PHAR 7633 Chapter 19
Multi-Compartment Pharmacokinetic Models

Student Objectives for this Chapter

- To draw the scheme and write the differential equations appropriate to a multi-compartment pharmacokinetic model
- To recognize and use the integrated equations for these models to calculate parameter values and for dosage regimen calculations
- To calculate the parameters of these models using the method of residuals

So far we have talked about the pharmacokinetics of drugs in terms of a one compartment model. We have assumed that the drug, once administered is mixed instantaneously in the blood and that the drug distributes throughout the body rapidly reaching equilibrium throughout the tissue into which the drug enters. We have in essence considered that the body acts as a well mixed container.

![Figure 19.1.1 Linear Plot of Cp Versus Time for a One-Compartment - IV Bolus](http://www.boomer.org/c/p4/c19/c19.html)

With first order drug elimination we found that the plasma concentration will fall monoexponentially with time following IV bolus administration.
And the log of the plasma concentration will fall as a straight line.

Commonly we find with real data, especially if we have a number of early data points, that the log Cp versus time plot is not a straight line. We see an initial early deviation from the straight line, followed by a log-linear phase. The initial phase is a more rapid drop in plasma concentration before settling into the log-linear fall in plasma concentration.

This suggests that the body is not behaving as a single well mixed compartment. There appears, mathematically, to be distribution between two (or more) compartments. That is we don't have instantaneous equilibrium between the drug in all the various tissues of the body. In the next approximation we can consider that the body is behaving as two distinct compartments. These compartments can be called the central compartment and the peripheral compartment. Exact anatomical assignment to these compartments is not always possible. However, generally the rapidly perfused tissues often belong in the central compartment.
Intravenous Administration

Scheme or diagram

Figure 19.2.1 Two Compartment Pharmacokinetic Model

Differential equation

The differential equation for drug in the central compartment following intravenous bolus administration is:

$$ \frac{dX_1}{dt} = -kel \cdot X_1 - k_{12} \cdot X_1 + k_{21} \cdot X_2 $$

Equation 19.2.1 Differential Equation for the Central Compartment

The $kel \cdot X_1$ term describes elimination of the drug from the central compartment, while the $k_{12} \cdot X_1$ and $k_{21} \cdot X_2$ terms describe the distribution of drug between the central and peripheral compartments. Writing differential equations can be reviewed in Chapter 2.

Integrated equation

Integration of this equation (using Laplace transforms) leads to a biexponential equation for plasma concentration as a function of time, Equation 19.2.2

$$ Cp = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} $$

Equation 19.2.2 Integrated Equation for Plasma Concentration versus Time

$$ Cp = \frac{\text{Dose} \cdot (\alpha - k_{21})}{V_1 \cdot (\alpha - \beta)} \cdot e^{-\alpha \cdot t} + \frac{\text{Dose} \cdot (k_{21} - \beta)}{V_1 \cdot (\alpha - \beta)} \cdot e^{-\beta \cdot t} $$

Equation 19.2.3 Integrated Equation for $Cp$ versus Time including $k_{21}$ and $V_1$

with $\alpha > \beta$ and
Equation 19.2.4 Calculating values for A and B

\[ A = \frac{Dose \cdot (\alpha - k21)}{V1 \cdot (\alpha - \beta)} \]

\[ B = \frac{Dose \cdot (k21 - \beta)}{V1 \cdot (\alpha - \beta)} \]

The A, B, \( \alpha \), and \( \beta \) terms were derived from the micro-constants during the integration process. They are functions of the micro-constant \( k12, k21, kel \) and \( V1 \)

Using the substitutions for the sum and product of \( \alpha \) and \( \beta \).

\( \alpha + \beta = kel + k12 + k21 \)

\( \alpha \cdot \beta = kel \cdot k21 \)

If we know the values of \( kel, k12 \) and \( k21 \) we can calculate \( \alpha + \beta \) as well as \( \alpha \cdot \beta \). Substituting these values into Equation 19.2.3 gives us values for \( \alpha \) and \( \beta \).

\[ \alpha, \beta = \frac{(\alpha + \beta) \pm \sqrt{(\alpha + \beta)^2 - 4 \cdot \alpha \cdot \beta}}{2} \]

Equation 19.2.5 Converting from \( kel, k12 \) & \( k21 \) to \( \alpha \) & \( \beta \)

Note, in this equation, \( \alpha \) is calculated when '+' is used in the numerator and \( \beta \) is calculated when '-' is used in place of the '±'. Thus \( \alpha \) is greater than \( \beta \).

