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

Print: ____________________________ Sign: ____________________________

Name: ____________________________

UFID: ____________________________

PHA 5128
Spring 2008
First Exam (Version A) - answers

Total points for exam 100 points (15 questions)
**Question #1:** (5 points)

Drug X is given as a 200 mg dose TID given i.v. bolus. The concentration-time profile for the first three doses is shown. This patient has a clearance of 24L/hr. Another patient came in and was starting on the same dosing regimen. However, this patient had a clearance 6 L/hr. What would his concentration-time profile look like for this patient?

(Vd=18L for both patients)

A) [Concentration vs Time graph]

B) [Concentration vs Time graph]

C) [Concentration vs Time graph]

D) [Concentration vs Time graph]
**Question #2:** (5 points)

Propranolol is a high-extraction drug and only undergoes liver metabolism. It is combined with phenobarbital. Phenobarbital is a known enzyme inducer. How would you change the dose of propranolol to account for this. Choose the best choice.

A) Increase the dose because the clearance is decreased.

**B) Leave the dose the same because clearance does not significantly change.**

C) Decrease the dose because clearance is increased.

D) Increase the dose because clearance is significantly increased.
An 80 kg patient receives 500 mg theophylline i.v. by bolus injection every 8 hr. Assume that Vd = 0.5 L/kg and \( t_{1/2} = 6.4 \) hr. Predict steady state peak and trough concentration.

A) \( \text{Cmax}=16.52 \text{mg/L}, \text{Cmin}=5.89 \text{mg/L} \)
B) \( \text{Cmax}=21.61 \text{mg/L}, \text{Cmin}=5.89 \text{mg/L} \)

C) **Cmax=21.61mg/L, Cmin=9.11mg/L**

D) \( \text{Cmax}=26.22 \text{mg/L}, \text{Cmin}=9.11 \text{mg/L} \)

\( K_e = \frac{0.693}{6.4 \text{hr}} = 0.108 \text{hr}^{-1} \)

\[
\text{Cmax} = \frac{D}{V_d(1-e^{-k_e \tau})} = 500 \text{ mg/((0.5L/kg*80kg)*(1-e^{-0.108hr^{-1}*8hr}))}=21.61 \text{mg/L}
\]

\[
\text{Cmin} = \text{Cmax} e^{-k_e \tau} = 21.6 \text{mg/L} * e^{-0.108hr^{-1}*8hr}=9.11 \text{mg/L}
\]
Question #4: (5 points)

What is the minimum extraction ratio for renal filtration if neither active reabsorption nor active secretion takes place? Assume renal blood flow 1200 ml/min, glomerular filtration rate (GFR) 120 ml/min, the urine flow rate 1.2 ml/min.

A) \( E_{\text{Ren}} = 1 \)

B) \( E_{\text{Ren}} = \frac{\text{GFR}}{\text{renal blood flow}} \)

C) \( E_{\text{Ren}} = \frac{\text{urine flow}}{\text{renal blood flow}} \)

D) \( E_{\text{Ren}} = \frac{\text{urine flow}}{\text{GFR}} \)

E) Not enough information to determine.
**Question #5:** (10 points)

Mike, a 25 years old male patient (5’1”, 80kg, \(C_{\text{creat}}=1.2\text{mg/dl}\)), needs to be treated with gentamicin. Assuming linear pharmacokinetics (\(V_d=0.25\text{L/kg}\), \(\text{Cl}=C_{\text{creat}}\)) and an infusion time of 30 minutes. Calculate the daily dose and dose interval that will produce a steady state peak concentration of 10 mg/L and trough concentration of 1 mg/L.

(Use \(k_e = \text{Cl}/V_d\))

![](https://latex.codecogs.com/png.latex?%5Cbegin%7Balign%7D%5Ctext{A)}%20160\text{mg},%206\text{hr} \\
\text{B)}%20360\text{mg},%206\text{hr} \\
\text{C)}%20520\text{mg},%2012\text{hr} \\
\text{D)}%20480\text{mg},%208\text{hr} \\
\text{E)}%20160\text{mg},%208\text{hr}%5Cend%7Balign%7D)

