CHAPTER 5

I.V. Infusion

OBJECTIVES

1. Given patient drug concentration and/or amount vs. time profiles, the student will calculate (III) the relevant pharmacokinetic parameters available ($V_d$, $K$, $k_m$, $k_r$, $AUC$, Clearance, MRT) from IV infusion data.

   - I.V. Infusion dosing for parent compounds
   - Plasma concentration vs. time profile analysis
   - Rate vs. time profile analysis
   - Professional communication of IV Infusion information
   - Computer aided instruction and simulation
   - Metabolite (active vs. inactive)
5.1 Parent compound

5.1.1 PLASMA

Valid equations:

\[ C_p = \frac{Q}{K \cdot V_d} (1 - e^{-Kt}) \quad \text{or} \quad \text{(EQ 5-1)} \]

\[ C_p = \frac{Dose}{K \cdot V_d \cdot T_{infusion}} (1 - e^{-Kt}) \quad \text{(EQ 5-2)} \]

at any time during the infusion

\[ (C_p)_{ss} = \frac{Q}{K \cdot V_d} \quad \text{(EQ 5-3)} \]

at steady state (t is long)

\[ C_p = C_{p(term)} \cdot e^{-Kt} \quad \text{(EQ 5-4)} \]

after termination of infusion

Where \( C_p \) is the plasma concentration

\[ Q = \frac{Dose}{T_{infusion}} \]

is the infusion rate shown in equation 5-1 and equation 5-2.

\[ C_{p(term)} = \frac{Q}{K \cdot V_d} (1 - e^{-K_t_{infusion}}) \] is the plasma concentration when the infusion is stopped.

Rewriting equation 5-4 to an equation which may be used by a computer results in:

\[ \frac{C_p}{Q} = \frac{1}{e^{K \cdot T} - e^{K \cdot T^*}} \quad \text{(EQ 5-5)} \]

where \( T^* = (T - T_{iv}) \) for \( T > T_{iv} \)

and \( T^* = 0 \) for \( T < T_{iv} \).
Using The Scientist®’s Unit function makes the change in $T^*$ straight forward. In The Scientist®, Unit(+) = 1 and Unit(-) = 0, so defining $T^* = (T - T_{iv}) \cdot \text{UNIT}(T - T_{iv})$ meets these needs.

This equation is utilized in The Scientist®’s companion product PKAnalyst® also by MicroMath. Since the route of administration is an infusion and we would know how much we gave ($Dose$), how fast we gave it ($Q$), and over how long the infusion lasted ($T_{iv}$), the only other variables in the equation are $K$ and $V_d$. PKAnalyst asks for $T_{iv}$ and yields $DoverV\left(\frac{Dose}{V_d}\right)$ and $K$ as parameters resulting from non-linear regression analysis. Dividing $Dose$ by $\frac{Dose}{V_d}$ yields $V_d$.

**Utilization:**

You should be able to determine the infusion rate necessary to obtain a desired plasma concentration. Rearranging equation 5-3 results in:

$$K \cdot V_d \cdot (C_p)_{ss} = Q \quad \text{(EQ 5-6)}$$

You should be able to determine how long it would take to get to a desired plasma concentration. Using equation 5-1 and equation 5-3, it looks like it will take forever to get exactly to steady state because in order for

$$(C_p)_{ss} = \frac{Q}{K \cdot V_d} = \frac{Q}{K \cdot V_d} (1 - e^{-Kt}), e^{-Kt} \to 0 \text{ which occurs when } t = \infty.$$  

So, how close is close enough? If $(C_p) = 0.95 \cdot (C_p)_{ss}$, that’s good enough in most people’s estimation. So in order to find out how long it will take we use equation 5-1, setting $(C_p) = 0.95 \cdot (C_p)_{ss}$ and solve for time. Thus:

$$(C_p) = 0.95 \cdot (C_p)_{ss} = \frac{Q}{K \cdot V_d} (1 - e^{-Kt}) \quad \text{which results in}$$

$$0.95 = (1 - e^{-Kt})$$

$$0.95 - 1 = -e^{-Kt}$$

$$\ln (0.05) = -Kt$$
or about 4.32 half lives to get to 95% of steady state. Generalizing, then, the number of half-lives it takes to get to steady-state is equal to the logarithm of the inverse of how close is close (in this case, 5% or 0.05 = 20) divided by the logarithm of two.

Changing infusion rates:

Occasionally, it is necessary to change infusion rates to stabilize the patient. If a patient were started on an infusion rate, Q1, and then at some subsequent time, T>T*, the infusion rate was changed to Q2, the equation for the concentration after the change would be:

\[
C_p = \frac{Q_1}{K \cdot V} \cdot (1 - e^{-k \cdot (T^* - T)}) \cdot e^{-k \cdot (T - T^*)} + \frac{Q_2}{K \cdot V} \cdot (1 - e^{-k \cdot (T - T^*)})
\]  

(EQ 5-8)

Assuming equilibrium was reached at infusion rate Q1, we could simplify equation 5-8 by setting T = 0 at the time of the rate change (thus we would be interested in the time after the change) resulting in:

\[
C_p = \frac{Q_1}{K \cdot V} \cdot e^{-k \cdot T} + \frac{Q_2}{K \cdot V} \cdot (1 - e^{-k \cdot T})
\]  

(EQ 5-9)

Under these conditions, it would be useful to determine the time to reach the new equilibrium. As before, within 5% is close enough. Thus if we are coming down (lowering the Cp, i.e. Q2 < Q1), we would want \( C_p = 1.05 \frac{Q_2}{K \cdot V} \) and if we were going up (raising the Cp, i.e. Q2 > Q1), we would want \( C_p = 0.95 \frac{Q_2}{K \cdot V} \). Taking the first condition we find:

\[
C_p = 1.05 \frac{Q_2}{K \cdot V} = \frac{Q_1}{K \cdot V} \cdot e^{-k \cdot T} + \frac{Q_2}{K \cdot V} \cdot (1 - e^{-k \cdot T})
\]  

(EQ 5-10)

Rearranging and solving for T results in:
Similarly, under the second condition, we would find:

\[
T = \frac{\ln \left( \frac{-0.05 \cdot Q2}{Q1 - Q2} \right)}{-K}
\]  

(EQ 5-12)

