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Multiple Oral Dose Administration

Student Objectives for this Chapter

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

- be able to use the integrated equations for multiple oral dose administration to calculate plasma concentration or calculate appropriate multiple dose regimen
- be able to define, use, and calculate the parameter:
  - average plasma concentration, $\overline{Cp}$
- be able to use the $\overline{Cp}$ equation to calculate or adjust an appropriate dosing regimen
- be able to use the superposition principle to calculate Cp after non uniform IV or oral dosing regimen

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So far we have looked at multiple IV bolus dose administration. In an analogous fashion, equations can be developed which enable you to calculate the plasma concentration achieved following multiple oral administration. To start, the plasma concentration achieved following a single oral dose can be given by:

$$Cp = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left[e^{-kel \bullet t} - e^{-ka \bullet t}\right]$$

Equation 15.2.1 Cp after a Single Oral Dose

This can be converted to an equation describing plasma concentration at any time following n equal doses with constant dosing interval t using a "multiple dose function".

$$e^{-k \bullet t} \rightarrow \left[\frac{1 - e^{-n \bullet k \bullet \tau}}{1 - e^{-k \bullet \tau}}\right] \bullet e^{-k \bullet t}$$

Equation 15.2.2 Multiple Dose Function

$$Cp = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left(\left[\frac{1 - e^{-n \bullet kel \bullet \tau}}{1 - e^{-kel \bullet \tau}}\right] \bullet e^{-kel \bullet t} - \left[\frac{1 - e^{-n \bullet ka \bullet \tau}}{1 - e^{-ka \bullet \tau}}\right] \bullet e^{-ka \bullet t} \right)$$

Equation 15.2.3 Cp after a Single Oral Dose - Uniform Dose and Interval, τ
General Equation

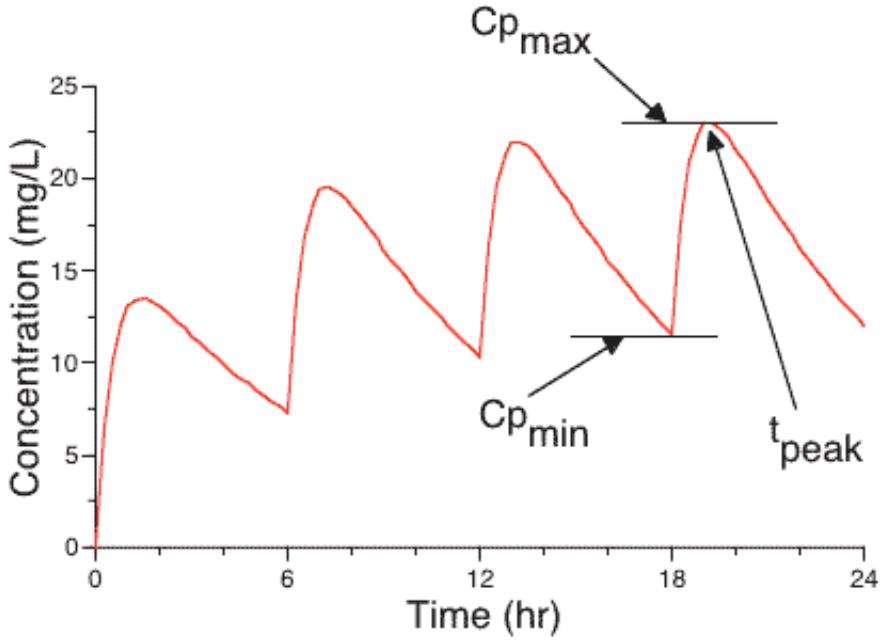

Figure 15.2.1 Plot of Cp *versus* Time for Multiple Oral Doses showing Cp_{max} and Cp_{min}

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

The plasma concentration *versus* time curve described by this equation is similar to the IV curve in that there is accumulation of the drug in the body to some plateau level and the plasma concentrations fluctuate between a minimum and a maximum value.

The Cpmax value could be calculated at the time t = t_{peak} after many doses (as n approaches ∞) but it is complicated by the need to determine the value for t_{peak}.

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Cp_{min} Equation

Starting with equation 26.2.3 we can derive an equation for Cp_{min} which can be more easily determined at t = 0 or t = t. Thus at t = 0 and n approaches ∞ as $e^{-n \bullet k \bullet \tau}$ approaches 0.

$$Cp_{min} = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left(\left[\frac{1}{1 - e^{-kel \bullet \tau}} \right] - \left[\frac{1}{1 - e^{-ka \bullet \tau}} \right] \right)$$

Equation 15.3.1 Cp_{min} after Many Oral Doses - Version 1

This can be further simplified if we assume that the subsequent doses are given after the plasma concentration has peaked and $e^{-ka \bullet \tau}$ is close to zero. That is the next dose is given after the absorption phase is complete.

