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One Compartment Linear Model

Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to draw the schemes and write the differential equations for a one compartment pharmacokinetic model after IV infusion administration
- be able use the integrated equations for drug concentrations during and after an IV infusion administration to calculate parameter values and suitable dosing regimens including IV infusion alone, fast/slow IV infusion or infusion/bolus dosage regimens
- be able to calculate kel and V from data collected after a single IV infusion
- be able to define, use, and calculate the parameters:
    - k0 (infusion rate constant)
    - D (infusion duration)

Hospital patients will commonly receive drugs by intravenous infusion. The inconvenience of administering the drug over a long time is not a real problem with bedridden patients. Some may already be receiving intravenous fluids. If a drug is chemically stable and is compatible with the intravenous fluid it may be added to the fluid and thereby be given by slow infusion.

Some drugs cannot be given by rapid intravenous injection. Therefore they may be given by slower IV infusion over 15 or 30 minutes. For example, IV phenytoin must be given slowly, no greater than 50 mg/min (and preferably 25 mg/min or less) in adults. Much slower in neonates. Phenytoin's poor solubility requires alkaline pH control and/or a co-solvent which can produce adverse effects when given too quickly.

References

- Intravenous Phenytoin Administration instructions from Virtual Hospital
- Phenytoin sodium injection dosing Information from Abbott India

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Continuous IV Infusion - Steady State

The Model

Giving the drug by infusion changes the drug concentration *versus* time curve. The equations used to describe the drug concentration are different.

The model can be described schematically.

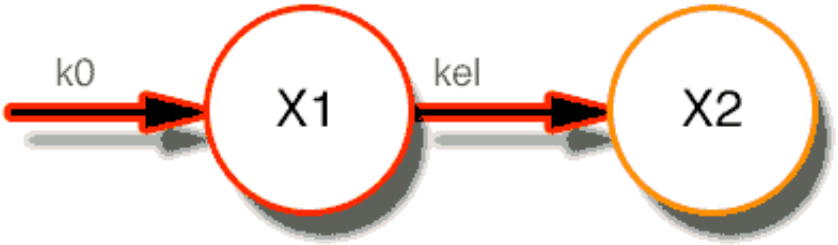

Figure 6.2.1 Scheme for One Compartment Intravenous Infusion

In Figure 6.2.1 we have added an infusion rate constant, k0, to the diagram presented earlier, (Figure 4.4.1). This is a zero order process so the units of k0 are amount per time, for example 25 mg/min.

Differential and Integrated equation

The differential equation for V • Cp is then:

$$\frac{dX_1}{dt} = k0 - kel \bullet X_1$$

Equation 6.2.1 Differential Equation for Drug amount During an IV Infusion

Equation 6.2.1 is the differential equation during the infusion period and it can be integrated to give Equation 6.2.2 using Laplace transforms.

$$X_1 = \frac{k0}{kel} \bullet \left[1 - e^{-kel \bullet t}\right]$$

Equation 6.2.2 Integrated Equation for Drug Amount in the body *versus* Time

and after dividing both sides by the apparent volume of distribution, V.

$$Cp = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet t}\right]$$

Equation 6.2.3 Integrated Equation for Drug Concentration *versus* Time

---

Equation 6.2.3 can be used estimate the drug concentration at various times after an infuion is started OR to calculate the infusion rate needed to achive a desired drug concentration.

Javascript Calculators using Equation 6.2.3

Calculator 6.2.1 Calculate Cp Given k0, kel and V at time t

Enter your own values into each field

k0 (zero order mass/time)	100
kel (first order reciprocal time)	0.15
V (volume)	10
t (time)	1
	Calculate Cp at time t
Cp (mass/volume) is:	

Calculator 6.2.2 Calculate k0 required to give Cp at time t

Enter your own values into each field

Desired Cp (mass/volume)	10
kel (first order reciprocal time)	0.15
V (volume)	10
t (time)	1
	Calculate Required k0
k0 (mass/time) is:	

You may notice that Equation 6.2.3 for Cp is quite similar to Equation 5.3.4 that we used before for the cumulative amount of drug excreted into urine. As you might expect the plot of Cp would be similar in shape.