IBW = 50 + (2.3)*(Height in inches > 60) = 50 + 2.3 = 52.3 kg

Clinically obese: if TBW > 120%IBW

80 kg > 1.2*52.3 = 62.76 kg \(\Rightarrow\) clinically obese \(\Rightarrow\) use ABW

\[
\text{ABW} = \text{IBW} + 0.4(\text{TBW-IBW}) = 52.3 + 0.4(80-52.3) = 63.38 \text{ kg}
\]

\[
\text{Cl}_{\text{Cr}} = \frac{[(140-\text{age})*\text{(weight)}]}{72*\text{SCr}} = \frac{[(140-25)*63.4]}{72*1.2} = 84.4 \text{ ml/min} = 5.06 \text{ L/h (use ABW)}
\]

\[
V_d = 0.25*63.4 = 15.9 \text{ L (use ABW)}
\]

\[
k_e = \frac{\text{Cl}}{V_d} = \frac{5.06}{15.9} = 0.318 \text{ h}^{-1} \\
\tau = \frac{\ln \left( \frac{C_{\text{max}}}{C_{\text{min}}} \right)}{k_e} + T = \frac{\ln \left( \frac{10}{1} \right)}{0.318} + 0.5 = 7.7 \text{ hr} \approx 8 \text{ hr}
\]

\[
D_{\text{daily}} = 3 \cdot C_{\text{max}} \cdot \text{Cl} \cdot T \cdot \frac{\left(1-e^{-k_e \cdot \tau} \right)}{\left(1-e^{-k_e \cdot T} \right)} = 3 \cdot 10 \cdot 5.06 \cdot 0.5 \cdot \frac{\left(1-e^{-0.318 \cdot 1.8} \right)}{\left(1-e^{-0.318} \right)} \approx 480\text{mg}
\]
**Question #6:** (5 points)

A longer half-life of a drug will cause

A) a larger total body clearance.

B) more fluctuation can be expected at steady state.

C) a shorter dosing interval to maintain a certain fluctuation.

**D) a longer time to reach steady state.**

E) a larger volume of distribution.
Question #7: (10 points)

J.D. is a 25 years old male. He is currently taking 200 mg/day of a drug X that is 50% excreted into the urine. How would you modify the dose, if the patient develops renal problems and his serum creatinine rises from 1 to 2.5 mg/dl?

A) 40mg/day
B) 80mg/day
C) 140mg/day
D) 180mg/day
E) 240mg/day

\[
\begin{align*}
C_{ss} &= \frac{D_{old}}{CL_{old}} = \frac{D_{new}}{CL_{new}} \Rightarrow D_{new} = D_{old} \cdot \frac{CL_{new}}{CL_{old}} \\
CL_{new} &= \frac{CL_{NR} + CLcr_{new}}{CL_{old} + CLcr_{old}} = \frac{CL_{NR}}{CL_{NR} + CLcr_{old}} + \frac{CLcr_{new}}{CL_{NR} + CLcr_{old}} \\
&= f_{NR} + f_{R} \cdot \frac{CLcr_{old}}{CLcr_{old} + CLcr_{old}} = f_{NR} + f_{R} \cdot \frac{CLcr_{new}}{CLcr_{old}} \\
\therefore D_{new} &= D_{old} \cdot (f_{NR} + f_{R} \cdot \frac{CLcr_{new}}{CLcr_{old}}) \\
&= 200 \text{ mg} \cdot [0.5 + 0.5 \cdot \frac{1}{2.5}] = 140 \text{ mg/day}
\end{align*}
\]
Question #8: (10 points)

W.G. is a 30-year-old female who suffered a severe burn that has since been infected by *S. aureus*. To treat her infection she is given 150mg of gentamicin by a half hour infusion every 8 hours. She was started on her first infusion at 10:00 am and at 11:00 am a plasma sample is taken and yields a $C_{\text{p* max}}$ of 9.8 $\mu$g/ml. In order to determine $C_{\text{p* min}}$, another plasma sample is taken at 5:30pm (1.6$\mu$g/ml). Please calculate her respective $V_d$.

A) 9.98L

B) 16.01L

C) 11.08L

D) 14.56L

E) 13.85L

$$k_e = \frac{\ln \left( \frac{C_{\text{p* max}}}{C_{\text{p* min}}} \right)}{t_{\text{min}} - t_{\text{max}}} = \frac{\ln \left( \frac{9.8}{1.6} \right)}{17.5 - 11} = 0.38 h^{-1}$$

$$C_{\text{p* max}} = \frac{C_{\text{p* max}}}{e^{-k_e (t_{\text{max}} - t_{\text{min}})}} = \frac{9.8 \mu g}{mL}{e^{-0.38 h^{-1} \times 0.5 h}} = 11.27 \mu g/mL$$

$$C_{\text{p* min}} = C_{\text{p* min}} \times e^{-k_e (t_{\text{min}} - t_{\text{min}})} = 1.6 \frac{\mu g}{mL} \times e^{-0.38 h^{-1} \times 0.5 h} = 1.39 \frac{\mu g}{mL}$$

$$V_d = \frac{Dose}{k_e \times T} \left( \frac{1 - e^{-k_e \times T}}{C_{\text{p* max}} - C_{\text{p* min}} \times e^{-k_e \times T}} \right)$$

$$= \frac{150 \mu g}{0.28 h^{-1} \times 0.5 h} \times \frac{1 - e^{-0.38 h^{-1} \times 0.5 h}}{11.27 - 1.39 \times e^{-0.38 h^{-1} \times 0.5 h}}$$

$$= 13.85L$$
Question #9: (5 points)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume of Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>0.15 L/kg</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.25 L/kg</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>0.60 L/kg</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1.1 L/kg</td>
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<tr>
<td>Digoxin</td>
<td>7.3 L/kg</td>
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<tr>
<td>Azithromycin</td>
<td>31 L/kg</td>
</tr>
</tbody>
</table>

Which of the following statements, based on the given volumes of distribution, are true?

