

# PHAR 7632 Chapter 14

## Multiple IV Bolus Dose Administration

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### Multiple IV Bolus Dose Administration

#### Student Objectives for this Chapter

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

- understand and be able to describe drug accumulation after repeated dose administration
- be able to use the integrated equations for drug concentration after multiple IV bolus doses
- be able to calculate suitable dosing regimens including loading dose, maintenance dose, and dosing interval
- be able to define, use, and calculate the parameters:
  - dosing interval,  $\tau$
  - accumulation factor, R
  - maximum plasma concentration,  $C_{p_{\max}}$
  - minimum plasma concentration,  $C_{p_{\min}}$
- be able to calculate suitable multiple dose regimen to achieve desired  $C_{p_{\min}}$  and  $C_{p_{\max}}$  values

This Chapter will consider drug pharmacokinetics after multiple IV bolus dose administration. But, first a review of the equations for a single dose administration.

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### Single Dose Review

### IV Bolus

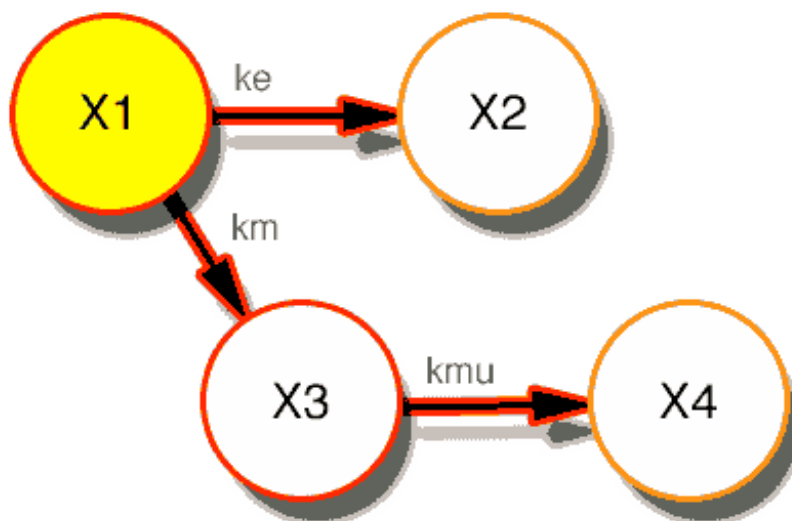


Figure 14.2.1 A Diagram Illustrating a One Compartment Model - IV Bolus

This model can be defined using both differential and integrated equations.

$$\frac{dC_p}{dt} = -k_e \cdot C_p - k_m \cdot C_p = -k_{el} \cdot C_p$$

Equation 14.2.1 Differential Equation describing a One Compartment Model - IV Bolus

$$C_p = C_p^0 \cdot e^{-k_{el} \cdot t} = \frac{Dose}{V} \cdot e^{-k_{el} \cdot t}$$

Equation 14.2.2 Integrated Equation describing a One Compartment Model - IV Bolus

or in clearance terms

$$\frac{dX}{dt} = -CL \cdot C_p \text{ or } C_p = \frac{Dose}{V} \cdot e^{-CL \cdot t / V}$$

