1. Calculate the extraction ratio of phenylbutazone in an 80 kg patient, given the following information: liver blood flow is 1.5 L/min; $t_{1/2} = 50$ h; $V_d = 0.1$ L/kg; no non-hepatic elimination. (5 points)

For hepatic clearance,

$Cl_H = E_H \cdot Q_H$

Where $E_H$ is the extraction ratio and $Q_H$ is hepatic blood flow. In order to calculate $E_H$ using this expression, we must know $Cl_H$. Although $Cl_H$ is not given, enough information is provided to calculate it.

For a 70 kg patient,

$Vd = \frac{0.1L}{kg} \cdot 80kg = 8.0L$

The half-life may be used to find $k_e$.

$k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{50hr} = 0.014hr^{-1}$

Clearance may now be calculated:

$Cl = k_e \cdot Vd$

$= (0.014 \text{ hr}^{-1}) \cdot (8.0L)$

$= 0.112 \frac{L}{hr} \cdot \frac{1000ml}{L} \cdot \frac{1hr}{60\text{ min}} = 1.87 \text{ ml/min}$

Actually, total body clearance is calculated from this expression. Since the problem states "no non-hepatic elimination", we may assume $Cl_H = 1.87 \text{ ml/min}$. 
The extraction ratio is then

\[ E_\mu = \frac{C_\mu}{Q_\mu} \]

\[ = \frac{1.87 \text{ ml/min}}{1500 \text{ ml/min}} = 0.0012 \]

a) 0.074
b) 0.112
c) **0.0012**
d) 0.9988
e) 0.8
2. In most cases, aminoglycoside is given by \textit{i.v.} short term infusion. However, for a certain group of patients, a bolus dose model could be used satisfactorily for prediction of the aminoglycoside concentrations. These patients are:

(5 pts)

a. young adults  
b. children  
c. patients with decreased liver function  
d. men  
e. patients with decreased renal function
3. A patient was given 80 mg gentamicin over 30 minutes (i.v.) from 9:30 to 10:00 am. The following two serum levels were measured: 6.5 μg/ml at 10:30 am and 1.2 μg/ml at 5:00 pm. Calculate the peak concentration at 10:00 AM and the trough concentration at 5:30 PM. (5 points)

the elimination rate constant $k$

$$k = \frac{\ln 6.5}{6.5} = 0.26 h^{-1}$$

the peak concentration at 10:00 am

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

the trough concentration at 5:30 pm

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

a. $C_{\text{max}} = 7.9 \mu g/ml; C_{\text{min}} = 0.99 \mu g/ml$
b. $C_{\text{max}} = 8.43 \mu g/ml; C_{\text{min}} = 0.93 \mu g/ml$
c. $C_{\text{max}} = 7.4 \mu g/ml; C_{\text{min}} = 1.05 \mu g/ml$
d. $C_{\text{max}} = 91.1 \mu g/ml; C_{\text{min}} = 1.05 \mu g/ml$
e. $C_{\text{max}} = 5.5 \mu g/ml; C_{\text{min}} = 0.55 \mu g/ml$
4. M.P. is a 40 year old male, 65 kg, 5’10”, intermittent asthmatic who presents to the emergency room with severe dyspnea, coughing, and wheezing. He is treated there with aerosol albuterol, but only partially clears. He is then given 400 mg of IV aminophylline (S = 0.8) over 30 minutes. Thirty minutes after the loading dose was administered (60 minutes from time zero) the theophylline concentration was 15 µg/ml. He has normal liver, kidney, and cardiac function and is afebrile. He is not receiving any other drugs. After the loading dose, M.P. was started on an IV theophylline constant infusion of 55 mg/hr, Solu-Medrol IV and albuterol nebulization. Eight hours after the first serum level, a second level was 9 µg/ml.

