Name: _____ ID _____

PHA 5128
First Exam
Spring 2009

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

_____
Signature

Question
1. _____/5pts
2. _____/5pts
3. _____/10pts
4. _____/5pts
5. _____/5pts
6. _____/10pts
7. _____/15pts
8. _____/10pts
9. _____/5pts
10._____/10pts
11._____5pts
12. _____/10pts
13. _____/5pts

Total _____/100 pts

1. Which of the following statements regarding body weight is likely to be **False?** (5pts)

   A. Oral bioavailability increases with increasing body weight.

   B. Volume of distribution increase as body weight increases for a lipophilic drug.

   C. Creatinine clearance is based on body weight.

   D. An obese subject is more likely to receive an overdose than a patient with an ideal body weight for a weakly lipophilic drug given mg/kg.

   E. Changes in drug distribution in obese subject can be the result of increased cardiac output, blood volume, and plasma or tissue binding.

2. A patient who has had an adverse reaction to Drug X requires that the plasma drug concentration not ever exceed 40 mg/L. If Drug X has half life of 8 hrs and clearance of 4 L/hr, what is the best i.v. loading dose that will give the maximum blood levels but still avoid an adverse reaction (5pts)?

A. 2500 mg

B. 2200 mg

C. 2000 mg

D. 1700 mg

E. 1000 mg

$t_{1/2}$ = ln2*V/CL ➔V = 8 hr*4 L/hr/ln(2) = 46.2 L;

V = D/Co ➔Dose = 46.2 L * 40 mg/L = 1847 mg; Thus, answer D.

3. The average steady state plasma concentration after administering an 800 mg sustained release theophylline product every 24 hours to a 78 kg male subject (5 feet 2 inch) is 15 ug/mL. The volume of distribution is 40 L. What is the drug's approximate half-life? (10pts)

A. 12 hrs

B. 24 hrs

C. 6 hrs

D. 8 hrs

E. 16 hrs

CL= F*D / (Cave ss * tau) = 800 / (15 *24) = 2.22 L/h
Ke= Cl/ Vd = 2.22 / 40 = 0.0555 /hr
T1/2 = 0.693/0.0555 = 12.46 hrs ~ 12 hrs

4. One hour after the end of a 30 min intravenous infusion of 200 mg gentamicin, the plasma level was 8 µg/ml. Nine hours after the end of the infusion the plasma level was 3 µg/ml. Predict the plasma level 12 hours after the dose was started. Only one single dose was given. The drug has 50% oral bioavailability (F=0.5). (5pts)

A. 2.2 ug/ml

B. 4.6 ug/ml

C. 1.15 ug/ml

D. 0.6 ug/ml

E. Not enough information to calculate the answer

The difference between the two samples was 8 hours… one hour after end of infusion and nine hours after end of infusion .
Ke = Ln (8/3) / 8 = 0.123 / hr

12 hours after dose was started would be 2.5 hours after last sample….(12 – 9.5 =2.5)

C= 3 exp(-0.123 * 2.5)
C = 2.31ug/ ml

5. Drug A has half-life of 12 hours and is given 200mg every 12 hours by IV route. Another drug B in the same class has a half life of 24 hours and is given 100 mg every 24 hours by IV route. Which of the following statement is correct? (5pts)

A. Drug A and B will take equally long to reach the steady state with current dosing.

B. Drug B will take longer than drug A to reach steady state

C. Drug A will take longer than drug B to reach steady state

D. With current dosing intervals these drugs will never reach steady state.

E. Not enough information to decide which drug reaches steady state first

6. How will an increase in tissue binding affect the AUC, C_{max}, and half-life ($t_{1/2}$) of a high-extraction drug? (please note that ↔ means no change) (10pts).

A: High extraction drug: ↑ AUC, ↓ Cmax, ↓ $t_{1/2}$

B: High extraction drug : ↔ AUC, ↑ Cmax, ↔ $t_{1/2}$

C: High extraction drug : ↔ AUC, ↓ Cmax, ↑ $t_{1/2}$

D: High extraction drug : ↓ AUC, ↔ Cmax, ↑ $t_{1/2}$

E: High extraction drug: ↑ AUC, ↑ Cmax, ↓ $t_{1/2}$

7. JS is a 70-year-old, 85 kg, 5'6'' man with gram-negative sepsis. His serum creatinine is 1.5mg/dL and has been stable since hospital admission. Compute a gentamicin dosing regimen to provide a steady-state peak concentration of 9 µg/mL and a steady-state trough concentration of 1.5 µg/mL after short-term infusion (30min).

