PHAR 7632 Chapter 19

Multi-Compartment Pharmacokinetic Models

return to the Course index
previous | next

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.

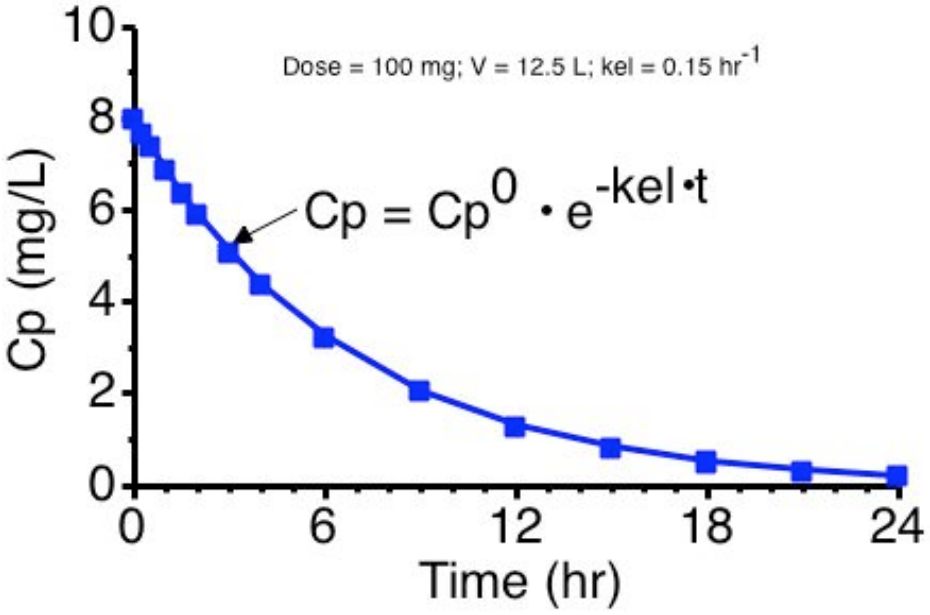


Figure 19.1.1 Linear Plot of Cp Versus Time for a One-Compartment - IV Bolus

With first order drug elimination we found that the plasma concentration will fall monoexponentially with time following IV bolus administration.

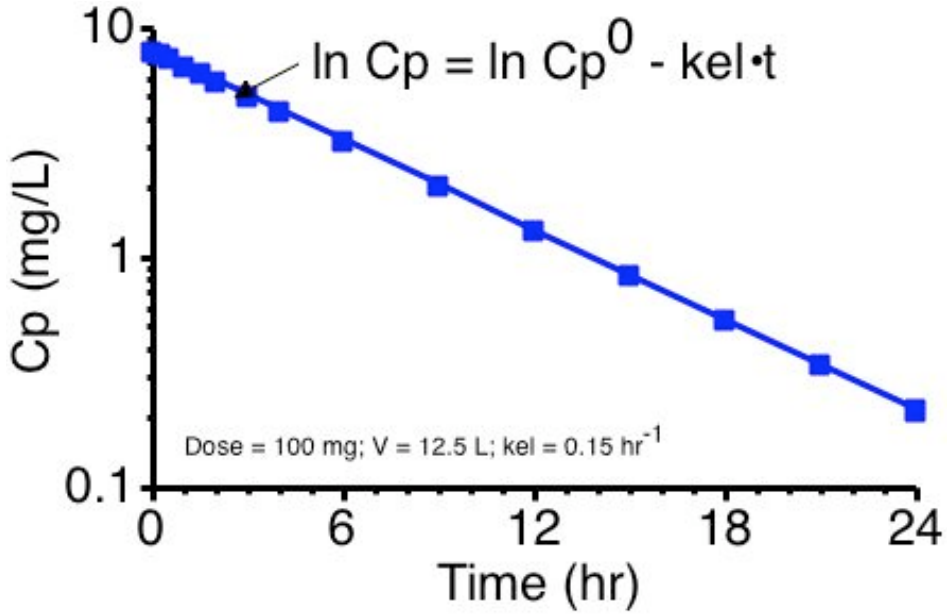


Figure 19.1.2 Semi-Log Plot of Cp Versus Time

And the log of the plasma concentration will fall as a straight line.

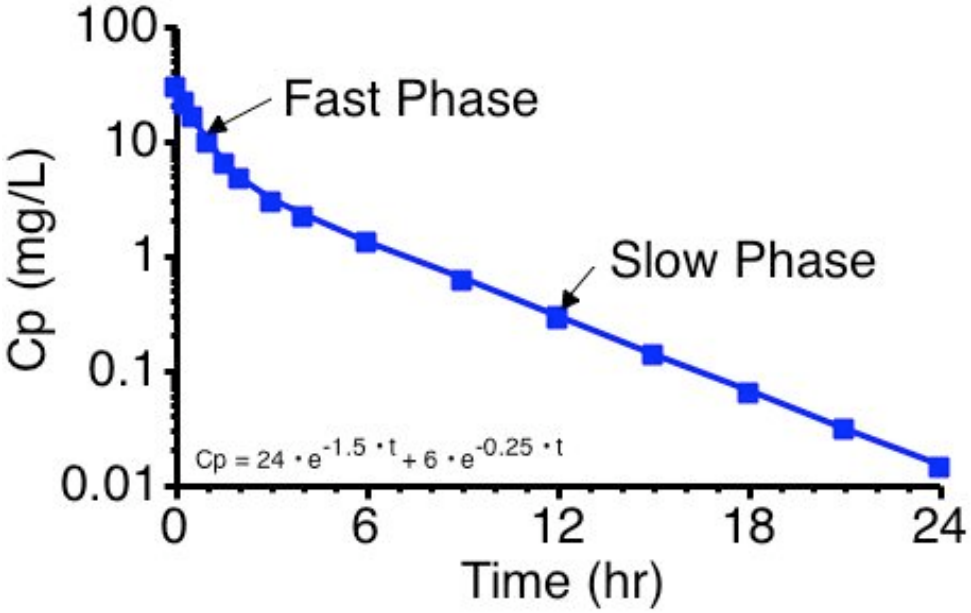


Figure 19.1.3 Semi-Log Plot of Cp Versus Time. Two-Compartment - IV Bolus. Note Fast and Slow Processes

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.