Equation 14.2.3 Equations describing a One Compartment Model - IV Bolus

## IV Infusion

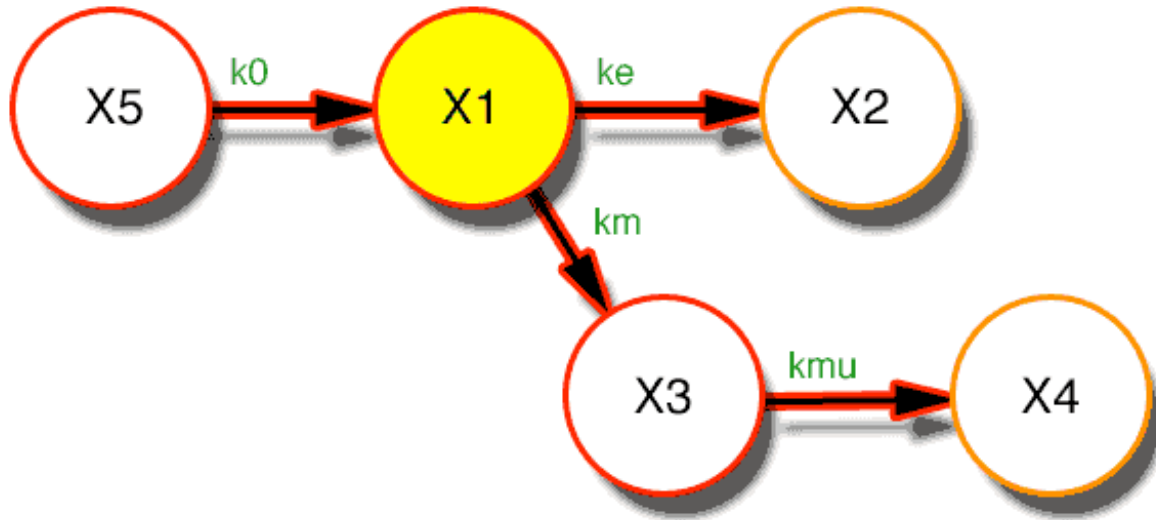


Figure 14.2.2 A Diagram Illustrating a One Compartment Model - IV Infusion

This model can be defined using both differential and integrated equations.

### During an Infusion

$$\frac{dC_p}{dt} = \frac{k_0}{V} - k_{el} \cdot C_p$$

Equation 14.2.4 Differential Equation describing a One Compartment Model - IV Infusion

$$C_p = \frac{k_0}{k_{el} \cdot V} \cdot [1 - e^{-k_{el} \cdot t}]$$

Equation 14.2.5 Integrated Equation describing a One Compartment Model - IV Infusion

### At Steady State

$$\frac{dC_p}{dt} = 0 \text{ or } C_p = \frac{k_0}{k_{el} \cdot V}$$

Equation 14.2.6 Equation describing a One Compartment Model - IV Infusion

### After an IV Infusion

$$\frac{dC_p}{dt} = -k_{el} \cdot C_p$$

Equation 14.2.7 Differential Equation describing a One Compartment Model - IV Infusion

$$Cp = \frac{k_0}{k_{el} \cdot V} \cdot [1 - e^{-k_{el} \cdot T}] \cdot e^{-k_{el} \cdot (t-T)}$$

Equation 14.2.8 Integrated Equation describing a One Compartment Model - IV Infusion

### Oral (Extravascular)

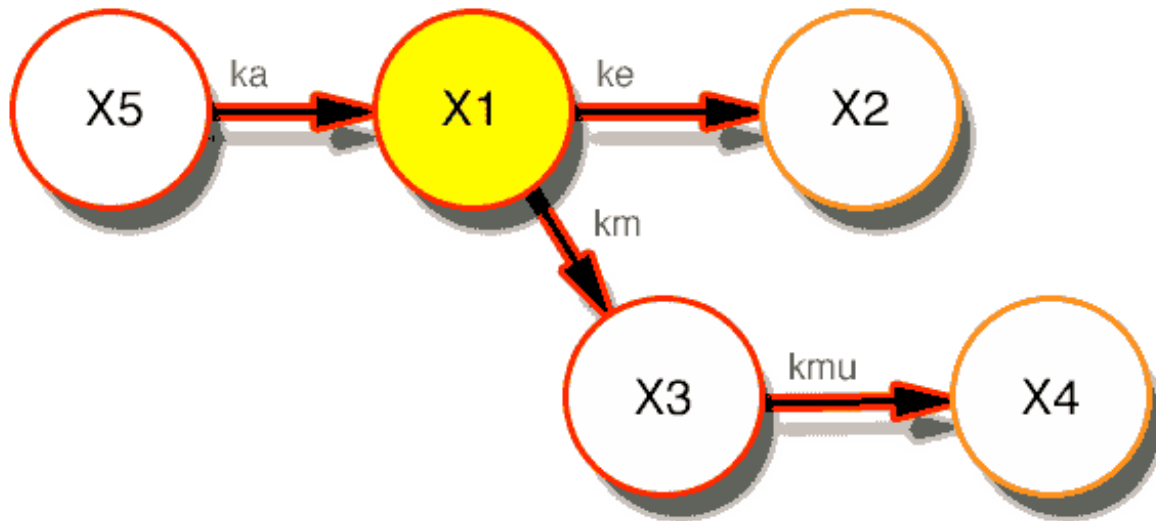


Figure 14.2.3 A Diagram Illustrating a One Compartment Model - Oral

This model can be defined using both differential and integrated equations.

$$\frac{dCp}{dt} = \frac{ka \cdot X5}{V} - k_{el} \cdot Cp$$

Equation 14.2.9 Differential Equation describing a One Compartment Model - Oral

$$Cp = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - k_{el})} \cdot [e^{-k_{el} \cdot t} - e^{-ka \cdot t}]$$

Equation 14.2.10 Integrated Equation describing a One Compartment Model - Oral

After a single IV bolus dose drug concentrations appear with an exponential decline on linear graph paper and a straight line on semi-log graph paper. With an IV infusion of duration  $T$  there is a steady increase to  $C_p^T$  followed by an abrupt exponential decline in concentration. After a single oral administration the curve around the peak concentration is smoother.