Once we have values for \( \alpha \) and \( \beta \) we can calculate values for A and B using Equation 19.2.4.

An example calculation (from the homework)

"A drug follows first order (i.e. linear) two compartment pharmacokinetics. After looking in the literature we find a number of parameter values for this drug. These numbers represent the micro constants for this drug. In order that we can calculate the drug concentration after a single IV bolus dose these parameters need to be converted into values for the macro constants. The \( kel \) and \( V1 \) for this drug in this patient (90.5 kg) are 0.192 hr\(^{-1}\) and 0.39 L/kg, respectively. The \( k12 \) and \( k21 \) values this drug are 1.86 and 1.68 hr\(^{-1}\), respectively. What is the plasma concentration of this drug 1.5 hours after a 500 mg, IV Bolus dose. In order to complete this calculation first calculate the appropriate A, B, \( \alpha \) and \( \beta \) values."

Since \( \alpha + \beta = kel + k12 + k21 = 0.192 + 1.86 + 1.68 = 3.732 \)

and

\( \alpha \times \beta = kel \times k21 = 0.192 \times 1.68 = 0.32256 \)

Now:

\[ \alpha = \frac{[(a+b) + \sqrt{(a+b)^2 - 4axb}]}{2} = \frac{[3.732 + \sqrt{(3.732)^2 - 4 \times 0.32256}]}{2} = \frac{3.732 + 3.5549}{2} = 3.643 \text{ hr}^{-1} \]

\[ \beta = \frac{[3.732 - 3.5549]}{2} = 0.08853 \text{ hr}^{-1} \]

A = \( \frac{Dose \times (\alpha - k21)}{[V1 \times (\alpha - b)]} = \frac{500 \times (3.643 - 1.68)}{[90.5 \times 0.39]} = \frac{(3.643 - 0.08853)}{[35.295]} = 7.824 \) mg/L

B = \( \frac{Dose \times (k21 - b)}{[V1 \times (\alpha - b)]} = \frac{500 \times (1.68 - 0.08853)}{[35.295]} = 6.343 \) mg/L

The last step is

\[ Cp = \alpha \times e^{(-\alpha \times t)} + \beta \times e^{(-\beta \times t)} = 7.824 \times e^{(-3.643 \times 1.5)} + 6.343 \times e^{(-0.08853 \times 1.5)} = 7.824 \times 0.004234 + 6.343 \times 0.8756 = 0.0331 + 5.5542 = 5.59 \) mg/L
Later in this chapter we will use equations for the reverse process of converting $\alpha, \beta, A$ and $B$ into values for $k_{12}, k_{21}, k_{el}$ and $V_1$. 
## Calculator 19.2.1 Calculate A, B, α and β

<table>
<thead>
<tr>
<th>Dose:</th>
<th>500</th>
</tr>
</thead>
<tbody>
<tr>
<td>V₁:</td>
<td>25</td>
</tr>
<tr>
<td>kel:</td>
<td>0.2</td>
</tr>
<tr>
<td>k₂₁:</td>
<td>1.5</td>
</tr>
<tr>
<td>k₁₂:</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Calculate**

<table>
<thead>
<tr>
<th>A is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>α is:</td>
</tr>
<tr>
<td>B is:</td>
</tr>
<tr>
<td>β is:</td>
</tr>
</tbody>
</table>

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PHAR 7633 Chapter 19

Multi-Compartment Pharmacokinetic Models

Parameter Determination

Method of residuals

Values for kel, k12, k12 and other parameters can be determined by first calculating A, B, α, and β. For this we can use the method of residuals (in a similar fashion to determining ka and kel for the one compartment model after oral administration). Starting with the equation for Cp.

\[ Cp = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]

Equation 19.3.1 Concentration versus time after an IV Bolus Dose, Two Compartment Model

By definition α is greater than β then as t approaches ∞, \( e^{-\alpha \cdot t} \) approaches 0 faster than \( e^{-\beta \cdot t} \). Therefore if the ratio α/β is large enough (greater than 5) the terminal data points will fall on the line

\[ Cp_{late} = B \cdot e^{-\beta t} \]

Equation 19.3.2 Equation for \( Cp_{late} \) versus time

This equation is similar to the equation for the late plasma concentration values after oral administration with a one compartment model. This will be a straight line if plotted on semi-log graph paper.