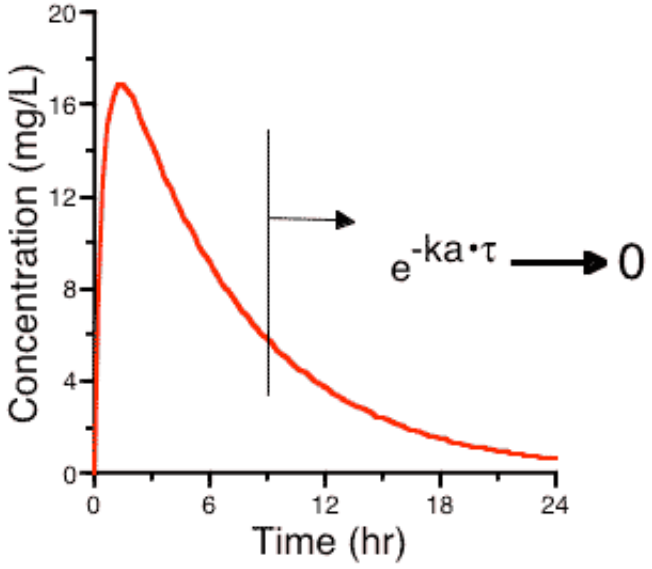


Figure 15.3.1 Plot Cp *versus* Time after a Single Dose showing Possible Time of Second Dose

Cp_{min} then becomes:

$$Cp_{min} = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left[\frac{e^{-kel \bullet \tau}}{1 - e^{-kel \bullet \tau}} \right]$$

Equation 15.3.2 Cp_{min} after Many Oral Doses - Version 2

The relationship between loading dose and maintenance dose and thus drug accumulation during multiple dose administration can be studied by looking at the ratio between the minimum concentration at steady state and the concentration at the end of the first dosing interval,τ, after the first dose. [Assuming $e^{-ka \bullet \tau}$ is close to zero].

$$\frac{Cp_{min}}{Cp_1^{\tau}} = \frac{\frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left[\frac{e^{-kel \bullet \tau}}{1 - e^{-kel \bullet \tau}} \right]}{\frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet e^{-kel \bullet \tau}}$$

Equation 15.3.3 Ratio Between Cp after First and Last Dose

Which can be simplified to give:

$$\frac{Cp_{min}}{Cp_1^{\tau}} = \frac{1}{1 - e^{-kel \bullet \tau}} = \frac{1}{(1 - R)}$$

Equation 15.3.4 Ratio Between Cp after First and Last Dose

This turns out to be the same equation as for the multiple IV bolus doses. Therefore we can estimate a loading dose just as we did for an IV multiple dose regimen.

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

Equation 15.3.5 Loading Dose Equation

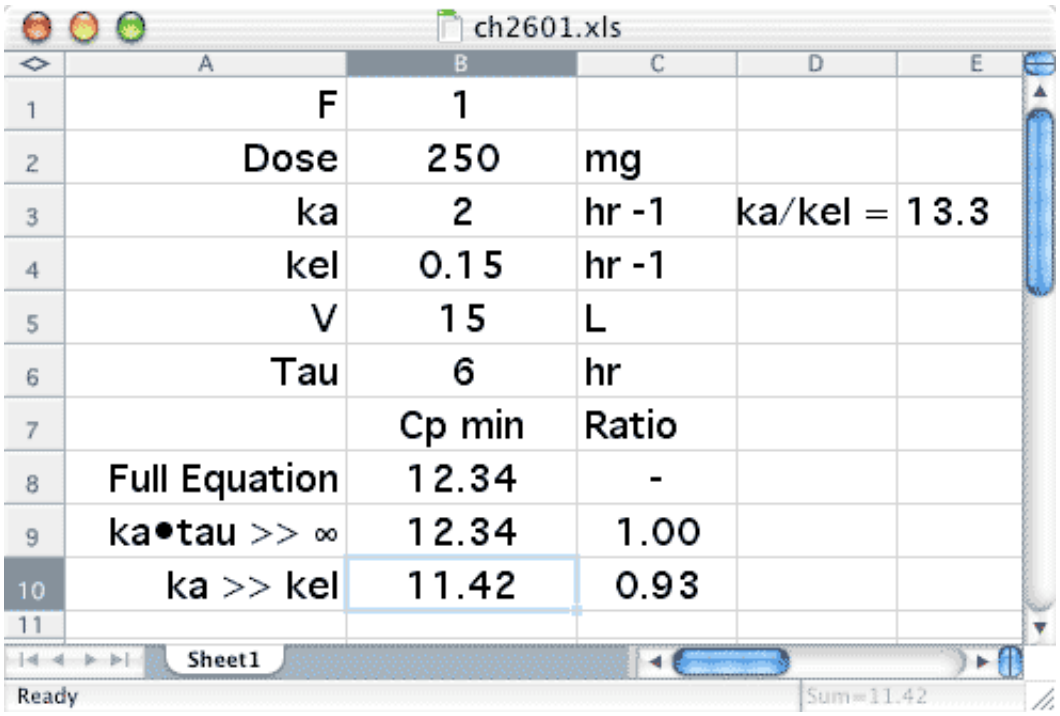
This equation holds if each dose is given after the absorption phase of the previous dose is complete.

