer zone of the kidney is called the cortex and the inner is called medulla.

The two kidneys represent about 0.5% of the total body weight, receive approximately 20–25% of the cardiac output, and serve endocrine and nonendocrine functions. Nonendocrine functions including filtration and excretion of metabolic waste products (urea and ammonia), regulation of necessary electrolytes, fluid and acid-base balance. In addition, the kidney has two endocrine functions: secretion of renin which regulates blood pressure and secretion of erythropoietin that stimulates red blood cell production.

![Diagram of nephron](http://dx.doi.org/10.5772/61573)

**Figure 15. Structure of nephron**

The nephrons are the basic functional units of the kidney responsible for the removal of metabolic waste and maintenance of water and electrolyte balance. There are 1–1.5 million nephrons in each kidney.

Each nephron is composed of a renal corpuscle and a renal tubule specialized for reabsorption and secretion. The renal corpuscle is composed of a glomerulus inside a bowman’s capsule,
which is the nephron’s initial filtering component. The renal tubule, containing the tubular fluid filtered through the glomerulus, consists of proximal convoluting tubule, loop of henle (descending and ascending limb), and distal convoluting tubule. After passing through the renal tubule, the filtrate continues to the collecting duct, which is not part of the nephrons.

The volume of blood flowing through the kidney (renal vasculature) per unit time is referred to as the renal blood flow (RBF), which exceeds 1.2 L/min or 1700 L/day, while, the renal plasma flow (RPF) is the renal blood flow minus the volume of red blood cells.

N.B: Hematocrit (Hct) is the fraction of blood cells in the blood which is about 45% of the total blood volume.

\[
RPF = RBF \times (1 - Hct)
\]

The glomerular filtration rate (GFR) in a normal adult male subject is approximately 125 ml/min, so about 180 L of fluid per day is filtered through the kidney. The average urine volume is 1–1.5 L, which accounts for the reabsorption of 99% of the fluid volume filtered at the glomerulus.

5.9. Renal Drug Excretion

The mechanisms of renal drug excretion may include any combination of the following:

1. Glomerular filtration of unbound drug
2. Active tubular secretion of free and protein-bound drug
3. Tubular passive/active reabsorption

**Glomerular filtration:** Most drugs (ionized or nonionized) are readily filtered from the blood unless they are tightly bound to large molecules such as plasma protein or have been incorporated into red blood cells. The hydrostatic pressure within the glomerular capillaries is the major driving force for glomerular filtration. Inulin and creatinine are examples of drugs that are eliminated by filtration only and that could be used to measure the GFR.

**Active tubular secretion:** This process involves transport of the drug against a concentration gradient from the blood capillaries around the nephron to the nephron lumen, which is characterized by the following: it is carrier-mediated, requires energy, the carrier is saturable, and competition for the same carrier could occur. Iodopyracet (Diodrast) and β-aminohippuric acid (PAH) are common examples of drugs used to measure active tubular secretion, since both are filtered by the glomeruli and secreted by the tubular cells.

N.B: The process of drug protein binding has very little effect on the elimination t½ of the drug excreted mostly by active secretion, while for drugs that are excreted only by glomerular filtration, the elimination half-life may be changed markedly according to the binding affinity of these drug for plasma proteins. Since drug protein binding is a reversible process, drug bound to plasma protein rapidly dissociates into a free drug that is secreted by kidneys. This
behavior is very common for some of the penicillins that are extensively bound to plasma protein, but their elimination half-lives are short, which could be attributed to rapid elimination by active secretion.

**Figure 16.** Mechanisms of renal drug excretion through nephron

**Tubular reabsorption:** Drug moves from nephron lumen to blood by passive diffusion (Fick’s Law is applied) or sometimes by an active process. Most drugs are weak acids or weak bases and hence the reabsorption of such drugs is influenced by the pH of the renal tubule fluid and the drug pKa, as both will affect the ratio of dissociated (ionized) to the undissociated (nonionized). The drug pKₐ is constant, but the normal urinary pH may vary from 4.5 to 8.0, depending on diet, pathophysiology, and drug intake. The undissociated drug is easily reabsorbed from the renal tubule back to the body.