Please use the aminoglycoside k_e equation from the equation sheet for k_e. ($k_e = 0.00293(CL_{creat}) + 0.014$) Cl_{creat} is in mL/min for this equation. (15pts)

A. 200mg every 12 hours

B. 140mg every 24 hours

C. 180mg every 12 hours

D. 180mg every 24 hours

E. 140mg every 12 hours

IBW=50kg+2.3kg*6''=63.8 kg→ obese patient, use ABW

ABW=IBW + 0.4* (TBW-IBW) = 63.8kg+ 0.4*(85-63.8)=72.28kg

$$CL_{creat} = \frac{(140 - age) \times ABW}{72 \times Cp_{creat}} = \frac{(140 - 70) \times 72.28kg}{72 \times 1.5mg/dl} = 46.85ml/\min = 2.81L/h$$

$$k_e = 0.00293(CL_{creat}) + 0.014 = 0.00293 * 46.85ml/\min + 0.014 = 0.15h^{-1}$$

Estimate the volume of distribution (Vd)

$$V_d = 0.25L/kg * 72.28kg = 18.07L$$

Calculate the dosing interval:

$$\tau = \frac{\ln\left[\frac{C_{\max}(desired)}{C_{\min}(desired)}\right]}{k_e} + T = \frac{\ln\left[\frac{9\mu g/mL}{1.5\mu g/mL}\right]}{0.15h^{-1}} + 0.5h = 12.44\text{h} \approx 12\text{h}$$

Calculate the dose:

$$D = C_{\max}(desired) \cdot k_e \cdot V_d \cdot T \frac{(1 - e^{-k_e \tau})}{(1 - e^{-k_e T})} =$$

$$9\mu g/ml \times 0.15h^{-1} \times 18.07L \cdot 0.5h \frac{(1 - e^{-0.15 \times 12h})}{(1 - e^{-0.15 \times 0.5h})} = 141mg$$

8. H.M., a 65-year-old, 5'5'', 60 kg woman with a serum creatinine of 1mg/dL, has been started on 1g of vancomycin administered as a 1 hr infusion q12h for the treatment of a staphylococcal infection. Calculate the steady-state peak concentration.

Vd=0.178*age+ 0.22 TBW +15. Please calculate k_e using the provided Vd equation and creatinine clearance. (10pts)

A. Cmax_ss = 24 µg/mL

B. Cmax_ss = 50 mg/L

C. Cmax_ss = 24 mg/L

D. Cmax_ss = 32 µg/mL

E. Cmax_ss = 39 µg/mL

$$CL_{creat} = \frac{(140 - age) \times ABW}{85 \times Cp_{creat}} = \frac{(140 - 65) \times 60kg}{85 \times 1mg/dl} = 52.94ml/\min = 3.18L/h$$

Vd=0.178*age+ 0.22 TBW +15=0.178*65+0.22*60+15=39.77L

$$k_e = CL/V_d = 3.18l/h/39.77L = 0.08h^{-1}$$

$$\text{Cpeak} = \frac{D}{Cl \times T}(1 - e^{k_e T}) = \frac{1000mg}{3.18L/h * 1h}(1 - e^{-0.08 \times 1}) = 24.18mg/L$$

$$C_{peak,ss} = 24.18/(1 - e^{-k_e \tau}) = 24.18/(1 - e^{-0.08 \times 12}) = 39.2mg/L$$

9. Please choose the correct answer: (5pts)

a) Bioavailability is defined as the rate and extent to which the active ingredient is absorbed from a drug product
b) Bioequivalence is the presence of a significant difference in rate and extent to which the active ingredient from a pharmaceutical alternative becomes available
c) Bioequivalent products are therapeutically interchangeable
d) Bioequivalence studies are required for all strengths of a pharmaceutical alternative

Answers:

A. a,b
B. b,c
C. b,c,d
D. a,c
E. all of the above

10. D.H., a 5'5", 60 kg, 40-year-old female, with a serum creatinine of 1.0 mg/dL is being treated for a presumed hospital-acquired, nafcillin-resistent S. aureus infection. What is the recommended vancomycin treatment according to vancomycin dosing nomogram below? (10pts)

