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

_______________________________
Name

Total points for exam **100pts (13 questions)**
Question #1: (5 points)

Vancomycin concentration-time profile can be described via a three compartment model. Which profile will represent a 1-hr infusion of vancomycin in the following graph?

A)  
B)  
C)  
D)  
E)
Question #2: (5 points)

Which of the following statements about body weight in pharmacokinetics are correct?

1) We can roughly assume liver and kidney function are proportional to body weight.

2) Effects of obesity on volume of distribution depend on the lipophilicity of the drug.

3) Physical and chemical properties of drugs determine the impact of body weight on pharmacokinetics.

4) In general, we should always use IBW for drug recommendations.

5) Weakly or moderately lipophilic drugs are poorly distributed in obese patients.

A) 1, 2, 3, 4 & 5
B) 1, 2 & 4
C) 1, 2, 3, & 5
D) 1, 3, 4 & 5
E) 2, 3, 4 & 5
high extraction drug $\Rightarrow CL = Q_H \leftrightarrow$

$V_d = V_p + V_T \cdot \frac{f_u}{f_{u,T}}$ & $f_{u,T} \downarrow \Rightarrow V_d \uparrow$

$AUC_{0-\infty} = \frac{D}{CL} \Rightarrow AUC_{0-\infty} \leftrightarrow$

$C_{\text{max}} = C_0 = \frac{D}{V_d} \Rightarrow C_{\text{max}} \downarrow$

$T_{1/2} = \frac{\ln 2}{ke} = \frac{\ln 2}{CL/Vd} = \frac{\ln 2 \cdot V_d}{CL} \Rightarrow T_{1/2} \uparrow$
**Question #3:** (5 points)

T.S. is a 67 kg 65 year old male receiving 1.5 mg/kg Phenobarbital every 12 hours for the past 2 months. However this patient’s seizures are not controlled and it was decided to start this patient on a concomitant therapy of carbamazepine. Calculate the daily maintenance dose to produce a target steady state concentration of 6 mg/L using the immediate release formulation. Later the results come back from the lab and the level of carbamazepine was 4mg/L. What dose should be given to get the desired serum concentration?

A) 1200mg/day, 1800mg/day  
B) 400mg BID, 1800mg/day  
C) 1200mg/day, 2400mg/day  
D) 600mg/day, 2400mg/day  
E) 1200mg/day, 500 BID

\[ MD = \frac{C_{\text{pss}} \times \text{Cl} \times \tau \times (S \times F)}{(S \times F) = 6 \text{mg/L} \times 0.1 \text{L/hr/kg} \times 67 \text{kg} \times 24 \text{hr}/(0.8 \times 1) = 1206 \text{mg} - 1200 \text{mg} \]  
4mg/L/6mg/L=1200mg/Xmg X=1800mg
Question #4 (5 points)

Make a dosing recommendation for chronic use of a drug with a total body clearance of 25mL/min and a volume of distribution of 100L. The drug is completely and rapidly absorbed. The therapeutic range is 20-30μg/mL. You have 500mg tablets available to dispense.

A) 2 tablets q 12 hours  
B) 1 tablet q 24 hours  
C) 3 tablets q 8 hours  
D) 2 tablets q 24 hours  
E) 1 tablet q 12 hours

1) Since the question states that the drug is completely absorbed, we will assume an oral dosing regimen.
2) Since the drug is absorbed fast, the i.v. bolus equation is sufficient to determine dose and dosing interval.
3) Determine elimination rate constant:

\[ k_e = \frac{CL}{V_d} = \frac{25\text{mL/min} \cdot 60\text{min}}{100L \cdot 1000mL/1L} = 0.015h^{-1} \]

4) Determine the dosing interval:

\[ \tau = \frac{\ln\left(\frac{C_{pss}(\text{max})}{C_{pss}(\text{min})}\right)}{k_e} = \frac{\ln\left(\frac{30μg/mL}{20μg/mL}\right)}{0.015h^{-1}} = 27.03h \sim 24h \]

For multiple i.v. administration, \(C_{\text{max,ss}}\) can be calculated by:
\[ C_{\text{max,ss}} = \frac{D}{V_{d}} \cdot \frac{1}{(1 - e^{-\frac{k_{\text{elu}}}{V_{d}}})} \]

By rearranging the equation the dose can be calculated.

\[ D = C_{p_{\text{ss,max}}} \cdot V_{d} \cdot \left(1 - e^{-\frac{k_{\text{elu}}}{V_{d}}}\right) = \]
\[ = 30 \text{mg} / \text{L} \cdot 100 \text{L} \cdot \left(1 - e^{-\frac{0.015h^{-1}}{24h}}\right) = 907 \text{mg} \]
Question #5: (5 points)

J.D., a 45 year-old, 87 kg male, with CHF, was admitted to the hospital for his arrhythmia. A bolus dose of lidocaine was given to achieve an immediate response ($C_0 = 3\text{mg/L}$). After the bolus, a followed 250 mg short-term infusion will start for 15 minutes. One hour after the bolus, a maintenance infusion will start. What might be the potential purpose to give the short-term infusion immediately?