We can further simplify Equation 15.3.2, if we assume that ka >> kel then (ka - kel) is approximately equal to ka and ka/(ka - kel) is approximately equal to one.

$$Cp_{min} = \frac{F \bullet Dose}{V} \bullet \left[\frac{e^{-kel \bullet \tau}}{1 - e^{-kel \bullet \tau}} \right]$$

Equation 15.3.6 Cp_{min} after Many Oral Doses - Version 3

Equation 15.3.6 is an even more extreme simplification. However, it can be very useful if we don't know the ka value but we can assume that absorption is reasonably fast. Equation 15.3.6 will tend to give concentrations that are lower than those obtained with the full equation (Equation 15.3.1). Thus any estimated fluctuation between Cp_{min} and Cp_{max} will be overestimated using the simplified equation.



Click on the figure
to download and use this Excel spreadsheet

Figure 15.3.2 Excel™ Spreadsheet Illustrating the Use of Three Cp_{min} Equations

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$Cp_{average}$ Equation

Another very useful concentration value for the calculation of oral dosing regimens is the average plasma concentration during a dosing interval at steady state, $\overline{Cp}$.

The average plasma concentration is defined as the area under the plasma concentration *versus* time curve during the dosing interval at steady state divided by the dosing interval.

Thus:

$$\overline{Cp} = \frac{AUC}{\tau} = \frac{\int_0^{\tau} Cp \bullet dt}{\tau}$$

Equation 15.4.1 Average Cp for a Dosing Interval at Steady State

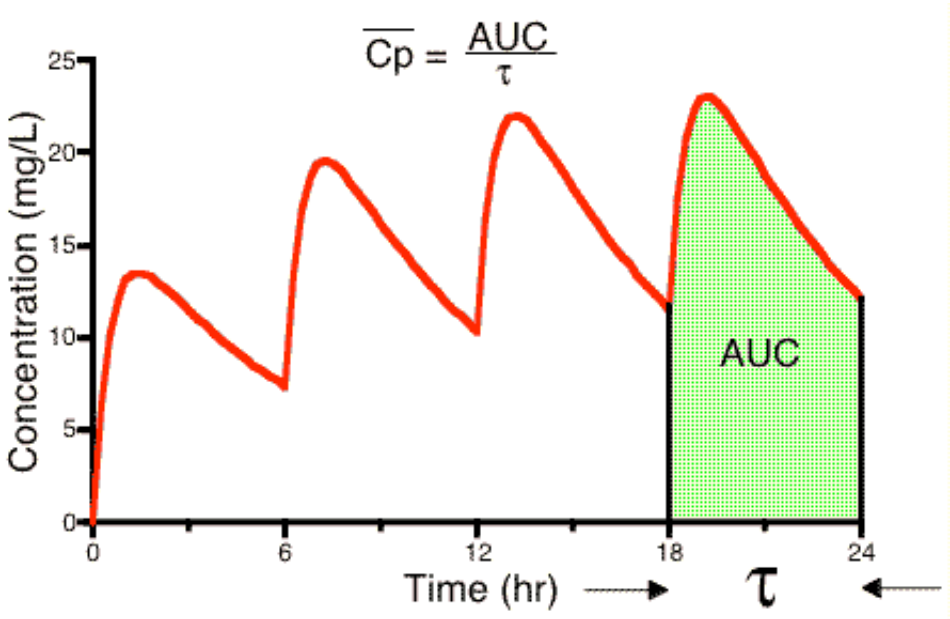

Figure 15.4.1 Plot of Cp *versus* Time after Multiple Oral Administration showing AUC at Steady State

Since,

$$AUC = \frac{F \bullet Dose}{kel \bullet V}$$

Equation 15.4.2 AUC Equation

from the equations developed during the Wagner-Nelson derivation or from the clearance (kel • V) equation.

$$\overline{Cp} = \frac{F \bullet Dose}{V \bullet kel \bullet \tau}$$

Equation 15.4.3 Average Cp for a Dosing Interval at Steady State

This works because the AUC during one dosing interval at steady state is the same as the AUC from zero to infinity after one single dose.

An interesting result of this equation is that we get the same average plasma concentration whether the dose is given as a single dose every dosing interval, τ, or is subdivided into shorter dosing intervals. For example 300 mg every 12 hours will give the same average plasma concentration as 100 mg every 4 hours. **However**, the difference between the maximum and minimum plasma concentration will be larger with less frequent dosing.