Combining equation 5-11 and equation 5-12 and rearranging results in:

\[
T = \frac{\ln \left( \frac{|Q1 - Q2|}{Q2} \cdot 20 \right)}{K} = \frac{\ln \left( \frac{|Q1 - Q2|}{Q2} \cdot 20 \right)}{0.693} \cdot t_{1/2}
\]  

(EQ 5-13)

Thus it is the absolute value of the difference of the two rates and the elimination rate constant which determine the length of time needed to establish a new equilibrium. Under the conditions of \( Q1 = 0 \), that is no previous infusion, and the difference is maximal equation 5-13 simplifies to equation 5-7. Under the conditions of \( Q1 = Q2 \), the equation is undifined and has no utility (as well as makes no sense, because the equation was designed to be used when there was a change in rate.) However, \( \lim_{Q2 \to Q1} T = 0 \), thus no change results in zero time to get to the new equilibrium. Similar to equation 5-7 as before, the generalization for the number of half-lives it takes to obtain the new steady-state is the logarithm of \( ( \text{the fractional difference of the rates (or the steady-state concentrations) times the inverse of how close is close) } \) devided by the logarithm of \( 2 \).

As pharmacokinetic equations are additive, you should be able to determine a loading dose (by I.V. bolus, for example) and a maintenance dose (infusion rate) for a patient to establish an equilibrium. If, for example, you want to give a loading dose followed by an IV infusion, the generalization for the number of half-lives it takes to obtain the new steady-state is the logarithm of \( ( \text{the fractional difference of the concentrations, } C_p0 \text{ and } C_pss, \text{ times the inverse of how close is close) } \) devided by the logarithm of \( 2 \).
Discussion:

IV infusion is a controlled way to get drug into your patient. Using patient population average pharmacokinetic parameters (K, V_d) available in the drug monographs, you are able to make a professional judgement about:

1. the plasma concentration that you would like to achieve (from therapeutic range) and the time in which you would like to get there.
2. the infusion rate necessary to get to the target concentration, and
3. the time necessary to get there.

Example: Using population average pharmacokinetic parameters to make professional judgements.

As an example, theophylline is a bronchodilator used in asthma with a therapeutic range of 10 to 20 mg/L, a volume of distribution of 0.45 (0.3 - 0.7) L/kg and a half life of about 8 (6 - 13) hours for a non-smoking adult. Your patient weighs 200 pounds and meets these criteria. The physician decides to maintain him at 15 mg/L. What do you do?

Using population average parameters for K and V_d, equation 5-6 results in:

\[
\left( \frac{0.693}{8 \text{ hr}} \right) \cdot \left( \frac{0.45 \text{ L}}{\text{kg}} \cdot \frac{\text{kg}}{2.2 \text{ lb}} \cdot 200 \text{ lb} \right) \cdot \left( \frac{15 \text{ mg}}{L} \right) = 53.2 \text{ mg/hr}.
\]

For an eight hour IV infusion, you would need

\[\frac{53.2 \text{ mg/hr}}{8 \text{ hr}} = 425 \text{ mg of theophylline.}\]

IV Theophylline comes as aminophylline which is theophylline compound containing 85% theophylline and 15% ethylenediamine. So in order to get 425 mg of theophylline we have to give

\[425 \text{ mg theophylline} \cdot \frac{100 \text{ mg aminophylline}}{85 \text{ mg theophylline}} = 500 \text{ mg aminophylline}.
\]

So we prepare our IV infusion using Aminophylline U.S.P. for injection (500 mg aminophylline in 20 mL) by placing the contents of the ampule in 1000 mL of D5W and calculate the drip rate using an adult IV administration set which regulates the drip to 10 gtts/mL. Thus the drip rate is:

\[\frac{1020 \text{ ml}}{8 \text{ hr}} \cdot \frac{\text{hr}}{60 \text{ min}} \cdot \frac{10 \text{ gtts}}{\text{ml}} \sim \frac{21 \text{ gtts}}{\text{min}} \sim \frac{7 \text{ gtts}}{20 \text{ sec}}\]
How long to get to steady state?

After setting up the infusion, the doctor asks, “How long to steady state?”

Using equation 5-7, our patient who has an eight hour half life, will take about 4.32 · 8 hr = 34.6 hr to get to 95% of steady state. The patient doesn’t want relief in a day and a half. He needs to breathe NOW. What would you suggest?

Infusion takes too long. How do we get relief now? IV Bolus stat.

It might be possible to give him an IV Bolus dose stat which would get him to $(C_p)_{ss}$ right away. This is done by converting $(C_p)_{ss} = \frac{Dose}{V_d}$ to $V_d \cdot (C_p)_{ss} = Dose$.

$$\left(0.45 \frac{L}{kg} \cdot \frac{kg}{2.2 \text{ lb}} \cdot 200 \text{ lb}\right) \cdot \left(15 \frac{mg}{L}\right) = 613.6 \text{ mg Theophylline}$$

Converting to aminophylline yields:

$$613.6 \text{ mg Theophylline} \cdot \frac{100 \text{ mg aminophylline}}{85 \text{ mg theophylline}} \sim 725 \text{ mg aminophylline}.$$ Thus, if we gave a 725 mg IV bolus dose of aminophylline followed by a concomitant IV infusion of 500 mg aminophylline over 8 hours, our patient should get to steady state right away and stay there.

Some protocols require starting with faster infusion, then changing to a slower one to get to steady state faster.

Sometimes the physician might want to just increase the infusion rate (say double it for a short time, 2Q) to get to the target concentration faster and then just back the infusion down. If that is the protocol, the question becomes, “How long do you run the infusion in at the faster rate?” Thus:

$$(C_p)_{ss} = \frac{Q}{K \cdot V_d} = \frac{2Q}{K \cdot V_d} (1 - e^{-Kt}) \quad \text{which yields} \quad 1 = 2(1 - e^{-Kt}) \quad \text{and so}$$

$$\frac{1}{2} = 1 - e^{-Kt} \quad \text{Thus} \quad \frac{1}{2} - 1 = -e^{-Kt} . \quad \text{Taking the ln of both sides}$$

$$\ln (0.5) = -Kt$$

$$\frac{\ln (0.5)}{-K} = 0.693 t_i = t_i = t \quad \text{or that it will take one half-life to get to the target}$$

plasma concentration (which is the $C_p_{ss}$ obtained by the infusion rate of 1Q) if you run the infusion at a faster rate, 2Q. So for your patient, you might suggest an infusion of 1000 mg over 8 hours (2Q for one half life) to get to steady state quickly and then back off to 500 mg over 8 hours for the second 8 hours.
Clearance: New pharmacokinetic parameter