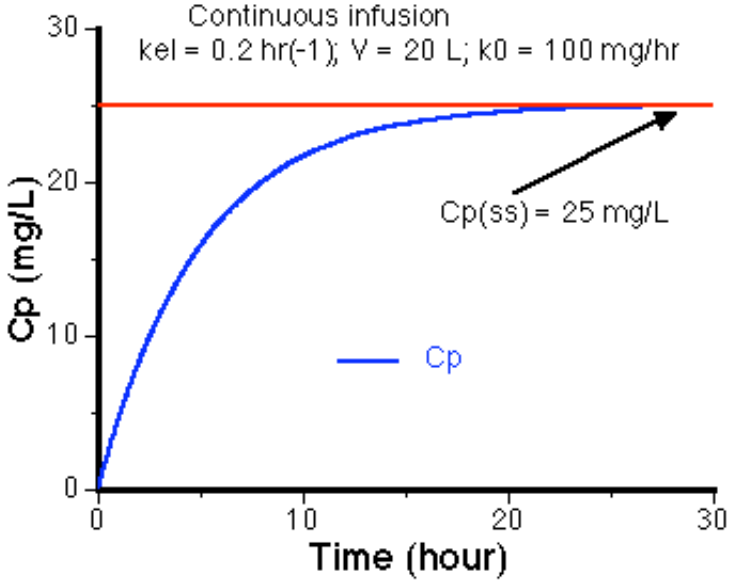

Figure 6.2.2 Linear Plot of Cp *versus* Time During a Continuous Infusion

Click on the figure to view the Java Applet window
Java Applet as a Semi-log Plot

If we continue the infusion indefinitely then we will approach a steady state plasma concentration when the rate of infusion will be

equal to the rate of elimination.

This is because the rate of infusion is constant whereas the rate of elimination will increase as the plasma concentration increases. At steady state the two rates become equal. We can determine the steady state concentration from the differential equation by setting the rate of change of Cp, i.e. dCp/dt = 0.

Then

$$\frac{V \bullet Cp}{dt} = 0 = k0 - kel \bullet V \bullet Cp^{ss}$$

therefore

$$Cp^{ss} = \frac{k0}{kel \bullet V} = \frac{k0}{CL}$$

Equation 6.2.4 Steady State Concentration after Continuous IV Infusion

This could also be calculated from the integrated equation by setting $e^{-kel \bullet t} = 0$ at $t = \infty$.

We can now calculate the infusion rate necessary to produce some desired steady state plasma level.

For Example:

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

First calculate kel from the $t_{1/2}$, kel = 0.693/4 = 0.17 hr^{-1}

then k0 = kel • V • Cp = 0.17 x 25 x 15 = 63.8 mg/hr

We would probably use an infusion of 60 mg/hr which would produce a Cp^{ss} value of:

Cp^{ss} = k0/(kel • V) = 60/(0.17 x 25) = 14.1 mg/L

Equation 6.2.4 can be used to calculate the steady state concentration after a continous infusion or the infusion rate constant required to achieve a required drug concentrstion.

Javascript Calculators using Equation 6.2.4

Calculator 6.2.3 Calculate Cp^{ss} Given k0, kel and V	
Enter your own values into each field	
k0 (zero order mass/time)	60
kel (first order reciprocal time)	0.17
V (volume)	25
	Calculate Cpss at time t
Cp^{ss} (mass/volume) is:	

Calculator 6.2.4 Calculate k0 required to give Cp^{ss}	
Enter your own values into each field	
Desired Cp^{ss} (mass/volume)	15
kel (first order reciprocal time)	0.17
V (volume)	25
	Calculate Required k0
k0 (mass/time) is:	

For practice try calculating concentrations or required infusion rates. Compare your answers with the computer! These problems includes calculation of drug concentration or required infusion rates during an IV infusion or at steady state.

