Question

1. _____/5 pts
2. _____/20 pts
3. _____/5 pts
4. _____/5 pts
5. _____/10 pts
6. _____/15 pts
7. _____/5 pts
8. _____/5 pts
9. _____/20 pts
10. _____/5 pts
11. _____/15 pts
Total _____/100 pts
1. A patient is admitted with an acute theophylline overdose. A serum level is measured at 45 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)?

\[
k_e = \frac{0.693}{8} = 0.0866 \text{ h}^{-1}
\]

\[
20 = 45 \cdot e^{-0.0866 \cdot t}
\]

\[
\ln 20 = \ln 45 - 0.0866 \cdot t
\]

\[
0.8109 = 0.0866 \cdot t
\]

\[
t = 9.4 \text{ h}
\]
2. A patient was given 80 µg gentamicin over 30 minutes (i.v.) from 9:30 to 10 am. During the elimination phase, two serum levels were measured:

At 10:30 am 6.5 µg/mL
At 5:00 pm 1.2 µg/mL

Calculate:

a. The elimination rate constant \( k_e \)

\[
k_e = \frac{\ln 6.5 - \ln 1.2}{6.5} = 0.26 \, h^{-1}
\]

b. The elimination half-life

\[
t_{1/2} = \frac{0.693}{0.26} = 2.7 \, h
\]

c. The peak concentration at 10:00 am

\[
C_{\text{max}} = \frac{6.5}{e^{-0.26 \cdot 0.5}} = 7.4 \, \mu g / mL
\]

d. The trough concentration at 5:30 pm

\[
C_{\text{min}} = 1.2 \cdot e^{-0.26 \cdot 0.5} = 1.05 \, \mu g/mL
\]

e. The volume of distribution

\[
V_d = \frac{D \cdot (1 - e^{-k \cdot T})}{k \cdot T \cdot (C_{\text{max}} - C_{\text{min}} \cdot e^{-k \cdot T})} = \frac{80 \cdot (1 - e^{-0.13})}{0.26 \cdot 0.5 \cdot (7.4 - 1.05 \cdot e^{-0.13})} = 11.6L
\]

f. The clearance

\[
CL = k_e \cdot V_d = 3.0 \, L/h \text{ or } 50 \, mL/min
\]
3. **What is a “deep compartment”**?

Peripheral body compartment with slow equilibration

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

- Assumption of constant formation of creatinine in the body from muscle
- Empirical relationship with age, weight and sex.

5. **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.**

**High E**

\[ CL = Q \]

\[ Cp_{ss} = \frac{ko}{Q} \text{ not affected by } PB \uparrow \]

\[ fu \cdot Cp_{ss} = \frac{fu \cdot ko}{Q} \text{ if } PB \uparrow, fu \cdot Cp_{ss} \downarrow \Rightarrow \text{ change dose} \]

**Low E**

\[ CL = fu \cdot CL_{int} \]

\[ Cp_{ss} = \frac{ko}{fu \cdot CL_{int}} \text{ if } PB \uparrow, fu \downarrow, Cp_{ss} \uparrow \]

\[ fu \cdot Cp_{ss} = \frac{ko}{CL_{int}} \text{ not affected by } PB \Rightarrow \text{no change in dose} \]

\[ fu \cdot Cp_{ss} \text{ is the therapeutically relevant free drug concentration} \]
6. 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 17 and a trough (after 12h) of 13 µg/mL. The average volume of distribution is 0.5 L/kg.

a. Calculate the clearance

$$\bar{C}_{p_{ss}} = \frac{F \cdot D}{CL \cdot \tau}$$

$$15 = \frac{400}{CL \cdot 12}$$

CL = 2.2 L/h

b. Calculate the elimination half-life

$$t_{1/2} = \frac{0.693 \cdot 70 \cdot 0.5}{2.2} = 11h$$

c. Interpret the results

flip-flop
7. Although it is well understood, that only the unbound concentration causes pharmacological effects and side effects, drug level monitoring is usually done on total serum concentrations. Discuss this procedure.

- Assumes constant fraction bound
- Free level monitoring is expensive and time consuming

8. Define the pharmacokinetic parameters $V_{d_{ss}}$ and $V_{d_{area}}$ and explain, why $V_{d_{area}}$ is always larger than $V_{d_{ss}}$.

$$V_{d_{ss}} \rightarrow V_d \text{ at steady state} \quad C_{central} = C_{peripheral} \text{ (free)}$$

$$V_{d_{area}} \rightarrow V_d \text{ during elimination phase} \quad C_{central} < C_{peripheral} \text{ (free)}$$

If $C_{central} \downarrow$, $V_d \uparrow$

9. A theophylline infusion is started at a rate of 30 mg/h in a patient with the following parameters.

$$CL = 3.5 \text{ L/h}$$
$$V_d = 35 \text{ L}$$

a. Calculate the expected steady state concentration

$$Cp_{ss} = \frac{30\text{mg/h}}{3.2\text{L/h}} = 8.6 \mu g / mL$$

b. Calculate the expected concentration after 12 hours

$$Cp = Cp_{ss} \cdot (1 - e^{-ke \cdot t}) \quad ke = \frac{3.5}{35} = 0.1 h^{-1}$$

$$Cp = 8.6 \cdot (1 - e^{-1.2}) = 6 \mu g / mL$$
c. Make a recommendation for dosing rate to bring the level at steady state to 15 µg/mL.

\[ k_0 = 15 \cdot 3.5 = 52.5 \text{ mg/h} \approx 50 \text{ mg/h} \]

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

\[ 10 = 15 \cdot e^{-0.1 \cdot t} \]

\[ -0.405 = -0.1 \cdot t \]

\[ t = 4.05 \text{ h} \]

10. Calculate the extraction ratio of phenylbutazone in a 77.0 kg patient, given the following information: liver blood flow, 1500 ml/min; half-life 50 h; \( V_d \), 0.1 l/kg; no non-hepatic elimination.

\[ k_e = \frac{0.693}{50} = 0.0139 h^{-1} \]

\[ V_d = 7.7 \text{ L} \]

\[ CL = 0.0139 \cdot 7.7 = 0.107 \text{ L/h} \]

\[ CL = Q \cdot E \quad E = \frac{CL}{Q} \]

\[ E = \frac{0.107}{90} = 0.0012 \]

11. Show the effect of changes in protein binding on the AUC of any drug given orally. Assume that the drug undergoes first pass metabolism.

\[ AUC = \frac{F \cdot D}{CL} \quad F = 1 - E = 1 - \frac{fu \cdot CL_{int}}{Q + fn \cdot CL_{int}} = \frac{Q}{Q + fn \cdot CL_{int}} \]

\[ AUC = \frac{Q \cdot D}{Q \cdot fu \cdot CL_{int}} = \frac{D}{fu \cdot CL_{int}} \rightarrow fb \uparrow \rightarrow AUC \uparrow \]