A) Lidocaine has very short terminal half life, so we need to keep infusing the drug to maintain the same drug effect

B) Lidocaine can cause pharmacodynamic tolerance, so we need to keep increasing the drug concentration to maintain the same drug effect

C) Lidocaine can cause seizures if the initial concentration is above 3 mg/L, so we need to increase the drug concentration slowly to achieve a higher therapeutic concentration

D) *Lidocaine has very rapid initial distribution, so we need to complement the drug losing from the central compartment to maintain the drug effect*

E) All of above
Question #6: (5 points)

A study was conducted to assess the effect of thyroid diseases on Digoxin pharmacokinetics. Three groups of subjects received the same amount of Digoxin via intravenous administration. Group I: (Subjects with Myxedema); Group II: (Subjects with Euthyroid state); Group III: (Subjects with Hyperthyroidism) Serum Digoxin concentrations were measured, and concentration-time profiles were assessed. Which of the following statement is FALSE?

A) Subjects with hyperthyroidism have the highest apparent volume of distribution.

B) If multiple doses are applied to the subjects, the time required to reach steady state will be the same for all three groups.

C) Both clearance and volume of distribution are affected by thyroid disease.

D) If subjects with hyperthyroidism have an increased glomerular filtration rate, and renal function is the major factor associated with digoxin clearance, patients with intrinsic renal failure will have a decreased digoxin clearance.

E) When multiple doses are required, hyperthyroid patients will take smaller loading doses in order to achieve the same steady state concentrations as those in euthyroid state.
**Question #7: (10 points)**

L.J., a 30 year old male, ($C_{p\text{Creat}} = 1.4 \text{mg/dL}$), was diagnosed congestive heart failure (CHF). He is 5'9" tall and weights 80 kg. At 9:30AM on the day of admission (day 1), L.J. was given an intravenous 0.75-mg of digoxin for his CHF. From day 2, He was continued on his outpatient maintenance doses orally (Formulation: tablets) (0.5 mg per day at 9:30 AM). On the fourth day, at 9:30 PM, 12 hour after his morning dose, a second digoxin sample was obtained, and what will be the predicted concentration for the second sample? How many oral doses did L.J. take already? (Assuming Digoxin is rapidly absorbed.)

**A)** $1.87 \text{ ng/mL}$ 3 doses

**B)** $1.48 \text{ ng/mL}$ 2 doses

**C)** $2.50 \text{ ng/mL}$ 3 doses

**D)** $1.77 \text{ ng/mL}$ 2 doses

**E)** $1.48 \text{ ng/mL}$ 3 doses

Given information:
Male with CHF, 30 yrs, 5'9", 80 kg, $C_{p\text{Creat}} = 1.4 \text{mg/dL}$
Bioavailability for Digoxin Tablets: 0.7
Clearance-factor: 0.75 from verapamil’s effect

$\text{IBW} = 50 \text{kg} + 2.3 \text{kg} \cdot (\text{Height} - 5')$
$\text{IBW} = 50 \text{kg} + 2.3 \cdot (9) = 70.7 \text{ kg} \rightarrow \text{TBW} < 1.2 \text{ IBW}$

$\text{Cl}_{\text{creat}} (\text{male}) = \frac{(140 - \text{age}) \cdot \text{weight}}{(72) \cdot C_{p\text{Creat}}}$

$\text{Cl}_{\text{creat}} (\text{male}) = \frac{(140 - 30) \cdot 80}{(72) \cdot 1.4} = 87.3 \text{ (mL/min)}$ (Use TBW for ClCreat)