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Continuous IV Infusion - Time to Reach Steady State

Another important factor is the time to reach the steady state concentration. The time to reach half the steady state can be derived:

Since

$$Cp^{ss} = \frac{k0}{kel \bullet V} = \frac{k0}{CL}$$

and

$$Cp = \frac{Cp^{ss}}{2} = Cp^{ss} \bullet \left[1 - e^{-kel \bullet t_{half}}\right]$$

then

$$\frac{Cp^{ss}}{2} = Cp^{ss} \bullet \left[1 - e^{-kel \bullet t_{half}}\right]$$

$$\frac{1}{2} = 1 - e^{-kel \bullet t_{half}}$$

$$\frac{1}{2} - 1 = -\frac{1}{2} = -e^{-kel \bullet t_{half}}$$

$$\frac{1}{2} = e^{-kel \bullet t_{half}}$$

or

$$2 = e^{kel \bullet t_{half}}$$

taking the **ln** of both sides

$$kel \bullet t_{half} = ln(2) = 0.693$$

Thus

$$t_{half} = \frac{0.693}{kel} = t_{1/2} \text{ for elimination}$$

Thus the approach to Cp^{ss} is exponential in nature and is controlled by the elimination process **NOT** the infusion process. NOTE however that the value of Cp^{ss} **IS** controlled by k0.

Halfway - 50%	to steady state	in	one	half-life
75%	to steady state	in	2	half-life
87.5%	to steady state	in	3	half-life
94%	to steady state	in	4	half-life

For theophylline with a $t_{1/2}$ equal to 4 hours the time to reach 94% of steady state will be 16 hours. We could calculate how long it might take to reach a therapeutic concentration. For theophylline this might be 10 mg/L

Thus

$$Cp = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet t}\right]$$

Using the values from before

k0 = 60 mg/hr; kel = 0.17 hr^{-1}; V = 25 L; and $C_{required}$ = 10 mg/L

$$10 = \frac{60}{0.17 \times 25}\left[1 - e^{-0.17 \bullet t}\right]$$

$$\frac{10 \times 0.17 \times 25}{60} = 0.708 = 1 - e^{-0.17 \bullet t}$$

thus

$$1 - 0.708 = 0.292 = e^{-0.17 \bullet t}$$

and taking the ln of both sides gives -0.17 * t = -1.231 or t = 7.24 hr

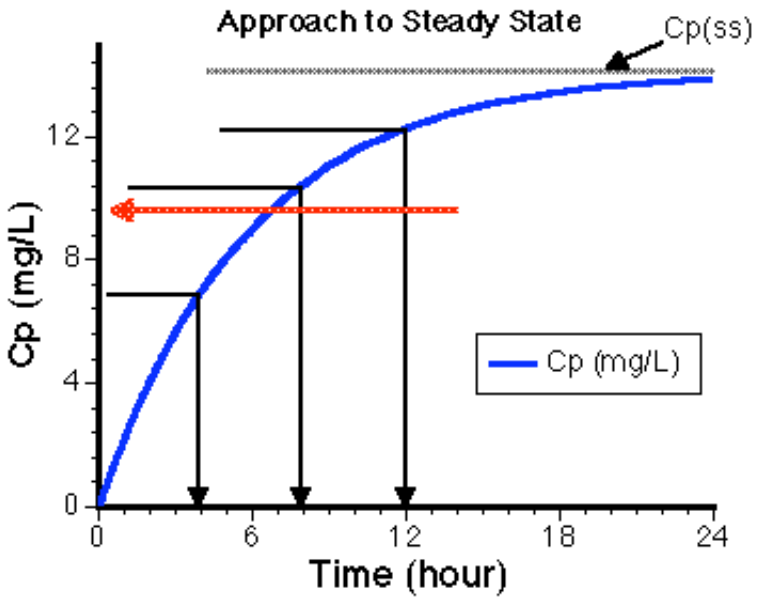

Figure 6.3.1 Plot of Cp *versus* Time showing Approach to Steady State

Thus if we started an infusion to achieve a steady state plasma concentration of approximately 15 mg/L (actually 14.1 mg/L) it would take 7.25 hours to reach a therapeutic level of 10 mg/L. This is probably too long so another strategy should be explored.