![Figure 19.3.1 Semi-Log Plot of Cp Versus Time Showing Cp_{late} Extrapolated Back to B](http://www.boomer.org/c/p4/c19/c19.html)

From the slope of this line a value of β can be determined.

\[ \beta = \frac{\ln(Cp_{late,1}) - \ln(Cp_{late,2})}{t_2 - t_1} \]

Equation 19.3.3 Determining β from the \( Cp_{late} \) Line

The units for β and α, below, are reciprocal time, for example min⁻¹, hr⁻¹, etc.
Biological half-life or Terminal half-life

The $t_{1/2}$ calculated as $0.693/\beta$ is often called the biological half-life or terminal half-life. It is the half-life describing the terminal elimination of the drug from plasma. [For the one compartment model the biological half-life was equal to $0.693/\text{kel}$].

The difference between the $C_p^{late}$ values (red line) at early times and the actual data at early times is again termed the 'residual'

$$\text{Residual} = C_p - C_p^{late} = A \cdot e^{-\alpha t}$$

Equation 19.3.4 Equation for Residual versus time


The slope of the residual line (green line) will provide the value of $\alpha$ and $A$ can be estimated as the intercept of the concentration axis (y-axis). A more accurate value for the $\alpha$ value can be determined by expanding the scale on the time axis (Figure 19.3.3). Don't forget to use the new time values when calculating $\alpha$ from the equation

$$\alpha = \frac{\ln(\text{Residual}_1) - \ln(\text{Residual}_2)}{t_2 - t_1}$$

Equation 19.3.5 Determining $\alpha$ from the Residual Line
Figure 19.3.3 Semi-Log Plot of Cp Versus Time Showing Residual Line and Cp Data - NOTE the expansion of the time axis (x axis)

Converting macro constants to micro constants

With A, B, α, and β determined using the method of residuals we can calculate the micro-constants from the equations.

\[
k_{21} = \frac{A \cdot \beta + B \cdot \alpha}{A + B}
\]

\[
k_{el} = \frac{\alpha \cdot \beta}{k_{21}}
\]

\[
k_{12} = \alpha + \beta - k_{21} - k_{el}
\]

Equation 19.3.6 Converting from A, B, α & β to kel, k12 & k21
Calculator 19.3.1 Calculate k10, k12, k21 and V₁

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose:</td>
<td>500</td>
</tr>
<tr>
<td>A:</td>
<td>24</td>
</tr>
<tr>
<td>(\alpha):</td>
<td>1.5</td>
</tr>
<tr>
<td>B:</td>
<td>6</td>
</tr>
<tr>
<td>(\beta):</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Calculate

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>(kel)</td>
<td></td>
</tr>
<tr>
<td>(k_{12})</td>
<td></td>
</tr>
<tr>
<td>(k_{21})</td>
<td></td>
</tr>
<tr>
<td>(V₁)</td>
<td></td>
</tr>
</tbody>
</table>

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Multi-Compartment Pharmacokinetic Models

Effect of k12 and k21 on Drug Concentration versus Time

Changing the Ratio of k12 to k21

From the k12 and k21 values we can assess the extent of distribution of drug into the peripheral compartment. The higher the ratio k12/k21 the greater the distribution of drug into the peripheral compartment. The larger the individual values of k12 and k21 the faster is the transfer between the central and peripheral compartments and the more the body behaves as a single compartment.

As the ratio increases the distribution phase is more pronounced. Conversely with the ratio 1/4 there is very little distribution phase. Also note that the β value or the slope of the terminal phase is changing even though the kel is fixed at 0.2 hr⁻¹.

Changing the Magnitude of k12 and k21 with the Same Ratio

With faster and faster distribution the initial drop in plasma concentration becomes quite rapid. If you were sampling every 30 minutes, the initial phase would be missed. The data would look just like a one compartment model. Redrawing the slow plot with k12/k21 (0.5/0.25) over 24 hours and gives a plot that is definitely still biexponential.
Simulate other concentration versus time curves after IV bolus administration with the two compartment pharmacokinetic model using macro constants (A, B, α and β)

Linear plot - Semi-log plot

or micro constants (kel, k12, k21, and V1)

Linear plot - Semi-log plot

Click on the figure to view as an interactive graph or a Semi-log Plot

Figure 19.4.2 Plot of Cp versus Time Showing the Effect of Different k12/21 Magnitudes
PHAR 7633 Chapter 19

Multi-Compartment Pharmacokinetic Models

Apparent Volumes of Distribution

The concentration of drug in the body is determined not only by the rate constant values but also by the apparent volume of distribution. In the case of the two compartment model a number of volume terms can be defined.