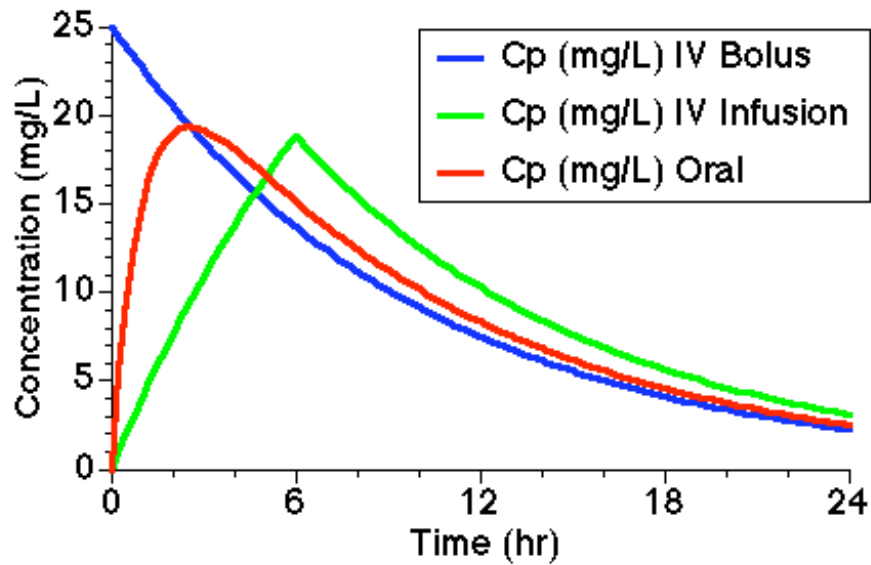


Figure 14.2.4 Linear Plot of Drug Concentration *versus* Time

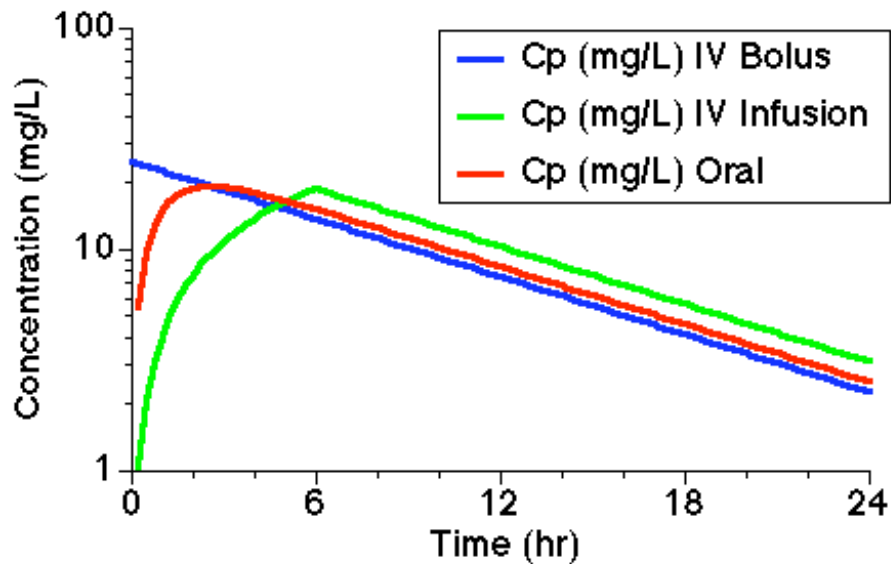


Figure 14.2.5 Semi-log Plot of Drug Concentration *versus* Time

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### Multiple Dose

With this refresher, drug pharmacokinetics after multiple dose administration may be easier to understand.

Aspirin given for a headache may be given as a single administration, whereas aspirin for arthritis will be given as a multiple dose. Antibiotics are usually given as a multiple dose regimen to produce and maintain effective plasma concentration. In fact, many drugs are given this way; anti-hypertensives, anti-epileptics etc.