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Combined Infusion and bolus administration

One reason we give a drug by IV is because we need a quick therapeutic response. One way to achieve a therapeutic concentration more quickly is to give a loading dose by rapid intravenous injection and then start the slower maintenance infusion.

For Drugs which can be given as a bolus

For example, using theophylline again.

To achieve Cp^{ss} = 14.1 mg/L; k0 = 60 mg/hr; V = 25 L; kel = 0.17 hr^{-1}.

A loading dose can be calculated from

$$Cp^0 = \frac{Dose}{V}$$

thus

DOSE = V • Cp^0 = 25 x 14.1 = 353 mg

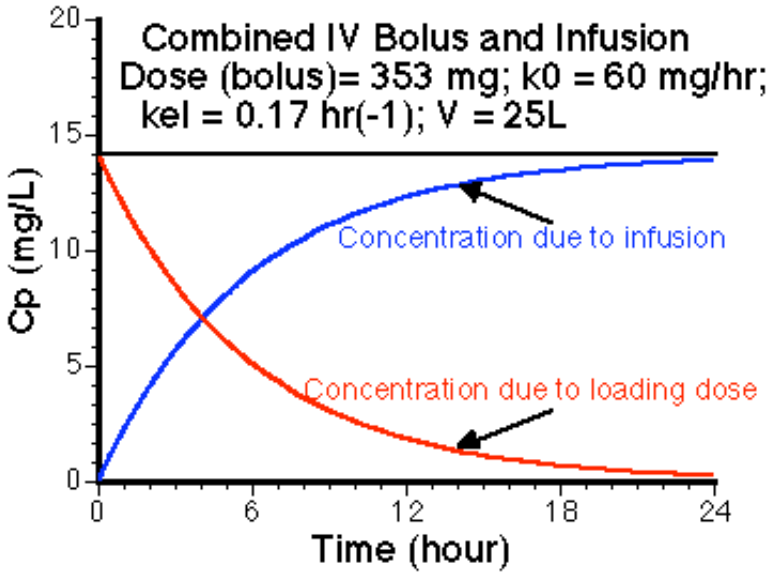

Figure 6.4.1 Linear Plot of Cp *versus* Time Showing Bolus, Infusion, and Combined Curves

Click on the figure to view the Java Applet window
Java Applet as a Semi-log Plot

The plasma concentration from the combined bolus and infusion regimen is shown as the black horizontal line in Figure 6.4.1

Javascript Calculators using Equation 6.2.3 and 4.5.2

Calculator 6.4.1 Calculate Cp given k0, Bolus Dose, kel and V at time t

Enter your own values into each field

k0 (zero order mass/time)	60
Dose (bolus dose - mass)	353
kel (first order reciprocal time)	0.17
V (volume)	25
t (time)	1
	Calculate Cp at time t
Cp from the bolus dose (mass/volume) is:	
Cp from the maintenance infusion (mass/volume) is:	
The total Cp (mass/volume) is:	

An IV bolus and maintenance infusion is one way to achieve a steady state plasma concentration rapidly and maintain it. However, we may not be able to give a bolus dose intravenously so another approach may be necessary.

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Combined Slow and Fast Infusion

Alternately we can give a loading dose by rapid infusion and then give a slower maintenance infusion once the plateau concentration is achieved.

For example, using the previous data

For theophylline, kel = 0.17 hr^{-1}; V = 25 L; with a required Cp = 14.1 mg/L

If we wish to give a loading infusion over 30 minutes we need to give the infusion at a rate which will produce Cp = 14.1 mg/L at 30 minutes. Therefore:-

$Cp^{30\ min}$ = 14.1 mg/L

$$Cp = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet t}\right]$$

$$14.1 = \frac{k0}{0.17 \times 25}\left[1 - e^{-0.17 \times 0.5}\right]$$

thus

k0 = 735 mg/hr

Therefore we need to give a dose of 367 mg over 30 minutes to achieve a plasma concentration of 14.1 mg/L at 30 minutes.