$\text{Cl}_{\text{Digoxin}} = 0.33 \text{mL/kg/min} \cdot \text{IBW} + 0.9 \cdot \text{Cl}_{\text{creat}} (\text{with} - \text{CHF})$
\[ CL = 0.33 \cdot 70.7 + 0.9 \cdot 87.3 = 101.9 \text{ (mL/min)} = 101.9 \text{ mL/min} \cdot 1440 \text{ min/day} \cdot \frac{1 \text{ L}}{1000 \text{ ml}} = 146.74 \text{ L/day} \]

\[ V_{\text{Digitoxin}} = 3.8 L / kg \cdot IBW + 3.1 \cdot Cl_{\text{Creat}} \]

\[ V_d = 3.8 \cdot 70.7 + 3.1 \cdot 87.3 = 539.3 \text{ (L)} \]

\[ k_e = \frac{CL}{V_d} = \frac{146.74}{539.3} = 0.27 \text{ days}^{-1} \]

\[ C = \frac{F \cdot D_1}{V_d} \cdot e^{-k_e \cdot t_1} + \frac{F \cdot D_2}{V_d} \cdot e^{-k_e \cdot t_2} + \frac{F \cdot D_3}{V_d} \cdot e^{-k_e \cdot t_3} + \frac{F \cdot D_4}{V_d} \cdot e^{-k_e \cdot t_4} \]

\[ = \frac{1.750 \mu g}{539.3 L} \cdot e^{-0.27 \cdot 3.5} + \frac{0.7 \cdot 500 \mu g}{539.3 L} \cdot e^{-0.27 \cdot 2.5} + \frac{0.7 \cdot 500 \mu g}{539.3 L} \cdot e^{-0.27 \cdot 1.5} + \frac{0.7 \cdot 500 \mu g}{539.3 L} \cdot e^{-0.27 \cdot 0.5} \]

\[ = 1.39(\mu g / L) \cdot 0.39 + 0.65(\mu g / L) \cdot [0.51 + 0.67 + 0.87] \]

\[ = 1.87(\mu g / L) \]
C.B. is a 10 year old 35kg male patient given valporic acid spinkles 250mg TID for his seizures. Calculate the fluctuation for this patient at steady state. Assume rapid absorption. Then calculate a new dosing regimen if the trough level came back from the lab and was 38.0 mg/L using the population targets.

A) \(F=3, \text{ Dose 230 mg every 12 hours}\)

B) \(F=2.1, \text{ Dose 300 mg every 6 hours}\)

C) \(F=1.5, \text{ Dose 150 mg every 6 hours}\)

D) \(F=2.1, \text{ Dose 230 mg every 6 hours}\)

E) \(F=2.1, \text{ Dose 150 mg every 12 hours}\)

\[
\begin{align*}
\text{Ke}=\text{Cl}/\text{Vd}=0.013/0.14=0.0929\text{hr}^{-1} \\
\text{Cmax} = \frac{D}{(Vd*(1-e^{-k_e*\tau}))} = 250\text{mg}/(0.14\text{L/kg}*35\text{kg}*(1-e^{-0.0929\text{hr}^{-1}*8\text{hr}})) = 97.3\text{mg/L} \\
\text{Cmin} = 97.3\text{mg/L}e^{-0.0929}\text{hr}^{-1}*8\text{hr} = 46.3\text{mg/L} \\
F = \frac{97.3\text{mg/L}}{46.3\text{mg/L}} = 2.1 \\
\text{Cmax} = \frac{D}{Vd} + \text{Cmin} = 250\text{mg}/(0.14\text{L/kg}*35\text{kg}) = 89.02\text{L/kg} \\
\text{Ke} = \ln(89.02/38.00)/8\text{hr} = 0.106\text{hr}^{-1} \\
\text{Tau} = \ln(100/50)/0.106\text{hr}^{-1} = 6.5\sim6\text{hr} \\
\text{Cmax} = \frac{D}{Vd*(1-e^{-k_e*\tau})} = 100\text{mg/L}*(0.14*35)*(1-e^{-0.106\text{hr}^{-1}*6}) = 230\text{mg} \\
\text{Dose 230mg every 6 hours}
\end{align*}
\]
R. S. is a 53 kg female patient (47 years) to receive 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/m\(^2\) dose of leucovorin q6h (four doses) followed by eight oral doses (q6h) of 20 mg. Predict when the methotrexate level will fall below 0.1 μM by using the typical half-life parameters? After the drug sampling report (14 μM (24h), 1.2 μM (48h) and 0.35 μM (60 h)), adjust your prediction according to data. (You can assume the plasma concentration already reached steady state after 24 hrs infusion.).