Multiple dose administration is a very common method of drug administration. Up to this point we can calculate the drug concentration in plasma at any time after a single dose. We will continue now by looking at the equations for multiple dose administration.

### Multiple IV Bolus

After a single dose administration we assume that there is no drug in the body before the drug is given and that no more is going to be administered. However, in the case of multiple dose administration we are expected to give second and subsequent doses before the drug is completely eliminated. Thus ACCUMULATION of the drug should be considered. On repeated drug administration the plasma concentration will be repeated for each dose interval giving a PLATEAU or STEADY STATE with the plasma concentration fluctuating between a minimum and maximum value.

We have already looked at the shape of the plasma concentration *versus* time curve following a single intravenous administration. If we assume instantaneous mixing we start off with an initial concentration,  $C_p^0$ , calculated as  $\text{Dose}/V$  and then we have a fall in concentration with time controlled by the elimination rate constant.

## Independent Doses

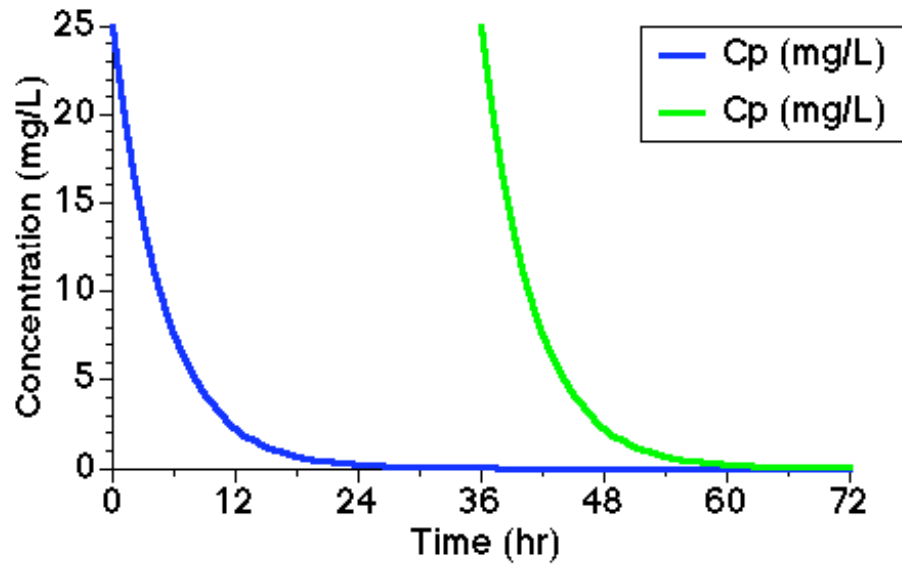


Figure 25.3.1 Drug Concentration after Two Independent IV Bolus Doses

If the doses are given far enough apart then the concentration will have fallen to approximately zero before the next dose. There will then be no accumulation of drug in the body.

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### Drug Accumulation

However if the second dose is given early enough so that not all of the first dose is eliminated then the drug will start to accumulate and we will get higher concentrations with the second and third dose. As an example we could consider a drug with a half-life of 6 hours. Giving a dose of 100 mg every six hours with an apparent volume of distribution of 25 liter, the  $C_p^0 = 4$  mg/liter (see Figure 14.4.1).

After six hours the plasma concentration will fall to 2 mg/liter. If we give the same dose again the plasma concentration will increase by 4 mg/liter from 2 mg/liter to 6 mg/liter. Then after another half-life (6 hours) the plasma concentration will fall to 3 mg/liter. Again, another dose will increase the plasma concentration by 4 mg/liter to 7 mg/liter. After another half-life the plasma concentration will be 3.5 mg/liter. After repeated drug administration every six hours the plasma concentration will accumulate until it fluctuates between a maximum and minimum value of 8 mg/liter and 4 mg/liter. In this example the dose was given every drug elimination half-life of 6 hours.