---

return to the Course index

previous | next

PHAR 7632 Chapter 19

Multi-Compartment Pharmacokinetic Models

return to the Course index
previous | next

Intravenous Administration

Scheme or diagram

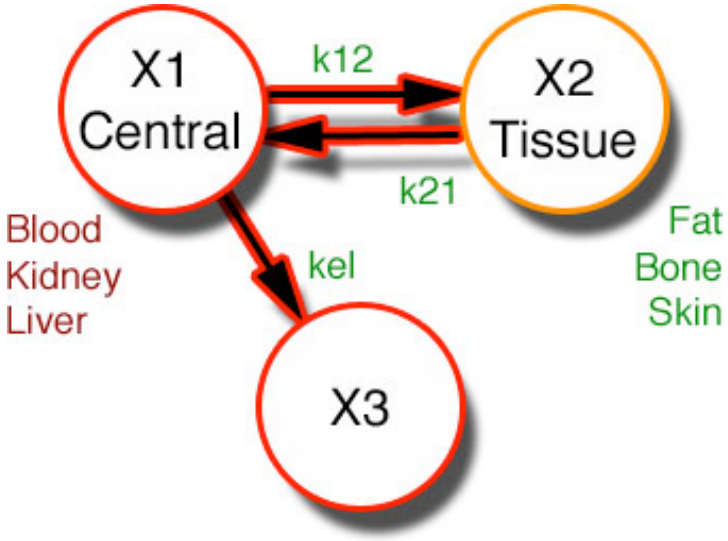


Diagram 19.2.1 Two Compartment Pharmacokinetic Model

Differential equation

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

$$\frac{dX1}{dt} = -kel \bullet X1 - k12 \bullet X1 + k21 \bullet X2$$

Equation 19.2.1 Differential Equation for the Central Compartment

The kel • X1 term describes elimination of the drug from the central compartment, while the k12 • X1 and k21 • X2 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.

That is,

$Cp = A \bullet e^{-\alpha \bullet t} + B \bullet e^{-\beta \bullet t}$ with $\alpha > \beta$.

The A, B, α, and β 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 α and β.

α + β = kel + k12 + k21

α • β = kel • k21

$$\alpha,\beta = \frac{(\alpha+\beta) \pm \sqrt{(\alpha+\beta)^2 - 4 \bullet \alpha \bullet \beta}}{2}$$

Note, in this equation, α is calculated when '+' is used in the numerator and β is calculated when '-' is used in place of the '±'. Thus α is greater than β.

We can then calculate values for A and B.

$$A = \frac{Dose \bullet (\alpha - k21)}{V_1 \bullet (\alpha - \beta)}$$

$$B = \frac{Dose \bullet (k21 - \beta)}{V_1 \bullet (\alpha - \beta)}$$

Later in this chapter we will use equations for the reverse process of converting α, β, A and B into values for k12, k21, kel and V_1.

Calculator 19.2.1 Calculate A, B, α and β

Dose:	500
V_1:	25
kel:	0.2
k21:	1.5
k12:	2.0
	Calculate
A is:	
α is:	
B is:	
β is:	

return to the Course index
previous | next

This page (http://www.boomer.org/c/p4/c19/c1902.html) was last modified: Saturday 31 Dec 2005 at 03:58 PM

PHAR 7632 Chapter 19

Multi-Compartment Pharmacokinetic Models

return to the Course index
previous | next

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.

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

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

$$Cp^{late} = B \bullet e^{-\beta \bullet t}$$

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.

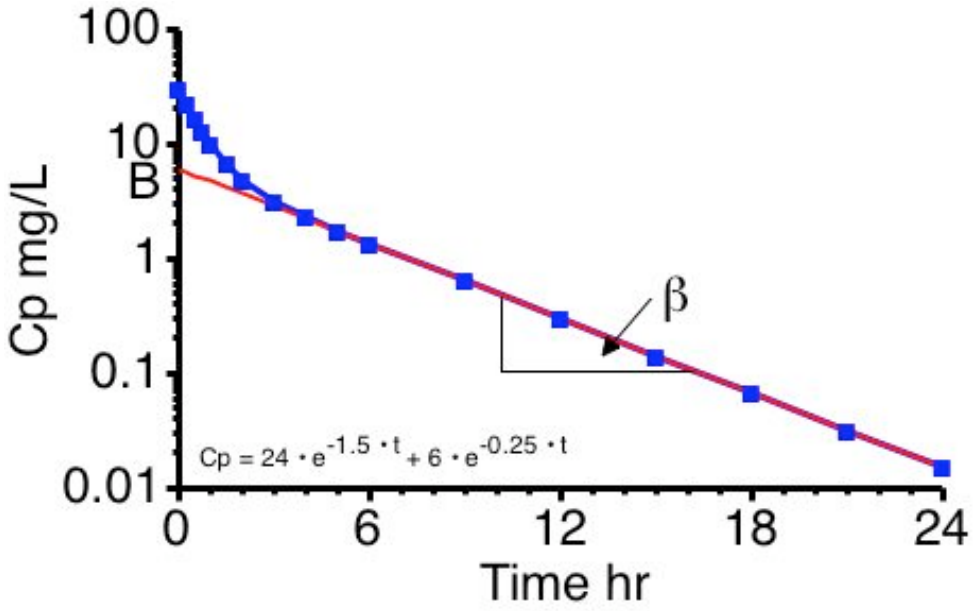


Figure 19.3.1 Semi-Log Plot of Cp Versus Time Showing Cp^{late} Extrapolated Back to B

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/β 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/kel].

