On my honor, I have neither given nor received unauthorized aid in doing this assignment.

**Typed Key**

**Name**

**Question**

1. _____/5 pts
2. _____/25 pts
3. _____/5 pts
4. _____/5 pts
5. _____/5 pts
6. _____/10 pts
7. _____/10 pts
8. _____/5 pts
9. _____/15 pts
10. _____/10 pts
11. _____/5 pts

Total _____/100 pts
1. (5 pts) A patient is admitted with an acute theophylline overdose. A serum level is measured at 53 µg/mL. Assuming an 8 hour half-life and no further drug absorption, how long does it take for the serum level to drop to the upper limit of the therapeutic range (20 µg/mL)?

\[ t_{1/2} = 8 \text{ h} \]

\[ k = \frac{0.693}{t_{1/2}} = 0.0866 \text{ h}^{-1} \]

\[ C = C_0 \cdot e^{-k \cdot t} \]

\[ 20 = 53 \cdot e^{-0.0866 \cdot t} \]

\[ \frac{20}{53} = e^{-0.0866t} \]

\[ \ln \left( \frac{20}{53} \right) = -0.0866 \cdot t \]

\[ t = \frac{\ln \left( \frac{20}{53} \right)}{-0.0866} = 11.3 \text{ h} \]
2. (25pts) A patient was given 80 mg gentamicin over 30 minutes (i.v.) from 7:30 to 8 am. During the elimination phase, two serum levels were measured:

At 8:30 am 6.0 µg/mL
At 3:00 pm 0.9 µg/mL

Calculate:

a. The elimination rate constant \( k \)

\[
ln\left(\frac{C_1}{C_2}\right) = \frac{ln\left(\frac{6.0}{0.9}\right)}{6.5} = 0.292 \, h^{-1}
\]

b. The elimination half-life \( t_{1/2} \)

\[
t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.292} = 2.4 \, h
\]

c. The peak concentration at 8:00 am

\[
C_{\text{max}} = \frac{C_{\text{max}}^*}{e^{-k\cdot t^*}} = \frac{6.0}{e^{-0.292\cdot0.5}} = 6.94 \, \mu g / mL
\]

d. The trough concentration at 3:30 pm

\[
C_{\text{min}} = C_{\text{min}}^* \cdot e^{-k\cdot t^*} = 0.9 \cdot e^{-0.292\cdot0.5} = 0.78 \, \mu g / mL
\]

e. The volume of distribution

\[
V_d = \frac{D}{k \cdot T \cdot \left(\frac{1 - e^{-k\cdot T}}{C_{\text{max}} - C_{\text{min}}^* \cdot e^{-k\cdot T}}\right)} = \frac{80}{0.292 \cdot 0.5 \cdot \left(\frac{1 - e^{-0.292\cdot0.5}}{6.94 - 0.78 \cdot e^{-0.292\cdot0.5}}\right)} = 547.95 \cdot \frac{0.136}{6.266} = 11.9 \, L
\]
f. The clearance

\[ CL = k \cdot V_d = 0.292 \cdot 11.9 = 3.47 \text{ L/h or 57.9 mL/min} \]
3. (5 pts) What is the difference between a "third compartment" and "third space fluids"?

Third compartment: Space in the body that equilibrates slowly with the central compartment

Third space fluids: Accumulation of water in the tissue (e.g. ascites, edema)

4. (5 pts) Explain why it is possible to use serum creatinine levels to determine renal function without measuring creatinine concentrations in the urine.

\[ \text{Clearance} = \frac{\text{Excretion Rate}}{\text{Serum Level}} \]

At steady state: Excretion Rate = Formation Rate

Assumption: Creatinine Formation Rate is constant

An empirical equation (Cockroft and Gault) is used to estimate creatinine clearance from serum creatinine.
5. (5 pts) Show for both high and low extraction drugs, how doubling the protein binding will affect the resulting unbound and total serum levels. What recommendations would you make for dose adjustments? Assume constant rate infusions and steady state.