1) Ibuprofen is primarily found in the blood due to extensive plasma protein binding

2) Gentamicin penetrates well into cells

3) Digoxin shows extensive tissue binding

4) Azithromycin is primarily found in the extracellular space fluid

5) Diazepam is a hydrophilic drug

A) 2, 4
B) 1, 3
C) 1, 2, 3
D) 3, 4, 5
E) None of the above

1) **TRUE** Ibuprofen shows a very high plasma protein binding (>99%). Consequently, most of the drug stays in the plasma, resulting in a small volume of distribution.

2) **FALSE** Gentamicin does not penetrate membranes very well. It accumulates therefore preferably in the extracellular fluid. (Exception: kidneys, ears)

3) **TRUE** Digoxin does bind extensively to muscle tissue.

4) **FALSE** Azithromycin accumulates in the lysosomes of the cells (Ion trapping) → is has a huge $V_d$

5) **FALSE** Diazepam is a very lipophilic drug that accumulates in fat tissue
X.Y. is a 71kg male patient. He receives for his *S. aureus* infection 500 mg gentamicin every 36 hours as an infusion. A blood sample was taken 10 hours after the start of the infusion. The respective concentration was determined to be 7mg/L. Please state which of the following statements is TRUE!

**A) The current dosing regimen is sufficient.**

B) The dosing regimen should be changed to 500mg every 24 hours.

C) The dosing regimen should be changed to 500mg every 48 hours.

D) There is not enough information given to answer this question.

E) None of the above.

\[
\frac{500 \text{ mg}}{71 \text{ kg}} \times \frac{7 \text{ mg}}{1 \text{ kg}}
\]

→ Nomogram for gentamicin can be used

\[
\frac{7 \text{ mg}}{\text{L}} = \frac{7 \text{ mg}}{\text{mL}} \text{ after 10 hours after the start of the infusion indicates a Q36h dosing regimen}
\]

→ The current dosing regimen is sufficient
**Question #11:** (10 points)

B.M. (male, 52-year-old, 105kg, 5’8” tall) with a serum creatinine of 2.5 mg/dL, is being treated with vancomycin for a presumed hospital-acquired, nafcillin-resistant S. aureus infection. What is his dosing regimen based on Nomogram?

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<th>60</th>
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</tbody>
</table>

Figure 1. Detroit Receiving Hospital and University Health Center vancomycin dosing nomogram. (Updated 5/99)

**A)** 1000 mg q12h

**B)** 1000mg q24h

**C)** 1000mg q8h

**D)** 500mg q8h

**E)** None of the above

**IBW =**50 + 2.3 ∙ (height in inches-60) kg = 50 + 2.3 ∙ 8 = 68.4kg

120%IBW = 68.4 ∙ 1.2 = 82.08 kg < TBW (105kg)
ABW = IBW + 0.4 · (TBW - IBW) = 68.4 + 0.4 · (105 - 68.4) = 83.04kg

Use ABW to calculate the $CL_{cr}$

$$CL_{cr} = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot Cp_{\text{creat}}} = \frac{(140 - 52) \cdot 83.04}{72 \cdot 2.5} = 40.6 \text{mL/min}$$

From Nomogram: 1000mg q24h
Question #12: (10 points)

S.W., a 64-year-old, 5’5”, 65kg woman with a serum creatinine of 1mg/dL, has been started on 1000mg of vancomycin over 1 hour infusion q12h for the treatment of staphylococcal infection. Calculate the steady-state peak and trough vancomycin concentration in this short-term infusion model.