It is important to realize what the steady state plasma concentration would be if we didn't turn this fast infusion off.

$$Cp^{ss} = \frac{k0}{kel \bullet V} = \frac{735}{0.17 \times 25} = 173\ \mathrm{mg/L}$$

which would be quite toxic.

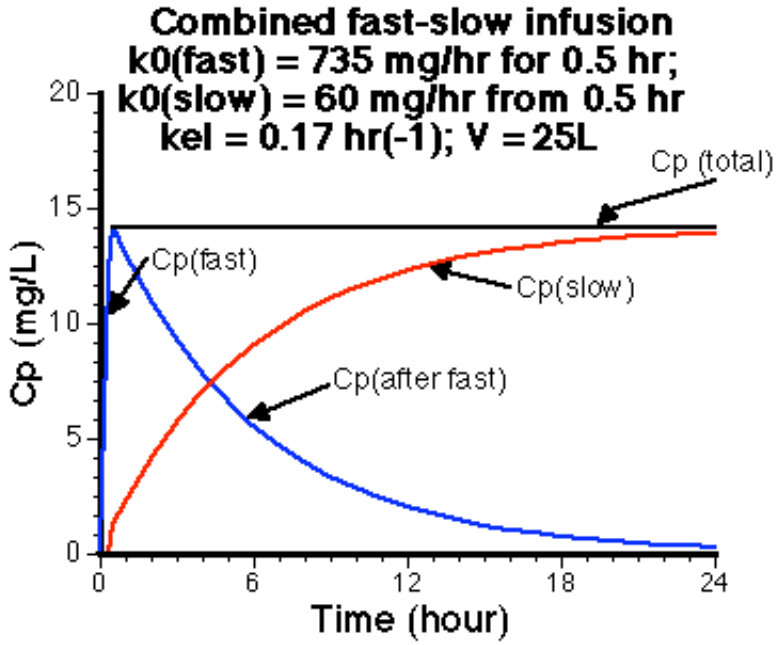

Figure 6.5.1 Linear Plot of Cp *versus* Time showing Combined and Separate Curves for Both Infusions

Click on the figure to view the Java Applet window
Java Applet as a Semi-log Plot

Consequently we would need to ensure that at 30 minutes the rapid infusion rate was slowed from 735 mg/hr to 60 mg/hr. One way to do this would be to only provide 367 mg (or 360 mg) in the infusion syringe at first.

The dosing regimen (or controlled sequence of drug administration) to achieve the desired plasma concentration is:-

a) a loading dose by IV infusion of 367 mg/30 minutes followed by

b) a maintenance IV infusion of 60 mg/hr

Javascript Calculators using Equation 6.2.3 and 6.6.3 (on the next page)

Calculator 6.5.1 Calculate Cp given fast and slow k0, kel and V at time t

Enter your own values into each field

Fast k0 (zero order mass/time)	735
Maintenance k0 (zero order mass/time)	60
Duration of fast infusion (time - same time units as rate constants)	0.5
kel (first order reciprocal time)	0.17
V (volume)	25
t (time)	1
	Calculate Cp at time t
Cp from the fast infusion (mass/volume) is:	
Cp from the maintenance infusion (mass/volume) is:	
The total Cp (mass/volume) is:	
WARNING The Cp if the fast infusion is not stopped (mass/volume) is:	

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Post Infusion

Before moving on we should look at the equation for plasma concentration after an infusion is stopped.

Remember that the equation for plasma concentration *versus* time during an IV infusion is:

$$Cp = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet t}\right]$$

Equation 6.6.1 Drug Concentration during an IV Infusion

If the infusion is continued indefinitely then the plasma concentration approaches a steady state plasma concentration.

$$Cp^{ss} = \frac{k0}{kel \bullet V} = \frac{k0}{CL}$$

If however the infusion is stopped the plasma concentration can be expected to fall.

Scheme or diagram

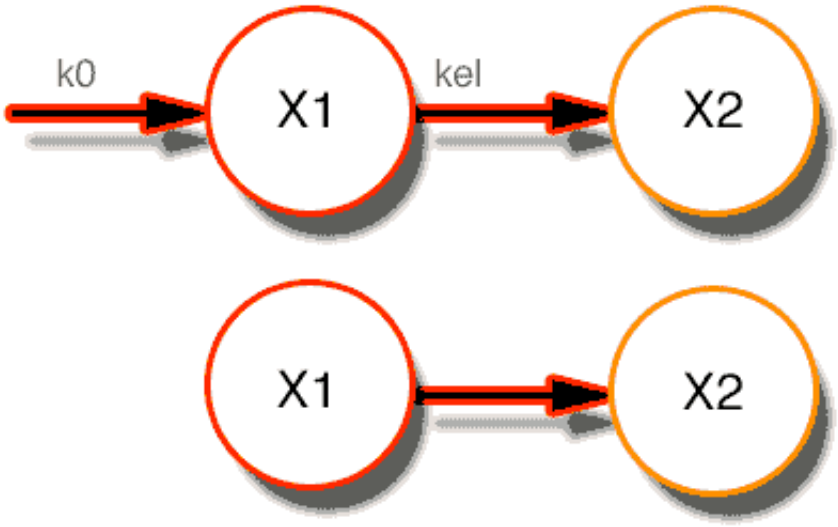

Figure 6.6.1 During and After an IV Infusion - One Compartment Model

The scheme shown to represent 'after the infusion is stopped' is the same as that for the bolus injection.

Equations

The equation for drug concentration *versus* time during an IV infusion is shown above as Equation 6.6.1. At the end of the infusion period when t = D the plasma concentration can be calculated as:-

$$Cp^{D} = \frac{k0}{kel \bullet V}\left[1 - e^{-kel \bullet D}\right]$$

Equation 6.6.2 Concentration at the End of an IV Infusion

Once the infusion is stopped all we have is first order elimination.

Then

$$Cp^{t} = Cp^{D} \bullet e^{-kel \bullet (t-D)}$$

Equation 6.6.3 Concentration after an IV Infusion has Stopped

where t is time counted from the start of the infusion. Thus t - D is the time since the end of the infusion. Then

$$Cp^{t} = \frac{k0}{kel \bullet V}\left[1 - e^{-kel \bullet D}\right] \bullet e^{-kel \bullet (t-D)}$$

Equation 6.6.4 Concentration during and after an IV Infusion

Equation 6.6.4 can be used as shown when t is greater than D (that is for drug concentrations after the infusion has stopped). Also, if t is less than or equal to D you should set D = t before using the equation. In this way the term $e^{-kel * (t-D)}$ becomes equal to 1 and can be dropped from the equation and the equation reverts to Equation 6.6.1.