Some drugs such as ascorbic acid and antacids, for example, sodium carbonate, may alter the urine pH. The former decreases (acidify) while the latter increases (alkalinize) the urinary pH when administered in large quantities. During excretion of these drug solutions, the urine pH may drastically change and alter other drug reabsorption and/or excretion by the kidney.

According to the Henderson–Hasselbalch equation, the percent of ionized to nonionized drug is the function of both pH and pKa, as follows:

For acidic drugs: \( pH = pK_a + \log \left[ \frac{\text{ionized}}{\text{unionized}} \right] \)
\[
\frac{[\text{ionized}]}{[\text{unionized}]} = 10^{(pH - pKa)}
\]

\[
\text{ionized} = [\text{unionized}] \cdot 10^{(pH - pKa)}
\]

*The fraction of acidic drug ionized = \[\frac{[\text{ionized}]}{[\text{ionized} + [\text{unionized}]]}\]

\[
= \frac{[\text{unionized}] \cdot 10^{(pH - pKa)}}{[\text{unionized}] \cdot 10^{(pH - pKa)} + [\text{unionized}]}
\]

\[
= \frac{10^{(pH - pKa)}}{1 + 10^{(pH - pKa)}}
\]

For basic drugs: \(pH = pKa + \log\left[\frac{[\text{unionized}]}{[\text{ionized}]}\right]\)

*The fraction of basic drug ionized = \(1 + \frac{10^{(pH - pKa)}}{10^{(pH - pKa)}}\)

The urine–plasma (U/P) ratio of weak acidic or basic drugs could be evaluated from the following:

For weak acids: \(U/P = 1 + \frac{10^{(pH_{\text{urine}} - pKa)}}{1 + 10^{(pH_{\text{plasma}} - pKa)}}\)

For weak bases: \(U/P = 1 + \frac{10^{(pKa - pH_{\text{urine}})}}{1 + 10^{(pKa - pH_{\text{plasma}})}}\)

**Example**

The pKa of a weak acidic drug is 5. Calculate the U/P at urinary pH of 3, 5, and 7, respectively.

**Solution**

For acidic drug, \(U/P = 1 + \frac{10^{(pH_{\text{urine}} - pKa)}}{1 + 10^{(pH_{\text{plasma}} - pKa)}}\)

<table>
<thead>
<tr>
<th>At pH = 3</th>
<th>At pH = 5</th>
<th>At pH = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>U/P = 1/252</td>
<td>U/P = 2/252</td>
<td>U/P = 101/252</td>
</tr>
</tbody>
</table>

**5.10. Drug Clearance**

As we mentioned for IV bolus administered drugs, Clearance or drug clearance is a pharmacokinetic term describing the process of drug elimination from the body without identifying the mechanism of this process. It refers to the volume of plasma fluid that is cleared of drug per unit time (volume approach, L/hr or ml/hr) or the amount of the drug eliminated from the
body per unit time (mass approach, mg/min or mg/hr). It may also be considered as the fraction of the drug $V_D$ that is excreted by the kidney per unit of time (fraction approach).

Practically, drug clearance (body clearance, total body clearance, or $Cl_T$) may also be expressed based on the plasma drug concentration as the elimination rate of the drug divided by the plasma drug concentration.

$$Cl_T = \frac{\text{Elimination rate}}{\text{Plasma concentration (Cp)}} = \frac{(dD_e/\text{dt})/C_p}{\mu g/\text{ml} / \mu g/\text{ml} = \text{ml/min}}$$

Since the drug elimination rate is a first-order process, so $dD_e/\text{dt}$ is equal to $k D_B$ or $k C_p V_D$.

$$Cl_T = k \cdot D_B/C_p = k \cdot C_p \cdot V_D/C_p = k \cdot V_D$$

**Example**

Calculate the elimination rate for penicillin if the plasma drug concentration is 2 µg/ml, assuming penicillin has a clearance of 15 ml/min.