\( V_d = 0.17 \cdot \text{age} + 0.22 \cdot \text{TBW} + 15 \)

\[ \begin{align*} 
A) & \quad C_{\text{peak,ss}} = 36.8 \text{ mg/L}, \quad C_{\text{trough,ss}} = 14.1 \text{ mg/L} \\
B) & \quad C_{\text{peak,ss}} = 39.2 \text{ mg/L}, \quad C_{\text{trough,ss}} = 16.7 \text{ mg/L} \\
C) & \quad C_{\text{peak,ss}} = 31.3 \text{ mg/L}, \quad C_{\text{trough,ss}} = 10.5 \text{ mg/L} \\
D) & \quad C_{\text{peak,ss}} = 30.4 \text{ mg/L}, \quad C_{\text{trough,ss}} = 12.6 \text{ mg/L} \\
E) & \quad C_{\text{peak,ss}} = 37.9 \text{ mg/L}, \quad C_{\text{trough,ss}} = 8.9 \text{ mg/L} 
\end{align*} \]

\[ \begin{align*} 
V_d & = 0.17 \cdot \text{age} + 0.22 \cdot \text{TBW} + 15 = 0.17 \cdot 64 + 0.22 \cdot 65 + 15 = 40.18 \text{L} \\
\text{IBW} & = 45 + 2.3 \cdot (\text{height in inches} - 60) \text{ kg} = 45 + 2.3 \cdot 5 = 56.5 \text{kg} \\
\text{TBW} & < 1.2 \times \text{IBW}, \text{ we will use TBW} \\
\text{CL} & = CL_{cr} = \frac{(140 - \text{age}) \cdot \text{weight}}{Cp_{\text{crea}}} \cdot \frac{85}{1.85} = \frac{140 - 64}{1.85} \cdot 65 = 58.12 \text{mL/min} = 3.49 \text{L/hr} \\
k_e & = \frac{\text{CL}}{V_d} = \frac{3.49 \text{L/hr}}{40.18 \text{L}} = 0.087 \text{hr}^{-1} \\
\text{Steady state peak and trough} \\
C_{\text{peak,ss}} & = \frac{D \cdot (1 - e^{-keT})}{\text{CL} \cdot T \cdot (1 - e^{-keT})} = \frac{1000 \cdot (1 - e^{-0.087 \cdot 1})}{3.49 \cdot 1 \cdot (1 - e^{-0.087 \cdot 12})} = 36.8 \text{ mg/L} \\
C_{\text{trough,ss}} & = C_{\text{peak,ss}} \cdot e^{ke(\tau - T)} = 36.8 \cdot e^{-0.087 \cdot 11} = 14.1 \text{ mg/L} 
\end{align*} \]
Question #13: (5 points)

Which of the following statements are true about vancomycin pharmacokinetics and pharmacodynamics?

1. Vancomycin exhibits time-dependent bacterial killing rather than concentration-dependent killing (as in aminoglycosides)
2. Monitor peak plasma concentrations for vancomycin efficacy rather than trough concentrations
3. Vancomycin has poor absorption from GI tract
4. Vancomycin is 80-90% eliminated by liver
5. Vancomycin has good tissue penetration except bile, eye, noninflamed meninges

A) 1, 2, 4  
B) 1, 2, 3  
C) 1, 3, 5  
D) 3, 4, 5  
E) None of the above

1. True  
2. False  
   Monitor trough plasma concentrations for vancomycin efficacy. 
   Vancomycin has slow distribution into peripheral tissues making it difficult to identify the true peak.  
3. True  
4. False  
   Vancomycin is 80-90% eliminated by kidneys
5. True
Question #14:  (5 points)

Compare creatinine production from muscle in a normal 30 year old and 90 year old male subject (total body weight for both of them: 75 kg) with a serum creatinine of 0.75 mg/dl, and make a conclusion which of the following statements is correct (please think about the Cockcroft-Gault-Equation).

A) Young subject produces less amount of creatinine per day than the old one because the elderly have more muscle.

B) Young subject produces more amount of creatinine per day than the old one because young people have more muscle.

C) The creatinine clearance is higher in the old subject due to the higher muscle mass.

D) The creatinine clearance is lower in the old subject due to the higher muscle mass.

E) They produce the same amount of creatinine per day due to the same weight.

\[ Cl_{\text{creat}} (\text{male}) = \frac{(140 - \text{age}) \cdot \text{weight}}{(72) \cdot C_{\text{pCreat}}} \]

⇒ Age increases, creatinine clearance decreases when body weight and serum creatinine concentration stay the same between them.

Amount of creatinine produced per day is: \[ Amount_{\text{creat}} = Cl_{\text{creat}} \cdot C_{\text{pCreat}} \cdot 24hr \]

⇒ Produce more amount of creatinine when creatinine clearance is higher and serum creatinine concentration is the same between them.
Question #15: (5 points)

Which of the following statements on bioavailability is correct?

A) Bioavailability reflects rate and extent of absorption.

B) The FDA requires the relative bioavailability is determined from steady-state plasma levels.

C) Differences in bioavailability always lead to difference in therapeutic activity.

D) In case of chronic dosing two tablets with equal rates of bioavailability should be considered bioequivalent.

E) In case of first order kinetics comparison of the amount of unchanged drug in the urine is a proper way to determine relative bioavailability.