14

Multiple intermittent infusions

Objectives

Upon completion of this chapter, you will have the ability to:

- calculate plasma drug concentrations during an intermittent infusion
- determine the dosing regimen (infusion rate \([Q]\) and the duration of infusion \([t_{inf}]\)) that will result in target plasma drug concentrations
- calculate a loading infusion rate
- apply theoretical pharmacokinetic principles to real-world intermittent infusion regimens of aminoglycosides and vancomycin
- adjust the method of calculating “peak” \((C_{PK})\) and trough \((C_{TR})\) plasma drug concentrations when these concentrations are not collected exactly at their scheduled times.

14.1 Introduction

Drugs administered by constant-rate intravenous infusion are frequently infused intermittently rather than continuously. The following example of a particular dosing regimen for the antibiotic vancomycin may be illustrative. In a particular patient, vancomycin was infused at a rate of 800 mg h\(^{-1}\) for 1 h, with a period of 12 h elapsing before this process was repeated. While drug was being infused, it was entering the body at a constant rate, namely 800 mg h\(^{-1}\) in this example. However, the lapse of 12 h between each 1 h infusion defines this process as an intermittent administration of drug.

Figure 14.1 is a graph, on rectilinear co-ordinates, of plasma vancomycin concentration for this regimen. In this figure we see the fairly rapid attainment (after approximately 36 h) of steady-state conditions, where successive peak drug concentrations \((C_{PK})_{ss}\) are equal to each other and successive trough concentrations \((C_{TR})_{ss}\) are equal to each other. We see also that the dosing interval \((\tau)\) can be measured either from peak to peak or from trough to trough. Finally, we see that the interval \(\tau\) comprises the time that the infusion is running \((t_{inf}\) which is 1 h in this example) plus the time that the infusion is not running (i.e. the time from the end of one infusion to the beginning of the next infusion \([\tau - t_{inf}]\): 11 h in this example.) Therefore, \(\tau - t_{inf}\) is also the length of time between the peak and trough times.

Figure 14.2 is the same data plotted on semi-logarithmic co-ordinates. At time zero, the plasma drug concentration would also equal zero. (A value of zero cannot be shown on the logarithmic y-axis of this graph; therefore, we have to imagine the plasma drug concentration coming up from zero for an infinitely long distance along the y-axis.) This figure also shows that the declining blood concentrations after
each short infusion exhibit a terminal linear segment. This occurs when distribution of drug to tissues has reached equilibrium. Finally, there is an extension of the terminal linear segment for 1 h beyond the commencement of the next short infusion. This is equal to \((C_{TR})_{ss}(e^{-K_{inf}})\), an expression which is found in the equation for calculation of the volume of distribution:

\[
V = \frac{(S)(Q)(1 - e^{-K_{inf}})}{(K)((C_{PK})_{ss} - (C_{TR})_{ss}e^{-K_{inf}})} \quad (14.1)
\]

Once steady state has been attained, the following equation can be used to calculate drug concentration at any time, \(t\), from the time of peak concentration up to the time of trough

Figure 14.1 Multiple intermittent infusions shown in a rectilinear plot. \(C_p\), plasma drug concentration; \((C_{PK})_{ss}\), peak drug concentration at steady state; \((C_{TR})_{ss}\), trough drug concentration at steady state; \(\tau\), dosing interval; \(t_{inf}\), time infusion is running.

Figure 14.2 Multiple intermittent infusion shown in a semilogarithmic plot. Abbreviations as in Fig. 14.1.
concentration (right before the next infusion is begun):

\[ C_{ss} = (C_{PK})_{ss} (e^{-K(t-t_{inf})}) \]  \hspace{1cm} (14.2)

Table 14.1 shows what happens when various values are substituted for \( t \) in the above equation. The numerical values in the table are based on a dosing interval equal to 8 h and an infusion time equal to 1 h.

### 14.2 Drug concentration guidelines

Table 14.2 presents target plasma steady-state peak and trough drug concentrations for four aminoglycoside antibiotics. These target values vary depending upon the severity of the patient’s infection but give a guideline when calculating the ideal dosing regimen for a particular patient in a particular condition. Below is a worked example of the determination of a multiple intermittent infusion dosing regimen for the aminoglycoside gentamicin.