**Solution**

$$\text{Elimination rate} = C_p \times Cl_T = 2 \times 15 = 30 \ \mu g/\text{min}$$

Using the previous penicillin example, assume that the plasma penicillin concentration is 10 µg/ml. Calculate the rate of drug elimination.

$$dD_e/\text{dt} = 10 \times 15 = 150 \ \mu g/\text{min}$$

**Example**

A 70-kg male patient has been administered a single oral dose of an antimalarial drug as a prophylactic treatment. If this drug has an elimination half-life of 3 hr and an apparent volume of distribution of 100 ml/kg, assuming that this drug follows a one-compartment kinetic model, determine the drug total body clearance in this patient.

**Solution**

$$k = 0.693/t_{1/2} = 0.693/3 = 0.231 \ \text{hr}^{-1}$$

$$C_T = k \cdot V_D = 0.231 \times 100 = 23.1 \ \text{ml/kg/hr}$$

and for 70 kg, $Cl_T = 23.1 \times 70 = 1617 \ \text{ml/hr}$
5.11. Physiologic/Organ Clearance

This term deals with any individual organ or tissue group involved in the process of drug removal from the body. If Q is the blood flow through this organ, Ca is the concentration of drug entering the organ (usually arterial drug concentration), Cv is the drug concentration leaving the organ (venous drug concentration), so the diagram that best describes this process will be:

\[
\text{Q Ca} \quad \text{Elimination Organ} \quad \text{Q Cv}
\]

\[
\text{Elimination Drug}
\]

Figure 17. Diagram that best describes the process of physiologic/Organ Clearance

Accordingly, the physiologic/organ clearance may be described as the blood volume fraction which contains a specific drug that flows through the organ and is eliminated of this drug per unit time. Accordingly, clearance is considered as the product of the blood flow (Q) to the organ, and the extraction ratio (ER):

Clearance = Q \cdot (ER)

ER is the fraction of drug extracted by the organ as drug passes through and is equal Ca – Cv divided by the entering drug concentration Ca, i.e., \( ER = \frac{(Ca - Cv)}{Ca} \)

\[
CI = Q \cdot \left[ \left( \frac{Ca - Cv}{Ca} \right) / Ca \right]
\]

It must be noted that clearance measurements using the physiologic approach require measurements of blood flow and extraction ratio to a specified organ or group of tissue, which is not so easy, and invasive techniques are needed to obtain these data.

5.12. Model-Independent Methods

These are noncompartment model approaches that help to determine certain pharmacokinetic parameters such as drug clearance and bioavailability (F). In these methods, no assumption for a specific compartment model is required to evaluate the data, which is the major advantage of these methods. In addition, no complicated methods are required to determine the studied pharmacokinetic parameters such as the volume of distribution and the elimination rate constant. These parameters can be calculated directly from the equation that best fits the plasma-drug-concentration time curve.

Clearance can be estimated directly from the plasma–time concentration curve by:
where $D_0$ is the dose and $[AUC]_0^\alpha = \int_0^\alpha C_p\,dt$.

Since $[AUC]_0^\alpha$ is calculated from the plasma-level time curve from 0 to infinity by the trapezoidal rule, no compartmental model is assumed.