Doubled fb =

\[ \text{fu}_\downarrow \]

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>Q (⁻)</td>
<td>fu · CL_{int} (⁻)</td>
</tr>
<tr>
<td>Css</td>
<td>( \frac{Ro}{Q} ) (⁻)</td>
<td>( \frac{Ro}{fu \cdot CL_{int}} ) (↑)</td>
</tr>
<tr>
<td>fu · Css</td>
<td>( \frac{fu \cdot Ro}{Q} ) (⁻)</td>
<td>( \frac{Ro}{CL_{int}} ) (⁻)</td>
</tr>
<tr>
<td>Dose</td>
<td>(↑)</td>
<td>(-)</td>
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</tbody>
</table>

(↑) increase
(-) no change
(⁻) decrease
6. (10 pts) After administration of a 400 mg theophylline sustained release product Q12H to a 70 kg patient, at steady state you measure a peak (after 4h) of 16 and a trough (after 12h) of 12 µg/mL. The average volume of distribution is 0.5 L/kg.

a. Calculate the clearance

\[ CL = \frac{D}{AUC} = \frac{400}{\frac{16 + 12}{2} \cdot 12} = \frac{400}{168} = 2.38 L/h \]

b. Calculate the elimination half-life

\[ t_{1/2} = \frac{0.693 \cdot V_d}{CL} = \frac{0.693 \cdot 35}{2.38} = 10.2 h \]

c. Interpret the results

This is a flip-flop case. Half-life cannot be calculated from the terminal slope.
7. (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 only half 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.
8. (5 pts) Define the pharmacokinetic parameters $V_{d_{ss}}$ and $V_{d_{area}}$ and explain why $V_{d_{area}}$ is always larger than $V_{d_{ss}}$.

$V_{d_{ss}}$ Volume of distribution at steady state
Central and peripheral compartment are in equilibrium (equal unbound concentrations)

$V_{d_{area}}$ Volume of distribution during the elimination phase. There is a concentration gradient from the peripheral to the central compartment. (unbound concentration is higher in the peripheral compartment, lower in the central compartment)

Lower concentration in central compartment
→ larger $V_d$

→ $V_{d_{area}} > V_{d_{ss}}$
9. (15 pts) A theophylline infusion is started at a rate of 30 mg/h in a patient with the following parameters.

\[ \text{CL} = 3 \text{ L/h} \]
\[ \text{Vd} = 40 \text{ L} \]

a. Calculate the expected steady state concentration

\[ C = \frac{R_o}{\text{CL}} = \frac{30}{3} \times 10 \frac{\mu g}{mL} \]

b. Calculate the expected concentration after 12 hours

\[ C = \frac{R_o}{\text{CL}} (1 - e^{-k \cdot t}) = 10 \times (1 - e^{-0.075 \cdot 12}) = 5.9 \frac{\mu g}{mL} \]

\[ k = \frac{\text{CL}}{\text{Vd}} = \frac{3}{40} = 0.075 h^{-1} \]

c. Make a recommendation for dosing rate to bring the level at steady state to 15 \mu g/mL.

\[ R_o = C \cdot \text{CL} = 15 \times 3 = 45 \text{ mg/h} \]

d. When therapy is discontinued, how long will the level stay above 10 \mu g/mL.

\[ C = C_o \cdot e^{-k \cdot t} \]
\[ 10 = 15 \cdot e^{-0.075 \cdot t} \]

\[ \ln \left( \frac{10}{15} \right) = -0.075 \cdot t \]

\[ t = 5.4 \text{ h} \]
10. (10 pts) If propranolol is combined with phenobarbital, its intrinsic clearance can double due to enzyme induction. Discuss (in detail) how this interaction will affect the average steady state concentration of propranolol.

a. after i.v. administration

\[ C_{ss} = \frac{R_o}{Q} \rightarrow \text{independent of } CL_{int} \]

\[ \rightarrow \text{no change} \]

b. after oral administration

\[ C_{ss} = \frac{D \cdot F}{CL \cdot \tau} = \frac{(1 - E) \cdot D}{CL \cdot \tau} = \frac{Q \cdot D}{fu \cdot CL_{int} \cdot Q \cdot \tau} = \]

\[ F = 1 - E = \frac{Q}{fu \cdot CL_{int} + Q} \sim \frac{Q}{fu \cdot CL_{int}} \bigg| \bigg| \frac{D}{fu \cdot CL_{int} \cdot \tau} \]

\[ CL \sim Q \]

\[ \rightarrow \text{if } CL_{int} \text{ is doubled, } C_{ss} \text{ is cut in half} \]
11. (5 pts) In a study the volume of distribution for diazepam was found to be 91L in a group of normal weight subjects (average weight 61 kg) and 292 L in a group of obese subjects (average weight 104 kg).

Discuss the results.

Normal: 91L/61 kg → 1.5 L/kg

Obese: 292 L/104 kg → 2.8 L/kg

Increase in BW: ~ 70%
In V_d: ~ 220%

Distribution in EBW more than in IBW

→ more than proportional increase in V_d due to high lipophilicity of diazepam