An Example - Part 1

With F = 1.0, V = 30 liter, $t_{1/2}$ = 6 hours or kel = 0.693/6 = 0.116 hr^{-1}, calculate the dose given every 12 hours that will achieve an average plasma concentration of 15 mg/L.

$$\text{Since } \overline{Cp} = \frac{F \bullet Dose}{V \bullet kel \bullet \tau}$$

$$Dose = \frac{\overline{Cp} \bullet V \bullet kel \bullet \tau}{F}$$

$$= \frac{15 \times 30 \times 0.116 \times 12}{1.0} = 624\ mg$$

We could now calculate the loading dose

$$R = e^{-kel \bullet \tau} = e^{-0.166 \times 12} = 0.25$$

$$\text{Loading Dose} = \frac{\text{Maintenance Dose}}{1 - R} = \frac{624}{1 - 0.25} = 832\ mg$$

To get some idea of the fluctuations in plasma concentration we could calculate the Cpmin value.

Assuming that ka >> kel and that $e^{-ka \bullet \tau}$ approaches 0 we can use Equation 26.2.6.

$$Cp_{min} = \frac{F \bullet Dose}{V} \bullet \left[\frac{e^{-kel \bullet \tau}}{1 - e^{-kel \bullet \tau}} \right]$$

$$Cp_{min} = \frac{1.0 \times 624}{30} \times \left[\frac{0.25}{1 - 0.25} \right] = 6.93\ mg/L$$

Therefore the plasma concentration would probably fluctuate between 7 and 23 mg/L (very approximate) with an average concentration of about 15 mg/L. [23 = 15 + (15 - 7), i.e. high = average + (average - low), very approximate!].

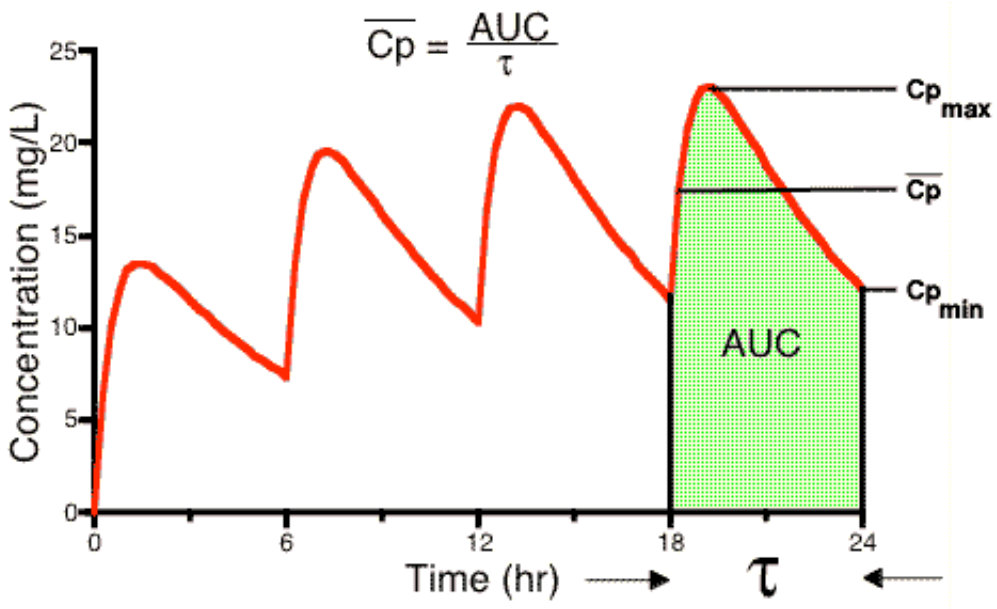

Figure 15.4.2 Figure Illustrating Cp_{max}, Cp_{min} and Cp(average)

An Example - Part 2

As an alternative we could give half the dose, 312 mg, every 6 hours to achieve:

$$Cp_{min} = \frac{1.0 \times 312}{30} \times \left[\frac{0.5}{1 - 0.5} \right] = 10.4\ mg/L$$

The $\overline{Cp}$ would be the same

$$\overline{Cp} = \frac{F \bullet Dose}{V \bullet kel \bullet \tau} = \frac{1 \times 312}{30 \times 0.116 \times 6} = 15\ mg/L$$

Thus the plasma concentration would fluctuate between about 10.4 to 20 with an average of 15 mg/L.

Some items to consider

Item 1. Changing the dosing interval and the dose in the same proportion should produce the same $Cp_{average}$ concentration. However, the Cp_{min} and Cp_{max} can vary considerably.

With F = 1.0, V = 30 liter, $t_{1/2}$ = 6 hours or kel = 0.693/6 = 0.116 hr^{-1}, a dose of 600 mg given every 12 hours will achieve an average plasma concentration of approximately 15 mg/L. Try simulating this regimen and also the alternate regimen of 1200 mg very 24 hours and 300 mg every 6 hours. Which regimen gives the least variation between Cp_{max} and Cp_{min}? Explore the problem as a Linear Plot - Java Applet

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Item 2. Metabolism can be subject to a number of factors, such as genetics, disease state and co-administration of other compounds. Other compounds may inhibit metabolism or induce metabolic activity. Some drugs are capable of inducing their own metabolism.