In summary, clearances may be expressed mathematically as:

$$\text{Physiologic or organ clearance} = \frac{Q}{Q_{ER}} = \frac{Q}{Q_{ER}}$$

$$\text{Noncompartmental clearance} = \frac{D_0}{[AUC]_0^\alpha}$$

5.13. Renal Clearance

Renal clearance utilizes the same concept for the clearance or the drug clearance previously illustrated, except that the drug is cleared by the kidney and so the volume, mass, or fraction approaches are also applicable here. It could be expressed also as the urinary drug excretion rate $(dDu/dt)$ divided by the plasma drug concentration:

$$Cl_k = \frac{\text{excretion rate}}{\text{plasma concentration}} = \left(\frac{dDu}{dt}\right) / C_p$$

For any drug cleared by the kidney, the rate of drug passing through the kidney must equal the rate of drug excreted in the urine.

$$Cl_k x C_p = Q x C_u$$

where $Cl_k$ is renal clearance, $C_p$ is plasma drug concentration, $Q$ is the rate of urine flow, and $C_u$ is the urine drug concentration.

$$Cl_k = \frac{Q x C_u}{C_p} = \frac{\text{excretion rate}}{C_p}$$

5.14. Excretion Mechanism (Comparison of Drug Excretion Methods)

Since the renal excretion is the urinary drug excretion rate $(dDu/dt)$ divided by the plasma drug concentration, the expression could be rephrased to include the drug excretion mechanisms as follows:
The excretion mechanism could be identified if the clearance value of the drug is compared to a well-recognized standard reference such as Inulin, which is a substance completely cleared through glomerular filtration only (clearance ratio). The following table illustrates identification of the mechanism:

<table>
<thead>
<tr>
<th>Clearance Ratio</th>
<th>Renal Excretion Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl drug/Cl Inulin &lt; 1</td>
<td>Drug is subjected to tubular reabsorption</td>
</tr>
<tr>
<td>Cl drug/Cl Inulin = 1</td>
<td>Drug is filtered only</td>
</tr>
<tr>
<td>Cl drug/Cl Inulin &gt; 1</td>
<td>Drug is subjected to active tubular secretion</td>
</tr>
</tbody>
</table>

**Example**

If glomerular filtration at rate 125 ml/min is the sole elimination mechanism for gentamicin and kanamycin from the body, assuming gentamicin and kanamycin have V<sub>D</sub> of 10 and 20 L, respectively, is there a difference in the drug clearances for each drug based on the classic and physiologic approaches? If not, describe pharmacokinetic parameters that could be used to differentiate between the two drugs.

**Solution**

Since the two drugs are eliminated from the body by glomerular filtration only, the classic and physiologic approaches will be the same and equal 125 ml/min.

For gentamicin: 
\[ k = \frac{Cl}{V_D} = \frac{125}{10000} = 0.0125 \text{ min}^{-1} \]
and 
\[ t_{1/2} = \frac{0.693}{0.0125} = 55.44 \text{ min} \]

For kanamycin: 
\[ k = \frac{125}{20000} = 0.00625 \text{ min}^{-1} \]
and 
\[ t_{1/2} = \frac{0.693}{0.00625} = 110.88 \text{ min} \]

So, there is an obvious difference between the elimination rate and half-life of the two drugs, although both have similar drug clearance.

**5.15. Determination of Renal Clearance by Graphical Methods**

It is possible to determine the renal clearance graphically by two methods:

1. If after administration of a drug, the drug excretion rate \((dDu/dt)\) versus the plasma concentration \((C_p)\) is plotted, the drug excretion rate is the slope of the curve, since

\[ Cl_R = \frac{excretion \ rate}{plasma \ concentration} = \frac{Glomerular \ filtration \ rate + tubular \ secretion \ rate - tubular \ reabsorption \ rate}{C_p} \]

Slope = renal clearance = \((dDu/\ dt) / C_p\)
Figure 18. A plot of the drug excretion rate \( (dD_u/dt) \) versus the plasma concentration \( (C_p) \)

2. Since the renal clearance \( Cl_R = (dD_u / dt) / C_p \), so \( Cl_R . C_p = dDu / dt \)

Rearranging and integration of the last equation will give:

\[
\int_0^{D_u} dD_u = Cl_R \int_Cp \ dt \quad \text{So,} \quad [D_u]_1^{t_2} = Cl_R [AUC]_1^{t_2}
\]

If a graph were plotted of the cumulative drug excreted in the urine versus the area under the plasma-level time curve, renal clearance is the slope of the curve.

