MULTICOMPARTMENT MODELS: INTRAVENOUS BOLUS ADMINISTRATION

Dr. Qutaiba Ahmed Al Aga
Assistant Professor
Faculty of Pharmacy
Philadelphia University-Jordan
Learning Outcomes

At the end of this lesson students will be able to

• Understand the compartmental modeling and it’s significance
• Understand drug absorption, distribution and elimination
• Understand drug clearance including (total, renal and hepatic clearance)
• Understand pharmacokinetics and biopharmaceutics after I.V bolus, I.V infusion, and
• oral administration of drugs.
• Understand protein binding and its effects
• Understand bioavailability and bioequivalence
• Understand Multiple dosage regimen
• Have a knowledge on biopharmaceutics considerations in dosage form design
TWO-COMPARTMENT OPEN MODEL

• Many drugs given in a single intravenous bolus dose demonstrate a plasma level-time curve that does not decline as a single exponential (first-order) process. 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.
• A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body, as is assumed for a one-compartment model.

• The central compartment represents the blood, extracellular fluid, and highly perfused tissues.

• The drug distributes rapidly and uniformly in the central compartment.

• A second compartment, known as the tissue or peripheral compartment, contains tissues in which the drug equilibrates more slowly.
• The drug in the tissues that have the highest blood perfusion equilibrates rapidly with the drug in the plasma. These highly perfused tissues and blood make up the central compartment. While this initial drug distribution is taking place, multicompartment drugs are delivered concurrently to one or more peripheral compartments composed of groups of tissues with lower blood perfusion and different affinity for the drug.
• A drug will concentrate in a tissue in accordance with the affinity of the drug for that particular tissue. For example, lipid-soluble drugs tend to accumulate in fat tissues.

• Drugs that bind plasma proteins may be more concentrated in the plasma, because protein-bound drugs do not diffuse easily into the tissues. Drugs may also bind with tissue proteins and other macromolecules, such as DNA and melanin.
• Tissue sampling is invasive, and the drug concentration in the tissue sample may not represent the drug concentration in the entire organ.
• *General Grouping of Tissues According to perfusion*

<table>
<thead>
<tr>
<th>Highly perfused</th>
<th>Slowly perfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart, brain, hepatic-portal system, kidney, and endocrine glands</td>
<td>Bone, ligaments, tendons, cartilage, teeth, and hair</td>
</tr>
</tbody>
</table>
Drug transfer between the two compartments is assumed to take place by first-order processes.
Plasma level-time curve for the two-compartment open model (single IV dose) described in (model A).
There are several possible two-compartment models

- Model A is used most often and describes the plasma level-time curve observed in the diagram below. By convention, compartment 1 is the central compartment and compartment 2 is the tissue compartment. The rate constants $k_{12}$ and $k_{21}$ represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 ($k_{12}$) and from compartment 2 to compartment 1 ($k_{21}$). The transfer constants are sometimes termed microconstants, and their values cannot be
• Model B assume that elimination occurs from the peripheral compartment model, as shown in (model B)
Model C assume that elimination occurs from the central and peripheral compartment model, as shown in (model C)
• The plasma level-time curve for a drug that follows a two-compartment model may be divided into two parts, (a) a distribution phase and (b) an elimination phase. The two-compartment model assumes that, at $t = 0$, no drug is in the tissue compartment. After an IV bolus injection, drug equilibrates rapidly in the central compartment.
• The distribution phase of the curve represents the initial, more rapid decline of drug from the central compartment into the tissue compartment (line a).

• Although drug elimination and distribution occur concurrently during the distribution phase, there is a net transfer of drug from the central compartment to the tissue compartment.

• The fraction of drug in the tissue compartment during the distribution phase increases up to a maximum in a given tissue, whose value may be greater or less than the plasma drug concentration.