### Table 14.1 Peak, trough and other points with respect to Equation 14.2

<table>
<thead>
<tr>
<th>Point described</th>
<th>( t = )</th>
<th>( t-t_{inf} = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (the highest point; it occurs immediately before the infusion is stopped)</td>
<td>( t_{inf} ) (e.g. ( t = 1 ) h)</td>
<td>( t_{inf} - t_{inf} = 0 ) (so ( t-t_{inf} ) always equals 0 at time of peak)</td>
</tr>
<tr>
<td>Points between peak and trough</td>
<td>( \tau &gt; t &gt; t_{inf} ) (e.g. ( t ) is between 1 and 8 h)</td>
<td>( 7 &gt; t-t_{inf} &gt; 0 ) (i.e. ( t-t_{inf} ) will range between 0 and 7 h for this example)</td>
</tr>
<tr>
<td>Trough (the lowest point; it occurs immediately before the next infusion is started)</td>
<td>( \tau ) (e.g. ( t = 8 ) h)</td>
<td>( \tau - t_{inf} ) (e.g. ( t-t_{inf} = 7 ) h)</td>
</tr>
<tr>
<td>Trough extends for 1 h into the next interval (serves as a baseline under the next peak)</td>
<td>( \tau + t_{inf} ) (e.g. ( t = 9 ) h)</td>
<td>( \tau ) (e.g. ( t-t_{inf} = 8 ) h)</td>
</tr>
</tbody>
</table>

\( \tau \), dosing interval (measured from peak to peak or from trough to trough); \( t_{inf} \), time infusion running; \( t-t_{inf} \), the time from the end of one infusion to the beginning of the next infusion (also the length of time between the peak and trough times).

### Table 14.2 Aminoglycoside target plasma levels

<table>
<thead>
<tr>
<th>Severity of infection</th>
<th>Gentamicin, tobramycin or netilmicin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target peak concentration (µg mL(^{-1}))</td>
<td>Less severe 5–8</td>
<td>20–25</td>
</tr>
<tr>
<td></td>
<td>Life-threatening 8–10(^a)</td>
<td>25–48</td>
</tr>
<tr>
<td>Target trough concentration (µg mL(^{-1}))</td>
<td>Less severe 0.5–1</td>
<td>1–4</td>
</tr>
<tr>
<td></td>
<td>Life-threatening 1–2(^a)</td>
<td>4–8</td>
</tr>
</tbody>
</table>

\(^a\) In select patients with life-threatening infections, netilmicin has been used with troughs 2–4 µg mL\(^{-1}\) and peaks 12–16 µg mL\(^{-1}\).
14.3 Example: determination of a multiple intermittent infusion dosing regimen for an aminoglycoside antibiotic

The aminoglycoside antibiotics display some two-compartment characteristics, but not as markedly as vancomycin. For a 1 h infusion, the true peak plasma gentamicin concentration (immediately after the infusion is stopped) is often used. The rationale for this is that distribution equilibrium for gentamicin is essentially complete in 1 h. However, for a 30 min infusion, it is common to wait for an additional 30 min after the infusion is stopped and to call this the gentamicin “peak” concentration.

Patient information:

- $t_{1/2} = 4.91 \text{ h}$
- $V = 0.25 \text{ L kg}^{-1}$
- height $= 200 \text{ cm}$
- weight $= 60 \text{ kg}$
- drug = gentamicin sulfate (for which the salt value ($S$) $\approx 1$).

1. An intermittent intravenous infusion dosing regimen needs to be designed that will achieve peak steady-state plasma drug concentrations of 6 $\mu$g mL$^{-1}$ and trough steady-state plasma drug concentrations of 1 $\mu$g mL$^{-1}$ for an infusion over 1 h.

2. Using convenient, practical values for infusion rate ($Q$) and dosing interval ($\tau$), what exact peak and trough steady-state plasma drug concentrations will be achieved?

3. Calculate a one-time-only loading infusion rate.

1. First solve for the interval $\tau$, using the following equation:

$$\tau = \frac{\ln \left( \frac{(C_{PK})_{ss}}{(C_{TR})_{ss}} \right) + t_{inf}}{K}$$

$$\tau = \frac{\ln \left( \frac{6 \text{ mg L}^{-1}}{1 \text{ mg L}^{-1}} \right)}{0.693/4.91 \text{ h}} + 1 \text{ h} = 13.7 \text{ h}$$

A convenient interval $= 12 \text{ h}$.