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

$$\text{Residual} = Cp - Cp^{late} = A \bullet e^{-\alpha \bullet t}$$

Equation 19.3.4 Equation for Residual *versus* time

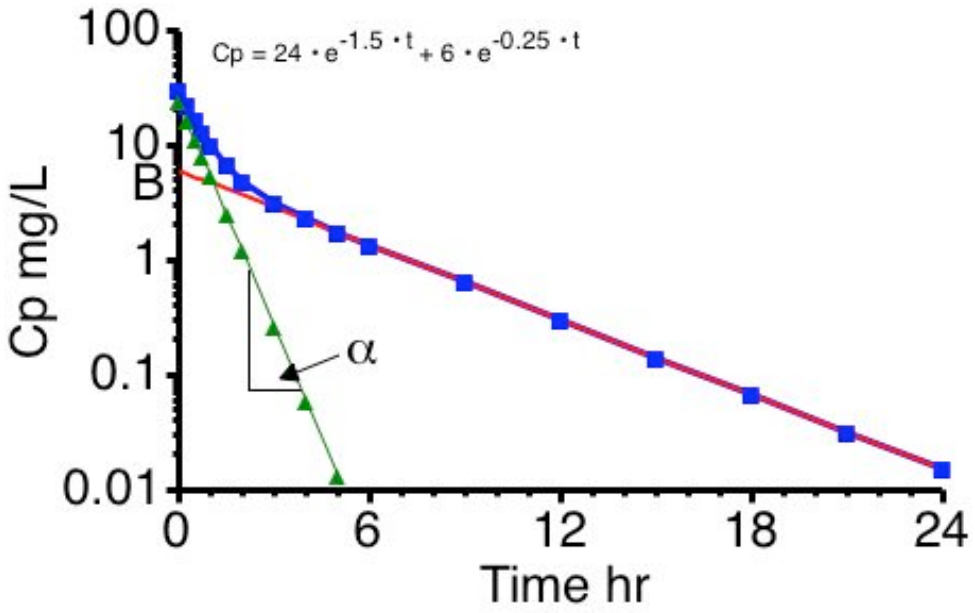


Figure 19.3.2 Semi-Log Plot of Cp Versus Time Showing Residual Line and Cp_{late} Line

Click on the figure to view as a Java Applet
or a Java Applet as a Linear Plot
Linear or Semi-log plots as a Tiger widget

The slope of the residual line (green line) will provide the value of α and A can be estimated as the intercept of the concentration axis (y-axis). A more accurate vlue for the α 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 α from the equation

$$\alpha = \frac{ln(Residual_1) - ln(Residual_2)}{t_2 - t_1}$$

Equation 19.3.5 Determining α from the Residual Line

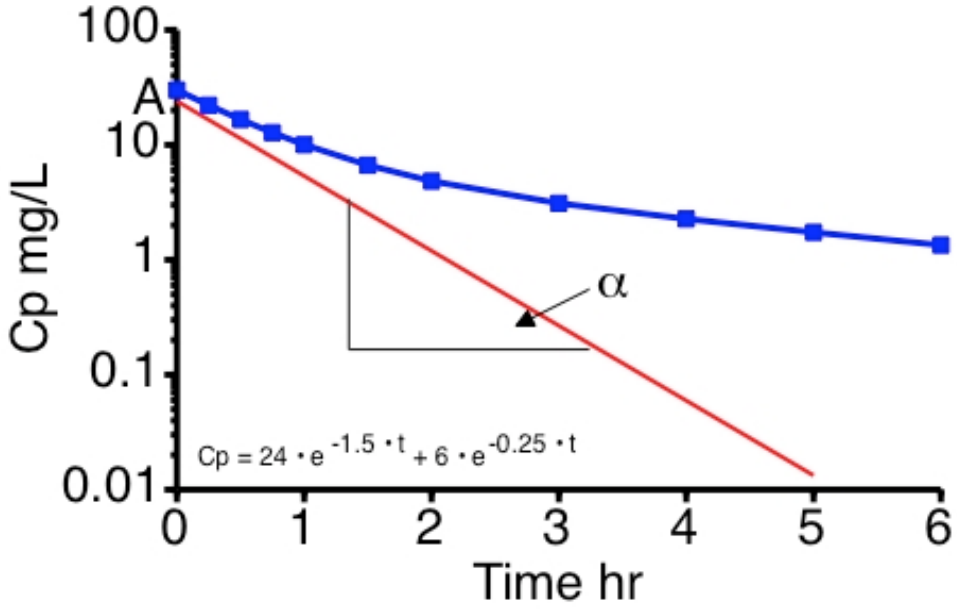


Figure 19.3.3 Semi-Log Plot of Cp Versus Time Showing Residual Line and Cp Data - NOTE the expansion of the time axis (x axis)

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.

$$k21 = \frac{A \bullet \beta + B \bullet \alpha}{A + B}$$

$$kel = \frac{\alpha \bullet \beta}{k21}$$

$$k12 = \alpha + \beta - k21 - kel$$

Calculator 19.3.1 Calculate k10, k12, k21 and V_1

Dose:	500
A:	24
α:	1.5
B:	6
β:	0.25
	Calculate
kel is:	
k12 is:	
k21 is:	
V_1 is:	

return to the Course index
previous | next

This page (http://www.boomer.org/c/p4/c19/c1903.html) was last modified: Saturday 31 Dec 2005 at 03:58 PM