A) Expected 75 hr after the infusion start; adjusted 101 hr after the infusion start
B) Expected 60 hr after the infusion start; adjusted 88 hr after the infusion start
C) Expected 75 hr after the infusion start; adjusted 70 hr after the infusion start
D) **Expected 75 hr after the infusion start; adjusted 88 hr after the infusion start**
E) Expected 60 hr after the infusion start; adjusted 70 hr after the infusion start

Calculate the expected MTX steady-state concentration (in μM).

\[
CL_{Cr} = \frac{(140 - 47) \cdot 53}{85 \cdot 1.6} = 36.2 \text{mL/min} \approx 2.2 L/h
\]
\[
CL_{MTX} = CL_{Cr} \cdot 1.6 = 2.2 L/h \cdot 1.6 = 3.48 L/h
\]
\[
C_{ss} = C_{36h} = \frac{R_o}{CL} = \frac{25 \text{mg/h}}{3.48 L/h} = 7.2 \text{mg/L} = \frac{7.2 \text{mg/L}}{0.454} = 15.9 \text{μM}
\]

Time to 0.5 μM:

\[
t = 36 + \frac{\ln \left(\frac{15.9}{0.5}\right)}{0.231} = 36 + 15 = 51 \text{h}
\]
The reported levels were 14 µM (24h), 1.2 µM (48h) and 0.35 µM (60 h). What recommendation would you make (show calculations)?

\[
C_{36} \approx C_{24} \approx C_{ss} \Rightarrow k_\alpha = \frac{\ln \left( \frac{C_{36}}{C_{48}} \right)}{48 - 36} = \frac{\ln \left( \frac{14}{1.2} \right)}{12} = 0.205 h^{-1}
\]

Time to 0.5 µM: \[
t = 36 + \frac{\ln \left( \frac{0.5}{0.205} \right)}{0.205} = 36 + 16 = 52 h
\]

\[
k_\beta = \frac{\ln \left( \frac{C_{52}}{C_{60}} \right)}{60 - 52} = \frac{\ln \left( \frac{0.5}{0.35} \right)}{8} = 0.045 h^{-1}
\]

Time to 0.1 µM: \[
t = 51 + \frac{\ln \left( \frac{0.5}{0.045} \right)}{0.045} = 52 + 36 = 88 h
\]
Question #10: (10 points)

J.D., a 45 year-old, 87 kg male, with CHF, was admitted to the hospital for his arrhythmia. Calculate a bolus dose of lidocaine that should achieve an immediate response ($C_0 = 3\text{mg/L}$). After the bolus, a followed 250 mg short-term infusion will start for 15 minutes. What is the plasma concentration 1 hour after the bolus? One hour after the bolus, a maintenance infusion will start. What is the maintenance infusion rate that will achieve the steady-state plasma lidocaine concentration of 3 mg/L for J.D?

A) Loading Dose = 90 mg, $C_{1h} = 2.63 \text{mg/L}$; Maintenance Dose = 108 mg/hr

B) Loading Dose = 150 mg, $C_{1h} = 3.85 \text{mg/L}$; Maintenance Dose = 108 mg/hr

C) Loading Dose = 150 mg, $C_{1h} = 2.63 \text{mg/L}$; Maintenance Dose = 67 mg/hr

D) Loading Dose = 90 mg, $C_{1h} = 3.85 \text{mg/L}$; Maintenance Dose = 108 mg/hr

E) Loading Dose = 90 mg, $C_{1h} = 2.63 \text{mg/L}$; Maintenance Dose = 67 mg/hr

For CHF: $Vc=0.3 \text{ L/kg}$ $Vd=0.9 \text{ L/kg TBW}$; $CL=0.36 \text{ L/h/kg IBW}$ (since no height information, we will use TBW)

\[
S = .87 \\
LD = \frac{S \cdot 0.3 \cdot 87}{0.87} = 90\text{mg} \\
C = \frac{S \cdot LD}{Vd} e^{-kt} + \frac{S \cdot R_d}{CL} (1 \cdot e^{-kt}) e^{-kt} \\
k = \frac{CL}{Vd} = \frac{.36}{.9} = .4\text{h}^{-1} \\
C_{1h} = \frac{.87 \cdot 90}{0.9 \cdot 87} e^{-.4 \cdot 1} + \frac{.87 \cdot 250}{.36 \cdot 87} (1 - e^{-.4 \cdot .25}) e^{-.4 \cdot .75} = .67 + 2.64 \cdot .74 = 2.63 \text{mg/L} \\
MD = \frac{0.36 \cdot 87 \cdot 3}{0.87} = 108 \text{mg/hr}
Question #11: (10 points)

