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

Name: ________________________  
SS#: _______________________

**PHA 5128**  
**First Exam**  
**Spring 2003**

Question

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

Total _____/100 pts
1. J.E., (m, 27y, 60 kg), is receiving 90 mg of tobramycin infused IV over 30 minute period q8h. His serum creatinine has increased from 1 mg/dL to 2 mg/dL over the past 24 hours. Since his renal function appears to be decreasing, three plasma samples were obtained to monitor serum tobramycin concentrations as follows: just before a dose; one hour after that same dose; and eight hours after that dose (two troughs and one peak level). The serum tobramycin concentrations at these times were 4 mg/L, 8 mg/L, and 4.5 mg/L, respectively. Calculate the volume of distribution, elimination rate constant, and clearance of tobramycin for J.E. Also, using the pharmacokinetic parameters calculated for J.E. above, develop a dosing regimen that will produce reasonable true peak (8 mg/L) and true trough (1 mg/L) concentration of tobramycin.

\[
k = \frac{\ln\left(\frac{8}{4.5}\right)}{7} = 0.0822 h^{-1}
\]
\[
C_{\text{max}} = \frac{8}{e^{-0.0822 \cdot 0.5}} = 8.34 \text{ mg/L}
\]
\[
t_{\frac{1}{2}} = \frac{0.693}{0.0822} = 8.43 h
\]
\[
V_d = \frac{90}{0.0822 \cdot 0.5} \cdot \frac{(1 - e^{-0.0822 \cdot 0.5})}{(8.34 - 4 \cdot e^{-0.0822 \cdot 0.5})} = 19.6 L
\]
\[
C l = k \cdot V_d = 0.0822 \cdot 19.6 = 1.61 \text{ L/h}
\]

True Peak = 8 mg/L
\[
\tau = \frac{1}{0.0822} \cdot 0.5 = 25.8 \rightarrow 24 h
\]
\[
D = 8 \cdot 0.0822 \cdot 19.6 \cdot 0.5 \cdot \frac{(1 - e^{-0.0822 \cdot 24})}{(1 - e^{-0.0822 \cdot 0.5})} = 138 mg \Rightarrow 140 mg \text{ q24h}
\]
2. V.S., (m, 45y, 80 kg) with a subtherapeutic theophylline (4 µg/mL) is admitted to the ICU. Based on average pharmacokinetics parameters (Vd = 0.5 L/kg, t_{1/2} = 8 h)), calculated an i.v. bolus loading dose and a maintenance dose (i.v. infusion) to increase the level to 15 µg/mL.

\[ V_d = 80 \times 0.5 = 40 \text{L} \]

\[ LD = (15 - 4) \times 40 = 440 \text{mg} \]

\[ CL = \frac{0.693}{8} \times 40 = 3.47 \text{L/h} \]

MD = 15 \times 3.47 = 52 \text{mg/h or 1248 mg/d}
3. Ceftriaxone has the following average pharmacokinetic parameters: CL 0.24 ml/min/kg, Vd 0.16 l/kg, fb 93%, Fren 49%. For a 70 kg, 50 yo male patient with a serum creatinine of 0.8 mg/dl, calculate the necessary intravenous daily dose to produce an average unbound serum concentration of 15 mg/l. How would you have to modify the dose, if the patient develops renal problems and his serum creatinine rises to 2.4 mg/dl?

$$CL = 0.24 \cdot 70 = 16.8 \text{ mL/min} = 1 \text{ L/h}$$
$$V_d = 0.16 \cdot 70 = 11.2 \text{ L}$$

$$CL_R = 0.49 \cdot 16.8 = 8.2 \text{ mL/min} = 0.49 \text{ L/h}$$

$$CL_{NR} = 0.51 \text{ L/h}$$

$$D = \frac{Cu \cdot CL \cdot \tau}{fu \cdot F} = \frac{15 \cdot 1.24}{0.07 \cdot 1} = 5.1 \text{ g}$$

new $$CL_R = 0.33 \cdot 0.49 = 0.16 \text{ L/h}$$

new CL = 0.51 + 0.16 = 0.67 L/h

new dose

$$D = \frac{15 \cdot 0.67 \cdot 24}{0.07 \cdot 1} = 3.4 \text{ g}$$
4. The hepatic clearance of a drug in a patient is reduced by 40% due to chronic viral hepatitis. The daily dose for the normal condition of this patient was 200mg. What should be the new daily dose of the drug in the patient? Assume that renal drug clearance ($fe = 0.6$) and plasma drug protein binding are not altered.

\[ RL = \text{residual liver function} = \frac{[Cl_h]_{\text{hepatitis}}}{[Cl_h]_{\text{normal}}} \]

\[ fe = \text{fraction of drug excreted uncharged} \]
\[ 1 - fe = \text{fraction of drug metabolized} \]
\[ [Cl_h]_{\text{hepatitis}} = RL \cdot [Cl_h]_{\text{normal}} \]

Substituting for $[Cl_h]_{\text{normal}}$ with $Cl_{\text{normal}}$ ($1 - fe$),
\[ [Cl_h]_{\text{hepatitis}} = RL \cdot Cl_{\text{normal}} (1 - fe) \]

Assuming no renal clearance deterioration due to hepatitis,

\[ Cl_{\text{hepatitis}} = [Cl_h]_{\text{hepatitis}} + [Cl_R]_{\text{normal}} = RL \cdot Cl_{\text{normal}} (1 - fe) + Cl_{\text{normal}} fe = Cl_{\text{normal}} [RL (1 - fe) + fe] \]

\[ \frac{\text{Dose}_{\text{hepatitis}}}{\text{Dose}_{\text{normal}}} = \frac{Cl_{\text{hepatitis}}}{Cl_{\text{normal}}} = RL(1 - fe) + fe \]