PHAR 7632 Chapter 19

Multi-Compartment Pharmacokinetic Models

return to the Course index
previous | next

Effect of k12 and k21

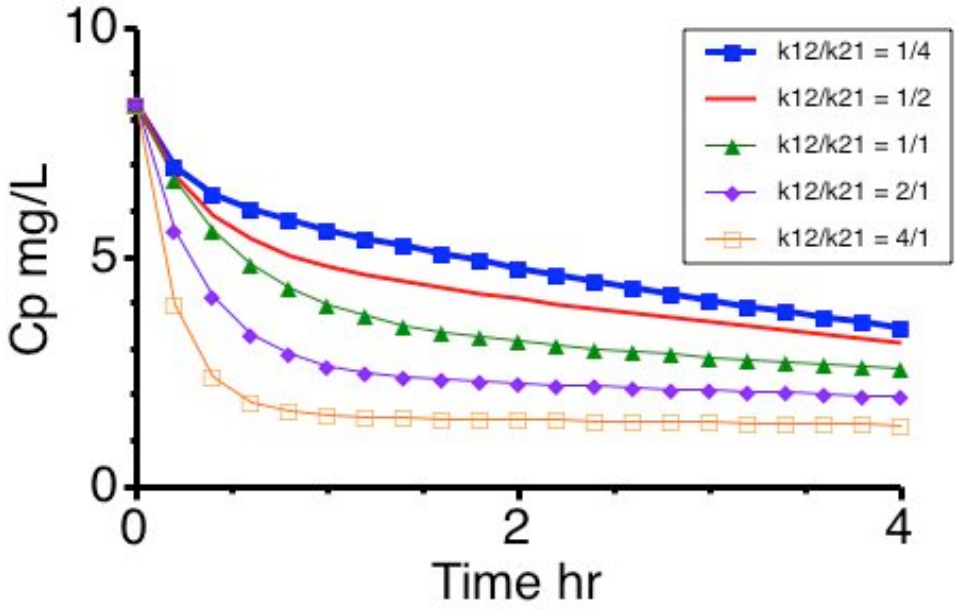


Figure 19.4.1 Plot of Cp versus Time Showing the Effect of Different k12/21 Ratio Values

Click on the figure to view as a Java Applet
or a Java Applet as a Semi-log Plot
Linear or Semi-log plots as a Tiger widget

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}.

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.

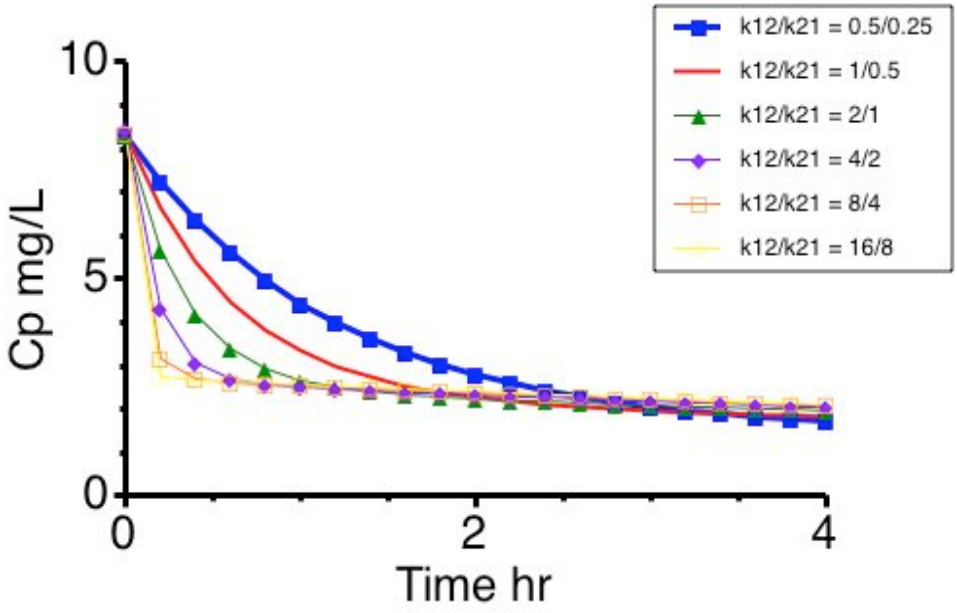


Figure 19.4.2 Plot of Cp versus Time Showing the Effect of Different k12/21 Magnitudes

Click on the figure to view as a Java Applet
or a Java Applet as a Semi-log Plot
Linear or Semi-log plots as a Tiger widget

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

---

return to the Course index
previous | next

This page (http://www.boomer.org/c/p4/c19/c1904.html) was last modified: Saturday 31 Dec 2005 at 03:58 PM

PHAR 7632 Chapter 19

Multi-Compartment Pharmacokinetic Models

return to the Course index
previous | next

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 been defined.

V_1

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

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

Equation 19.5.1 Apparent Volume of Central Compartment

This parameter is important because it allows the calculation of the highest plasma concentration or Cp^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:

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

Equation 19.5.2 Apparent Volume, V_{area}

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

V_{ss}

V_{ss}, V steady state defined as:

$$V_{ss} = V_1 \bullet \frac{k12 + k21}{k21}$$

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

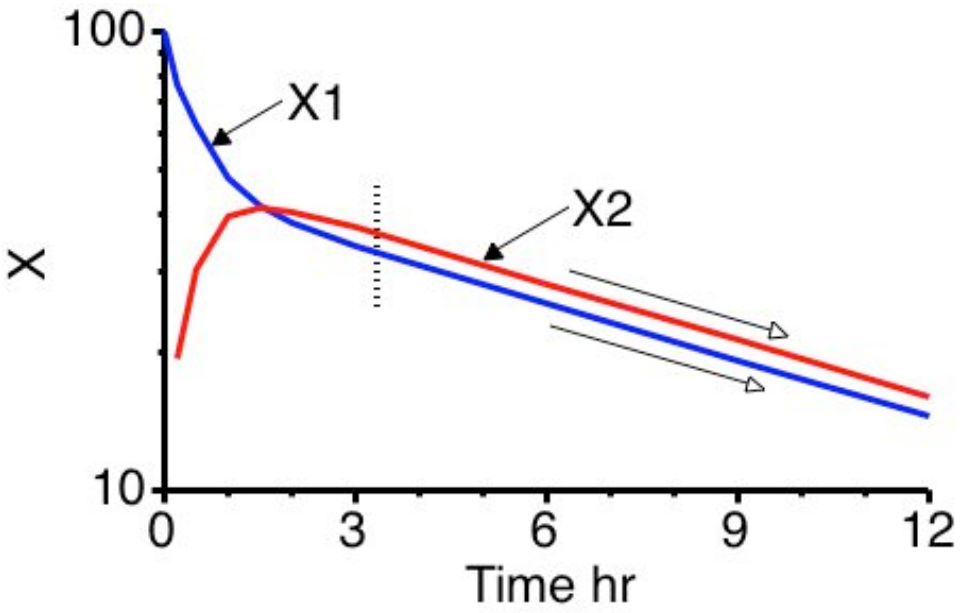


Figure 19.5.1 Plot of X1 (Plasma) and X2 (Tissue) Compartment Concentrations, Showing 'Steady State' with Both Lines Parallel

The relationship between volume terms is that:

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

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 19.5.1 Two Compartment Pharmacokinetics

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

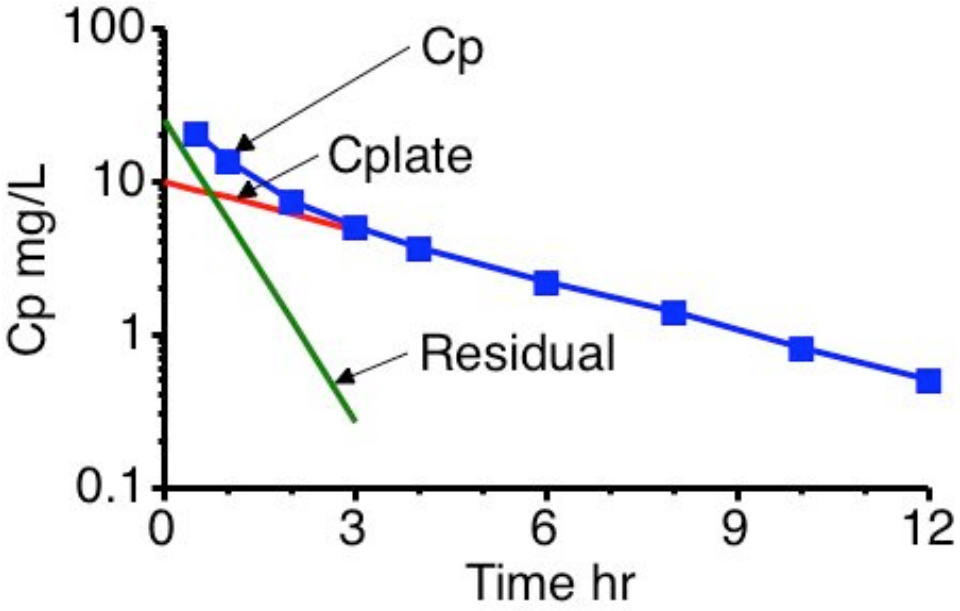


Figure 19.5.2 Plot of Cp versus Time Illustrating the Method of Residuals

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 $B \bullet e^{-\beta \bullet t}$.

Following it back to t = 0 gives B = 10 mg/L. From the slope of the line $\beta = 0.25\ hr^{-1}$. Cp^{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 mg/L and $\alpha = 1.51\ hr^{-1}$ Note that $\alpha/\beta = 6$, thus these values should be fairly accurate.

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

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

Therefore $Cp = 25 \bullet e^{-1.51 \bullet t} + 10 \bullet e^{-0.25 \bullet t}$

We can now calculate the micro-constants.

$$k21 = \frac{A \bullet \beta + B \bullet \alpha}{A + B} = \frac{25 \times 0.25 + 10 \times 1.51}{25 + 10} = 0.61\ hr^{-1}$$

$$kel = \frac{\alpha \bullet \beta}{k21} = \frac{1.51 \times 0.25}{0.61} = 0.62\ hr^{-1}$$

$$k12 = \alpha + \beta - k21 - kel = 1.51 + 0.25 - 0.61 - 0.62 = 0.53\ hr^{-1}$$

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

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

$$V_{area} = \frac{Dose}{\beta \bullet AUC} = \frac{500}{0.25 \times 58.3} = 34.3\ L$$

$$V_{ss} = V_1 \bullet \frac{k21 + k12}{k21} = 14.3 \times \frac{0.61 + 0.62}{0.61} = 26.7\ L$$

Notice that $V_{area} > V_{ss} > V_1$ [34.3 > 26.7 > 14.3]

Want more practice with this type of problem!

---

return to the Course index
previous | next

This page (http://www.boomer.org/c/p4/c19/c1905.html) was last modified: Saturday 31 Dec 2005 at 03:58 PM

PHAR 7632 Chapter 19

Multi-Compartment Pharmacokinetic Models

return to the Course index
previous | next

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:

$$\text{Dose} = V_1 \bullet Cp^0 \text{ (required)}$$

Equation 19.6.1 Equation for Loading Dose

To achieve an initial Cp of 20 mg/L given V_1 = 30 liter would require a DOSE = 20 * 30 = 600 mg.