$V_1$

The apparent volume of the central compartment, $V_1$ or $V_c$, can be calculated as:

$$V_1 = \frac{Dose}{A + B} = \frac{Dose}{C_p^0} \quad \text{(since } A + B = C_p^0)$$

Equation 19.5.1 Apparent Volume of Central Compartment

This parameter is important because it allows the calculation of the highest plasma concentration or $C_p^0$ after an IV bolus administration. This concentration may result in transient toxicity. $V_1$ can also be used in dose calculations.

$V_{area}$ ($= V_β$)

$V_{area}$ or $V_β$ is defined as:

$$V_{area} = \frac{Dose}{\beta \cdot AUC} = \frac{V_1 \cdot kel}{\beta} = \frac{Clearance}{\beta} = V_β$$

Equation 19.5.2 Apparent Volume, $V_{area}$

Because of the relationship with clearance and $\beta$ and with $V_1$ and $kel$ this parameter is quite useful in dosing calculations. This parameter can be readily calculated via AUC and $\beta$ values from the 'raw' data and is therefore commonly quoted.

$V_{ss}$

$V_{ss}$, $V$ steady state defined as:

$$V_{ss} = V_1 \cdot \frac{k_{12} + k_{21}}{k_{21}}$$

Equation 19.5.3 Apparent Volume, Steady State

This term relates the total amount of drug in the body at 'steady state' with the concentration in plasma or blood.
Figure 19.5.1 Plot of X1 (Plasma) and X2 (Tissue) Compartment Concentrations, Showing ‘Steady State’ with Both Lines Parallel

The relationship between volume terms is that:

$V_{\text{area}} > V_{ss} > V_1$

And for a one compartment model the values for all these parameters are equal.

**Example Calculation**

As an example we can look at the data in the table below.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Concentration (mg/L)</th>
<th>Cplate (mg/L)</th>
<th>Residual (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>20.6</td>
<td>8.8</td>
<td>11.8</td>
</tr>
<tr>
<td>1</td>
<td>13.4</td>
<td>7.8</td>
<td>5.6</td>
</tr>
<tr>
<td>2</td>
<td>7.3</td>
<td>6.1</td>
<td>1.2</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>4.7</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>3.7</td>
<td>3.7</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 19.5.1 Two Compartment Pharmacokinetics
The first two columns are the time and plasma concentration which may be collected after IV bolus administration of 500 mg of drug. These data are plotted (n) in Figure 19.5.2 above. At longer times, after 4 hours, out to 12 hours the data appears to follow a straight line on semi-log graph paper. Since $\alpha > \beta$ this terminal line is described by $B \cdot e^{-\beta \cdot t}$.

Following it back to $t = 0$ gives $B = 10 \text{ mg/L}$. From the slope of the line $\beta = 0.25 \text{ hr}^{-1}$. $C_p^{late}$ values at early times are shown in column 3 and the residual in column 4. The residual values are plotted (o) also 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.

$B = 10 \text{ mg/L}, \beta = (\ln 10 - \ln 0.5)/12 = 2.996/12 = 0.25 \text{ hr}^{-1}$

$A = 25 \text{ mg/L}, \alpha = (\ln 25 - \ln 0.27)/3 = 4.528/3 = 1.51 \text{ hr}^{-1}$

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

We can now calculate the micro-constants.

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

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

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

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

The AUC by the trapezoidal rule + $C_p^{last}/\beta = 56.3 + 2.0 = 58.3 \text{ mg.hr.L}^{-1}$. [Note the use of $\beta$] thus

$$V_{area} = \frac{Dose}{\beta \cdot AUC} = \frac{500}{0.25 \times 58.3} = 34.3 \text{ L}$$
\[ V_{ss} = V_1 \cdot \frac{k21 + k12}{k21} = 14.3 \times \frac{0.61 + 0.62}{0.61} = 26.7 \text{ } L \]

Notice that \( V_{\text{area}} > V_{ss} > V_1 \) [34.3 > 26.7 > 14.3]

Want more practice with this type of problem!
Dosage Calculations

Dosage calculations are complicated by the extra terms in the equations however some calculations are still reasonably straightforward. The dose required for a particular initial plasma concentration can be calculated if $V_1$ is known. Thus:

$$Dose = V_1 \cdot C_P^0 \text{ (required)}$$

**Equation 19.6.1 Equation for Loading Dose**

To achieve an initial $C_P$ of 20 mg/L given $V_1 = 30$ liter would require a DOSE = $20 \times 30 = 600$ mg.