Clearance \((Cl = K \cdot V_d)\) is a pharmacokinetic parameter which relates the fraction of the volume of distribution which is cleared of the drug per unit time. The volume of distribution is a mathematical construct which relates two knowns, the Dose of the drug and the resultant Concentration. In linear kinetics, the Dose is proportional to the Concentration, \(C \propto D\). The units of concentration are \(\frac{Mass}{Volume}\) while the units of dose are \(Mass\). So the units of the proportionality constant must be volume in order for the equation to balance. Thus, the volume of distribution is a hypothetical volume and not necessarily a real volume or physiological space. Consequently, clearance is the hypothetical volume of fluid from which the drug is irreversibly removed per unit time. So equation 5-3 can be rewritten:

\[
(C_p)_{ss} = \frac{Q}{Cl}
\]

**(EQ 5-14)**

and equation 5-14 can be rewritten to:

\[
Cl = \frac{Q}{(C_p)_{ss}}
\]

**(EQ 5-15)**

Thus, assuming steady state, the clearance can be calculated by dividing the infusion rate by the resultant steady state plasma concentration.

How do we calculate Clearance from IV infusion data?

How do we separate \(K\) and \(V_d\) out of Clearance?

How can we utilize the rate of change of plasma concentration to determine the pharmacokinetic parameters, \(K\) and \(V_d\)?

From our original model

\[
\frac{d}{dt}X = Q - (K \cdot X)
\]

**(EQ 5-16)**

and \(C_p = \frac{X}{V_d} \). Thus, \(V_d \cdot C_p = X\). Rewriting equation 5-16 yields:
$\frac{dC_p}{dt} = \frac{Q}{V_d} - K \cdot C_p$ and rearranging and incorporating equation 5-1 yields

$\frac{dC_p}{dt} = \frac{Q}{V_d} - K \cdot \left(\frac{Q}{K \cdot V_d}\right)(1 - e^{-Kt})$ which can be simplified to

$\frac{dC_p}{dt} = \frac{Q}{V_d} \cdot \frac{Q}{V_d} + \frac{Q}{V_d} \cdot e^{-Kt}$

or

$$\frac{dC_p}{dt} = \frac{Q}{V_d} e^{-Kt}$$  \hspace{1cm} (EQ 5-17)

Thus a plot of $\frac{dC_p}{dt}$ vs. t (actually, $\frac{\nabla C_p}{\nabla t}$ vs. $t_{mid}$ exactly like we did in urinary rate graphs) of the ascending portion of the plasma profile would result in a straight line with a slope of $-K$ and an intercept of $\frac{Q}{V_d}$.  


5.2 Problems

Equations needed for solving the problems:

1. \( k \) from the slope of the terminal portion of the graph of \( C_p \) vs. \( T \)

2. \( t_{1/2} = \frac{0.693}{k} \)

3. Volume of distribution from \( C_p = \frac{Q}{K \cdot V_d} (1 - e^{-Kt}) \)

4. Clearance \( Cl = K \cdot V_d \)

5. You wish to maintain a plasma concentration of \( C_{P_{ss}} \).
   a. Calculate the infusion rate necessary to maintain
      \[ C_{P_{ss}} \cdot Q = C_{P_{ss}} \cdot K \cdot V_d \]
   b. Suggest a loading dose which would give you \( C_{P_{ss}} \) immediately.
      \[ Dose_{loading} = C_{P_{ss}} \cdot V_d \]
   c. How long will it take to reach steady state?
      \[ T_{95} = 4.32 \cdot T_{1/2} \]
   d. Find the plasma concentration if the infusion is discontinued at time = \( T_{dc} \) hours.
      \[ C_{P_{dc}} = \frac{Q}{K \cdot V_d} (1 - e^{-(K \cdot T_{dc})}) \]
   e. Find the plasma concentration \( T_{post} \) hours after infusion is discontinued at time = \( T_{dc} \) hours.
      \[ C_{P_{post}} = C_{P_{dc}} \cdot e^{-(K \cdot T_{post})} \]
Acyclovir (225.21 g/Mole) is an antiviral drug used in the treatment of herpes simplex, varicella zoster, and in suppressive therapy. In this study, patients were given varying doses of acyclovir over one hour by infusion. Acyclovir distributes uniformly into the plasma and tissues such that the plasma concentration is representative of tissue concentration. Acyclovir is 30% metabolized and 70% renally excreted. The following data was obtained from an intravenous infusion dose of 2.5 mg/kg over one hour where the patient weighed 70 kg.

**TABLE 5 - 1. Acyclovir**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (umol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>7</td>
</tr>
<tr>
<td>0.5</td>
<td>12</td>
</tr>
<tr>
<td>0.75</td>
<td>17</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. k
2. $t_{1/2}$
3. Volume of distribution
4. Clearance
5. You wish to maintain a plasma concentration of 25 umol/L.
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 25 umol/L.
   b. Suggest a loading dose for the patient which would give you Cpss immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 5 hours.
   e. Find the plasma concentration 2 hours after infusion is discontinued at time = 5 hours.
“Acyclovir” on page 11

1. \( k = 0.751 \text{ hr}^{-1} \) (from slope of graph).
2. \( t_{1/2} = 0.923 \text{ hr} \) (from slope of graph).
3. Volume of distribution = 26.2 L
4. Clearance = 19.67 l/hr
5. You wish to maintain a plasma concentration of 25 \( \text{umol/L} \).
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 25 \( \text{umol/L} \) = 111 mg/hr
   b. Suggest a loading dose for the patient which would give you \( C_{pss} \) immediately. 148 mg
   c. How long will it take to reach steady state? 4 hr
   d. Find the plasma concentration if the infusion is discontinued at time = 5 hours. = 25 \( \text{umol/L} \)
   e. Find the plasma concentration 2 hours after infusion is discontinued at time = 5 hours. = 5.6 \( \text{umol/L} \)
Aminophylline is used in the treatment of bronchospasm. In this study, aminophylline was given by intravenous infusion to patients with a mean weight of 75.7 kg. The doses given were chosen to maintain a between 10 - 20 mg/L based on desirable body weight. The doses were given at a rate of 0.5 mg/kg/hour (Theophylline) for 84 hr. The following set of data was collected.