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

Cp^0 = 500/16 = 31.3 mg/L

If the A, B, α, and β 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.:

$$k0 = Cp^{ss} \bullet Cl = Cp^{ss} \bullet V_1 \bullet kel = Cp^{ss} \bullet V_{area} \bullet \beta$$

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 kel is 0.2 hr^{-1} then the required infusion rate can be readily determined.

k0 = 30 x 15 x 0.2 = 90 mg/hr

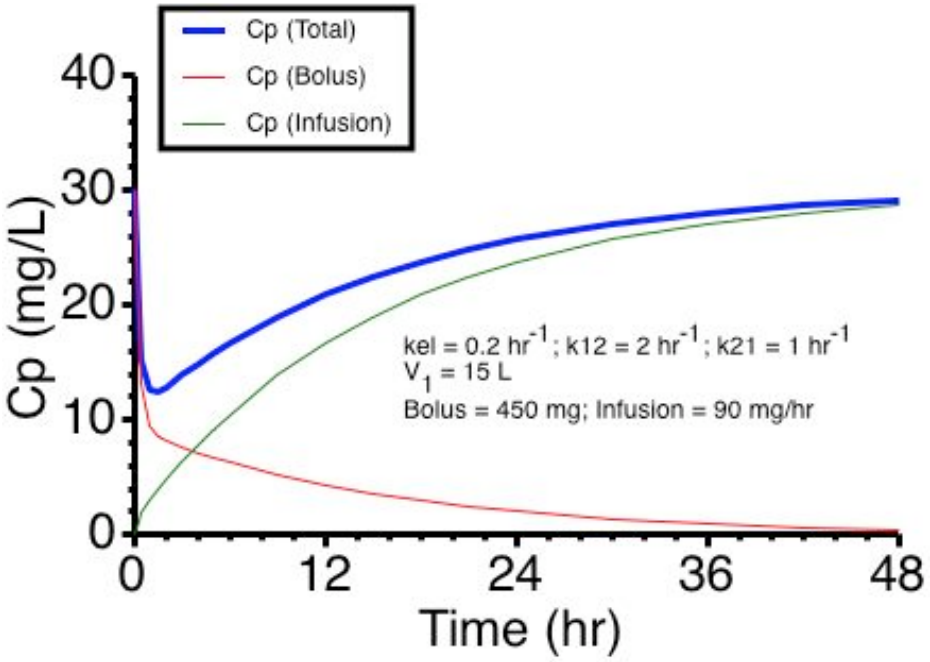


Figure 19.6.1 Linear Plot of Cp Versus Time With IV Bolus and Infusion

Click on the figure to view as a Java Applet
or a Java Applet as a Semi-log Plot
Linear or Semi-log plots as a Tiger widget

Since the time to reach the steady state concentration is controlled by the β 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 L, kel = 0.2 hr^{-1}, and required Cp = 30 mg/L

Bolus DOSE = 15 x 30 = 450 mg and

Infusion Rate = k0 = 30 x 15 x 0.2 = 90 mg/hr

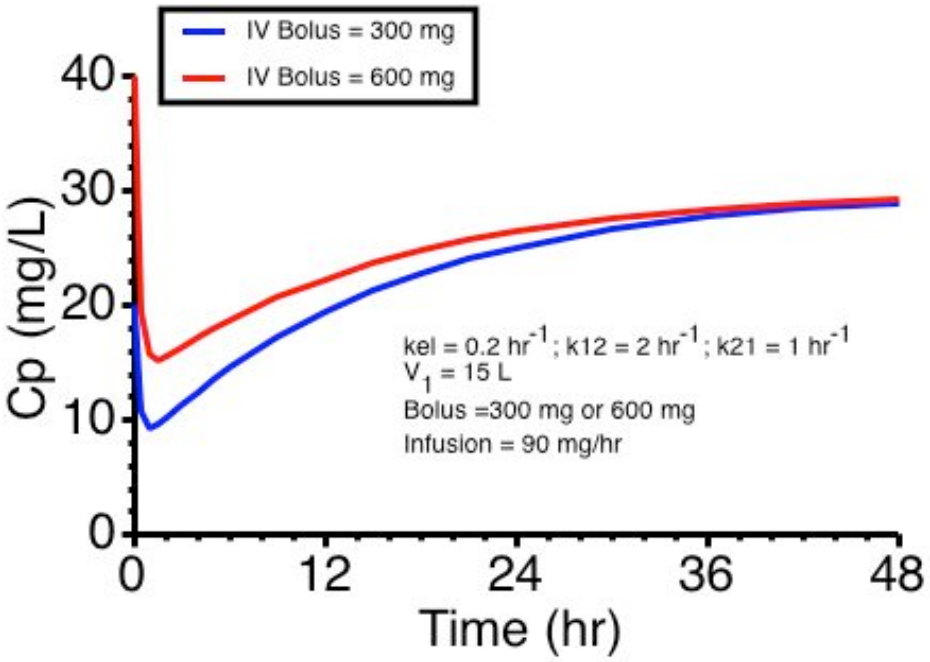


Figure 19.6.2 Linear Plot after an IV Infusion and a Higher or Lower Bolus Dose

As you can see (Figure 19.6.1 above) this gives quite a dip in the Cp 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.

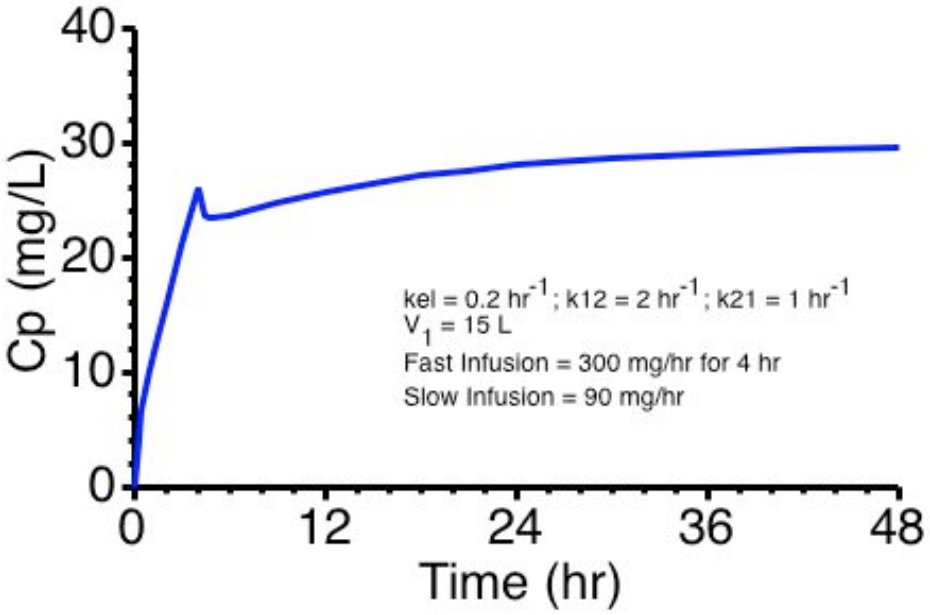


Figure 19.6.3 Linear Plot of Cp *versus* Time With Fast and Slow Infusion

Click on the figure to view as a Java Applet
or a Java Applet as a Semi-log Plot
Linear or Semi-log plots as a Tiger widget

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.