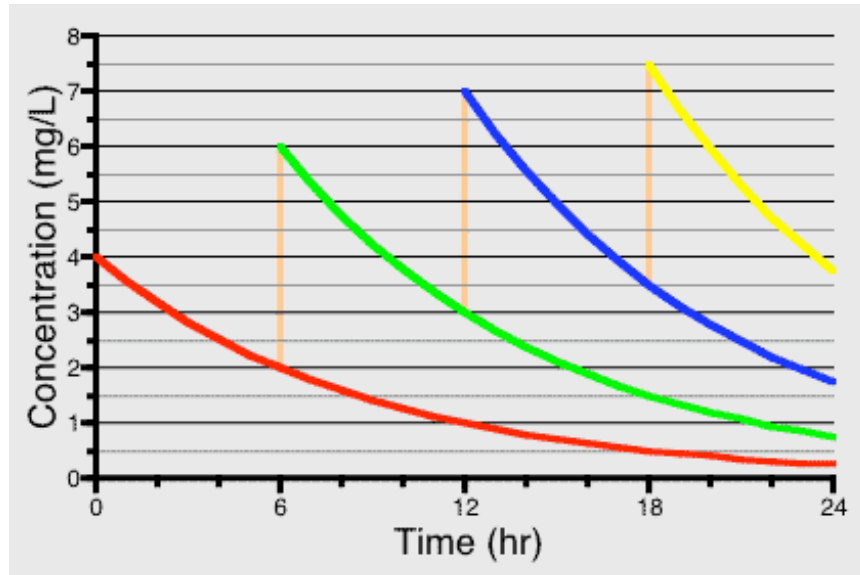


Figure 14.4.1 Linear Plot of  $C_p$  versus Time Showing Doses Every Six Hours

Click on the figure to view the Java Applet window  
Java Applet as a [Semi-log Plot](#)

With each dose, drug accumulated until the amount of drug eliminated during each dosing interval was equal to the amount of the dose. In the first interval plasma concentrations fall from 4 to 2 mg/L. Continuing for a number of doses gives the following table.

**Table 14.4.1 Drug Concentration Accumulation During Multiple IV Bolus Dose Administration**

Start		End	Concentration lost during dosage interval
4	-->	2 mg/L	2 mg/L
6	-->	3	3
7	-->	3.5	3.5
7.5	-->	3.75	3.75
	...		
8	-->	4	4 <- which is the same as the concentration increase caused by each dose

There is a limit to drug accumulation because as the plasma concentration increased the amount of drug eliminated during the dosing interval will also increase as the rate of elimination is equal to the amount of the drug in the body multiplied by the rate constant for a first order elimination. (Compare this with the case of a continuous infusion).

So far we can see that if we give repeated doses before the body can eliminate the previous doses then we will get accumulation of the drug. We have also seen that when we have first order elimination this accumulation will not proceed indefinitely but will approach a steady state.

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### Development of General Equation

We can now consider a general equation which could describe the plasma concentration at any time after multiple IV bolus drug administration.

#### Concentration at the end of the first dosing interval

$$Cp_1^\tau = Cp_1^0 \bullet e^{-kel \bullet \tau}$$

Equation 14.5.1 Cp after the First Dose

where  $Cp$  time since last dose  
dose number

This gives the plasma concentrations at the end of first interval, where  $\tau$  is the dosing interval in hours.

#### Concentration at the start of the second interval

$$Cp_2^0 = Cp_1^\tau + Cp_1^0 = Cp_1^0 \bullet e^{-kel \bullet \tau} + Cp_1^0$$

Equation 14.5.2 Cp at the Start of the Second Interval

#### Concentration at the end of the second dose interval

$$Cp_2^\tau = [Cp_1^0 \bullet e^{-kel \bullet \tau} + Cp_1^0] \bullet e^{-kel \bullet \tau}$$

Equation 14.5.3 Cp at the End of the Second Interval

and so on.

It will help if we define the parameter,  $R = e^{-kel \bullet \tau}$ , which is the fraction of the initial plasma concentration remaining at the end of the dosing interval.

Then

$$Cp_2^\tau = Cp_1^0 \bullet R + Cp_1^0 \bullet R^2$$

Equation 14.5.4 Cp at the End of the Second Interval

$$Cp_3^0 = Cp_1^0 + Cp_1^0 \bullet R + Cp_1^0 \bullet R^2$$

Equation 14.5.5 Cp at the Start of the Third Interval

this is a geometric series with each term R times the preceding term.

$$Cp_n^0 = Cp_1^0 + Cp_1^0 \cdot R + Cp_1^0 \cdot R^2 + \dots + Cp_1^0 \cdot R^{n-1}$$

Equation 14.5.6 Cp at the Start of the nth Interval

$$Cp_n^\tau = Cp_1^0 \cdot R + Cp_1^0 \cdot R^2 + Cp_1^0 \cdot R^3 + \dots + Cp_1^0 \cdot R^n$$

