Chapter 4 Answers and solutions

Short Answer Question

1. The curves should be similar those of Figures 4.16 and 4.17. The curve representing the short elimination half-life should rise rapidly to steady state with large fluctuations between the peaks and trough concentrations. The long elimination half-life curve should show a slower, exponential rise towards steady state with less fluctuation between peak and trough concentrations, because there will be less drug eliminated in the dosage interval. The slopes of the decay from peak to trough should become steeper because the rate of elimination will be higher at higher concentrations.

Multiple Choice Questions (Answer TRUE or FALSE)

1. When a drug that is eliminated according to first-order kinetics is injected into a one compartment model:
   (a) FALSE. In first-order reactions the rate is proportional to the concentration and therefore declines as the concentration decreases.
   (b) TRUE. The decay is exponential and \( C_t = C_0 \exp(-\lambda t) \).
   (c) TRUE. See (b).
   (d) TRUE. Because it is an intravenous injection the amount at \( t = 0 \), \( X_0 \), must be the dose, and so \( V = \text{Dose}/C_0 \).
   (e) TRUE. The rate of elimination is the amount present, \( X_t \), multiplied by the rate constant, \( \lambda \). The amount is the plasma concentration multiplied by the volume of distribution, so rate of elimination = \( (V.C_t)\lambda \).

2. For a drug eliminated according to first-order kinetics, the half-life is:
   (a) TRUE. This an important, in fact unique, feature of first-order elimination.
   (b) FALSE. Half-life is inversely proportional to \( \lambda \); \( t_{1/2} = \ln 2/\lambda \).
   (c) TRUE. The larger the volume of distribution the greater the half-life, as there is a larger volume to be cleared of drug.
   (d) FALSE. Half-life is inversely proportional to \( CL \) – the larger the clearance the sooner half of the drug will be eliminated.
   (e) FALSE. Lipophilic drugs have large volumes of distribution and so tend to have long elimination half-lives.

3. A drug showing first-order elimination kinetics from a one-compartment model has a half-life of 6 hours. This means that after:
   (a) TRUE. Half of the dose will be eliminated in \( 1 \times t_{1/2} \).
   (b) FALSE. Even if the extent of absorption of the oral dose is 100% it will take time to be absorbed and so 50 mg cannot be eliminated during the first 6 hours.
   (c) FALSE. The maximum rate of elimination is immediately after the injection, so more than 25 mg will be eliminated in the first 3 hours.
   (d) FALSE. 18 h is \( 3 \times t_{1/2} \), so the amount eliminated will be \( 50 + 25 + 12.5 = 87.5 \) mg
   (e) TRUE. The fraction remaining will be \( 1/2^N \), where \( N = \) number of half-times elapsed, i.e. \( 1/2^3 = 1/8 \)th.

4. Organ clearance, \( CL_{org} \):
   (a) TRUE. This is the definition of organ clearance.
   (b) FALSE. Unless otherwise stated, \( CL_{org} = \text{plasma flow rate} \times \text{extraction ratio} \).
   (c) FALSE. Extraction ratio is dimensionless, so the units of \( CL \) must be the units of flow rate, e.g. mL min\(^{-1}\).
(d) TRUE. Systemic (plasma, whole body) clearance is the sum of all the organ clearances and so if there is only one organ clearing the drug, this must equal systemic clearance.
(e) FALSE. This question does not say that we are considering the kidney.

5. Concerning a constant rate infusion \((R_0)\) of a drug eliminated according to first-order kinetics:
(a) TRUE. Because the rate of elimination is proportional to the amount of drug in the body, then as the amount increases due to the infusion, the rate of elimination increases until it equals the rate of infusion.
(b) FALSE. Drugs with short half-lives (high values of \(\lambda\)) will be eliminated faster and so reach steady-state conditions more quickly (see (a)).
(c) TRUE. While ever first-order kinetics apply, \(C^{ss} \propto R_0\).
(d) TRUE. The loading dose must be such that \(C^{ss}\) is obtained at the start of infusion. The amount will be \(V.C^{ss}\) (or \(R_0/\lambda\)).
(e) TRUE. The infusion curve is exponential and reaches 0.5 \(C^{ss}\) in \(1 \times t_1\), 0.75 \(C^{ss}\) in \(2 \times t_1\), etc. After 5 half-lives \(C_t \sim 0.969\).

