100 mg of a drug are given i.v. and p.o. to the same patient. The following plasma level concentrations are measured.

<table>
<thead>
<tr>
<th>Time [hrs]</th>
<th>( C_p ) i.v. [µg/ml]</th>
<th>( C_p ) oral [µg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>2.58</td>
<td>0.30</td>
</tr>
<tr>
<td>0.6</td>
<td>2.40</td>
<td>0.74</td>
</tr>
<tr>
<td>1.0</td>
<td>2.24</td>
<td>1.18</td>
</tr>
<tr>
<td>2.0</td>
<td>1.90</td>
<td>1.26</td>
</tr>
<tr>
<td>3.0</td>
<td>1.60</td>
<td>1.22</td>
</tr>
<tr>
<td>4.0</td>
<td>1.34</td>
<td>1.10</td>
</tr>
<tr>
<td>6.0</td>
<td>0.96</td>
<td>0.82</td>
</tr>
<tr>
<td>8.0</td>
<td>0.68</td>
<td>0.58</td>
</tr>
<tr>
<td>12.0</td>
<td>0.34</td>
<td>0.30</td>
</tr>
</tbody>
</table>

1. Determine the absolute bioavailability of the oral product.

To determine absolute bioavailability of an oral dosage form, the AUC after an oral dose must be compared to that after an IV bolus dose. For the same dose (here, 100 mg),

\[
F = \frac{AUC(oral)}{AUC(IV)}
\]

\[
K_e = \ln\left(\frac{c_2}{c_1}\right)/(t_2-t_1) = 0.18/hr^{-1}
\]

IV bolus dose

\[C_p(0) = 2.67 \, \mu g/ml \text{ from extrapolation}\]

Or by back calculating by using a point in the line representing the elimination phase.

\[C_p(0)=C/e^{(-k_e*t)}=\frac{2.58}{e^{-0.18*0.2}}=2.68\mu g/mL\]

\[AUC(0-0.2) = \frac{(2.68 + 2.58)\mu g/ml}{2} \cdot (0.2 - 0) hr = 0.53 \mu g/ml/hr\]
\[ AUC(0.2 - 12) = \frac{(2.58 + 2.4) \mu g / ml}{2} \cdot (0.6 - 0.2) hr + \ldots + \frac{(0.68 + 0.34) \mu g / ml}{2} \cdot (12 - 8) hr \]

\[ = 13.19 \mu g/ml/hr \]

\[ AUC(12 - \infty) = \frac{Cp(@12hr)}{k} = \frac{0.34 \mu g / ml}{0.18 hr^{-1}} = 1.90 \mu g / ml / hr \] (for calculating terminal AUC or AUClast-\(\infty\))

\[ AUC(0 - \infty) = 15.6 \mu g/ml/hr \]

**Oral Dose**

\[ Cp(0) = 0 \mu g/ml for a single oral dose \]

\[ AUC(0 - 0.2) = \frac{(0 + 0.3) \mu g / ml}{2} \cdot (0.2 - 0) hr = 0.03 \mu g / ml / hr \]

\[ AUC(0.2 - 12) = \frac{(0.3 + 0.74) \mu g / ml}{2} \cdot (0.6 - 0.2) hr + \ldots + \frac{(0.58 + 0.3) \mu g / ml}{2} \cdot (12 - 8) hr = 9.29 \mu g / ml \]

\[ AUC(12 - \infty) = \frac{Cp(@12hr)}{k} = \frac{0.3 \mu g / ml}{0.18 hr^{-1}} = 1.67 \mu g / ml / hr \]

\[ AUC(0 - \infty) = 11.0 \mu g/ml/hr \]

\[ F=11.0 \mu g/ml/hr/15.6 \mu g/ml/hr =0.71 \text{ (no units)} \]

2. From the above data calculate the CL and Vd.

From the IV bolus dose:  \( Cl=\frac{D/AUC}{100mg/15.6 \text{ mg/L/hr}} = 6.4L/hr \)

\( Vd=CL/ke = 6.4L/hr/0.18hr^{-1} = 35.6L \)
Or
\[ V_d = \text{Dose}/C_0 = 100\text{mg}/2.68\text{mg/L} = 37.3\text{L} \]
\[ \text{Cl} = \text{ke} \cdot V_d = 0.18\text{hr}^{-1} \cdot 1 \cdot 37.3 = 6.7\text{L/hr} \]

3. How do we know that the terminal slope of the oral dose is the elimination rate constant (ke) and this is not a flip flop situation?

