PHAR 7633 Chapter 15

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, $\overline{C_p}$
- be able to use the $\overline{C_p}$ equation to calculate or adjust an appropriate dosing regimen
- be able to use the superposition principle to calculate $C_p$ after non uniform IV or oral dosing regimen
Multiple Oral Dose Administration

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:

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

Equation 15.2.1 \( C_p \) 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".

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

Equation 15.2.2 Multiple Dose Function

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

\[ - \left[ \frac{1 - e^{-n \cdot ka \cdot \tau}}{1 - e^{-ka \cdot \tau}} \right] \cdot e^{-ka \cdot t} \]

Equation 15.2.3 \( C_p \) after a Single Oral Dose - Uniform Dose and Interval, \( \tau \) General Equation

Compare with IV Bolus Multiple Dose Equation 14.5.11
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 $C_{p\text{max}}$ value could be calculated at the time $t = t_{\text{peak}}$ after many doses (as $n$ approaches $\infty$) but it is complicated by the need to determine the value for $t_{\text{peak}}$.
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$C_{P_{min}}$ Equation

Starting with equation 15.2.3 we can derive an equation for $C_{P_{min}}$ which can be more easily determined at $t = 0$ or $t = t$. Thus at $t = 0$ and $n$ approaches $\infty$ as $e^{-n \cdot k \cdot \tau}$ approaches 0.

$$C_{P_{min}} = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \left( \frac{1}{1 - e^{-kel \cdot \tau}} - \frac{1}{1 - e^{-ka \cdot \tau}} \right)$$

Equation 15.3.1 $C_{P_{min}}$ 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 $e^{-ka \cdot \tau}$ 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](http://www.boomer.org/c/p4/c15/c15.html)
Cp\textsubscript{min} then becomes:

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

Equation 15.3.2 Cp\textsubscript{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, \(\tau\), after the first dose. [Assuming \(e^{-ka \cdot \tau}\) is close to zero].

$$\frac{Cp_{\text{min}}}{Cp_1} = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \frac{e^{-kel \cdot \tau}}{1 - e^{-kel \cdot \tau}} \cdot e^{-kel \cdot \tau}$$

Equation 15.3.3 Ratio Between Cp after First and Last Dose

Which can be simplified to give:

$$\text{Accumulation Factor} = \frac{Cp_{\text{min}}}{Cp_1} = \frac{1}{1 - e^{-kel \cdot \tau}} = \frac{1}{1 - R}$$

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 when ka is high if we assume that ka >> kel then (ka - kel) is approximately equal to ka and ka/(ka - kel) is approximately equal to one.
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 $C_{P_{\text{min}}}$ and $C_{P_{\text{max}}}$ will be overestimated using the simplified equation.

$$C_{P_{\text{min}}} = \frac{F \cdot \text{Dose}}{V} \cdot \left[ \frac{e^{-k_{el} \cdot \tau}}{1 - e^{-k_{el} \cdot \tau}} \right]$$

Equation 15.3.6 $C_{P_{\text{min}}}$ after Many Oral Doses - Version 3

Compare with IV Bolus Multiple Dose Equation 14.6.2

Equation 15.3.6 and 15.3.1 are provided above.

Click on the figure to download and use this Excel spreadsheet

**Figure 15.3.2 Excel™ Spreadsheet Illustrating the Use of Three $C_{P_{\text{min}}}$ Equations**

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Multiple Oral Dose Administration

$C_p_{\text{average}}$ 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, $C_p_{\text{average}}$, aka $\overline{C_p}$ or $C_p(\text{bar})$.

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:

$$\overline{C_p} = \frac{AUC_{SS}^{0-\tau}}{\tau} = \frac{\int_0^\tau C_p \bullet dt}{\tau}$$

Equation 15.4.1 Average $C_p$ for a Dosing Interval at Steady State

Since the AUC during one dosing interval at steady state is the same as the AUC from zero to infinity after the first dose,

$$AUC_{1}^{0-\infty} = AUC_{SS}^{0-\tau}$$

The AUC (first dose) from the equations developed during the Wagner-Nelson derivation or from the clearance ($kel \bullet V$) equation is given as Equation 15.4.2.
Equation 15.4.2 AUC Equation

\[ AUC_{1-\infty}^0 = \frac{F \cdot Dose}{kel \cdot V} = \frac{F \cdot Dose}{CL} \]

Equation 15.4.3 for the average concentration at steady state can be obtained from Equation 15.4.1 and 15.4.2.

\[ \bar{C}_p = \frac{F \cdot Dose}{V \cdot kel \cdot \tau} = \frac{F \cdot Dose}{CL \cdot \tau} \]

Equation 15.4.3 Average Cp for a Dosing Interval at Steady State

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, \( \tau \), 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.