From this data determine the following:

1. $k$
2. $t_{1/2}$
3. Volume of distribution
4. Clearance
5. You wish to maintain a plasma concentration of 15 mg/L in your patient.
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 15 mg/L.
   b. Suggest a loading dose for the patient which would give you $C_{P_{ss}}$ immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 5 hours.
   e. Find the plasma concentration 2 hours after infusion is discontinued at time = 5 hours.

### TABLE 5 - 2. Aminophylline

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration $\left(\frac{mg}{L}\right)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>30</td>
<td>11.6</td>
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<td>36</td>
<td>12.0</td>
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<td>4.6</td>
</tr>
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<td>100</td>
<td>3.2</td>
</tr>
</tbody>
</table>
“Aminophylline” on page 13

1. \( k = 0.085 \, \text{hr}^{-1} \)
2. \( t_{1/2} = 8.15 \, \text{hr} \)
3. \( V_d = 35.3 \, \text{L} \)
4. \( \text{Cl} = 3 \, \text{L/hr} \)
5a. \( Q = 45 \, \text{mg/hr} \)
5b. \( D_L = 530 \, \text{mg} \)
5c. \( t_{95\%}^{ss} = 35 \, \text{hr} \)
5d. \( C_p = 5.2 \, \text{mg/L} \)
5e. \( C_p = 4.4 \, \text{mg/L} \)
Carmustine (BCNU) is an antineoplastic agent with a molecular weight of 214.04 g.

In this study a 70 kg, 1.8 m² patient was given 600 mg/m² by intravenous infusion over 2 hours. The following data was obtained.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Plasma concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>.3</td>
</tr>
<tr>
<td>30</td>
<td>.5</td>
</tr>
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<td>60</td>
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<td>.5</td>
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<tr>
<td>142.5</td>
<td>.4</td>
</tr>
<tr>
<td>150</td>
<td>.3</td>
</tr>
</tbody>
</table>

From this data determine the following:
1. k
2. t₁/₂
3. V_d
4. Cl
5. A patient with a BSA of 1.8 m² is to be given BCNU by IV infusion. You wish to maintain a plasma concentration of 2 μM. Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 2 μM.
   b. Suggest a loading dose for the patient which would give youCss immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 10 minutes.
   e. Find the plasma concentration 1 hour after infusion is discontinued at time = 10 minutes.
“Carmustine” on page 15

1. \( k = 0.031 \text{ min}^{-1} \)
2. \( t_{1/2} = 22 \text{ min} \)
3. \( V_d = 198 \text{ L/M}^2 \)
4. \( Cl = 6.15 \text{ L/M}^2/\text{hr} \)
5. A patient with a BSA of 1.8 M\(^2\) is to be given BCNU by IV infusion. You wish to maintain a plasma concentration of 2 \( \mu\text{M} \). Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 2 \( \mu\text{M} \).
      \[ Q = C_{pss} \cdot V_d \cdot K = \frac{2 \mu\text{mole}}{L} \cdot \frac{214 \mu\text{g}}{\mu\text{mole}} \cdot \frac{mg}{1000 \mu\text{g}} \cdot \frac{198 L}{M^2} \cdot 1.8 M^2 \cdot 0.031 \text{min}^{-1} = \frac{4.73 mg}{min} \sim \frac{285 mg}{hr} \]
   b. Suggest a loading dose for the patient which would give you \( C_{pss} \) immediately.
      \[ \text{Dose} = C_{pss} \cdot V_d = \frac{2 \mu\text{mole}}{L} \cdot \frac{214 \mu\text{g}}{\mu\text{mole}} \cdot \frac{mg}{1000 \mu\text{g}} \cdot \frac{198 L}{M^2} \cdot 1.8 M^2 = 150 \text{mg} \]
   c. How long will it take to reach steady state? \( 4.32 \times T \frac{1}{2} = 97 \text{ min} \).
   d. Find the plasma concentration if the infusion is discontinued at time = 1 hr. = 0.36 mg/L
   e. Find the plasma concentration 1 hour after infusion is discontinued at time = 1 hr. = 0.056 mg/L
Cefotaxime is a third generation cephalosporin which is widely used as an antimicrobial in neonates, infants, and children. In this study, infants and children were given a 50 mg/kg dose of cefotaxime intravenously over 0.25 hour. The following data was collected:

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>0.05</td>
<td>35</td>
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<tr>
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<td>70</td>
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<td>80</td>
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<td>8</td>
</tr>
<tr>
<td>6.50</td>
<td>1.7</td>
</tr>
</tbody>
</table>

From this data, assuming that the patient weighs 30 kg, determine the following:

1. k
2. $t_{1/2}$
3. $V_d$
4. Cl
5. You wish to maintain a plasma concentration of 80 mg/L. Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 80mg/L.
   b. Suggest a loading dose for the patient which would give you $C_{pss}$ immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 0.25 hours.
   e. Find the plasma concentration 2 hours after infusion is discontinued at time = 0.25 hours.
1. \( k = 0.733 \text{ hr}^{-1} \)

2. \( t_{1/2} = 0.945 \text{ hr} \)

3. \( V_d = 0.276 \text{ L/kg} \)

4. \( Cl = 0.202 \text{ L/kg/hr} \)

4a. \( Q = 16.2 \text{ mg/kg/hr} \)

4b. \( D_L = 22.1 \text{ mg/kg} \)

4c. \( t^{ss}_{95\%} = 4.1 \text{ hr} \)

4d. \( C_p = 166 \text{ mg/L} \)

4e. \( C_p = 38 \text{ mg/L} \)
Ganciclovir is used against the human herpes viruses, cytomegalovirus retinitis, and cytomegalovirus infections of the gastrointestinal tract. In this study, twenty-seven newborns with cytomegalovirus disease were given 4 mg/kg of ganciclovir intravenously over one hour. Blood samples were taken and the data obtained is summarized in the following table:

**TABLE 5 - 5. Ganciclovir**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>3.10</td>
</tr>
<tr>
<td>1.5</td>
<td>4.50</td>
</tr>
<tr>
<td>2.0</td>
<td>3.80</td>
</tr>
<tr>
<td>3.0</td>
<td>2.90</td>
</tr>
<tr>
<td>4.0</td>
<td>2.30</td>
</tr>
<tr>
<td>6.0</td>
<td>1.50</td>
</tr>
<tr>
<td>8.0</td>
<td>0.88</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. \( k \)
2. \( t_{1/2} \)
3. \( V_d \)
4. \( Cl \)