Equation 14.5.7 Cp at the End of the nth Interval

these two sums are sums of geometric series and they can be simplified to give

$$Cp_n^0 = Cp_1^0 \cdot \left[ \frac{1 - R^n}{1 - R} \right] = \frac{Dose}{V} \cdot \left[ \frac{1 - e^{-n \cdot kel \cdot \tau}}{1 - e^{-kel \cdot \tau}} \right]$$

Equation 14.5.8 Cp at the Start of the nth Interval

$$Cp_n^\tau = Cp_1^0 \cdot \left[ \frac{1 - R^n}{1 - R} \right] \cdot R = \frac{Dose}{V} \cdot \left[ \frac{1 - e^{-n \cdot kel \cdot \tau}}{1 - e^{-kel \cdot \tau}} \right] \cdot e^{-kel \cdot \tau}$$

Equation 14.5.9 Cp at the End of the nth Interval

Starting with the first equation (Equation 14.5.8) we can calculate drug concentration in blood or plasma at any time following uniform multiple IV bolus administration.

$$Cp_n^t = Cp_n^0 \cdot e^{-kel \cdot t}$$

Equation 14.5.10 Cp at time, t, after the nth IV Bolus Dose

where here t = time since the last dose.

$$Cp_n^t = \frac{Dose}{V} \cdot \left[ \frac{1 - e^{-n \cdot kel \cdot \tau}}{1 - e^{-kel \cdot \tau}} \right] \cdot e^{-kel \cdot t}$$

Equation 14.5.11 Cp at time, t, after the nth IV Bolus Dose  
General Equation

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#### $C_{p_{max}}$ and $C_{p_{min}}$

More useful equations can be derived from this general equation. These are equations to calculate the maximum and minimum plasma concentration after many doses. That is as  $n$  approaches  $\infty$ ,  $R^n (= e^{-n \cdot kel \cdot \tau})$  approaches 0 and with  $t = 0$  or  $t = \tau$ . These are the limits of the PLATEAU CONCENTRATIONS.

$$C_{p_{\infty}^0} = C_{p_{max}} = \frac{Dose}{V} \bullet \left[ \frac{1}{1 - e^{-kel \cdot \tau}} \right] = \frac{Dose}{V \bullet (1 - R)}$$

Equation 14.6.1  $C_p$  Immediately after Many Doses

$$C_{p_{\infty}^{\tau}} = C_{p_{min}} = \frac{Dose}{V} \bullet \left[ \frac{e^{-kel \cdot \tau}}{1 - e^{-kel \cdot \tau}} \right] = \frac{Dose \bullet R}{V \bullet (1 - R)}$$

Equation 14.6.2  $C_p$  Immediately before Many Doses

An example may be helpful:  $t_{1/2} = 4$  hr; IV dose 100 mg every 6 hours;  $V = 10$  liter

$$\text{Therefore } C_{p_1^0} = \frac{100}{10} = 10 \text{ mg/L}$$

What are the  $C_{p_{max}}$  and  $C_{p_{min}}$  values when the plateau values are reached

$$kel = \frac{0.693}{4} = 0.17 \text{ hr}^{-1}$$

$$R = e^{-kel \cdot \tau} = e^{-0.17 \times 6} = 0.35$$

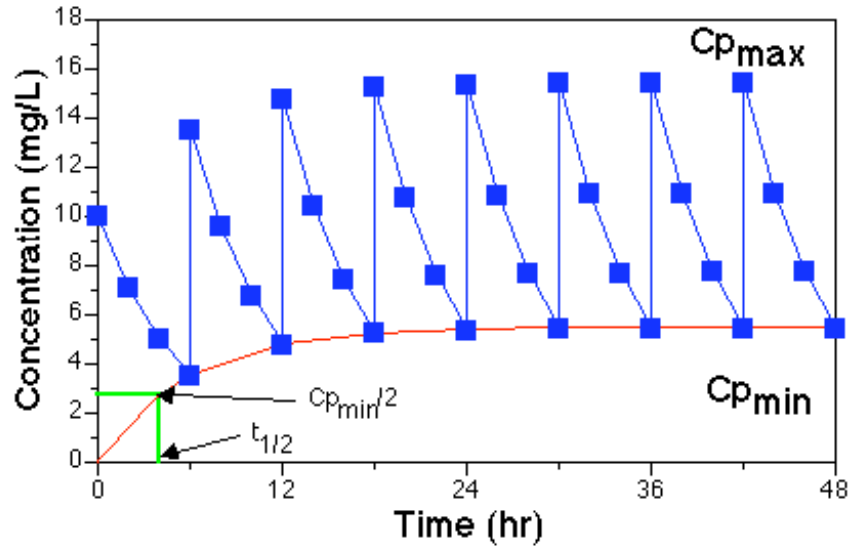
therefore

$$C_{p_{max}} = \frac{C_{p_1^0}}{(1 - R)} = \frac{10}{1 - 0.35} = 15.5 \text{ mg/L}$$