Since \( \bar{C}_p = \frac{F \cdot Dose}{V \cdot kel \cdot \tau} \)

\[ Dose = \bar{C}_p \cdot V \cdot kel \cdot \tau \cdot \frac{F}{15 \times 30 \times 0.116 \times 12 \times 1.0} = 624 \text{ mg} \]

We could now calculate the loading dose

\[ R = e^{-kel \cdot \tau} = e^{-0.116 \times 12} = 0.25 \]

Loading Dose = \( \frac{624}{1 - 0.25} = 832 \text{ mg} \)

To get some idea of the fluctuations in plasma concentration we could calculate the \( Cp_{min} \) value.

Assuming that \( ka << kel \) and that \( e^{-ka \cdot \tau} \) approaches 0 we can use Equation 26.2.6.

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

An Example - Part 2

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

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

The \( \overline{C_P} \) would be the same

\[ \overline{C_P} = \frac{F \cdot Dose}{V \cdot kel \cdot \tau} = \frac{1 \times 312}{30 \times 0.116 \times 6} = 15 \text{ mg/L} \]

Thus the plasma concentration would fluctuate between about 10.4 to 20 with an average of 15 mg/L, Figure 15.4.2. The exact equation was used for the calculation in Figure 15.4.2.

![Figure 15.4.2 Figure Illustrating \( C_{p_{\text{max}}}, C_{p_{\text{min}}} \) and \( C_p(\text{average}) \)](http://www.boomer.org/c/p4/c15/c15.html)

Some items to consider
Item 1. Changing the dosing interval and the dose in the same proportion should produce the same \( C_{p_{\text{average}}} \) concentration. However, the \( C_{p_{\text{min}}} \) and \( C_{p_{\text{max}}} \) can vary considerably.

With \( F = 1.0 \), \( V = 30 \) liter, \( t_{1/2} = 6 \) hours or \( kel = 0.693/6 = 0.116 \text{ hr}^{-1} \), 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 \( C_{p_{\text{max}}} \) and \( C_{p_{\text{min}}} \)? Explore the problem as a Plot - Interactive graph. (IE Version)

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 \( F = 0.8 \), \( V = 1.4 \text{ L/hr} \), \( CL = 0.028 \text{ L/Kg/hr} \). 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 \( kel = 0.02 \text{ hr}^{-1} \) and \( V = 100 \text{ L} \). 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 Plot - Interactive graph. (IE Version)

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, enzyme 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 theophylline 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 Plot - Interactive graph. (IE Version)

References


Practice problems involving \( C_{p_{\text{average}}} \), \( C_{p_{\text{max}}} \) and \( C_{p_{\text{min}}} \) 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\(^{-1}\).

\[
C_p^1 = \frac{200}{15} \cdot e^{-0.15 \times t} = 0.364 \text{ mg/L at } 24 \text{ hr}
\]

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

\[
C_p^2 = \frac{300}{15} \cdot e^{-0.15 \times (t-6)} = 1.344 \text{ mg/L}
\]

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

\[
C_p^3 = \frac{100}{15} \cdot e^{-0.15 \times (t-18)} = 2.710 \text{ mg/L}
\]

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

\[
C_p = C_p^1 + C_p^2 + C_p^3 = 4.42 \text{ mg/L}
\]

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.

![Drug Concentration after Three IV Bolus Doses](Figure 15.5.1 Drug Concentration after Three IV Bolus Doses)

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

\[ C_p^0 \]

Total drug concentration just after the first dose

\[ C_p^6 = 13.33 \times e^{-0.15 \times 6} = 5.42 \text{ mg/L} \]

Total drug concentration just before the second dose

\[ C_p^0 = 5.42 + \frac{300}{15} = 25.42 \text{ mg/L} \]

Total drug concentration just after the second dose

\[ C_p^{12} = 25.42 \times e^{-0.15 \times 12} = 4.20 \text{ mg/L} \]

Total drug concentration just before the third dose

\[ C_p^0 = 4.20 + \frac{100}{15} = 10.87 \text{ mg/L} \]
\[ C_{p3}^6 = 10.87 \times e^{-0.15 \times 6} = 4.42 \text{ mg/L} \]

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

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.
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 if patient stays asleep.
This regimen can be explored further using an Excel spreadsheet illustrating the superposition principle.

![Excel Spreadsheet Illustrating the Superposition Principle](c1506.xls)

**Figure 15.5.4 Excel™ Spreadsheet Illustrating the Superposition Principle - Multiple Oral Doses AT Steady State**

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

### Student Objectives for this Chapter

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