From the oral dose \[ \ln(0.82/0.58)/(8-6) = 0.17. \] The slope of the terminal phase oral is ~equal to the slope of the terminal phase i.v. Therefore ka must be larger than ke and the slope of the terminal phase of the oral dose truly represents the elimination phase.

4. K.L., a 85 kg male smoker with chronic obstructive pulmonary disease, is to be started on an oral regimen of aminophylline (85% of which is theophylline). The pharmacokinetic parameters for this patient are \( V_d \) (0.5 L/kg), \( \text{CL} \) (80 mL/h/kg) and \( F \) (1.0).

Design an oral dosage regimen of aminophylline (100- and 200 mg tablets are marketed) for this patient to attain and maintain a plasma concentration within the therapeutic range (10-20 \( \mu \text{g/ml} \)) and average steady state target of 15mg/L. The absorption of theophylline is complete and rapid.

\[ \text{CL} = 6.8 \text{ L/h}, \quad V_d = 42.5 \text{ L} \]
\[ k = \frac{6.8}{42.5} = 0.16h^{-1} \]
\[ \tau = \frac{\ln\left(\frac{20}{10}\right)}{0.16} = 4.3h \rightarrow 4h \]
\[ D = \frac{\bar{C} \cdot CL \cdot \tau}{F} = \frac{15 \cdot 6.8 \cdot 4}{0.85} = 480mg \rightarrow 500mg \] (Two 200mg tablets and 1 100mg tablet)

Since a 4 hours dosing interval is not very practical a sustained released product may be recommended.

5. How will the following parameters change for a drug that is a high extraction drug eliminated by hepatic clearance only if the free fraction in plasma is changed from 0.8 to 0.2. Indicate increase, decrease, or remain the same (half point each).

A. \( V_d \) decrease
B. $E_H$ remain the same

D. $Cl$ remain the same

E. $K_e$ increase

6. Drug A is administered as a 250 mg IV bolus dose. 2 hours after administration the concentration in plasma is 4 mg/L and 10 hours after administration the concentration in plasma is 1 mg/L. This lipophilic drug is cleared by the liver and this patient has a liver blood flow of 80 L/hr. The tissue protein binding is 0.6.

A. Calculate $C_0$ (2 pts)

$$K_e = -\text{slope}$$

$$K_e = -(\ln 1 \text{ mg/L} - \ln 4 \text{ mg/L})/(10 - 2) = 0.173 \text{ hr}^{-1}$$

$$C = C_0 e^{-K_e t}$$

$$C_0 = \frac{C}{e^{-K_e t}}$$

$$C_0 = 4 \text{ mg/L}/(e^{-0.173 \text{ hr}^{-1} \times 2 \text{ hr}}) = 5.65 \text{ mg/L}$$

B. Calculate $V_d$ (1 pts)

$$V_d = \frac{\text{Dose}}{C_0}$$

$$V_d = \frac{250 \text{ mg}}{5.65 \text{ mg/L}} = 44.2 \text{ L}$$

C. Is this a high extraction drug or low extraction drug? (1 pt)

$$Cl = K_e V_d$$

$$Cl = 0.173 \text{ hr}^{-1} \times 44.2 \text{ L} = 7.65 \text{ L/hr}$$

If this drug were a high extraction drug, than the clearance would be close to liver blood flow, 80L/hr. However, it is much lower indicating that this drug is a low extraction drug.

E. If this drug were coadministered with Drug B, which is known to caused enzyme induction for the enzymes responsible for the metabolism of Drug A, would you expect to see a change in clearance? (1 pt)

Yes, this would change clearance. Since clearance of a low extraction drug is dependent on the fraction of free drug and intrinsic clearance.