Calculate M.P.’s total body clearance, a second IV loading dose to increase his level from 9 µg/ml to 15 µg/ml, and a IV aminophylline infusion rate to maintain the concentration at 15 µg/ml. (10 points)

\[ V_d = \frac{Dose \cdot F \cdot S}{C_p} = \frac{400 \cdot 1 \cdot 0.8}{15} = 21.3 \text{L} \]

\[ CL = \frac{2 \cdot R_0}{(C_1 + C_2)} + \frac{2 \cdot Vd \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)} = \frac{2 \cdot 55}{9 + 15} + \frac{2 \cdot 21.3 \cdot (15 - 9)}{(15 + 9) \cdot 8} = 4.58 + 1.33 = 5.9 \text{L/hr} \]

\[ LD = \frac{\Delta C_p \cdot Vd}{S \cdot F} = \frac{6 \cdot 21.3}{0.8} = 160 \text{mg} \]

\[ MD = \frac{Cp,ss \cdot CL \cdot 15}{S \cdot F} = \frac{15 \cdot 5.9}{0.8} = 110 \text{ mg/hr} \]

a.) CL = 5.9 L/hr; LD = 400 mg; MD = 110 mg/hr  
b.) CL = 3.67 L/hr; LD = 160 mg; MD = 94 mg/hr  
c.) CL = 1.33 L/hr; LD = 120 mg; MD = 90 mg/hr  
d.) CL = 5.9 L/hr; LD = 160 mg; MD = 110 mg/hr  
e.) CL = 10 L/hr; LD = 160 mg; MD = 94 mg/hr
5. N.R. is a 53 kg female patient (47 years old) on methotrexate therapy. Her serum creatinine is 1.6 mg/dL. She is treated with a loading dose (20 mg) followed by an infusion of 25 mg/h over 36 hours. She will then receive a 10 mg/m² dose of leucovorin q6h (four doses) followed by eight oral doses (q6h) of 20 mg.

Calculate the expected MTX steady-state concentration (in µM), and the predicted concentrations at 24, 48 and 60 hours after the start of the infusion. (10 points)

\[
\begin{align*}
CL_{cr} &= \frac{(140 - 47) \cdot 53}{85 \cdot 1.6} = 36.2 \text{mL/min} \approx 2.2L/h \\
CL_{MTX} &= CL_{cr} \cdot 1.6 = 2.2L/h \cdot 1.6 = 3.48L/h \\
C_{ss} &= \frac{R_0}{CL} \cdot \frac{25mg/h}{3.48L/h} = \frac{7.1mg/L}{L} \quad \Rightarrow \\
MTX / \mu M &= \frac{MTX/\text{mg/L}}{0.454} = \frac{7.2mg/L}{0.454} = 15.6 \mu M
\end{align*}
\]

24 h: \( 15.6 \mu M \)

48 h: \[ Cp = 15.6\mu M \cdot e^{-0.23112} = 1.0\mu M \]

\[
\ln\left(\frac{15.6}{0.5}\right) = 15h \quad \Rightarrow \quad 0.5\mu M \text{ at } 51 \text{ h}
\]

60 h: \[ Cp = 0.5\mu M \cdot e^{-0.069-9} = 0.27\mu M \]

a.) \( C_{ss} = 7.2 \mu M \); \( C_{24} = 15.6 \mu M \); \( C_{48} = 1.0 \mu M \); \( C_{60} = 0.27 \mu M \)
b.) \( C_{ss} = 7.2 \mu M \); \( C_{24} = 15.6 \mu M \); \( C_{48} = 10 \mu M \); \( C_{60} = 0.06 \mu M \)
c.) \( C_{ss} = 15.6 \mu M \); \( C_{24} = 15.6 \mu M \); \( C_{48} = 1.0 \mu M \); \( C_{60} = 0.001 \mu M \)
d.) \( C_{ss} = 7.2 \mu M \); \( C_{24} = 7.2 \mu M \); \( C_{48} = 0.45 \mu M \); \( C_{60} = 0.27 \mu M \)
e.) \( C_{ss} = 15.6 \mu M \); \( C_{24} = 15.6 \mu M \); \( C_{48} = 1.0 \mu M \); \( C_{60} = 0.27 \mu M \)
6. J.T., a 55 year-old, 70 kg, 5’9”, male, was admitted to the coronary care unit with a diagnosis of heart failure, probable myocardial infarction (MI), and premature ventricular contractions (PVCs). Calculate a bolus dose of lidocaine that should achieve a concentration of 3 mg/L. Calculate a maintenance infusion rate that will achieve a steady-state plasma lidocaine concentration of 2 mg/L for J.T. (5 points)

\[ LD = \frac{3 \cdot 0.3 \cdot 70}{0.87} = 72mg \approx 70 \text{ mg} \]