Substituting with $RL = 0.6$ and $fe = 0.6$:

\[ \frac{\text{Dose}_{\text{hepatitis}}}{\text{Dose}_{\text{normal}}} = \frac{Cl_{\text{hepatitis}}}{Cl_{\text{normal}}} = 0.6(1 - 0.6) + 0.6 = 0.84 \text{ (or 84%)} \]

\[ \text{Dose}_{\text{hepatitis}} = 168 \text{mg} \]
5. MW is a 65 year old male (75.3 kg, \( \text{CL}_{\text{Cr}} \) 26.7 mL/min) admitted to the Shands hospital with a probable urosepsis in need of parenteral tobramycin. A dose of 450 mg q36h is administered as a one-hour infusion (from 8-9am). Following the third dose of this regimen the tobramycin concentrations were determined as 19.8 µg/mL (11am) and 5.2 µg/mL (11pm).

a) What would be the expected trough concentration right before the next dose at 8 pm?

\[
k = \frac{\ln\left(\frac{19.8}{5.2}\right)}{12} = 0.111 \text{ h}^{-1}
\]

\[
C_{\text{min}} = 5.2 \cdot e^{-0.111 \cdot 21} = 0.51 \mu g / mL
\]
b) Based on the observations, make appropriate changes in this patient's dose regimen of tobramycin.

Measured levels are not on scale.

Calculate at 8 h:

\[ C = 19.8 \cdot e^{-0.1115} = 11.37 \mu g/mL \]

\[ \Rightarrow \text{increase dosing interval (\( \tau \)) to 48 h.} \]
\[ \Rightarrow 7\text{mg/kg q48h} \]
6. Monica (27 years old, 66 kg) was admitted to emergency room with severe acute asthma. She was given 300mg i.v. aminophylline (which is 85% theophylline) over 30 minutes followed by a maintenance infusion of i.v. aminophylline of 60mg/h. One half hour after the end of the loading dose a theophylline level of 12 µg/mL was monitored. Eight hours after the first serum level, a second level was 16 µg/mL. Make a recommendation.

Calculate volume of distribution:

\[ V_d = 0.5L / kg \cdot 66kg = 33L \]

Use Chiou equation to calculate clearance:

\[
CL = \frac{2 \cdot 60 \cdot 0.85}{12 + 16} + \frac{2 \cdot 33 \cdot (12 - 16)}{(12 + 16) \cdot (9 - 1)} = 3.643L/h + (-1.179L/h) = 2.464L/h
\]

Calculate average plasma concentration on that regimen:

\[ MD = Cp_{ss} \cdot CL \]

\[
Cp_{ss} = \frac{60 \cdot 0.85}{2.464} = 20.7mg/L \quad \Rightarrow \text{concentration is too high (range is 10-20 mg/L)}
\]

Calculate maintenance dose using an average concentration of 15mg/L:

\[ MD = \frac{15 \cdot 2.464}{0.85} = 43.48mg/h \]

\[ \Rightarrow \text{give 45mg/h} \]
7. RJ, a 65 year old male (70kg, CL=0.04L/kg/h, Vd=0.5L/kg), is seen in the emergency room with asthma that is unresponsive to epinephrine.

a) Estimate a loading dose of aminophylline that will produce a plasma theophylline concentration of 15 mg/L.

\[ Vd = 0.5 \text{L/kg} \cdot 70 \text{kg} = 35 \text{L} \]

\[ LD = \frac{15 \cdot 35}{0.85} = 617.6 \text{mg} \quad \Rightarrow \quad 600 \text{mg} \]

b) What would be the aminophylline infusion rate that will maintain an average steady-state level of 15 mg/L?

Calculate clearance:

\[ CL = 0.04 \cdot 70 = 2.8 \text{L/h} \]

\[ MD = \frac{15 \cdot 2.8 \cdot 1}{0.85} = 49.41 \text{mg} \quad \Rightarrow \quad 50 \text{mg/h aminophylline} \]

c) Estimate RJ’s theophylline half-life

\[ t_{1/2} = \frac{0.693 \cdot 35}{2.8} = 8.66 \text{h} \]
8. JW, a 55 year old female (55kg, SrCr=1.3mg/dL, CL=35mL/min), has been empirically started on 500mg of vancomycin every 8h for treatment of a hospital-acquired staphylococcal infection. What would be the expected steady-state peak and trough vancomycin concentrations for JW? Discuss the results.

\[ Vd = 0.7L / kg \cdot 55kg = 38.5L \]

\[ k_e = \frac{2.1}{38.5}0.055h^{-1} \quad \Rightarrow \quad t_{\frac{1}{2}} = \frac{0.693}{0.055} = 12.6h \]

\[ C_{\text{max}} = \frac{500}{38.5 \left(1 - e^{-0.055 \cdot 8}\right)} = \frac{12.99}{0.36} = 36.08mg / L \]

\[ C_{\text{min}} = 36.08 \cdot e^{-0.055 \cdot 8} = 23.2mg / L \]

The peak concentration is in the desired dose range of 25-40mg/L.
The trough concentration is well above the recommended plasma concentration range of 5-15mg/L. The suggestion would be to increase the dosing interval (q12h) and monitoring plasma concentrations of vancomycin.