---

return to the Course index
previous | next

PHAR 7632 Chapter 19

Multi-Compartment Pharmacokinetic Models

return to the Course index
previous | next

Oral Administration

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

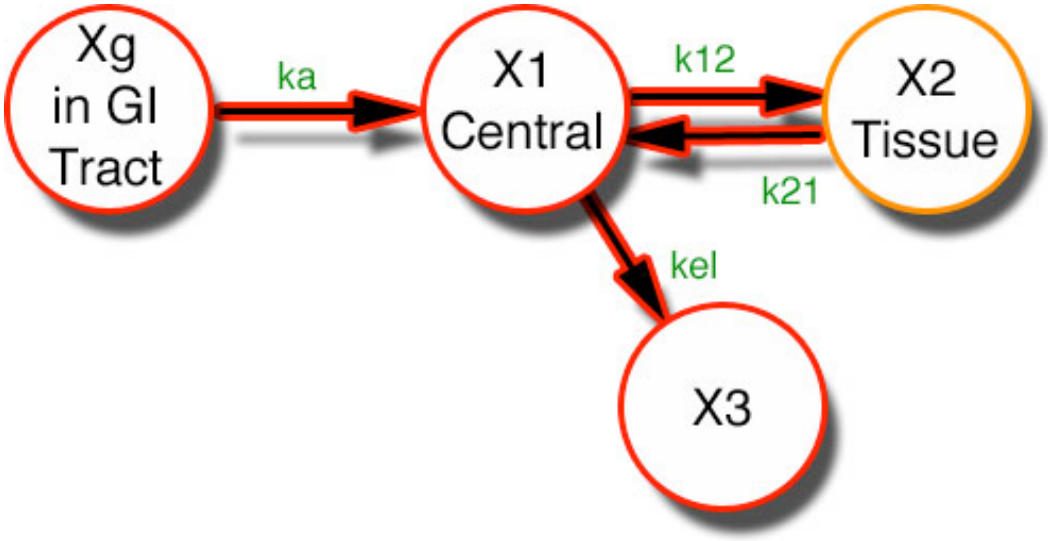


Diagram 19.7.1 Scheme for Oral Two-Compartment Pharmacokinetic Model

The model is shown in Diagram 19.7.1.

$$\frac{dX1}{dt} = ka \bullet Xg + k21 \bullet X2 - (k12 + kel) \bullet X1$$

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

Differential equation

$$Cp = A \bullet e^{-\alpha \bullet t} + B \bullet e^{-\beta \bullet t} + C \bullet e^{-ka \bullet t}$$