In order to solve for the infusion rate $Q$, the following equation is used:

$$Q = \frac{(C_{PK})_{ss}VK}{1 - e^{-Kr}}$$

$$Q = (6 \text{ mg L}^{-1})(0.25 \text{ L kg}^{-1}) \times (60 \text{ kg})(0.141 \text{ h}^{-1}) \left( \frac{1 - e^{- (0.141)(12)}}{1 - e^{- (0.141)(1)}} \right)$$

$$= 78.7 \text{ mg h}^{-1}$$

A round number is 80 mg h$^{-1}$.

So, the infusion would be of 80 mg h$^{-1}$ for 1 h. This would be repeated every 12 h.

2. Because of rounding off, the peak will not be exactly 6$\mu$g mL$^{-1}$, nor will the trough be exactly 1$\mu$g mL$^{-1}$.

To calculate the peak value, rearrange Eq. 14.4 as follows:

$$(C_{PK})_{ss} = \frac{Q}{VK} \left( \frac{1 - e^{-Kr}}{1 - e^{-Kr_t}} \right)$$

Then,

$$(C_{PK})_{ss} = \frac{80 \text{ mg h}^{-1}}{(15 \text{ L})(0.141 \text{ h}^{-1})} \times \left( \frac{1 - e^{- (0.141)(1)}}{1 - e^{- (0.141)(12)}} \right) = 6.10 \text{ mg L}^{-1}$$

To calculate the trough value, use:

$$(C_{TR})_{ss} = (C_{PK})_{ss}(e^{-K(t_{inf})})$$

So,

$$(C_{TR})_{ss} = (6.10 \text{ mg L}^{-1})(e^{- (0.141)(12 - 1)}) = 1.29 \text{ mg L}^{-1}$$

3. A one-time-only loading infusion rate avoids waiting to achieve a steady state; a single loading infusion rate that, exactly 1 h (when it is discontinued), will provide the desired steady-state peak drug concentration of 6$\mu$g mL$^{-1}$ is calculated by:

$$Q_L = \frac{(C_{PK})_{desired}(V)(K)}{1 - e^{-Kr_{inf}}}$$
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\[ Q_d = \frac{(6 \text{ mg L}^{-1})(15 \text{ L})(0.141 \text{ h}^{-1})}{1 - e^{-(0.141)(1)}} \]
\[ = 96.5 \text{ mg h}^{-1} \]
\[ \approx 100 \text{ mg h}^{-1} \text{ for 1 h only, given one time only.} \]

**Adjusting for the severity of infection**

In light of the guidelines (Table 14.2), suppose the patient in the dosing regimen calculation above was categorized as having a less-severe, non-life-threatening infection. In this case, it would be important not to risk possible side effects from the calculated trough steady-state concentration of 1.29 mg L\(^{-1}\). Since the peak concentration is acceptable, the trough concentration can be lowered by judiciously increasing the dosing interval. The calculations can be reworked substituting a dosing interval of 16 h for the original interval of 12 h. First Eq. 14.4 is used to solve for the new infusion rate:

\[ Q = (6 \text{ mg L}^{-1})(0.25 \text{ L kg}^{-1})(60 \text{ kg}) \]
\[ \times (0.141 \text{ h}^{-1})\left(\frac{1 - e^{-(0.141)(16)}}{1 - e^{-(0.141)(1)}}\right) \]
\[ = 86.4 \text{ mg h}^{-1} \]

Rounded off to the nearest 10 mg h\(^{-1}\), \( Q = 90 \text{ mg h}^{-1} \). If the infusion rate is 90 mg h\(^{-1}\) and the new dosing interval is 16 h, but the original infusion length of 1 h is unchanged, what changes would be expected in the steady-state peak and trough concentrations?