\[ MD = \frac{0.36 \cdot 70 \cdot 2}{60 \cdot 0.87} = 0.97mg / \text{min} \]

a.) LD = 189 mg; MD = 0.97 mg/min
b.) LD = 70 mg; MD = 0.97 mg/min
c.) LD = 70 mg; MD = 1.38 mg/min
d.) LD = 121 mg; MD = 1.61 mg/min
e.) LD = 314 mg; MD = 0.97 mg/min
7. A 23 year old female patient weighing 60 kg, has been taking uncoated (rapidly absorbed) theophylline tablets, 200 mg q 6 hr, with satisfactory response. Recently, steady-state theophylline plasma concentrations were determined to be 15 mg/L 1 hour after administration (peak) and 8.2 mg/L 6 hours after administration (trough). For this case, assume that F=1. (10 points)

Estimate the average steady-state theophylline concentration with this regimen.

\[
K = (\ln 8.2 - \ln15)/1-6 = 0.121 \text{ hr}^{-1}
\]

\[
C = \frac{D}{V} \left( \frac{1}{1 - e^{-0.121*6}} \right) * e^{-0.121*1}
\]

\[
15 = \frac{200}{V} \left( \frac{1}{1 - e^{-0.121*6}} \right) * e^{-0.121*1}
\]

\[
V = 22.8 \text{ L.}
\]

\[
Cl = k * V = 0.121 * 22.8 = 2.76 \text{ L/hr}
\]

\[
Css = \frac{D * F}{\tau * CL} = \frac{200 * 1}{6 * 2.76} = 12 \text{ mg/L}
\]

**a.** \(Css = 12 \text{ mg/L}\)

**b.** \(Css = 9.2 \text{ mg/L}\)

**c.** \(Css = 5.8 \text{ mg/L}\)

**d.** \(Css = 20 \text{ mg/L}\)

**e.** \(Css = 0.55 \text{ mg/L}\)
8. A.H. (55 years old, 58 kg, SrCr = 2.5 mg/dL, female) was admitted to the hospital and was diagnosed with congestive heart failure. She had been taking 0.25 mg digoxin qd for 3 months. The digoxin plasma concentration was determined to be 5 μg/L. How long will it take for the concentration to fall back to 1 μg/L? (10 points)

\[
C_l_{C_r\text{ (female)}} = (0.85)\frac{(140 - 55)(58)}{(72 * 2.5)} = 23.3 ml / min
\]

\[
C_l(CHF\text{ patients}) = (0.33 * 58) + (0.9 * 23.3) = 40.11 ml / min = 57.8 L / day
\]

\[
V = (3.8 * 58) + (3.1 * 23.3) = 293 L
\]

\[
k = \frac{C_l}{V} = \frac{57.8}{293} = 0.197\text{ day}^{-1}
\]

\[
\ln\left(\frac{C_1}{C_2}\right) = \ln\left(\frac{5}{1}\right)
\]

\[
t = \frac{\ln\left(\frac{C_1}{C_2}\right)}{k} = \frac{\ln\left(\frac{5}{1}\right)}{0.197} = 8.15 \text{ days}
\]

a.) 11.22 days
b.) 7.66 days
c.) 6.71 days
d.) **8.15 days**
e.) 11.75 days
9. Calculate the sodium phenytoin loading dose required to achieve a plasma concentration 15 mg/L in a 75 kg male. (5 pts)

\[
\text{Loading dose} = \frac{V_d \cdot C}{S \cdot F}
\]

\[V_d = 0.65 \text{ L/kg} \times 75 \text{ kg} = 48.75 \text{ L}\]

\[S = 0.92 \quad F = 1\]

\[\text{Loading dose} = \frac{48.75 \times 15}{0.92} = 795 \text{ mg} \sim 800 \text{ mg}\]

a. 600 mg  
b. 400 mg  
c. 1000 mg  
\textbf{d. 800 mg}  
e. 850 mg
10. For the above mentioned patient (question 9), 300mg/day phenytoin was given as maintenance dose, the steady state concentration was found to be 9 mg/L. Then the maintenance dose was increased to 350 mg/day, the steady state concentration was later found to be 22 mg/L. This level was decided to be too high for this patient, so the maintenance dose was discontinued. How long would it take for the concentration to drop to 15 mg/L after discontinuation of dose? (10 pts)