Answers:

A. 500 mg q8h

B. 1000mg q8h

C. 500mg q12h

D. 1000mg q12h

E. 500mg q24h

$$\text{IBW} = 45.5 + 2.3 \bullet 5 = 57 \text{ kg}$$

$$\text{TBW} < 120\% \text{ IBW} \Rightarrow use\ TBW$$

$$CL_{cr} = \frac{(140 - age) \cdot TBW}{Cpcr \cdot 85} = \frac{(140 - 40) \cdot 60}{1.0 \cdot 85} = 70.6mL / \min$$

Cl_{cr} (ml/min) → / Weight (kg) ↓	30	40	50	60	70	80	90	100	≥ 110
50	500 q24h	500 q24h	500 q12h	500 q12h	500 q12h	500 q12h	500 q12h	500 q8h	500 q8h
55	500 q24h	500 q24h	500 q12h	500 q12h	500 q12h	500 q12h	500 q12h	500 q8h	500 q8h
60	500 q24h	500 q24h	500 q12h	500 q12h	1000 q12h	1000 q12h	1000 q12h	500 q8h	500 q8h
65	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h
70	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h
75	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h
80	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h
85	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h
90	1000 q24	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
95	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
100	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
105	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
≥ 110	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h

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

11. Which combination of the following factors makes the serum creatinine level a good choice to estimate renal function? (5pts)

1) Creatinine is endogenous
2) Creatinine is only eliminated by kidney
3) Creatinine is not bound to protein in plasma
4) Creatinine urinary excretion rate is not affected by diseases
5) Creatinine is constantly formed by muscle

A) all of the above
B) 1, 2, & 4
C) 1, 2, 3, & 5
D) 1, 3, 4, & 5
E) 2, 3, 4 & 5

12. A 150 mg dose of an antibiotic drug is administered orally to 12 healthy volunteers and the following information was obtained: $AUC_{0\text{-infinity}}$ = 25 mg*hr/L, plasma half-life = 9 hrs, bioavailability = 0.75, and cumulative amount of drug eliminated unchanged in the urine = 90 mg. What is the renal clearance of this drug? (10pts)

A. 4.5 L/hr
B. 2.7 L/hr
C. 3.6 L/hr
D. 6.0 L/hr
E. More data is needed to determined renal clearance

Plasma CL = Dose*F/AUC = 150 mg * 0.75/25 mg*hr/L = 4.5 L/hr
Faction Excreted in urine = 90 mg/(150 mg*0.75)=0.8
Renal CL = 4.5 L/hr*0.8 = 3.6 L/hr

13. You've been given clinical data of a well absorbed drug (Drug ABC) from an escalating dose study with four dose levels. The drug has a total clearance of 7.5 L/hr, what is the renal clearance of this drug given the information below? (5pts)

Dose level	1	2	3	4
Urinary excretion rate at steady state (mg/hr):	20	60	200	500
Corresponding blood ABC concentration at steady state (mg/L):	4	12	40	100

A. 2 L/hr
B. 5 L/hr
C. 0.75 L/hr
D. 1.38 L/hr
E. Cannot be determined

Renal CL = rate of excretion/plasma conc = 20 mg/hr / 4 mg/L = 5 L/hr

Aminoglycosides

Vd [L/kg]	0.25
CL [L/h/kg]	CL_{Cr}
$t_{1/2}$ [h]	2-3
% renal	100
F	-
S	-
C_{max} [mg/L]	>8-10·MIC
C_{min} [mg/L]	<2 (G, T)
	<10 (A)

Dosing Weight

if TBW>1.2·IBW: IBW + 0.4·(TBW-IBW)

Third Space Fluids: Add to Vd (1L/kg)

Dettli Equation:
$k=0.00293 \cdot CL_{Cr}[ml/min]+0.014\ [h^{-1}]$

Vancomycin Pharmacokinetics

Poor absorption from GI tract (oral only used for *C. difficile* colitis)

Vd=0.17·age+0.22·TBW+15 [L] (or 0.7 L/kg)

Good tissue penetration
(except bile, eye, noninflamed meninges)

80-90% eliminated by kidneys

$t_{1/2}$	Adults:	6-7 hours
	Infants/Children:	2-4 hours
	Newborn:	6-10 hours