Using Eq. 14.5, the calculation is:

\[ (C_{PK})_{ss} = \left(\frac{90 \text{ mg h}^{-1}}{(15 \text{ L})(0.141 \text{ h}^{-1})}\right) \]
\[ \times \left(\frac{1 - e^{-(0.141)(16)}}{1 - e^{-(0.141)(1)}}\right) = 6.25 \text{ mg L}^{-1} \]

which is a modest increase.

Next, using Eq. 14.6, the calculation is:

\[ (C_{TR})_{ss} = (6.25 \text{ mg L}^{-1})(e^{-(0.141)(16 - 1)}) \]
\[ = 0.754 \text{ mg L}^{-1} \]

Since this falls between 0.5 and 1 mg L\(^{-1}\), the regimen is acceptable.

**14.4 Dose to the patient from a multiple intermittent infusion**

Table 14.3 shows the dose to the patient from two multiple intermittent infusion regimens which differ in the length of the infusion. This table makes use of the equation:

\[ X_0 = Q/t_{inf} \] (14.7)

Notice in this table that \( X_0/t_{inf} = Q \), the infusion rate, which was the same for both regimens in the

<table>
<thead>
<tr>
<th>Dosing regimen</th>
<th>Infusion rate ( [Q] ) [mg h(^{-1})]</th>
<th>Infusion time ( [t_{inf}] ) [h]</th>
<th>Dosing interval ( [\tau] ) [h]</th>
<th>Dose (mg)</th>
<th>Dose/( \tau ) (proportional to average steady-state drug concentration) [mg h(^{-1})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg h(^{-1}) given over 1 h every 12 h</td>
<td>100</td>
<td>1</td>
<td>12</td>
<td>100</td>
<td>100/12 = 8.333</td>
</tr>
<tr>
<td>100 mg h(^{-1}) given over 0.5 h every 12 h</td>
<td>100</td>
<td>0.5</td>
<td>12</td>
<td>50</td>
<td>100/12 = 4.167</td>
</tr>
</tbody>
</table>
example above; whereas \( X_0/t \) was lower for the shorter infusion time regimen. This indicates that \((C_{ave})_{ss}\) will also be lower, since \((C_{ave})_{ss} = \frac{SF}{K} \left( \frac{X_0}{t} \right)\).

### 14.5 Multiple intermittent infusion of a two-compartment drug: vancomycin “peak” at 1 h post-infusion

In Fig. 14.2, plasma concentrations of vancomycin plotted versus time were plotted using semi-logarithmic co-ordinates. Even though this figure was graphed using a logarithmic \(y\)-axis, the post-infusion plasma drug concentration shows curvature for a period of time, until finally settling down to a straight line. This initial curvature indicates the presence of a multi-compartment drug. Vancomycin is, in fact, a classical two-compartment drug. In theory, use of a two-compartment equation would exactly characterize the vancomycin plasma concentration versus time curve. However, in practice, it is rare to have enough plasma concentration data on a patient to be able to calculate the two-compartment parameters. So, instead, a usable “peak” plasma vancomycin concentration (on the more nearly linear part of the curve) is drawn, assayed, and recorded at 1 h after the end of the infusion.

Figure 14.3 is a semilogarithmic plot showing the point on the declining plasma drug concentration curves at which sufficient linearity is reached to use simple one-compartment equations. This occurs at approximately 1 h after each short infusion has ended. Curvature of the graph before this time prevents the true peak concentration (immediately after the infusion ends) to be used in calculations. The concentration 1 h post-infusion is the usable peak level \((C_{PK})_{ss}\). In this figure, lines (with slope proportional to the elimination rate constant) are extended downward from the true peak concentration and from \((C_{PK})_{ss}\) to the concentration immediately before the next short infusion. The line originating from the 1 h post-infusion “peak” level is a closer estimate of the actual plasma vancomycin concentration curve. The slope of the line from the useable peak level to the trough value at steady state yields an apparent one-compartment, first-order elimination rate constant, which can be denoted \(K\).

**Modification of equations for the time from the end of the infusion to the “peak”**

The multiple intermittent infusion equation must be modified to reflect the use of the “peak” concentration for vancomycin, as defined above. The modified equation for steady-state peak plasma drug concentration is as follows:

\[
(C_{PK})_{ss} = \frac{(Q)(1 - e^{-K_{int}})(e^{-Kt})}{(V)(K)(1 - e^{-Kr})}
\]  

(14.8)

**Figure 14.3** Effect of choice of time of “peak” vancomycin concentration on estimate of trough level. \(C_p\), plasma drug concentration.
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1. Calculate a dosing interval and a volume of distribution of 35 L.