• At maximum tissue concentrations, the rate of drug entry into the tissue equals the rate of drug exit from the tissue.
The fraction of drug in the tissue compartment is now in equilibrium (distribution equilibrium) with the fraction of drug in the central compartment, and the drug concentrations in both the central and tissue compartments decline in parallel and more slowly compared to the distribution phase. This decline is a first-order process and is called the elimination phase or the beta phase (line b).
Since plasma and tissue concentrations decline in parallel, plasma drug concentrations provide some indication of the concentration of drug in the tissue. At this point, drug kinetics appears to follow a one-compartment model in which drug elimination is a first-order process described by $b$ (also known as beta).
Method of Residuals
The method of residuals (also known as feathering or peeling) is a useful procedure for fitting a curve to the experimental data of a drug when the drug does not clearly follow a one-compartment model. For example, 100 mg of a drug was administered by rapid IV injection to a 70-kg, healthy adult male. Blood samples were taken periodically after the administration of drug, and the plasma fraction of each sample was assayed for drug. 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>43.00</td>
</tr>
<tr>
<td>0.5</td>
<td>32.00</td>
</tr>
<tr>
<td>1.0</td>
<td>20.00</td>
</tr>
<tr>
<td>1.5</td>
<td>14.00</td>
</tr>
<tr>
<td>2.0</td>
<td>11.00</td>
</tr>
<tr>
<td>4.0</td>
<td>6.50</td>
</tr>
<tr>
<td>8.0</td>
<td>2.80</td>
</tr>
<tr>
<td>12.0</td>
<td>1.20</td>
</tr>
<tr>
<td>16.0</td>
<td>0.52</td>
</tr>
</tbody>
</table>
When these data are plotted on semilogarithmic graph paper, a curved line is observed. The curved-line relationship between the logarithm of the plasma concentration and time indicates that the drug is distributed in more than one compartment.

\[ C_p = 45e^{-1.8t} + 15e^{-0.21t} \]
As shown in the biexponential curve, the decline in the initial distribution phase is more rapid than the elimination phase. The rapid distribution phase is confirmed with the constant $a$ being larger than the rate constant $b$. Therefore, at some later time the term $A.e^{-at}$ will approach zero, while $B. e^{-bt}$ will still have a value. At this later time Equation will reduce to:

\[ W \quad C_p = B e^{-bt} \]

In common logarithms, is

\[ \log C_p = \frac{-bt}{2.3} + \log B \]
The rate constant can be obtained from the slope \((-b/2.3)\) of a straight line representing the terminal exponential phase. The t 1/2 for the elimination phase (beta half-life) can be derived from the following relationship:

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

In the sample case considered here, \(b\) was found to be 0.21 hr\(^{-1}\). From this information the regression line for the terminal exponential or \(b\) phase is extrapolated to the y-axis; the y intercept is equal to B, or 15 g/mL.

Values from the extrapolated line are then subtracted from the original experimental data points and a straight line is obtained. This line represents the rapidly distributed \(a\) phase.
## Application of the method of Residual

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>$C_p$ observed plasma level</th>
<th>$\dot{C}_p$ extrapolated plasma concentration</th>
<th>$C_p - \dot{C}_p$ residual plasma concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>43.0</td>
<td>14.5</td>
<td>28.5</td>
</tr>
<tr>
<td>0.5</td>
<td>32.0</td>
<td>13.5</td>
<td>18.5</td>
</tr>
<tr>
<td>1.0</td>
<td>20.0</td>
<td>12.3</td>
<td>7.7</td>
</tr>
<tr>
<td>1.5</td>
<td>14.0</td>
<td>11.0</td>
<td>3.0</td>
</tr>
<tr>
<td>2.0</td>
<td>11.0</td>
<td>10.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4.0</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.0</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.0</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• The new line obtained by graphing the logarithm of the residual plasma concentration \((C_p - C'_p)\) against time represents the \(a\) phase. The value for \(a\) is 1.8 hr\(^{-1}\), and the \(y\) intercept is 45 g/mL. The elimination \(t_{\frac{1}{2}}\) is computed from \(b\) and has the value of 3.3 hr.

• At any given time, the plasma concentration can be calculated by:

\[
C_p = Ae^{-at} + Be^{-bt}
\]
A number of pharmacokinetic parameters may be derived by proper substitution of rate constants $a$ and $b$ and y intercepts $A$ and $B$ into the following equations:

$$k = \frac{ab(A + B)}{Ab + Ba}$$

$$k_{12} = \frac{AB(b - a)^2}{(A + B)(Ab + Ba)}$$

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

$k_{12}$ and $k_{21}$ are first-order rate constants that govern the rate of drug change in and out of the tissues.
The volume of the central compartment is useful for determining the drug concentration directly after an IV injection into the body. In clinical pharmacy, this volume is also referred to as Vi or the initial volume of distribution as the drug distributes within the plasma and other accessible body fluids. This volume is generally smaller than the terminal volume of distribution after drug distribution to tissue is completed.
• At zero time \( t = 0 \), all of the drug in the body is in the central compartment. \( C^0_p \) can be shown to be equal to \( A + B \) by the following equation

\[
C_p = Ae^{-at} + Be^{-bt}
\]

• At \( t = 0 \), \( e^0 = 1 \). Therefore

\[
C^0_p = A + B
\]

\[
V_p = \frac{D_0}{A + B}
\]
APPARENT VOLUME OF DISTRIBUTION AT STEADY STATE

At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment.

