1. (20 pt.) The following table shows the pharmacokinetic properties of cefuroxime:

<table>
<thead>
<tr>
<th></th>
<th>Cefuroxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL [L/h]</td>
<td>6.8</td>
</tr>
<tr>
<td>Vd [L]</td>
<td>14</td>
</tr>
<tr>
<td>F_{oral}</td>
<td>0.68</td>
</tr>
<tr>
<td>F_{b}</td>
<td>0.33</td>
</tr>
<tr>
<td>F_{ren}</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Calculate the total daily oral dose necessary to maintain an average unbound concentration of 20 mg/L in plasma and urine. Assume a urine flow of 1 ml/min.

\[
C = \frac{F \cdot D}{CL \cdot 24} = \frac{Cu}{fu}
\]

\[
D = \frac{Cu \cdot CL \cdot 24}{F \cdot fu} = \frac{20 \cdot 6.8 \cdot 24}{0.68 \cdot 0.67} = 7.2g
\]

**urine**

\[
\frac{dE}{dt} = 20 \mu g / min = 1.2 mg / h
\]

\[
CL_{ren} = 0.96 \cdot 6.8 = 6.5 L/h = \frac{dE}{\frac{dt}{C}}
\]

\[
C = \frac{1.2}{6.5} = 0.18 mg / L
\]

\[
D = \frac{C \cdot CL \cdot 24}{F} = \frac{0.18 \cdot 6.8 \cdot 24}{0.68} = 43 mg
\]
2. (25pts) A patient was given 100 mg gentamicin over 30 minutes (i.v.) from 6:00 to 6:30 am. During the elimination phase, two serum levels were measured:

At 8:00 am 9.3 pg/mL
At 5:00 pm 0.5 pg/mL

Calculate:

a. The elimination rate constant \( k \)

\[
ln\left(\frac{9.3}{0.5}\right) \quad k = \frac{\ln\left(\frac{9.3}{0.5}\right)}{9} = 0.325\text{h}^{-1}
\]

b. The elimination half-life

\[
t_{1/2} = \frac{0.693}{0.325} = 2.1h
\]

c. The peak concentration at 6:30 am

\[
C_{\text{max}} = \frac{9.3}{e^{-0.325 \cdot 1.5}} = 15.1\mu g / mL
\]

d. The trough concentration at 6:00 pm

\[
C_{\text{min}} = 0.5 \cdot e^{-0.325 \cdot 1} = 0.3\mu g / mL
\]

e. The volume of distribution

\[
V_d = \frac{100}{0.325 \cdot 0.5} \cdot \left(1 - e^{-0.325 \cdot 0.5}\right) = 6.2L
\]

f. The clearance

\[
CL = 0.325 \cdot 6.2 = 2\text{ L/h or 34 mL/min}
\]
3. (10 pts) A high-extraction drug was given by i.v. bolus injection. Sketch the profiles for the following changes (all other primary parameters remaining constant):

<table>
<thead>
<tr>
<th>Decreased Vd</th>
<th>Decreased CL</th>
<th>Decreased $f_a$</th>
<th>Decreased $f_{aT}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

4. (10 pts) In a study to compare the pharmacokinetics of 250 mg lignocaine after oral administration in old and young subjects, the following results were obtained:

Lignocaine is a high-extraction drug. Interpret the results.

Difference is due to first-pass effect, not clearance. First-pass effect depends on intrinsic clearance, whereas clearance is dependent on liver blood flow.
5. (20 pt.) Ciprofloxacin has a total body clearance of 6 mL/min/kg. 65% of the absorbed drug is renally eliminated, the remainder is hepatically eliminated. The plasma protein binding is 40%. The oral bioavailability is 60%. The volume of distribution is 1.8 L/kg.

For a 70 kg patient, calculate

a. the total body clearance

\[ \text{CL} = 6.70 \times 70 = 420 \text{ mL/min} = 25.2 \text{ L/h} \]

b. the renal clearance

\[ \text{CL}_{\text{ren}} = 0.65 \times 25.2 = 16.4 \text{ L/h} \text{ or } 273 \text{ mL/min} \]

c. the elimination half-life

\[ V_d = 1.8 \times 70 = 126 \text{ L} \]

\[ t_{1/2} = \frac{0.693 \times V_d}{CL} = \frac{0.693 \times 126}{25.2} = 3.5 \text{ h} \]

d. the hepatic extraction ratio

\[ E_H = \frac{CL_{\text{H}}}{Q} = \frac{8.8}{90} = 0.1 \]

e. the intrinsic hepatic clearance

\[ 0.1 = \frac{0.6 \times CL_{\text{int}}}{90 + 0.6 \times CL_{\text{int}}} \]

\[ 9 + 0.06 \times CL_{\text{int}} = 0.6 \times CL_{\text{int}} \]

\[ CL_{\text{int}} = \frac{9}{0.54} = 16.7 \text{ L/h} \]
f. the fraction of the absorbed drug excreted by tubular secretion

\[ \text{CL}_{\text{ren}} = 273 \text{ mL/min} \]

\[ \text{GFR} = 125 \text{ mL/min} \]

\[ F_T^S = \frac{11.9}{25.2} = 0.47 \]

\[ \text{CL}_{\text{TS}} = 273 - 75 = 198 \text{ mL/min} = 11.9 \text{ L/h} \]

\[ \text{CL}_{\text{GFR}} = 125 \cdot 0.6 = 75 \]

g. the expected oral bioavailability assuming complete absorption and first-pass effect

\[ F = 1 - E_H = 0.9 \]

6. (10 pts) Theophylline is administered as a constant rate infusion over 2 days. A plasma concentration profile is obtained which is shown in the two figures below.

a. In the graph below, add the expected curve for a patient with equal clearance but twice the volume of distribution
b. In the graph below, add the expected curve in a smoker with equal volume of distribution but twice the clearance.

![Graph showing drug concentration over time]

7. (5 pts) In a study the volume of distribution for diazepam was found to be 13 L in a group of normal weight subjects (average weight 55 kg) and 19 L in a group of obese subjects (average weight 104 kg).

Discuss the results.

Normal

\[ Vd = \frac{13}{55} = 0.24 L/kg \]

Obese

EBW = 105 - 55 = 49 kg

Additional \[ Vd = \frac{6}{49} = 0.12 L/kg \] (only 50% of IBW)

→ the uptake is 50% of that in IBW

\[ Vd = 0.24 \cdot (IBW + 0.5 \cdot EBW) \]