$$C_{p_{min}} = \frac{C_{p_1^0} \bullet R}{(1 - R)} = C_{p_{max}} \bullet R = 15.5 \times 0.35 = 5.4 \text{ mg/L}$$

therefore the plasma concentration will fluctuate between 15.5 and 5.4 mg/liter during each dosing interval when the plateau is reached.

We can now calculate the plasma concentration at any time following multiple IV bolus administration and we can calculate the  $C_{p_{max}}$  and  $C_{p_{min}}$  values.



**Figure 14.6.3 Plot of  $C_p$  versus Time showing Time to Approach 50% of Plateau during Multiple Dose Regimen**

Click on the figure to view the Java Applet window  
Java Applet as a [Semi-log Plot](#)

It can be shown that the time to reach a certain fraction of the plateau concentration is dependent on the drug elimination half-life only, much the same as for the approach to steady state during an IV infusion. Thus we may again have a problem with an excessive time required to reach the plateau. Therefore we may want to determine a suitable loading dose to achieve steady state rapidly.

In the previous example  $C_{p_{max}} = 15.5$  mg/liter

A suitable loading dose would be  $C_{p_{max}} \bullet V = 15.5 \times 10 = 155$  mg as a bolus would give  $C_p = 15.5$  mg/liter, followed by 100 mg every 6 hours to maintain the  $C_{p_{max}}$  and  $C_{p_{min}}$  values at 15.5 and 5.5 mg/liter, respectively.

In summary:

The IV bolus loading dose to quickly achieve a required drug concentration,  $C_{p_{max}}$ , can be calculated as  $C_{p_{max}} \bullet V$

Rewriting Equation 14.6.1 with Dose expressed more explicitly as the Maintenance Dose.

$$C_{p_{max}} = \frac{\text{Maintenance Dose}}{V \bullet (1 - R)}$$

**Equation 14.6.3  $C_{p_{max}}$**

$$\text{Loading Dose} = \frac{\text{Maintenance Dose}}{(1 - R)}$$

Equation 14.6.4 Loading Dose

or

$$\text{Maintenance Dose} = \text{Loading Dose} \bullet (1 - R)$$

Equation 14.6.5 Maintenance Dose

We can try another example of calculating a suitable dosing regimen.

Consider  $V = 25$  liter and  $k_{el} = 0.15 \text{ hr}^{-1}$  for a particular drug and we need to keep the plasma concentration between 35 mg/liter (MTC) and 10 mg/liter (MEC).

What we need is the maintenance dose, the loading dose, and the dosing interval.

From Equations 14.6.1 and 14.6.2

$$\frac{C_{p_{max}}}{C_{p_{min}}} = \frac{Dose}{V \bullet (1 - R)} \bullet \frac{V \bullet (1 - R)}{Dose \bullet R} = \frac{1}{R}$$

Equation 14.6.6 R from  $C_{p_{max}}$  and  $C_{p_{min}}$ 

therefore

$$R = \frac{C_{p_{min}}}{C_{p_{max}}} = \frac{10}{35} = 0.286 = e^{-k_{el} \bullet \tau}$$

taking the ln of both sides

$$-k_{el} \bullet \tau = -1.252 = -0.15 \bullet \tau$$

$$\tau (\text{dosing interval}) = 8.35 \text{ hr}$$

A dosing interval of 8 hours would be more reasonable. Thus with  $\tau = 8 \text{ hr}$  and  $k_{el} = 0.15 \text{ hr}^{-1}$

$$R = e^{-k_{el} \bullet \tau} = e^{-8 \times 0.15} = 0.301$$

From Equation 14.6.3

$$\text{Maintenance Dose} = C_{p_{max}} \bullet V \bullet (1 - R)$$

Equation 14.6.7 Maintenance Dose

$$\text{Maintenance dose} = 35 \times 25 \times (1 - 0.301) = 612 \text{ mg}$$

Again a more realistic maintenance dose would be 600 mg every 8 hours.