Carbamazepine is a drug which can induce its own metabolism during the first few days of therapy (Hawkins Van Tyle and Winter, 2004). After the first dose, carbamazepine pharmacokinetic parameters include F = 0.8, V = 1.4 L/hr, Cl = 0.028 L/Kg/hr. After 3 to 5 days carbamazepine metabolism is induced such that the Cl becomes 0.064 L/Kg/gr. For a 70 Kg patients pre-induction (first-dose) parameter values are kel = 0.02 hr^{-1} and V = 100 L. After induction the kel changes to 0.045 hr^{-1}. Dose adjustment during the first few days can be difficult. Using post induction parameters for initial dosage regimen could cause toxic concentrations. For example, try the simulation again with a dose regimen of 600 mg every 12 hours with both pre and post induction kel values. The typical therapeutic plasma concentration range is 4 - 12 mg/L. Explore the problem as a Linear Plot - Java Applet

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Item 3. Theophylline has been studied extensively. It has been used commonly and has been the subject of therapeutic drug monitoring (TDM) because of its variable pharmacokinetic parameters and narrow therapeutic window. Theophylline parameter values vary considerably with disease state, enyzme status (drug co-administration or smoker status) and formulation factors. Currently, the therapeutic window ranges from 5 to 20 mg/L whereas earlier a range of 10 to 20 mg/L had been used. Average plasma concentration targets includes values around 10 mg/L or in the range 8 to 15 mg/L (Aminimanizani and Winter, 2004).

Theophylline is marketed in a number of oral dosage forms. Rapid release tablets generally are rapidly and completely absorbed with F close to 1.0 and ka values above 2 hr^{-1}. The apparent volume of distribution is approximately 0.5 L/Kg (ideal body weight, IBW). Average values of theopylline clearance approximate 0.04 L/Kg/hr (based on IBW). A number of factors can influence this average clearance value. For example; smoking x 1.6, cimetidine co-administration x 0.6, phenytoin co-administration 1.6, congestive heart failure x 0.5 (depending on status), cystic fibrosis x 1.5, hepatic cirrhosis x 0.5. Considering a 70 Kg (IBW) non-smoker patient the expected V and kel might be 35 L and 0.08 hr^{-1}. For a patient that smokes the kel would be expected to be approximately 0.125 hr^{-1}. Try adjusting the parameter values according to these covariates and adjust the dosing regimen to maintain appropriate therapeutic concentrations. Explore the problem as a Linear Plot - Java Applet

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References

- Hawkins Van Tyle, J. and Winter, M.E. 2004 Chapter 2 "Carbamazepine" in **Basic Clinical Pharmacokinetics**, 4th ed., Winter, M.E., Lippincott Williams & Wilkins, Baltimore, MD
- Aminimanizani, A. and Winter, M.E. 2004 Chapter 12 "Theophylline" in **Basic Clinical Pharmacokinetics**, 4th ed., Winter, M.E., Lippincott Williams & Wilkins, Baltimore, MD

Practice problems involving $Cp_{average}$, Cp_{max} and Cp_{min} at steady state after uniform multiple dose Oral doses.

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Superposition Principle

The superposition principle can be used when all the disposition processes are linear. The disposition processes are distribution, metabolism and excretion (DME). That is, the processes that occur after the drug is absorbed. Thus, the superposition principle can be used when the DME processes are linear or first-order. According to this approach concentrations after multiple doses can be calculated by adding together the concentrations from each dose. Also, doubling the dose will result in the concentrations at each time doubling. This is not true when disposition processes are non-linear.

For example, calculate drug concentration at 24 hours after the first dose of 200 mg. The second dose of 300 mg was given at 6 hours and the third dose of 100 mg at 18 hours. The apparent volume of distribution is 15 L and the elimination rate constant is 0.15 hr^{-1}.

$$Cp^1 = \frac{200}{15} \bullet e^{-0.15 \times t} = 0.364\ mg/L \text{ at } 24 \text{ hr}$$

The concentration from the first dose at 24 hours after the administration of the first dose

$$Cp^2 = \frac{300}{15} \bullet e^{-0.15 \times (t-6)} = 1.344\ mg/L$$

The concentration from the second dose at 24 hours after the administration of the first dose

$$Cp^3 = \frac{100}{15} \bullet e^{-0.15 \times (t-18)} = 2.710\ mg/L$$

The concentration from the third dose at 24 hours after the administration of the first dose

$$Cp = Cp^1 + Cp^2 + Cp^3 = 4.42\ mg/L$$

The total concentration from all three doses at 24 hours after the administration of the first dose. This method involved calculating the contribution from each dose at a time 24 hours after the first dose.

The result of this calculation is shown graphically in Figure 15.5.1.