M.D, an 82 kg male, became nauseated after receiving i.v. aminophylline 90mg/h for several days. A plasma sample for theophylline was obtained and the infusion was discontinued. Ten hours later a second plasma sample was obtained. The reported plasma theophylline concentrations were 36μg/mL and 18μg/mL, respectively. Estimate the hourly dose of aminophylline required to maintain the plasma theophylline concentration at 15mg/L. (Use aminophylline S = 0.85, V_d = 0.5L/kg)

A) 40mg/h
B) 60mg/h
C) 58mg/h
D) 50mg/h
E) 70mg/h

\[
\begin{align*}
\ln \frac{C_1}{C_2} &= \frac{\ln 36}{\ln 18} \\
&= 0.693 \\
&= 0.0693h^{-1}
\end{align*}
\]

\[
V_d = 0.5L/kg \times 82kg = 41L
\]

CL = K_e * V_d = 0.0693h^{-1} * 41L = 2.84L/h

\[
MD = \frac{CL \cdot C^{\infty}}{F \cdot S} = \frac{2.84L/h \cdot 15mg/L}{1 \cdot 0.85} = 50.11mg/h \approx 50mg/h
\]
**Question #12:** (10 points)

O.S., a 50-year-old, 60 kg male patient, received a liver transplantation a year ago. Currently, he is taking cyclosporine 200 mg orally as the solution BID. His steady-state cyclosporine trough concentration is 400 ng/mL. In order to achieve a new steady-state cyclosporine trough concentration of 200 ng/mL, what will be the modified dose regimen if the same cyclosporine formulation is applied? If cyclosporine is given to O.S. intravenously every day, what will be the dose regimen? (Assuming bioavailability of cyclosporine is 0.3)

\[ Dose_{\text{new, oral}} = \frac{200 \text{ng/mL}}{400 \text{ng/mL}} \cdot 200 \text{mg} = 100 \text{mg} \quad (100 \text{mg BID}) \]

\[ Dose_{\text{new, IV}} = \frac{200 \text{ng/mL}}{400 \text{ng/mL}} \cdot 200 \text{mg} \cdot \frac{0.3}{1} = 30 \text{mg} \quad (30 \text{ mg BID}) \]

**A)**  Oral → 100 mg BID; I.V. → 30 mg BID

**B)**  Oral → 100 mg QD; I.V. → 30 mg QD

**C)**  Oral → 100 mg BID; I.V. → 300 mg BID

**D)**  Oral → 100 mg QD; I.V. → 300 mg BID

**E)**  Oral → 100 mg BID; I.V. → 30 mg QD
Question #13: (10 points)

A.S., a 59-year-old, 67 kg female, was admitted to the ER with a diagnosis of tachyarrhythmia. A.S. has a history of mild chronic renal failure, a serum creatinine of 1.7mg/dL. A.S. developed premature ventricular contractions (PVCs) which were unresponsive to lidocaine. Calculate a parenteral loading dose of procainamide designed to achieve a plasma concentration of around 7mg/L and an i.v. maintenance infusion rate that will maintain an average plasma concentration of 6mg/L.

A) Loading Dose = 1200 mg; Maintenance infusion rate = 184 mg/min
B) Loading Dose = 1100 mg; Maintenance infusion rate = 150 mg/min
C) Loading Dose = 1200 mg; Maintenance infusion rate = 3.1 mg/min
D) Loading Dose = 1100 mg; Maintenance infusion rate = 2.5 mg/min
E) Loading Dose = 1200 mg; Maintenance infusion rate = 150 mg/min

\[
V_d = 2 \cdot 67 = 134L \\
LD = \frac{C_p \cdot V_d}{F \cdot S} = \frac{7 \cdot 134}{1 \cdot 0.87} = 1078.2mg \approx 1100mg \\
CL_{Cr} = \frac{(140 - 59) \cdot 67}{85 \cdot 1.7} = 37.56mL/min \approx 2.25L/h \\
CL_{renal} = 3 \cdot 2.25 = 6.75L/h \\
CL_{acet} = 0.13 \cdot 67 = 8.71L/h \\
CL_{other} = 0.1 \cdot 67 = 6.7L/h \\
CL_{total} = 6.75 + 8.71 + 6.7 = 22.16L/h \\
MD = \frac{C_{ss,ave} \cdot CL}{S} = \frac{6 \cdot 22.16}{0.87} = 152.83mg/h \approx 150mg/h = 2.5mg/min
\]