The trough equation must be modified as well:

\[
(C_{TR})_{ss} = (C_{PK'})_{ss} \left( e^{-K(t_{inf} - t')} \right)
\]  

(14.9)

The equation for volume of distribution then becomes:

\[
V = \frac{(S)(Q)(1 - e^{-Kt_{inf}})(e^{-Kt'})}{(C_{PK'})_{ss}(K)(1 - e^{-Kt})}
\]

\[
= \frac{(S)(Q)(1 - e^{-Kt_{inf}})(e^{-Kt_{inf}})}{(C_{PK'})_{ss}(K)(1 - e^{-Kt})}
\]

(14.10)

The only difference in these two equations is whether one prefers the notation \( t' \) or \( t_{wait} \), both of which terms stand for the same thing.

### 14.6 Vancomycin dosing regimen problem

Now we are able to solve a vancomycin problem. A patient has a vancomycin elimination half life of 8 h (elimination rate constant, 0.08663 h\(^{-1}\)) and a volume of distribution of 35 L.

1. Calculate a dosing interval \( \tau \) to achieve a steady-state plasma drug “peak” concentration (measured 1 h after the end of the infusion) equal to 30 mg L\(^{-1}\) and a steady-state plasma drug trough concentration equal to 11 mg L\(^{-1}\). Use a 1 h infusion duration for doses <1000 mg, and a 2 h infusion duration for doses ≥1000 mg. The following equation is used:

\[
\tau = \frac{\ln \left( \frac{C_{PK'}}{C_{TR}} \right)_{ss}}{K} + t_{inf} + t'
\]

(14.11)

where \( t' \) is the time from the end of the infusion to the “peak” and \( t_{inf} \) is the the duration of the infusion.

2. Calculate a multiple intermittent infusion rate, \( Q \), that will deliver a “peak” steady-state plasma vancomycin concentration of 30 mg L\(^{-1}\), assuming that the salt form correction factor \( S \) is 1.0. Equation 14.8 is rearranged to solve for \( R \).

First, Eq. 14.11 is used to solve for \( \tau \). Tentatively \( t_{inf} = 1 \) h is used until the magnitude of the dose is known.

\[
\tau = \frac{\ln \left( \frac{30}{11} \right)}{0.08663} + 1 + 1 = 13.6 \text{ h.}
\]

For practical purposes, \( \tau = 12 \) h is used.

Second, the multiple intermittent infusion rate is calculate using:

\[
Q = \frac{(C_{PK'})_{ss}(V)(K)(1 - e^{-Kt})}{(1 - e^{-Kt_{inf}})(e^{-Kt'})}
\]

\[
= \frac{(30 \text{ mg L}^{-1})(35 \text{ L})(0.08663 \text{ h}^{-1})(1 - e^{-0.08663(12)})}{(1 - e^{-0.08663(1)})(e^{-0.08663(2)})}
\]

\[
Q = 773 \text{ mg h}^{-1}.
\]

For practical purposes, an infusion rate of 800 mg h\(^{-1}\) is used.

Since each dose to the patient will equal 800 mg, there is no need to go back and redo the calculations based on a \( t_{inf} = 2 \) h.

Since values for \( \tau \) and \( Q \) were rounded off, the expected values of the steady-state peak and trough concentrations need to be calculated.

This is done using a simple proportion for the “peak” calculation.

\[
(C_{PK})_{ss} = \text{(rounded off} \frac{Q}{\text{calculated} Q})\text{)(target peak)}
\]

\[
= (800/773)(30\text{ mg L}^{-1}) = 31.05\text{ mg L}^{-1}.
\]

This is close to the desired “peak” value.