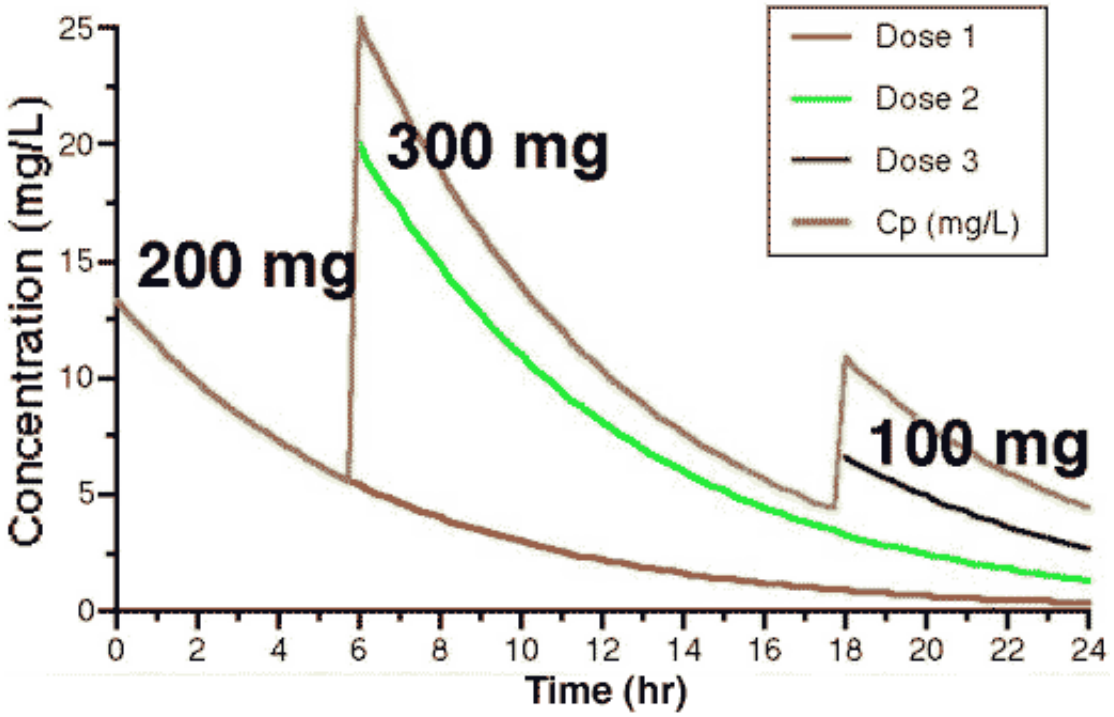


Figure 15.5.1 Drug Concentration after Three IV Bolus Doses

Another approach is to work through the dosing regimen dose by dose.

$$Cp_1^0 = \frac{200}{15} = 13.33\ mg/L$$

Total drug concentration just after the first dose

$$Cp_1^6 = 13.33 \times e^{-0.15 \times 6} = 5.42\ mg/L$$

Total drug concentration just before the second dose

$$Cp_2^0 = 5.42 + \frac{300}{15} = 25.42\ mg/L$$

Total drug concentration just after the second dose

$$Cp_2^{12} = 25.42 \times e^{-0.15 \times 12} = 4.20\ mg/L$$

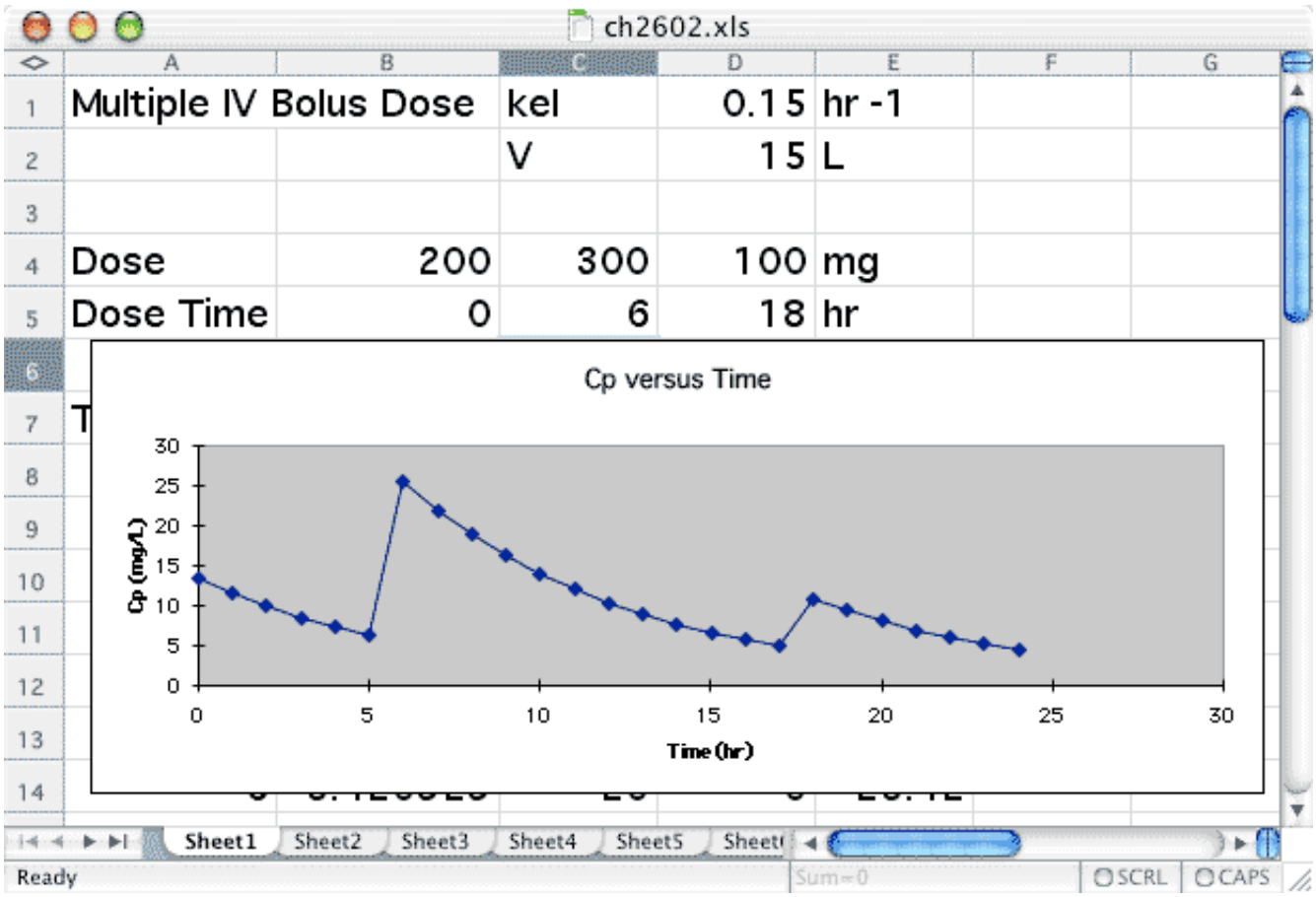
Total drug concentration just before the third dose