By plotting cumulative drug excreted in the urine from \( t_1 \) to \( t_2 \), \( [D_u]_{t_1}^{t_2} \) versus \( [AUC]_{t_1}^{t_2} \), an equation similar to that previously mentioned could be obtained, in which the slope is equal to the renal clearance: \( [D_u]_{t_1}^{t_2} = Cl_R [AUC]_{t_1}^{t_2} \)

Figure 19. A plot of the cumulative drug excreted in the urine versus the area under the plasma-level time curve
Important Considerations

1. Body clearance \( (Cl_T) \), renal clearance \( (Cl_R) \), and hepatic clearance \( (Cl_h) \) can be calculated according to the following expressions:

\[
Cl_T = k \cdot V_D \quad Cl_R = ke \cdot V_D \quad Cl_h = km \cdot V_D
\]

2. Total body clearance \( (Cl_T) \) is equal to the sum of renal clearance and hepatic clearance:

\[
Cl_T = Cl_R + Cl_h \quad k_v D = ke V_D + km V_D \quad k = ke + km
\]

5.16. Fraction of Drug Excreted

The fraction of drug excreted unchanged in the urine \( (f_e) \) is equal to the ratio of the total amount of unchanged drug excreted in the urine \( D^{\alpha_u} \), to the fraction of the dose absorbed, \( FD_0 \):

\[
f_e = D^{\alpha_u} / FD_0
\]

It was found that \( (f_e) \) is also equal to \( ke/k \):

\[
f_e = D^{\alpha_u} / FD_0 = ke / k
\]

Problem

I) A single oral dose of antibiotic (500 mg) was given. The drug is 90% systemically available. The total amount of unchanged drug recovered in the urine was found to be 300 mg, and the total amount of metabolite recovered in the urine was 150 mg. The drug has an elimination half-life of 3.3 hr and its apparent volume of distribution is 1000 ml. Calculate the total body clearance, renal clearance, and nonrenal clearance.

Solution

1. \[
k = 0.693 / 3.3 = 0.21 \text{ hr}^{-1}
\]

\[
Cl_T = k_v D = 0.21 \times 1000 = 210 \text{ mL/hr}
\]

2. Since \( ke / k = D^{\alpha_u} / FD_0 \)

\[
ke = (300 / 450)(0.21) = 0.14 \text{ hr}^{-1}
\]

\[
Cl_R = ke V_D = 0.14 \times 1000 = 140 \text{ mL/hr}
\]

3. \[
Cl_h = Cl_T - Cl_R \quad Cl_h = 210 - 140 = 70 \text{ mL/hr}
\]

II) An analgesic drug was given to an elderly patient by IV bolus injection at a dose of 500 mg. The apparent volume of distribution and the elimination half-life of this drug were estimated to be 21 L and 6 hr, respectively. Urine samples were collected from the patient for 48 hr, and the amount of unchanged drug recovered was found to be 400 mg. Determine the fraction of the dose excreted unchanged from this drug in the urine. Calculate \( k \), \( ke \), \( Cl_T \), \( Cl_R \), and \( Cl_h \).
Solution

\[ f_e = \frac{400}{500} = 0.8 \quad k = \frac{0.693}{6} = 0.1155 \text{ hr}^{-1} \]

\[ ke = f_k k = 0.8 \times 0.115 = 0.0924 \text{ hr}^{-1} \]
\[ Cl_T = k V_D = 0.1155 \times 21 = 2.34 \text{ L/hr} \]
\[ Cl_R = ke V_D = 0.0924 \times 21 = 1.94 \text{ L/hr} \]
\[ Cl_i = Cl_T - Cl_k = 2.34 - 1.94 = 0.49 \text{ L/hr} \]

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