A patient is to be given ganciclovir by IV infusion to an infant weighing 6.1 kg. You wish to maintain a plasma concentration of 5.5 mcg/mL. Determine the following:

a. Calculate the infusion rate necessary to maintain a plasma concentration of 5.5mcg/mL.
b. Suggest a loading dose for the patient which would give you Cpss immediately.

c. How long will it take to reach steady state?

d. Find the plasma concentration if the infusion is discontinued at time = 1 hour.

e. Find the plasma concentration 2 hours after infusion is discontinued at time = 1 hour.
1. \[ k = 0.255 \text{ hr}^{-1} \]
2. \[ t_{1/2} = 2.72 \text{ hr} \]
3. \[ V_d = 0.687 \text{ L/kg} \]
4. \[ Cl = 0.175 \text{ L/kg/hr} \]

5a. \[ Q = C_{p_{ss}} \cdot V_d \cdot K = \frac{5.5 \mu g}{ml} \cdot \frac{mg}{1000 \mu g} \cdot \frac{1000 ml}{L} \cdot \left( \frac{0.687 L}{kg} \cdot 6.1 kg \right) \cdot \frac{0.255}{hr} = \frac{5.9 mg}{hr} \]

5b. \[ D_L = C_{p_{ss}} \cdot V_d = \frac{5.5 \mu g}{ml} \cdot \frac{mg}{1000 \mu g} \cdot \frac{1000 ml}{L} \cdot \left( \frac{0.687 L}{kg} \cdot 6.1 kg \right) = 23 mg \]

5c. \[ T_{ss}^{95\%} = 4.32 \cdot t_{1/2} = 11.75 \text{ hr} \]

5d. \[ C_{p_{term}} = \frac{Q}{K} \cdot V_d (1 - e^{-Kt}) = \frac{5.9 mg}{hr} \cdot \frac{0.255}{hr} \cdot \frac{0.687 L}{kg} \cdot 6.1 kg \cdot (1 - e^{-K \cdot 1 hr}) = \frac{1.24 mg}{L} \]

5e. \[ C_p = C_{p_{term}} \cdot e^{-K \cdot 2 hr} = \frac{1.24 mg}{L} \cdot 0.6 = \frac{0.74 mg}{L} \]
Gentamicin

Problem Submitted By: Maya Lyte
Problem Reviewed By: Vicki Long


Gentamicin is an aminoglycoside antibiotic which is frequently used in the treatment of gram-negative bacilli infections. Since it has a low therapeutic index, it is important to determine proper dosage regimens. In this study, patients on peritoneal dialysis received a 30 minute intravenous infusion of 80 mg gentamicin in 100 mL of 5% dextrose in water. The following data was collected:

**TABLE 5 - 6. Gentamicin**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration ($\mu g/mL$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>5.68</td>
</tr>
<tr>
<td>1.50</td>
<td>5.15</td>
</tr>
<tr>
<td>3.70</td>
<td>4.80</td>
</tr>
<tr>
<td>7.35</td>
<td>3.99</td>
</tr>
<tr>
<td>11.30</td>
<td>3.35</td>
</tr>
<tr>
<td>24.00</td>
<td>2.02</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. k
2. $t_{1/2}$
3. Vd
4. Cl
5. A patient is to be given gentamicin by IV infusion. You wish to maintain a plasma concentration of 5.2 $\mu g/mL$. Determine the following:

a. Calculate the infusion rate necessary to maintain a plasma concentration of 5.2 $\mu g/mL$

b. Suggest a loading dose for the patient which would give you Cpss immediately.

c. How long will it take to reach steady state?

d. Find the plasma concentration if the infusion is discontinued at time = 0.5 hours.

e. Find the plasma concentration 2 hours after infusion is discontinued at time = 0.5 hours.
1. \( k = 0.0431 \text{ hr}^{-1} \)
2. \( t_{1/2} = 16.1 \text{ hr} \)
3. \( V_d = 14.5 \text{ L} \)
4. \( Cl = 0.625 \text{ L/hr} \)
5a. \( Q = 3.25 \text{ mg/hr} \)
5b. \( D_L = 75 \text{ mg} \)
5c. \( t_{95\%}^{ss} = 69.6 \text{ hr} \)
5d. \( C_p = 0.11 \text{ mg/L} \)
5e. \( C_p = 0.10 \text{ mg/L} \)
Human Monoclonal Anti-lipid A antibody (HA-1A)  


HA-1A is an immunoglobulin antibody. In this study, patients received a 250 mg intravenous infusion of HA-1A over 15 minutes. Serum levels were measured before and after infusion and the following data was collected:

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>0.75</td>
<td>80</td>
</tr>
<tr>
<td>1.00</td>
<td>75</td>
</tr>
<tr>
<td>2.00</td>
<td>74</td>
</tr>
<tr>
<td>5.00</td>
<td>65</td>
</tr>
<tr>
<td>15.00</td>
<td>50</td>
</tr>
<tr>
<td>25.00</td>
<td>40</td>
</tr>
<tr>
<td>48.00</td>
<td>21</td>
</tr>
<tr>
<td>72.00</td>
<td>10</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. \( k \)
2. \( t_{1/2} \)
3. \( V_d \)
4. \( Cl \)

5. A patient is to be given HA-1A by IV infusion. You wish to maintain a plasma concentration of 100 µg/mL. Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 100 µg/mL.
   b. Suggest a loading dose for the patient which would give you \( C_{PSS} \) immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 1 hour.
   e. Find the plasma concentration 3 hours after infusion is discontinued at time = 1 hour.
1. \( k = 0.0282 \text{ hr}^{-1} \)
2. \( t_{1/2} = 24.4 \text{ hr} \)
3. \( V_d = 3.2 \text{ L} \)
4. \( Cl = 0.09 \text{ L/hr} \)
5a. \( Q = 9 \text{ mg/hr} \)
5b. \( D_L = 320 \text{ mg} \)
5c. \( t_{ss}^{95\%} = 105 \text{ hr} \)
5d. \( C_p = 2.78 \text{ mg/L} \)
5e. \( C_p = 2.56 \text{ mg/L} \)
Ifosfamide

Problem Submitted By: Maya Lyte
AHFS 12:34.56 Antivirals
Problem Reviewed By: Vicki Long
GPI: 1234567890 Antivirals


Ifosfamide is an agent which has shown some pharmacological response in the treatment of cancer. In this study, a 5 g/m² dose of ifosfamide was infused over 30 minutes. The median BSA for the subjects was 1.8 m². The following data was obtained:

**TABLE 5 - 8. Ifosfamide**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.5</td>
<td>285.0</td>
</tr>
<tr>
<td>1</td>
<td>260.0</td>
</tr>
<tr>
<td>2</td>
<td>220.0</td>
</tr>
<tr>
<td>4</td>
<td>160.0</td>
</tr>
<tr>
<td>6</td>
<td>112.0</td>
</tr>
<tr>
<td>8</td>
<td>80.0</td>
</tr>
<tr>
<td>10</td>
<td>60.0</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. k
2. \( t_{1/2} \)
3. \( V_d \)
4. Cl
5. A patient is to be given ifosfamide by IV infusion. The patient has a BSA 1.8 M². You wish to maintain a plasma concentration of 336 µg/mL. Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 336 µg/mL
   b. Suggest a loading dose for the patient which would give you Cpss immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 20 min.
   e. Find the plasma concentration 2 hours after infusion is discontinued at time = 20min.
1. \( k = 0.1716 \text{ hr}^{-1} \)
2. \( t_{1/2} = 4.04 \text{ hr} \)
3. \( V_d = 16.6 \text{ L/M}^2 \)
4. \( Cl = 2.85 \text{ L/hr/M}^2 \)
5a. \( Q = 1.725 \text{ g/hr} \)
5b. \( D_L = 10 \text{ g} \)
5c. \( t_{95\%}^{ss} = 17.5 \)
5d. \( C_p = 18.7 \text{ mg/L} \)
5e. \( C_p = 13.25 \text{ mg/L} \)
Isosorbide 5-mononitrate (5-ISMN) is a metabolite of isosorbide dinitrate. In this study, the kinetics of isosorbide 5-mononitrate were looked at in 12 healthy patients after an intravenous infusion of 20 mg at 8 mg/hour for 2.5 hours. This drug follows one-compartment, open model kinetics. The following data was collected:

### TABLE 5 - 9. Isosorbide 5-mononitrate

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>40</td>
</tr>
<tr>
<td>0.50</td>
<td>91</td>
</tr>
<tr>
<td>0.75</td>
<td>141</td>
</tr>
<tr>
<td>1.00</td>
<td>181</td>
</tr>
<tr>
<td>1.50</td>
<td>239</td>
</tr>
<tr>
<td>2.00</td>
<td>305</td>
</tr>
<tr>
<td>2.50</td>
<td>351</td>
</tr>
<tr>
<td>3.00</td>
<td>335</td>
</tr>
<tr>
<td>3.50</td>
<td>303</td>
</tr>
<tr>
<td>4.50</td>
<td>257</td>
</tr>
<tr>
<td>5.50</td>
<td>216</td>
</tr>
<tr>
<td>7.50</td>
<td>162</td>
</tr>
<tr>
<td>9.50</td>
<td>117</td>
</tr>
<tr>
<td>11.50</td>
<td>77</td>
</tr>
<tr>
<td>14.50</td>
<td>47</td>
</tr>
<tr>
<td>18.50</td>
<td>24</td>
</tr>
<tr>
<td>26.50</td>
<td>7</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. $k$
2. $t_{1/2}$
3. $V_d$
4. $Cl$
5. A patient is to be given 5-ISMN by IV infusion. You wish to maintain a plasma concentration of 300 ng/mL. If the volume of distribution of 5-ISMN is 44.5, determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 300 ng/mL.
   b. Suggest a loading dose for the patient which would give you $C_{pss}$ immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 1 hour.
   e. Find the plasma concentration 2 hours after infusion is discontinued at time = 1 hour.
1. \( k = 0.168 \text{ hr}^{-1} \)
2. \( t_{1/2} = 4.125 \text{ hr} \)
3. \( V_d = 44.6 \text{ L} \)
4. \( Cl = 7.5 \text{ L/hr} \)
5a. \( Q = 2.25 \text{ mg/hr} \)
5b. \( D_L = 13.4 \text{ mg} \)
5c. \( t_{95\%}^{ss} = 17.8 \text{ hr} \)
5d. \( C_p = 46.4 \text{ ng/mL} \)
5e. \( C_p = 33.2 \text{ ng/mL} \)
Moclobemide


Moclobemide is reversibly inhibits the A-isoyme of the monoamine oxidase enzyme system. In this study, twelve patients received a 96.7 mg dose as an intravenous infusion over 20 minutes. Blood samples were obtained during the infusion and after the infusion was ended and the following data was obtained:

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.000</td>
</tr>
<tr>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>0.7</td>
<td>0.85</td>
</tr>
<tr>
<td>0.9</td>
<td>0.750</td>
</tr>
<tr>
<td>1.2</td>
<td>0.70</td>
</tr>
<tr>
<td>1.6</td>
<td>0.60</td>
</tr>
<tr>
<td>1.9</td>
<td>0.50</td>
</tr>
<tr>
<td>2.4</td>
<td>0.40</td>
</tr>
<tr>
<td>3.4</td>
<td>0.25</td>
</tr>
<tr>
<td>4.5</td>
<td>0.15</td>
</tr>
<tr>
<td>5.5</td>
<td>0.10</td>
</tr>
<tr>
<td>6.4</td>
<td>0.070</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. \( k \)
2. \( t_{1/2} \)
3. \( \text{Vd} \)
4. \( \text{Cl} \)
5. A patient is to be given moclobemide by IV infusion. You wish to maintain a plasma concentration of 1mg/L. Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 1mg/L.
   b. Suggest a loading dose for the patient which would give you \( \text{Cpss} \) immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 15 min.
   e. Find the plasma concentration 3 hours after infusion is discontinued at time = 15 mins.
1. \( k = 0.44 \text{ hr}^{-1} \)
2. \( t_{1/2} = 1.6 \text{ hr} \)
3. \( V_d = 90.4 \text{ L} \)
4. \( Cl = 39.8 \text{ L/hr} \)
5a. \( Q = 40 \text{ mg/hr} \)
5b. \( D_L = 90 \text{ mg} \)
5c. \( t_{ss}^{95\%} = 6.8 \text{ hr} \)
5d. \( C_p = 0.1 \text{ mg/L} \)
5e. \( C_p = 0.028 \text{ mg/L} \)
Obidoxime is an agent which is used as an antidote in organophosphate poisoning. In this study, the pharmacokinetics of obidoxime were studied in a 20 year old patient who attempted to commit suicide by ingesting Tamaron (60% methamidophos, an organophosphate, in ethylene glycol monethyl ether). She was given 4 mg/kg Obidoxime by intravenous infusion over 10 minutes and the following data was collected:

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Plasma concentration µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>45</td>
<td>15</td>
</tr>
<tr>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>120</td>
<td>11</td>
</tr>
<tr>
<td>150</td>
<td>9.3</td>
</tr>
<tr>
<td>180</td>
<td>8</td>
</tr>
<tr>
<td>240</td>
<td>6.1</td>
</tr>
<tr>
<td>300</td>
<td>4.6</td>
</tr>
</tbody>
</table>

From this data determine the following:
1. k
2. \( t_{1/2} \)
3. Vd
4. Cl
5. A patient is to be given obidoxime by IV infusion. The patient has a body weight of 60 kg. You wish to maintain a plasma concentration of 10 µg/mL. Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 10 µg/mL.
   b. Suggest a loading dose for the patient which would give you \( C_{pss} \) immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 30 minutes.
   e. Find the plasma concentration 1 hour after infusion is discontinued at time = 30 minutes.
“Obidoxime” on page 31

1. \( k = 0.00463 \text{ min}^{-1} \)
2. \( t_{1/2} = 150 \text{ min} \)
3. \( V_d = 0.22 \text{L/kg} \)
4. \( Cl = 1 \text{ mL/min} \)
5a. \( Q = 0.61 \text{ mg/min} \)
5b. \( D_L = 132 \text{ mg} \)
5c. \( t_{95\%}^{ss} = 10.8 \text{ hr} \)
5d. \( C_p = 1.3 \text{ mg/L} \)
5e. \( C_p = 0.98 \text{ mg/L} \)
Perindoprilat and other ACE inhibitors are used in the management of hypertension and chronic congestive heart failure. In this study, a 1 mg dose was infused over a one hour period. The following data was collected:

**TABLE 5 - 12. Perindoprilat**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Plasma concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>10</td>
<td>9.0</td>
</tr>
<tr>
<td>20</td>
<td>16.0</td>
</tr>
<tr>
<td>30</td>
<td>24.0</td>
</tr>
<tr>
<td>40</td>
<td>30.0</td>
</tr>
<tr>
<td>50</td>
<td>36.0</td>
</tr>
<tr>
<td>60</td>
<td>42.0</td>
</tr>
<tr>
<td>65</td>
<td>40.0</td>
</tr>
<tr>
<td>70</td>
<td>38.0</td>
</tr>
<tr>
<td>80</td>
<td>35.0</td>
</tr>
<tr>
<td>90</td>
<td>32.0</td>
</tr>
<tr>
<td>100</td>
<td>29.0</td>
</tr>
<tr>
<td>110</td>
<td>27.0</td>
</tr>
<tr>
<td>120</td>
<td>24.0</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. \( k \)
2. \( t_{1/2} \)
3. \( V_d \)
4. \( Cl \)
5. A patient is to be given perindoprilat by IV infusion. You wish to maintain a plasma concentration of 30 ng/ml. Determine the following:
   a. Calculate the infusion rate necessary to maintain a plasma concentration of 30 ng/mL.
   b. Suggest a loading dose for the patient which would give you \( C_{pss} \) immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 5 hours.
   e. Find the plasma concentration 2 hours after infusion is discontinued at time = 5 hours.
“Perindoprilat” on page 33

1.  \( k = 0.0087 \, \text{min}^{-1} \)
2.  \( t_{1/2} = 79.6 \, \text{min} \)
3.  \( V_d = 18.9 \, \text{L} \)
4.  \( Cl = 164 \, \text{mL/min} \)
5a.  \( Q = 5 \, \mu\text{g/min} \)
5b.  \( D_L = 0.57 \, \text{mg} \)
5c.  \( t_{ss}^{95\%} = 5.73 \, \text{hr} \)
5d.  \( C_p = 27.8 \, \text{ng/mL} \)
5e.  \( C_p = 9.8 \, \text{ng/mL} \)
**Sulfonamides**

(Problem 5 - 13)

**Problem Submitted By:** Maya Lyte  
**Problem Reviewed By:** Vicki Long  
**AHFS 12:34.56 Antivirals**  
**GPI: 1234567890 Antivirals**


This study looks at the affinity of sulfonamides for carbonic anhydrase. Doses of 8 micromoles/kg were administered via the jugular vein cannula in approximately 0.5 mL of PEG 400 over 5 minutes at a constant rate. Samples were collected during the infusion period and for 30 minutes afterward. The following set of data was collected:

**TABLE 5 - 13. Sulfonamides**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Plasma concentration (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>17.0</td>
</tr>
<tr>
<td>4.0</td>
<td>31.0</td>
</tr>
<tr>
<td>5.0</td>
<td>37.0</td>
</tr>
<tr>
<td>7.5</td>
<td>32.0</td>
</tr>
<tr>
<td>9.0</td>
<td>28.0</td>
</tr>
<tr>
<td>12.0</td>
<td>22.5</td>
</tr>
<tr>
<td>15.0</td>
<td>18.0</td>
</tr>
<tr>
<td>18.0</td>
<td>14.0</td>
</tr>
<tr>
<td>23.0</td>
<td>11.0</td>
</tr>
<tr>
<td>30.0</td>
<td>6.5</td>
</tr>
<tr>
<td>35.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. \(k\)
2. \(t_{1/2}\)
3. \(V_d\)
4. \(Cl\)
5. A 70-kg patient is to be given a sulfonamide by IV infusion. You wish to maintain a plasma concentration of 30 µM. Determine the following:
   a. Calculate the infusion rate which would be necessary to maintain the plasma concentration of 30 µM.
   b. Suggest a loading dose for the patient which would give you \(C_{pss}\) immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 4 hours.
   e. Find the plasma concentration 30 minutes after stopping infusion at time = 4 hours.
“Sulfonamides” on page 35

1. \( k = 0.0705 \text{ min}^{-1} \)
2. \( t_{1/2} = 9.8 \text{ min} \)
3. \( V_d = 0.18 \text{ L/kg} \)
4. \( Cl = 12.7 \text{ mL/min/kg} \)
5a. \( Q = 26.9 \text{ µmole/min} \)
5b. \( D_L = 380 \text{ µmole} \)
5c. \( t_{95\%}^{ss} = 42 \text{ min} \)
5d. \( C_p = 30 \text{ µmole/L} \)
5e. \( C_p = 3.6 \text{ µmole/L} \)
Terodiline

Problem Submitted By: Maya Lyte
Problem Reviewed By: Vicki Long


Terodiline is an agent which works as an anticholinergic and a calcium antagonist. It is used to treat incontinence. It is metabolized into p-Hydroxyterodiline, which is further metabolized to 3,4-dihydroxyterodiline. The parent drug and all of its metabolites are excreted into the urine as well as the feces. A patient is given 12.5 mg of Terodiline by IV infusion at a rate of 1 mL/ minute for 5 minutes. The following data is collected:

TABLE 5 - 14. Terodiline

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration</th>
<th>μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.000</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>50.000</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>75.000</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>100.000</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>125.000</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>150.000</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>175.000</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>200.000</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>225.000</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

From this data determine the following:

1. k
2. $t_{1/2}$
3. Vd
4. Cl
5. A patient is to be given terodiline by IV infusion. You wish to maintain a plasma concentration of 40 mcg/L. Determine the following:
   a. Calculate the infusion rate necessary to maintain the plasma concentration of 40 mcg/L.
   b. Suggest a loading dose for the patient which would give you Cpss immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 5 hours.
   e. Find the plasma concentration 2 hours after stopping infusion if the infusion ended at time = 5 hours.
“Terodiline” on page 37

1. $k = 0.0136 \, \text{hr}^{-1}$
2. $t_{1/2} = 50.9 \, \text{hr}$
3. $V_d = 283 \, \text{L}$
4. $Cl = 3.85 \, \text{L/hr}$
5a. $Q = 0.154 \, \text{mg/hr}$
5b. $D_L = 11.32 \, \text{mg}$
5c. $t_{ss}^{95\%} = 220 \, \text{hr}$
5d. $C_p = 2.63 \, \mu \text{g/L}$
5e. $C_p = 2.56 \, \mu \text{g/L}$
Tinidazole


Tinidazole is an antimicrobial similar to metronidazole which is used in the treatment of trichomoniasis, giardiasis, amoebiasis, and anaerobic infections. This study focuses on the pharmacokinetics of tinidazole in patients suffering from severe renal failure. Twelve patients received 800 mg of tinidazole dissolved in 400 mL of dextrose monohydrate solution as an intravenous infusion at a rate of 60 mg/min. Blood samples were taken and the following data was obtained:

### TABLE 5 - 15. Tinidazole

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.9</td>
</tr>
<tr>
<td>3</td>
<td>13.1</td>
</tr>
<tr>
<td>6</td>
<td>11.2</td>
</tr>
<tr>
<td>12</td>
<td>8.9</td>
</tr>
<tr>
<td>24</td>
<td>5.1</td>
</tr>
<tr>
<td>48</td>
<td>2.1</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. $k$
2. $t_{1/2}$
3. $V_d$
4. $Cl$
5. A patient is to be given tinidazole by IV infusion. Determine the following:
   a. Calculate the infusion rate necessary to maintain the plasma concentration of 25 mg/L.
   b. Suggest a loading dose for the patient which would give you $C_pss$ immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 1 hour.
   e. Find the plasma concentration 2 hours after stopping infusion if the infusion was stopped at time = 1 hour.
1. $k = 0.04136 \text{ hr}^{-1}$
2. $t_{1/2} = 16.75 \text{ hr}$
3. $V_d = 54.7 \text{ L}$
4. $Cl = 2.26 \text{ L/hr}$
5a. $Q = 56.6 \text{ mg/hr}$
5b. $D_L = 1.37 \text{ g}$
5c. $t_{ss}^{95\%} = 72.4 \text{ hr}$
5d. $C_p = 1 \text{ mg/L}$
5e. $C_p = 0.93 \text{ mg/L}$
**Tobramycin**


Most persons with cystic fibrosis (CF) become colonized with Pseudomonas aeruginosa in their bronchial secretions within their second decade of life. These patients require frequent treatment with potent antipseudomonal antibiotics such as Tobramycin. In this study, an intravenous infusion of 2.5 mg/kg tobramycin was given over 35 minutes. The following data was collected:

**TABLE 5 - 16. Tobramycin**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Plasma concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>8.00</td>
</tr>
<tr>
<td>60</td>
<td>6.00</td>
</tr>
<tr>
<td>90</td>
<td>4.50</td>
</tr>
<tr>
<td>150</td>
<td>2.50</td>
</tr>
<tr>
<td>270</td>
<td>0.75</td>
</tr>
</tbody>
</table>

From this data determine the following:

1. $k$
2. $t_{1/2}$
3. $V_d$
4. $Cl$
5. A patient is to be given tobramycin by IV infusion. The patient has a body weight of 70 kg. You wish to maintain a plasma concentration of 10 mg/L. Determine the following:
   a. Calculate the infusion rate necessary to maintain the plasma concentration of 10 mg/mL.
   b. Suggest a loading dose for the patient which would give you $C_{pss}$ immediately.
   c. How long will it take to reach steady state?
   d. Find the plasma concentration if the infusion is discontinued at time = 30 minutes.
   e. Find the plasma concentration 1 hour after stopping infusion if the infusion was stopped at time = 30 minutes.
“Tobramycin” on page 41

1. \( k = 0.01 \) min\(^{-1} \)
2. \( t_{1/2} = 69.3 \) min
3. \( V_d = 0.269 \) L/kg
4. \( Cl = 2.7 \) mL/min
5a. \( Q = 0.027 \) mg/kg/min = 1.62 mg/kg/hr
5b. \( D_L = 2.7 \) mg/kg
5c. \( t^{ss}_{95\%} = 300 \) min = 5 hr
5d. \( C_p = 2.6 \) mg/L
5e. \( C_p = 1.43 \) mg/L