$$Cp_3^0 = 4.20 + \frac{100}{15} = 10.87\ mg/L$$

Total drug concentration just after the third dose

$$Cp_3^6 = 10.87 \times e^{-0.15 \times 6} = 4.42\ mg/L$$

Total drug concentration 6 hours after the third dose. This answer can also be calculated using an Excel spreadsheet illustrating the superposition principle.



Click on the figure
to download and use this Excel spreadsheet

Figure 15.5.2 Excel™ Spreadsheet Illustrating the Superposition Principle - Multiple IV Doses

Non-uniform dosing intervals

Prior to this Chapter the calculations we have looked at consider that the dosing intervals are quite uniform, however, commonly this ideal situation is not adhered to completely.

Dosing three times a day may be interpreted as take with meals, the plasma concentration may then look like the plot in Figure 60. The ratio between Cpmax and Cpmin is seven fold (8.2/1.1 = 7.45) in this example.

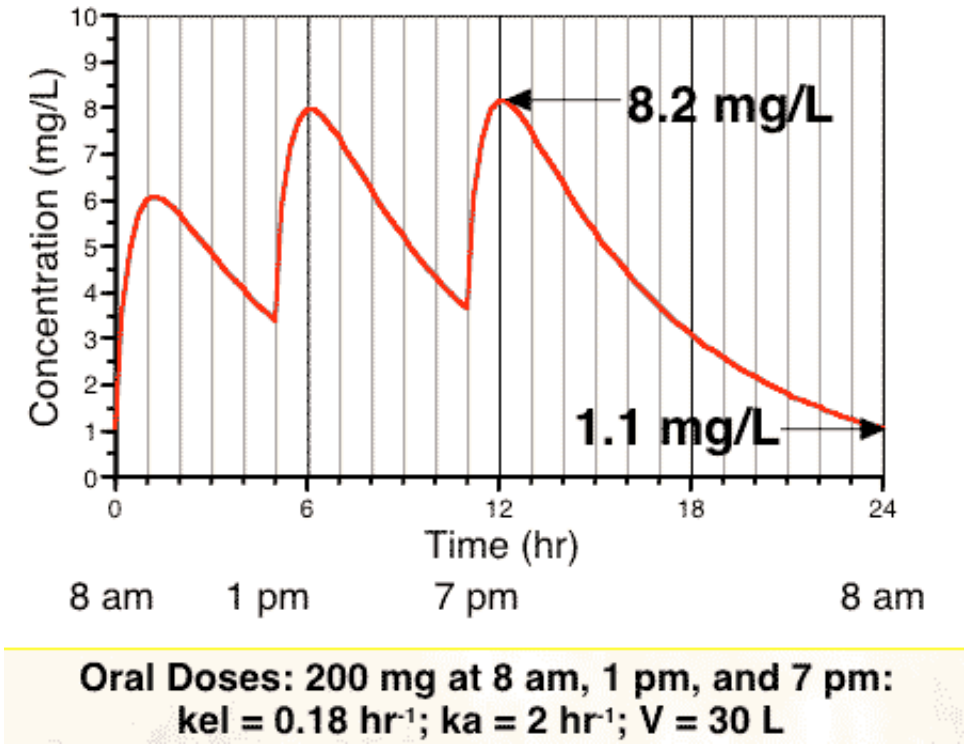


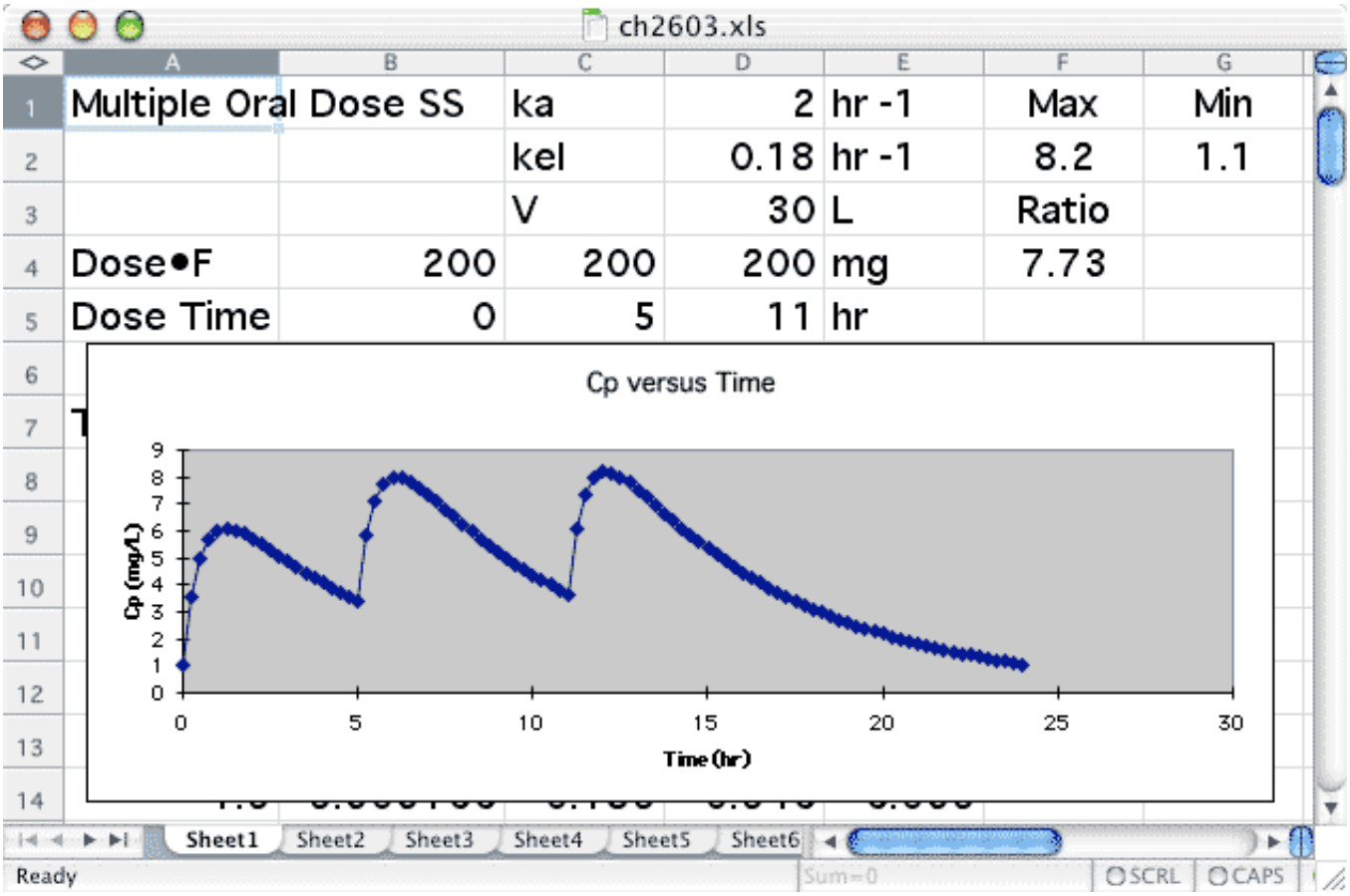
Figure 15.5.3 Cp *versus* Time during Dosing at 8 am, 1 pm, and 7 pm

However this regimen may be acceptable if

1) the drug has a wide therapeutic index

2) there is no therapeutic disadvantage to low overnight plasma concentrations, e.g., analgesic of patient stays asleep.

This regimen can be explored further using an Excel spreadsheet illustrating the superposition principle.



Click on the figure
to download and use this Excel spreadsheet

Figure 15.5.4 Excel™ Spreadsheet Illustrating the Superposition Principle - Multiple Oral Doses

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Other practice problems involving the calculation of Cp at three times during a uniform dosing interval with Linear or Semi-log graphical answers or calculation of Cp at three times during a non-uniform dosing interval with Linear or Semi-log graphical answers

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Student Objectives for this Chapter

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