6. A drug is eliminated from the body according to Michaelis-Menten kinetics. This means that:
(a) FALSE. Michaelis-Menten kinetics are not zero order. In fact the concept of order is of little help because it changes throughout the elimination.
(b) TRUE. Phenytoin shows Michaelis-Menten kinetics in its normal therapeutic range.
(c) FALSE. Steady-state concentrations will be disproportionately higher than would be expected for drugs eliminated by first-order kinetics.
(d) FALSE. Steady-state conditions will be achieved – see (c).
(e) TRUE. Because high concentrations tend towards zero-order kinetics then it follows that the half-life increases as the concentration increases.

7. The following take the units indicated:
(a) FALSE. First-order rate constant have units of reciprocal time \((\lambda \propto 1/t_1)\). For the rate of elimination, \(X, \lambda\), to have the correct units the rate constant must have units of time\(^{-1}\).
(b) TRUE. The apparent volume of distribution takes units of volume. It is sometimes normalized for body weight (e.g. L kg\(^{-1}\)).
(c) FALSE. Zero-order rate constants take the units of rate, e.g. g h\(^{-1}\).
(d) TRUE. Logarithms are dimensionless – so \(\ln(C_0)\) is dimensionless. This is why the units for the slope of a \(\ln C\) versus \(t\) plot are time\(^{-1}\). However, note the convention \(\ln(C/\text{mg mL}^{-1})\); the units refer to the concentration not the logarithm. This allows the correct units to be applied when taking antilogarithms.
(e) FALSE. A ratio of concentrations must be dimensionless.

Calculations
1. Plotting the \(\ln(\text{Concentration} / \text{mg L}^{-1})\) versus time data gives:

\[\text{Question 1}\]

\[\begin{array}{c|c}
\text{Time / h} & \text{ln}(C / \text{mg L}^{-1}) \\
0 & 5 \\
1 & 4 \\
2 & 3 \\
3 & 2 \\
\end{array}\]

(a) **One compartment and first-order decay** – The number of compartments is given by the number of exponential terms describing the decay (decline) in concentrations. There is clearly only one

exponential phase, as shown by the single declining line on the \(\text{ln}(C)\) versus \(t\) plot. It difficult to be sure that there is only one exponential when looking at the \(C\) vs \(t\) plot. Because it is exponential decay first-order equations can be used.

(b) **Kinetic parameters**

(i) The **elimination rate constant** is given by the slope of the line \(-1.39\ h^{-1} \times -1\), or from the half-life (see (ii)) \(0.693/0.5 = 1.39\ h^{-1}\). Linear regression gave \(-1.387 = -1.39\ h^{-1}\) (3 sig. fig.). Note that the gradient has units and that \(\lambda\) is slope (which is negative) multiplied by minus 1, so \(\lambda\) is positive. Rate constants cannot be negative.

(ii) Inspection of the time-concentration data reveals the **half-life** to be 0.5 h. Or from the rate constant, \(0.693/1.39 = 0.499\ h^{-1}\).

(iii) Inspection of the data shows that \(C_0 = 100\ mg\ L^{-1}\) (50 \(\times\) 2). The intercept from the ln plot is 4.6. The antilog of ln\(C_0\) = \(e^{4.6}\) = 99.5 mg L\(^{-1}\).

The **volume of distribution** = \(Dose/C_0 = 1500/100 = 15\ L\) (0.214 L kg\(^{-1}\)).

(iv) **Whole body (or plasma) clearance** is given by: \(CL = V\lambda\). \(15 \times 1.39 = 20.9\ L\ h^{-1}\)

(c) **Deductions**

(i) The volume of distribution is \(15/75 = 1/5 = 0.2\ L\ kg^{-1}\). This is approximately equal to extracellular fluid volume. The drug does not penetrate cells.

(ii) As the drug appears to be in ECF it is very unlikely that there is any plasma protein binding.

(iii) Practically all the drug (1455/1500 = 0.97) was recovered unchanged in the urine, thus \(CL_{\text{ren}}\) is a good estimate of systemic clearance, \(CL\).

\(CL = 20.9 \times 1000/60 = 348\ mL\ min^{-1}\). We can conclude that the drug is eliminated in the urine, and furthermore it must be actively secreted from the PCT because \(CL_{\text{ren}}\) exceeds GFR in this patient (~ 110 mL min\(^{-1}\)).

2. **Intravenous/intramuscular comparison**

(a) The ln \(C\) data should be plotted as a function of time. This allows the terminal slope to be calculated, graphically or by linear regression of last three points as shown below. The i.v. data are shown for comparison.