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

where A + B + C = 0

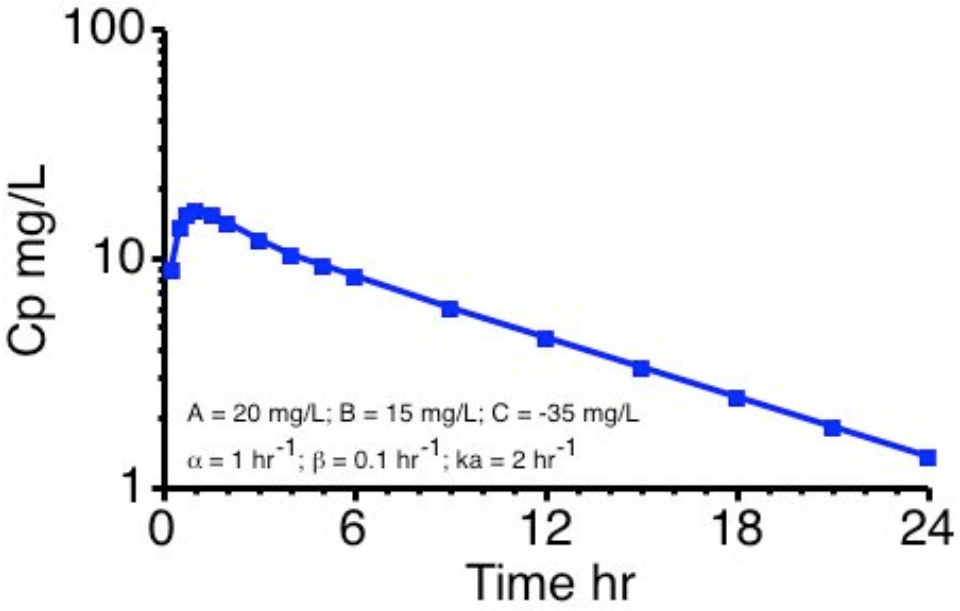


Figure 19.7.1 Semi-Log Plot Showing Pronounced Distribution

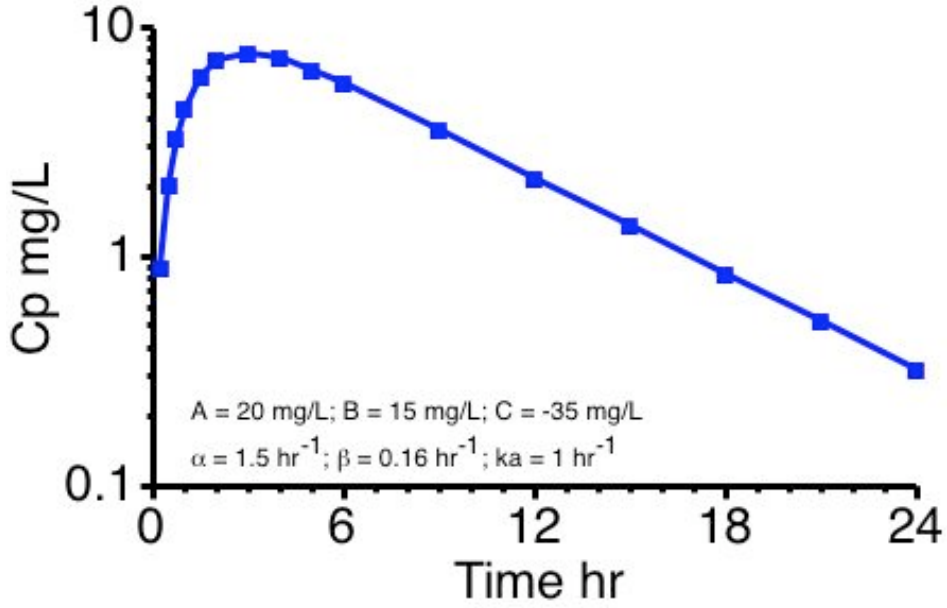


Figure 19.7.2 Semi-Log Plot Without Distribution Phase Evident

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 $Cp_{average}$.

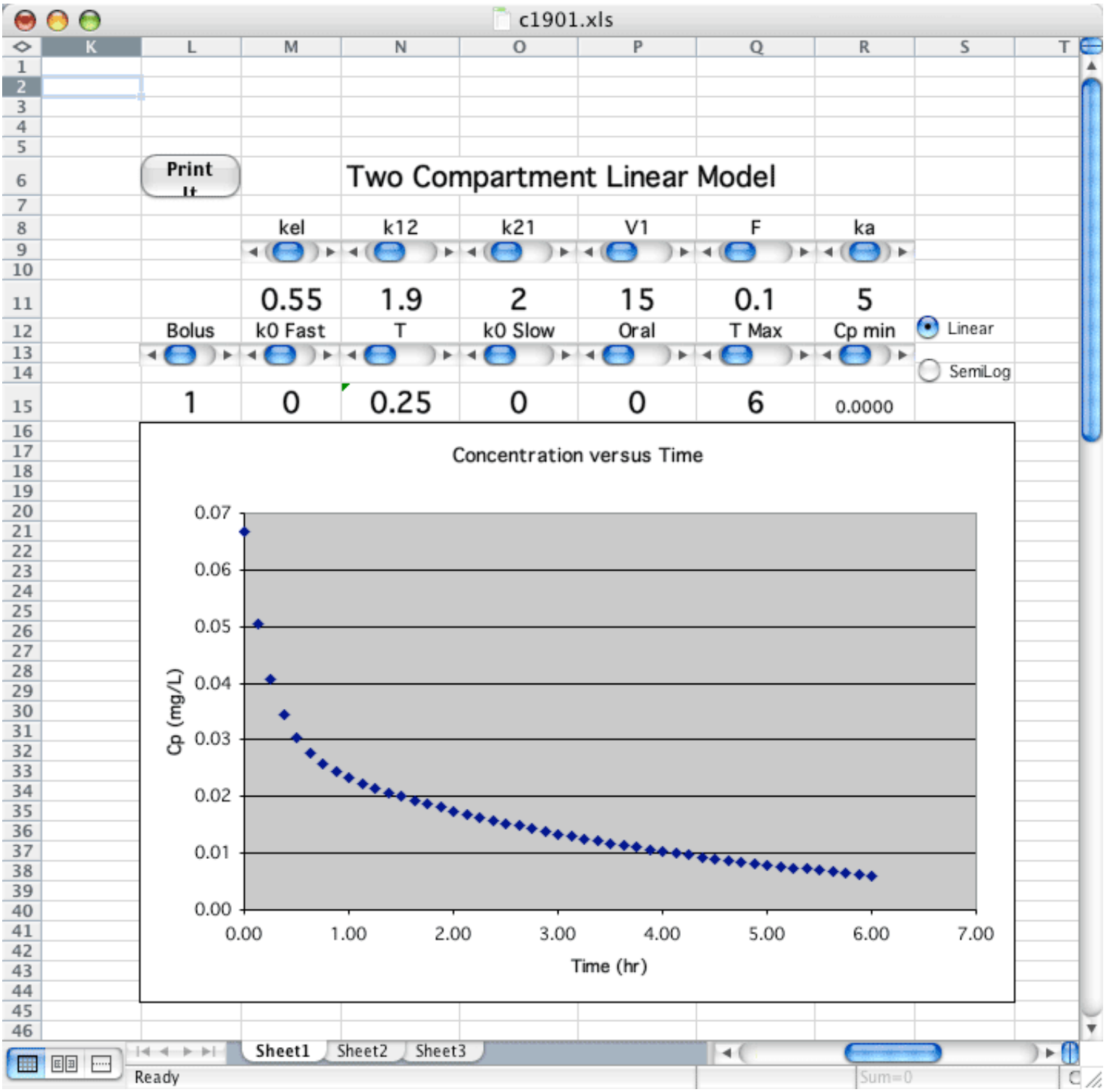
$$\overline{Cp} = \frac{F \bullet Dose}{Cl \bullet \tau} = \frac{F \bullet Dose}{kel \bullet V_1 \bullet \tau} = \frac{F \bullet Dose}{\beta \bullet V_\beta \bullet \tau}$$

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 Cp versus time after IV Bolus, IV Infusion (fast), IV Infusion (slow), and/or Oral can be downloaded by clicking on the figure below.



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.

---

return to the Course index
previous | next

This page (http://www.boomer.org/c/p4/c19/c1907.html) was last modified: Saturday 31 Dec 2005 at 03:58 PM