This term is used for the calculation of the loading dose

\[
(V_D)_{ss} = \frac{D_p + D_t}{C_p}
\]
VOLUME OF DISTRIBUTION BY AREA

This term is used for the calculation of the clearance

\[(V_D)_β = (V_D)_{area} = \frac{D_0}{b[AUC]_0}\]

\[(V_D)_β = \frac{\text{clearance}}{b}\]
Questions
1. Do you agree with the following statements for a drug that is described by a two-compartment pharmacokinetic model? At peak $C_t$, the drug is well equilibrated between the plasma and the tissue compartment, $C_p = C_t$, and the rates of drug diffusion into and from the plasma compartment are equal.

2. What happens after peak $C_t$?

3. Why is a loading dose used?

4. What is $V_i$? How is this volume related to $V_p$?

5. What population factors could affect the concentration of azithromycin?
FREQUENTLY ASKED QUESTIONS

• What is the apparent volume of distribution, and why are there so many different volumes of distribution?

Apparent volumes of distribution are not real tissue volumes, but rather reflect the volume in which the drug is contained. For example,

\[ V_p = \text{initial or plasma volume} \]

\[ V_t = \text{tissue volume} \]

\[ (V_D)_{SS} = \text{steady-state volume of distribution (most often listed in the literature) the steady state drug concentration multiplied by } (V_D). \] SS yields the amount of drug in the body. \((V_D)_{SS}\) is a volume usually determined from area under the curve (AUC), and differs from \((V_D)_{SS}\) somewhat in magnitude. \((V_D)\) multiplied by b gives clearance of the drug.
If physiologic models are better than compartment models, why not just use physiologic models? A physiologic model is a detailed representation of drug disposition in the body. The model requires blood flow, extraction ratio, and specific tissue and organ size. This information is not often available for the individual. Thus, the less sophisticated compartment models are used more often.
• Can I just learn clearance and forget about the other pharmacokinetic parameters, because clearance is the term most often used in clinical pharmacy?

Clearance is used to calculate the steady-state drug concentration and to calculate the maintenance dose. However, clearance alone is not useful in determining the maximum and minimum drug concentrations in a multiple-dosing regimen.
What is the error if I assume a one-compartment model instead of a two-compartment or multicompartment model?

If the two-compartment model is ignored and the data are treated as a one-compartment model, the estimated values for the pharmacokinetic parameters are distorted. For example, during the distributive phase, the drug declines rapidly according to distribution half-life, while in the elimination (terminal) part of the curve, the drug declines according to $b$ elimination half-life.
What kind of improvement in terms of patient care or drug therapy was made using the compartment model?

Compartment models have been used to develop dosage regimens and for the development of pharmacodynamic models. Compartment models have improved the dosing of drugs such as digoxin, gentamicin, lidocaine, and many others. The principal use of compartment models in dosing is to simulate a plasma drug concentration profile based on pharmacokinetic (PK) parameters. This information allows comparison of PK parameters in patients with only two or three points to a patient with full profiles using generated PK parameters.
• H.W.

• After a single IV bolus dose of 1000 mg of an antiarrhythmic drug, the following concentrations were obtained:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>120</td>
</tr>
<tr>
<td>0.5</td>
<td>84</td>
</tr>
<tr>
<td>1.0</td>
<td>53</td>
</tr>
<tr>
<td>2.0</td>
<td>29</td>
</tr>
<tr>
<td>4.0</td>
<td>18</td>
</tr>
<tr>
<td>6.0</td>
<td>15</td>
</tr>
<tr>
<td>8.0</td>
<td>12.5</td>
</tr>
<tr>
<td>12.0</td>
<td>8.8</td>
</tr>
</tbody>
</table>

a. Using the method of residuals, calculate the following parameters: $t_{1/2\alpha}$, $t_{1/2\beta}$, $k$, $k_{12}$, $k_{21}$, $C^0_p$ and $V_p$.

b. What will be the amount of drug remaining in the body after 15 h? Assuming the $(VD)_{ss} = 10$ liter
Recommended Books

- Clinical Pharmacokinetics Concepts and Application s. MALCOIM ROWIAND and THOMASN. TOZER., 1994, 3rd edition. LipPINCOTT WILLIAMS&WILKINS
Happy Thanksgiving