\[ t = \frac{K_m \cdot \ln \left( \frac{C_1}{C_2} \right) + C_1 - C_2}{V_{\text{max}}} \cdot V_d \]

\[ V_{\text{max}} = D_1 \cdot D_2 \cdot (C_2 - C_1) / (C_2 \cdot D_1 - C_1 \cdot D_2) = 300 \cdot 350 \cdot (22 - 9) / (22 \cdot 300 - 9 \cdot 350) = 1365000 / (6600 - 3150) = 395.65 \text{ mg} \]

\[ K_m = C \cdot (V_{\text{max}} - \text{Dose}) / \text{Dose} = 22 \cdot (395.65 - 350) / 350 = 2.87 \text{ mg/L} \]

\[ T = (K_m \cdot \ln(C_0/C_1) + (C_0 - C_1)) \cdot V_d / V_{\text{max}} = (2.87 \cdot \ln(22/15) + 22 - 15) \cdot 48.75 / 395.65 = 0.998 \text{ day} = 24 \text{ hr} \]

a. 0.998 hr
b. 48 hr
c. **24 hr**
d. 4 hr
e. 12 hr
11. A 35 years old, 58 kg female is to be given carbamazepine as an anticonvulsant agent. Calculate a daily dose to achieve average steady state plasma concentration of 5 mg/L.

\[ Dose = \frac{Cl \times Cpss \times \tau}{(S \times F)} \]

\[ F=0.8 \quad S=1.0 \quad Cl=0.064 \text{ L/kg} \]  

\[ Dose = \frac{0.064 \text{ L/kg} \times 58 \text{ kg} \times 5 \text{ mg/L} \times 24 \text{ hr/day}}{1 \times 0.8} = 556.8 \text{ mg/day} \]

a. 400 mg/day  
b. 200 mg/day  
c. 700 mg/day  
**d. 550 mg/day**  
e. 800 mg/day
12. A 40 year old, 75 kg male has been receiving 200mg/day (100 mg BID) of phenobarbital (S=1) for the past 25 days. The phenobarbital plasma concentration just before the morning dose on Day 26 was reported to be 28 mg/L. What would be the predicted concentration at that time if assuming average pharmacokinetic parameters for V_d and Cl of this patient. (10 pts)

\[ Cl = 0.004 \text{L/kg/hr} \times 24 \times 75 = 7.2 \text{ L/day} \]
\[ V_d = 0.7 \times 75 = 52.5 \text{ L} \]
\[ Ke = \frac{Cl}{V_d} = \frac{7.2}{52.5} = 0.137/\text{day} \]
\[ t_{1/2} = \frac{0.693}{0.137} = 5.058 \text{ day} \]
so after 25 (about 5 half-life) days, the steady state should be achieved.
\[ C_{pss \ min} = S \times F \times \text{Dose} \times \exp(-Ke \times t) / [V_d \times (1-\exp(-Ke \times \tau))] \]
\[ = 100 \times \exp(-0.137 \times 0.5) / [52.5 \times (1-\exp(-0.137 \times 0.5))] \]
\[ = 100 \times 0.934 / (52.5 \times 0.066) \]
\[ = 26.95 \text{mg/L} \]

a. 17 mg/L
b. 21 mg/L
c. 27 mg/L
d. 37 mg/L
e. 11 mg/L
13. M.A., a 78 kg liver transplant patient, is receiving 400 mg of cyclosporine QD as an IV infusion. Currently, his hepatic function tests appear to be stable, and for the past three days he has been improving clinically with steady-state trough cyclosporine concentrations of approximately 220 µg/L. What would be an appropriate oral cyclosporine dose for M.A.? (5 pts)

\[
Dose_{\text{new}} = \frac{cp_{\text{desired}}}{cp_{\text{ss\ current}}} \cdot \frac{F_{\text{current}}}{F_{\text{new}}}
\]

\[
Dose_{\text{current}} = \frac{220 \mu g \ / \ L}{220 \mu g \ / \ L} \cdot \frac{1.0}{0.3} \cdot 400 \text{mg} = 1333 \text{mg} \approx 1300 \text{mg / day}
\]

a. 1300 mg/day
b. 1500 mg/day
c. 900 mg/day
d. 500 mg/day
e. 300 mg/day