Equation 14.9 is used to obtain the trough value:

\[
(C_{TR})_{ss} = (31.05\text{ mg L}^{-1})(e^{-0.08663(12)} - 1) = 13.06\text{ mg L}^{-1}.
\]

This predicted trough level is higher than the desired trough of 11 mg L\(^{-1}\). If it is deemed too high, the dosing interval would need to be increased. For example, increasing the interval to 16 h would produce a trough level equal to 9.23 mg L\(^{-1}\).
14.7 Adjustment for early or late drug concentrations

In the real world, “peak” and trough blood concentrations after a multiple intravenous infusion at steady state are not always taken exactly at the appropriate time. For example, a delayed “peak” plasma drug concentration will be deceptively low, while an early trough concentration will be falsely high. A mathematical technique is needed to adjust these readings so that judgements can be made on the suitability of the dosing regimen for the patient.

As long as we are in the post-distribution phase of the drug concentration–time curve (the part that is linear when the data for the curve are plotted using a logarithmic y-axis), there is a simple way of adjusting the observed drug concentrations to yield the corresponding “peak” and trough concentrations. This method relies on the fact that the drug concentration is declining monoexponentially in the post-distribution phase of the curve. Therefore, for two points on this curve:

\[ (C_p)_{LO} = (C_p)_{HI} (e^{-\lambda t}) \]

where \((C_p)_{LO}\) is the lower of the two points; \((C_p)_{HI}\) is the higher of the two points; \(\lambda\) is a general symbol for the first-order rate constant of disappearance of drug from the plasma.

Since we are approximating two-compartment kinetics by employing a one-compartment equation in the terminal (i.e. elimination) phase of the plasma drug concentration versus time curve, the elimination rate constant \(K\) can be substituted for \(\lambda\), to give:

\[ (C_p)_{LO} = (C_p)_{HI} (e^{-K t}) \]

Specifically, if a “peak” plasma concentration \((C_p)_{HI}\) is sampled somewhat late (e.g. 1.5 h late), the above equation can be used to adjust \((C_p)_{HI}\) to the (higher) plasma drug concentration that would have been recorded if the concentration had been collected on time. Then,

\[ (C_p)_{TR} = (C_p)_{LO} (e^{-Kt}) \]

where \((C_p)_{TR}\) is a more accurate estimate of the trough concentration than was \((C_p)_{HI}\). This process can be described as sliding up the plasma concentration curve from right to left by exactly \(t = t_{PKlate} = 1.5\ h\).

Similarly, if a trough plasma concentration \((C_p)_{LO}\) is sampled somewhat early (e.g. 2 h early), this concentration will be falsely high; so the equation can be used to adjust \((C_p)_{LO}\) to the (lower) plasma drug concentration that would have been recorded if the concentration had been collected on time. Then,

\[ (C_p)_{TR} = (C_p)_{LO} (e^{-Kt}) \]

where \((C_p)_{TR}\) is a more accurate estimate of the trough concentration than was \((C_p)_{LO}\). This process can be described as sliding down the plasma concentration curve from left to right by exactly \(t = t_{TRearly} = 2.0\ h\).

Next, we ought to consider whether any other possibilities exist besides the two cases just described. For example, could a “peak” concentration need adjustment because it was collected too early? In fact, this case would represent a real problem since the drug concentration would have been collected in a part of the curve where distribution is still going on. Adjusting the observed concentration with the monoexponential equation would not be appropriate in this case since it would generate an erroneous estimate of the “peak” concentration.

What about a trough being collected too late? Well... The right time to collect a trough concentration is immediately before the next infusion is begun. Therefore, collecting a trough too late would imply that it was collected during the next dose (while plasma drug concentration is rising!) Needless to say, this is not done.

This leaves the following four possibilities.

A. Both “peak” and trough concentrations are collected on time according to the guidelines for the particular drug.

B. The trough concentration is sampled too early.

C. The “peak” concentration is sampled late.

D. A combination of scenarios B and C occur, where the trough concentration is sampled...
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### Table 14.4 Adjustment for early and late collection of plasma drug concentrations