To check this regimen

$$C_{p_{max}} = \frac{Dose}{V \bullet (1 - R)} = \frac{600}{25 \times (1 - 0.301)} = 34.3 \text{ mg/L}$$

or

$$C_{p_{min}} = C_{p_{max}} \bullet R = 34.3 \times 0.301 = 10.3 \text{ mg/L}$$

This regimen would be quite suitable as the maximum and minimum values are still within the limits suggested. All that remains is to calculate a suitable loading dose.

Loading dose =  $C_{p_{max}} \bullet V = 35 \times 25 = 875$  mg either 875, 850 or 800 mg

This answer can be expressed graphically.

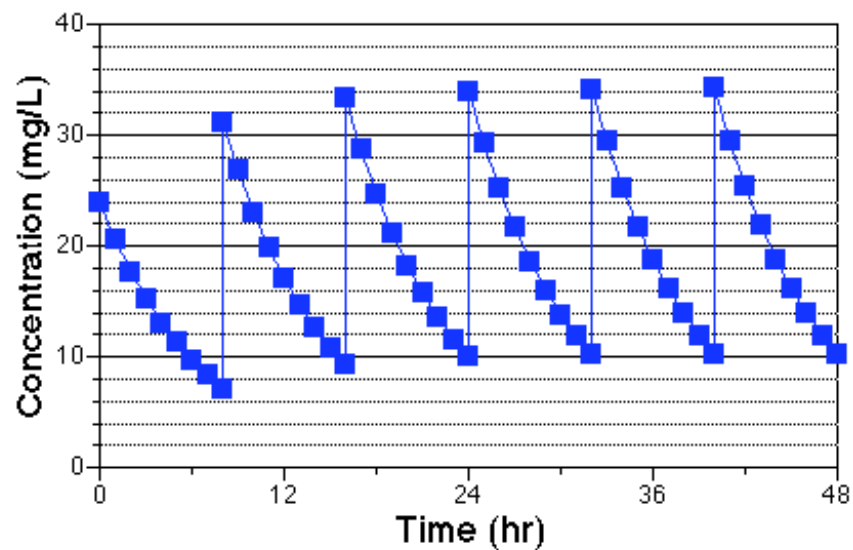


Figure 14.6.4 Plasma Concentration after Multiple IV Bolus Doses

**Calculator 14.6.1 Calculate a suitable multiple IV bolus dosage regimen for specified  $C_{p_{min}}$  and  $C_{p_{max}}$** [Click to generate a new question](#)

Patient  (weight  Kg) is to receive a drug by multiple IV bolus doses. For optimal treatment drug concentration should be kept between  $C_{p_{max}}$   mg/L and  $C_{p_{min}}$   mg/L. This drug has an apparent volume of distribution of  L/Kg and an elimination rate constant of   $hr^{-1}$  (Clearance =  L/kg.hr).

First calculate the dosing interval, tau.

[Click to find the value of tau](#)

Tau  hour.

Enter a new (rounded) value for tau.  hr.

The next step is to calculate a suitable maintenance and loading dose.

[Click to find suitable doses](#)

Start with a loading dose of  mg as an IV Bolus and a maintenance dose of  mg as an IV Bolus every  hour.

**Calculator 14.6.2 Calculate  $C_{p_{min}}$  and  $C_{p_{max}}$  after Multiple IV Bolus Doses**[Click to generate a new question](#)

Patient  (weight  Kg) has received  mg of a drug as an IV Bolus every  hours. This drug has an apparent volume of distribution of  L/Kg and an elimination rate constant of   $hr^{-1}$  (Clearance =  L/kg.hr). Calculate the  $C_{p_{min}}$  and  $C_{p_{max}}$  at steady state.

[Click to find out the answer](#)

$C_{p_{min}}$   mg/L

$C_{p_{max}}$   mg/L

[Practice problems involving  \$C\_{p\_{max}}\$  and  \$C\_{p\_{min}}\$](#)  at steady state after uniform multiple dose IV bolus doses. [Another practice problems involving  \$C\_{p\_{max}}\$  and  \$C\_{p\_{min}}\$](#)  at steady state after uniform multiple dose IV bolus doses. [A third practice problems involving  \$C\_{p\_{max}}\$  and  \$C\_{p\_{min}}\$](#)  at steady state after uniform multiple dose IV bolus doses.

Other practice problems involving the calculation of  $C_p$  at three times during a uniform dosing interval with [Linear](#) or [Semi-log](#) graphical answers or calculation of  $C_p$  at three times during a non-uniform dosing interval with [Linear](#) or [Semi-log](#) graphical answers

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