Alternately if a dose of 500 mg is given and the $V_1$ value is 16 L, the expected $C_P^0$ can be calculated.

$$C_P^0 = 500/16 = 31.3 \text{ mg/L}$$

If the $A$, $B$, $\alpha$, and $\beta$ values are known or calculated, then the plasma concentration at any time after a single IV dose can be calculated.

The plasma concentration achieved after a continuous IV infusion is given by the same equation described for the one compartment model, i.e.:

$$k_0 = C_P^{ss} \cdot CL = C_P^{ss} \cdot V_1 \cdot k_\text{el} = C_P^{ss} \cdot V_{area} \cdot \beta$$

**Equation 19.6.2 Equation for Maintenance Infusion Rate**

If a plasma concentration of 30 mg/L is required and $V_1 = 15$ L and $k_\text{el}$ is 0.2 hr$^{-1}$ then the required infusion rate can be readily determined.

$k_0 = 30 \times 15 \times 0.2 = 90 \text{ mg/hr}$
Since the time to reach the steady state concentration is controlled by the $\beta$ value this could mean a slow approach to the desired value, thus an IV bolus loading dose may be useful. Unfortunately this calculation is not straight forward as you will see if you explore the applet.

With $V_1 = 15 \text{ L}$, $k_e l = 0.2 \text{ hr}^{-1}$, and required $C_p = 30 \text{ mg/L}$

Bolus DOSE $= 15 \times 30 = 450 \text{ mg}$ and

Infusion Rate $= k_0 = 30 \times 15 \times 0.2 = 90 \text{ mg/hr}$

As you can see (Figure 19.6.1 and 19.6.2 above) this gives quite a dip in the $C_p$ versus time curve.

With Bolus DOSEs, either 600 or 300 mg (shown in Figure 19.6.2) the curves may or may not be better depending on the therapeutic range of the drug.
Another alternative is to give a fast infusion followed by the maintenance infusion. Here 1200 mg was given over 4 hours (at 300 mg/hr) before switching to the slower 90 mg/hr maintenance rate.

Try a dosing problem with a drug following a two compartment pharmacokinetic model.
Multi-Compartment Pharmacokinetic Models

Oral Administration

Following oral administration of a drug with two compartment characteristics, \( C_p \) is described by an equation with three exponential terms.

\[
\frac{dX_1}{dt} = ka \cdot X_g + k_{21} \cdot X_2 - (k_{12} + k_{el}) \cdot X_1
\]

Equation 19.7.1 Differential Equation for Drug Amount in the Body after Oral Administration

Differential equation

\[
C_p = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} + C \cdot e^{-k_a \cdot t}
\]

Equation 19.7.2 Integrated Equation for Drug Amount in the Body after Oral Administration

where \( A + B + C = 0 \)
Figure 19.7.1 Semi-Log Plot Showing Pronounced Distribution

Figure 19.7.2 Semi-Log Plot Without Distribution Phase Evident
Bioavailability

Bioavailability calculations are the same as for the one compartment model, i.e., by comparison of AUC or U∞. These apply for any linear system. Also if α, β, and ka are sufficiently separated the method of residuals can be applied (twice) to determine values for these three parameters.

Average Plasma Concentration

The average plasma concentration equation can also be used to calculate appropriate dosing regimens. For example if an average plasma concentration of 20 mg/L is required and V1 = 15 L, kel = 0.15 hr⁻¹, F = 0.9 and a dosing interval of 12 hours is to be used then the required dose can be calculated from the equation for Cp_average.

\[
\frac{C_p}{Dose} = \frac{F \cdot Dose}{CL \cdot \tau} = \frac{F \cdot Dose}{kel \cdot V_1 \cdot \tau} = \frac{F \cdot Dose}{\beta \cdot V_\beta \cdot \tau}
\]

Equation 19.7.3 Equation for Average Plasma Concentration

The required dose can be calculated using Equation 19.7.3 and the data provided. Thus

\[
Dose = \frac{20 \times 15 \times 0.15 \times 12}{0.9} = 600 \text{ mg every 12 hours}
\]
An Excel spreadsheet to calculate $C_p$ versus time after IV Bolus, IV Infusion (fast), IV Infusion (slow), and/or Oral can be downloaded by clicking on the figure below.

![Excel spreadsheet](c1901.xls)

Click on the figure to download and use this Excel spreadsheet

**Figure 19.7.3 Excel™ Spreadsheet Illustrating Concentrations calculated according to a Two Compartment Model**

WARNING: this spreadsheet does include some macros for printing and changing Y-axis scaling.

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