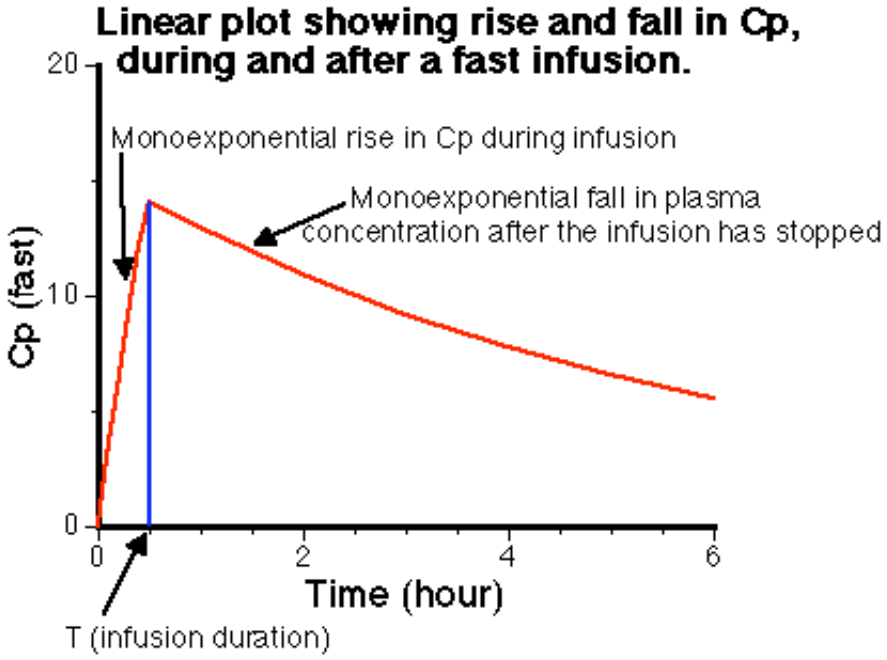

Figure 6.6.2 Linear Plot of Cp *versus* Time for Interrupted Infusion. Showing Mono exponential Rise and Fall

Click on the figure to view the Java Applet window

If we use the previous example data, V = 25 L; kel = 0.17 hr^{-1}; D = 0.5 hour; and k0 = 735 mg/hr, what would be the plasma concentration be at 4.5 hours (t = 4.5 hours). That is if we stop the loading infusion and don't start the maintenance infusion.

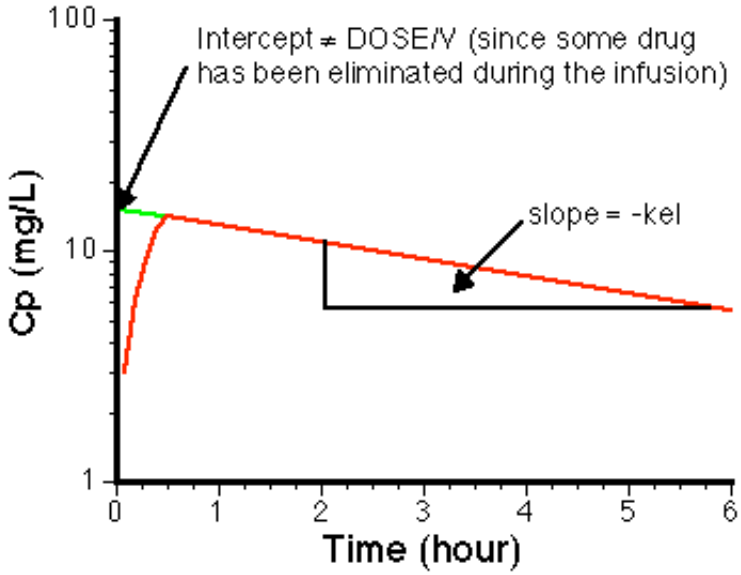

Figure 6.6.3 Semi-log Plot of Cp *versus* Time. NOTE: Intercept is not Cp^0

Click on the figure to view the Java Applet window

$$Cp^t = \frac{k0}{kel \bullet V}\left[1 - e^{-kel \bullet D}\right] \bullet e^{-kel \bullet (t-D)}$$

$$Cp^t = \frac{735}{0.17 \times 25}\left[1 - e^{-0.17 \times 0.5}\right] \times e^{-0.17 \times (4.5-0.5)}$$

$$\boldsymbol{Cp^t = 14.1 \times 0.5 = 7.05}\ \mathrm{mg/L}$$

Thus 4 hours after the infusion was stopped the drug concentration has fallen to half the value at the end of the infusion. Did you remember that the drug half-life was 4 hours.

Example Calculation

Following a two-hour infusion of 100 mg/hr plasma samples were collected and analysed for drug concentration. Calculate kel and V.