![Comparison of i.v. and i.m.](attachment:image)

(i) Plotting the i.m data on the same graph as the i.v. data should make the question a little easier. Inspection clearly shows that the terminal phase has a longer half-life after the i.m. dose. The slope of the construction line through the terminal points is \(-0.328\ h^{-1}\). The half-life of the terminal phase is \(0.693/0.328 = 2.11\ h\) (compared with 0.5 h after i.v. injection). Preparation B is a sustained-release (depot) i.m. preparation. The rate of release from the depot is rate limiting. Resolution to find the two rate constants is a useful exercise, but is unnecessary as it has can be estimated from the i.v. data in this instance.
(ii) The interval of one week is plenty for a drug with a half-life of 0.5 h, less than 1% remains after $7 \times t_{1/2} = 3.5$ h. After this time it is highly unlikely that any effects of enzyme induction or inhibition would be apparent.

(b) Bioavailability.

Usually, the trapezoidal method would be used. Inspection of the $C$ versus $t$ plots shows that $F$ is high.

![Graph showing concentration over time for different routes of administration](image)

In this exercise we can use the model to estimate the AUC values.

$AUC_{i.v.} = C_0/\lambda = 100/ 1.39 = 71.9$ mg h L$^{-1}$

$AUC_{p.o.} = \text{Intercept}/\lambda – \text{Intercept}/k_a = 28.9/0.5 – 28.9/1.39 = 57.8 20.8 = 76.6$

$F$ calculates as $76.6/71.9 = 1.06$. Thus the conclusion is that $F = 1$ because it cannot exceed 1.

Using the trapezoidal rule:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Conc$_{i.v.}$</th>
<th>Conc$_{i.m.}$</th>
<th>AUC$_{i.v.}$</th>
<th>AUC$_{p.o.}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>3.184116</td>
<td></td>
<td>21.3375</td>
<td>0.159206</td>
</tr>
<tr>
<td>0.25</td>
<td>70.7</td>
<td>7.007014</td>
<td></td>
<td>0.764335</td>
</tr>
<tr>
<td>0.5</td>
<td>50</td>
<td>11.38072</td>
<td>15.0875</td>
<td>2.298467</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>15.26007</td>
<td>18.75</td>
<td>6.660198</td>
</tr>
<tr>
<td>3</td>
<td>1.56</td>
<td>11.26641</td>
<td></td>
<td>12.93266</td>
</tr>
<tr>
<td>4</td>
<td>8.195286</td>
<td></td>
<td></td>
<td>9.730848</td>
</tr>
<tr>
<td>8</td>
<td>2.069473</td>
<td></td>
<td></td>
<td>20.52952</td>
</tr>
</tbody>
</table>

$C/A = 1.493126 \quad 5.946761$

$AUC \quad 76.18813 \quad 73.95147$

$F = 74.0/76.2 = 0.97$.

The question is based on benzylpenicillin (penicillin G), Preparation B being procaine penicillin. Penicillin is eliminated via the kidneys and a $CL > 125$ mL min$^{-1}$ indicates active tubular secretion which may be saturated by increasing doses. Thus $CL$ would fall with an increase in half-life. The apparent volume of distribution is equivalent to extracellular fluid volume so increasing doses are unlikely to affect this as there is no tissue or protein binding.
3. First-order input into single compartment

(a) Results using SLOPE and INTERCEPT functions in Excel with differing values of number of terminal points are shown below:

<table>
<thead>
<tr>
<th>Number of terminal points</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope (min⁻¹)</td>
<td>-0.143</td>
<td>-0.146</td>
<td>-0.153</td>
<td>-0.154</td>
<td>-0.151</td>
<td>-0.146</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.91</td>
<td>1.99</td>
<td>2.16</td>
<td>2.20</td>
<td>2.11</td>
<td>2.01</td>
</tr>
<tr>
<td>$C_0^\prime$ (μg mL⁻¹)</td>
<td>6.7</td>
<td>7.3</td>
<td>8.6</td>
<td>9.1</td>
<td>8.3</td>
<td>7.4</td>
</tr>
</tbody>
</table>

(b) Method of residuals

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\ln C_0^\prime$</td>
<td>2.70</td>
</tr>
<tr>
<td>$C_0^\prime$ (μg mL⁻¹)</td>
<td>14.9</td>
</tr>
<tr>
<td>$\lambda$ (min⁻¹)</td>
<td>0.171</td>
</tr>
<tr>
<td>$k_a$ (min⁻¹)</td>
<td>0.266</td>
</tr>
<tr>
<td>$C_0$ (μg mL⁻¹)*</td>
<td>5.28</td>
</tr>
<tr>
<td>* Assumes $F = 1$</td>
<td></td>
</tr>
</tbody>
</table>