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Adjustment for actual “peak” or trough value</th>
<th>Volume of distribution, V=</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: peak and trough levels collected on time and ( C_{p})LO = trough</td>
<td>( \Delta t = t_{inf} - t_{wait} )</td>
<td>( Q(1 - e^{-K_{inf}})(e^{-K_{wait}}) )</td>
</tr>
<tr>
<td>B: observed trough level ([C_{p}]_{LO}) sampled too early</td>
<td>Trough is ( C_{p})LO ( e^{-K_{trough}} )</td>
<td>( Q(1 - e^{-K_{inf}})(e^{-K_{wait}}) )</td>
</tr>
<tr>
<td>C: observed “peak” level ([C_{p}]_{HI}) sampled late</td>
<td>“Peak” is ( C_{p})HI ( e^{-K_{peak}} )</td>
<td>( Q(1 - e^{-K_{inf}})(e^{-K_{wait}}) )</td>
</tr>
<tr>
<td>D: trough sampled too early and “peak” sampled late</td>
<td>Trough is ( C_{p})LO ( e^{-K_{trough}} ); “Peak” is ( C_{p})HI ( e^{-K_{peak}} )</td>
<td>( Q(1 - e^{-K_{inf}})(e^{-K_{wait}}) )</td>
</tr>
</tbody>
</table>

\( K = \ln([C_{p}]_{HI}/[C_{p}]_{LO})/\Delta t \)

\( \Delta t \), time between high concentration sample \( [C_{p}]_{HI} \) and low concentration sample \( [C_{p}]_{LO} \); \( t_{inf} \), length of infusion; \( t_{wait} \), recommended time after infusion is stopped to wait until sampling (0.5 h for gentamicin and 1.0 h for vancomycin); \( t_{early} \), how much earlier than the recommended time the trough concentration was actually collected; \( t_{late} \), how much later than the recommended time the “peak” concentration was actually collected.

---

As shown above, early/late sampling will require the use of equations to adjust observed high and low concentrations to achieve more accurate estimates of the “peak” and trough concentrations. Early/late sampling will also have ramifications for the equations used to solve for the apparent volume of distribution and the elimination rate constant by using two steady-state plasma drug concentrations sampled after a multiple intravenous infusion. Table 14.4 summarizes these equations.

### Example problem: adjustment for early or late drug concentrations

In the vancomycin problem discussed in this chapter, what would be the effect of collecting the trough concentration 2.5 h before the end of the infusion (i.e. 2.5 h too early). The concentration recorded at that time was 16.2 mg L\(^{-1}\). This would be called \( (C_p)_{LO} \). The following questions need to be answered.

1. What is a more accurate estimate of the trough plasma vancomycin concentration in this patient?
2. Based on the measured \( (C_p)_{LO} \) value and the \( C_{PK} \) value of 31.05 mg L\(^{-1}\), what is this patient’s elimination rate constant?
3. What is an estimate of the patient’s volume of distribution?

Figure 14.4 will help to visualize the situation in this problem.

First, from Table 14.4, we obtain:

\[
(C_p)_{TR} = (C_p)_{LO}(e^{-K_{trough}})
\]

\[
(C_p)_{TR} = 16.2 \text{ mg L}^{-1}(e^{-0.08663 \times 2.5}) = 13.05 \text{ mg L}^{-1}.
\]

Notice that this agrees with the earlier estimate of \( (C_p)_{TR} \).
In order to calculate $K$, $\Delta t$ must be calculated first; this is the time between the $(C_p)^{PK}$ value and the $(C_p)_L$ value. Therefore,

$$\Delta t = \tau - t_{\text{inf}} - t_{\text{wait}} - t_{\text{TR early}} = 12 - 1 - 2.5 = 7.5 \text{ h}.$$ 

Then,

$$K = \frac{\ln \frac{C_{HI}}{C_{LO}}}{\Delta t} = \frac{\ln \frac{C_{PK}}{C_{LO}}}{\Delta t} = \frac{\ln \frac{31.05}{16.2}}{7.5} = 0.0867 \text{ h},$$

which is also in good agreement with the earlier estimate.

Finally, volume of distribution can be calculated from scenario B of Table 14.4.

$$V = \frac{(S)(Q)(1 - e^{-Kt_{\text{inf}}})(e^{-Kt_{\text{final}}})}{(C_{PK})_{ss}(K)(1 - e^{-K\tau})}$$

$$= \frac{(1)(800 \text{ mg h}^{-1})(1 - e^{-0.0867})(e^{-0.0867})}{(31.05 \text{ mg/L})(0.0867 \text{ h}^{-1})(1 - e^{-0.0867})}$$

$$= 35.0 \text{ L}.$$