Time (hr)	3	5	9	12	18	24
Cp (mg/L)	12	9	8	5	3.9	1.7

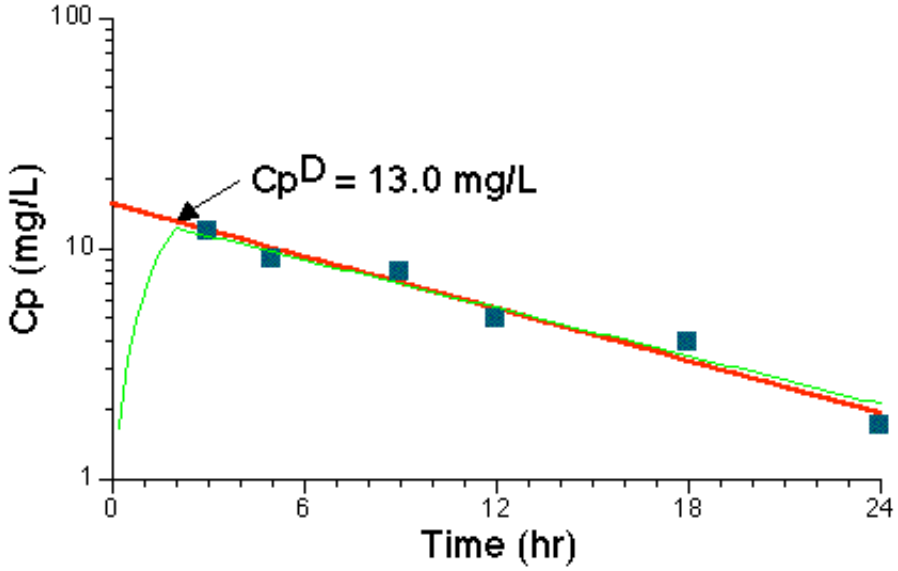

Figure 6.6.4 Plot of Cp *versus* Time after a Two-Hour Infusion

The red line drawn through the data points and back to the Y-axis represents the best-fit line.

$$Cp^D = 13.0 \text{ mg/L}$$

$$kel = \frac{ln(Cp^1) - ln(Cp^2)}{t^2 - t^1} = \frac{ln(13) - ln(1.9)}{24 - 2} = 0.087 \text{ hr}^{-1}$$

$$Cp^D = \frac{k0}{kel \bullet V}\left[1 - e^{-kel \bullet D}\right]$$

Rearranges to

$$V = \frac{k0}{kel \bullet Cp^D}\left[1 - e^{-kel \bullet D}\right]$$

$$V = \frac{100}{0.087 \times 13}\left[1 - e^{-0.087 \times 2}\right]$$

$$V = 88.4 \times [1 - 0.840] = 14.1\ L$$

Javascript Calculators using Equation 6.6.4

Calculator 6.6.1 Calculate kel and V given post infusion Cp *versus* time data

Enter a value for the infusion rate and duration (< 3 hr)

Infusion rate k0 (zero order mass/time)	100
Infusion duration < 3 (time)	2
	Generate a new Cp versus time data set
Cp at 4 hours (mg/L)	
Cp at 5 hours (mg/L)	
Cp at 6 hours (mg/L)	
Cp at 9 hours (mg/L)	
Cp at 12 hours (mg/L)	
Cp at 24 hours (mg/L)	
	Click here to see the answer
kel (first order reciprocal time)	
V (volume)	

Something to consider

Item 1. Which equation should you use. That is, is the simpler IV bolus dose equation close enough or is the 'full' IV infusion equation necessary. Winter (Winter 2004) suggests using the drug elimination half-life as a criteria. That is, if the infusion duration is less than 1/6th of the elimination half-life the simpler IV bolus equation is satisfactory, within 10%. When the infusion duration is longer the more complete IV infusion equation is better.

First try simulating concentration *versus* time after an IV bolus: Dose = 250 mg; D = 0 hr (IV Bolus); kel = 0.123 hr^{-1}; V = 25 L. Contrast this with an IV infusion of the same dose over an infusion duration of 1 or 2 hours. Explore the problem as a Linear Plot - Java Applet Winter 2004.

For practice try calculating required infusion rates and parameter values. Compare your answers with the computer! These problems include bolus/infusion and fast/slow infusion regimen calculations as well as parameters determinations from two post infusion drug concentrations.

For practice try estimating various parameter values from post infusion data. Compare your answers with the computer! These problems include graphing post infusion drug concentration data on semi-log graph paper and estimating parameters from the slope and intercept of the best-fit line.

References

- Winter, M.E. 2004 **Basic Clinical Pharmacokinetics**, 4th ed., Lippincott Williams & Wilkins, Baltimore, p 61-63

Student Objectives for this Chapter

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