Case Study #2 Answers  
PHA5128

Question #1: Salt factor  
   a) What does the salt factor stand for?  
      It is a correction factor that accounts for the acid/base of the drug in its salt form.

\[
S = \frac{\text{acid or base}[mg]}{\text{salt}[mg]}
\]

   b) When do you use a salt factor?  
      Basically, one always uses a salt factor. In order to keep it simple, we assumed it to be 1 so far. However, you need to take it into consideration as soon as a salt factor (S<1) or a difference in weight salt vs. acid/base is given.

Question #2: Bioequivalence  
   a) Which parameters are used to determine Bioequivalence?  
      \(C_{\text{max}}, AUC_{\infty}\)
   b) Which parameter characterizes the rate and which one the extent of availability?  
      rate \(\rightarrow t_{\text{max}}, (t_{\text{max}} \text{ is the time to reach } C_{\text{max}} \text{ parameters are linked})\)  
      extent \(\rightarrow AUC, (C_{\text{max}} \text{ given similar AUCs, a higher } C_{\text{max}} \text{ characterizes a greater extent})\)
   c) Drug X was administered as an i.v. bolus. Calculate AUC_{\infty} from the values given in the table below. Assume a 1-compartment body model and linear pharmacokinetics.

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Concentration (mcg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>110</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>
\[ AUC_{n \rightarrow t_2} = \frac{C_{t_2} + C_n}{2} \times (t_2 - t_1) \]

\[ AUC_{0h \rightarrow 4h} = \frac{50 \text{ mcg} \cdot \text{hr}}{L} + \frac{110 \text{ mcg} \cdot \text{hr}}{L} \times (4 \text{ hr} - 0 \text{ hr}) = 320 \text{ mcg} \cdot \text{hr} / L \]

\[ AUC_{4h \rightarrow 8h} = 144 \frac{\text{mcg} \cdot \text{hr}}{L} \]

\[ AUC_{8h \rightarrow 12h} = 64 \frac{\text{mcg} \cdot \text{hr}}{L} \]

\[ AUC_{12h \rightarrow 16h} = 30 \frac{\text{mcg} \cdot \text{hr}}{L} \]

\[ AUC_{16h \rightarrow 20h} = 14 \frac{\text{mcg} \cdot \text{hr}}{L} \]

\[ AUC_{20h \rightarrow \infty} = \frac{C_{20h}}{k_e^*} = \frac{2 \text{ mcg}}{L \cdot 0.2 \text{ hr}^{-1}} = 10 \frac{\text{mcg} \cdot \text{hr}}{L} \]

\[ AUC_{0 \rightarrow \infty} = AUC_{0h \rightarrow 4h} + AUC_{4h \rightarrow 8h} + AUC_{8h \rightarrow 12h} + AUC_{12h \rightarrow 16h} + AUC_{16h \rightarrow 20h} + AUC_{20h \rightarrow \infty} \]
\[ = (320 + 144 + 30 + 14 + 10) \frac{\text{mcg} \cdot \text{hr}}{L} = 582 \frac{\text{mcg} \cdot \text{hr}}{L} \]

**Question #3:** Cockroft and Gault

\( a) \) Give the equation(s) used to calculate \( Cl_{\text{creat}} \). Are there differences within a patient population?

Males: \[ Cl_{\text{creat}} = \frac{(140 - \text{age}) \cdot \text{BW}}{Cp_{\text{creat}} \cdot 72} \]

Females: \[ Cl_{\text{creat}} = \frac{(140 - \text{age}) \cdot \text{BW}}{Cp_{\text{creat}} \cdot 85} \]

Use IBW up to 120% TBW. If patients TBW exceeds 120% IBW use ABW.

\[ ABW = IBW + 0.4(TBW - IBW) \]

IBW\text{male} = 50kg+2.3kg for each inch over 5ft in height

IBW\text{female} = 45kg+2.3kg for each inch over 5ft in height
b) Patients A and B receive 1000mg of drug D per day, given as two 500mg tablets. Patient B was diagnosed with impaired renal function ($Cl_{\text{creat}} = 50\text{mL/min}$). Laboratory results further indicated that 80% of the drug is excreted into the urine. What would you do? Assume linear pharmacokinetics.

\[ D_{\text{pat}} = D_{\text{norm}} \cdot \left[ 1 - f_{\text{ren}} \cdot (1 - RF) \right] \]

\[ RF = \frac{Cl_{\text{creat}}^{\text{actual}}}{GFR} = \frac{50\text{mL/min}}{125\text{mL/min}} = 0.4 \]

\[ D_{\text{pat}} = 1000\text{mg} \cdot \left[ 1 - 0.8 \cdot (1 - 0.4) \right] = 520\text{mg} \]

Give only one tablet to patient B.

c) Explain the following graph.

The half-life for this particular drug is approximately 0.9 hours for patients with normal renal function. The half-life increases with decreasing renal function.