(c) Iterative fits:

<table>
<thead>
<tr>
<th></th>
<th>No weight</th>
<th>Weight = 1/C²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.E.</td>
<td>S.E.</td>
</tr>
<tr>
<td>$C_0$ (μg mL⁻¹)*</td>
<td>5.547 ± 0.4722</td>
<td>5.40 ± 0.327</td>
</tr>
<tr>
<td>$k_a$ (min⁻¹)</td>
<td>0.249 ± 0.0245</td>
<td>0.255 ± 0.021</td>
</tr>
<tr>
<td>$\lambda$ (min⁻¹)</td>
<td>0.1782 ± 0.0164</td>
<td>0.1744 ± 0.010</td>
</tr>
</tbody>
</table>

(d) $AUC$ and clearance values:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{(0,\infty)}$ (mg min mL⁻¹)</td>
<td>31.0</td>
</tr>
<tr>
<td>$CL/F$ (mL min⁻¹)</td>
<td>129</td>
</tr>
</tbody>
</table>

(e) $t_{max}$ and $C_{max}$

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{max}$ (min)</td>
<td>4.65</td>
</tr>
<tr>
<td>$C_{max}$ (μg mL⁻¹)*</td>
<td>2.38</td>
</tr>
</tbody>
</table>

(f) This exercise raises several interesting and important issues. Most of them arise from the relative sizes of the absorption and elimination rate constants ($k_a = 2\lambda$) and the duration of time that it was possible to measure accurate concentrations. According to Equation 4.23, only 75% of the dye will have been ‘absorbed’ into the larger volume by $t_{max}$. This produces marked curvature to the early part of the decay curve making it difficult to fit the data. This is seen in the results of the linear regression analysis of the terminal data points as the slope and intercept are reduced as earlier time points are added to the analysis.

The curvature of the decay curve is apparent when applying the method of residuals, when it is best to ‘feather’ the construction line to the data rather than drawing the line through the terminal points. Not collecting data for sufficient time to obtain an accurate assessment of the elimination rate constant results in an underestimate of the true value. It is often the case that it is not feasible to measure plasma concentrations for as long as would be desirable. This is pointed out in Chapter 11, when age and disease may prolong the half-life making it even more important to measure the decay for long times.

With extravascular administration the results must be viewed with caution. To calculate $C_0$, requires the assumption that $F = 1$ (we know it is in this case, but this is not usually so). Although the estimate of $CL/F$ is in good agreement with the nominal value of flow rate (130 mL min⁻¹), we
cannot take this as the value of systemic clearance unless we are confident that \( F = 1 \). \( CL/F \) should be described as oral clearance to make this clear.

4. Phenytoin example

(a) Substituting the values into Equation 4.5 gives:

\[
300 = V_{\text{max}} - 300K_m/5.3 = V_{\text{max}} - 56.60K_m
\]

\[
400 = V_{\text{max}} - 400K_m/9.2 = V_{\text{max}} - 43.48K_m
\]

Subtracting to eliminate \( V_{\text{max}} \) gives:

\[
100 = 13.12 K_m
\]

From which:

\[ K_m = 7.62 \text{ mg L}^{-1}. \]

Substituting for \( K_m \) gives:

\[ V_{\text{max}} = 300 + 56.60 \times 7.62 = 300 + 431 = 731 \text{ mg d}^{-1} \]

The problem can also be solved graphically; see (d) below.

(b) Substituting the values into Equation 4.5 to solve for \( R \):

\[ R = 731 - 7.62R/15 = 731 - 0.508R \]

\[ R + 0.508R = 731 \]

\[ R = 731/(1 + 0.508) = 485 \text{ mg d}^{-1}. \]

(c) Substituting the values into Equation 4.5 to solve for \( C^{ss} \):

\[
600 = 731 - 4572/C^{ss}
\]

\[
-131 = -4572/C^{ss}
\]

\[ C^{ss} = 34.9 \text{ mg L}^{-1} \]

Doubling the initial 300 mg per day dose in this patient would result in a steady-state serum concentration of 34.9 mg L\(^{-1}\). If the kinetics had been first-order then doubling any dose would double \( C^{ss} \), so if this were the case the concentration would be 10.6 mg L\(^{-1}\).

(d) The \( C^{ss} \) versus daily dose plot is shown below: