PHA 5127

Second Exam

Fall 2008

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

_____

Name

Put all answers on the bubble sheet

TOTAL _____/ 170 pts

Question Set I (True or False)

(25 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

Mark whether the following statements is true (A) or false (B). Drug A is cleared only by hepatic metabolism and has an intrinsic clearance of 0.8 L/h

1:     T   F   The oral bioavailability of this drug will be larger than 80%.

2:     T   F   Plasma protein binding will affect the oral bioavailability of this drug.

3:     T   F   The hepatic clearance of this drug is 1333 L/min.

4:     T   F   Plasma protein binding will affect the hepatic clearance of this drug.

5:     T   F   Drug B, known to induce enzymes, also responsible for metabolism of Drug A, will significantly affect the clearance of Drug A.

Question Set II

(25 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

Imagine a lipophilic unionized drug A with a volume of distribution of 108 L. When given by an iv bolus injection, the peak concentration of 0.18 **µg/ml** is observed (C_o). When given orally, the oral bioavailability is 1.9 %. Plasma Protein Binding is 50% (f_u=0.5).

Peak [µg/ml]	0.18
V [L]	108
F (%)	1.9
f_u	0.5

Mark whether the following statements are true (A) or false (B).

6:     T   F   The drug is highly metabolized in the liver.

7:     T   F Plasma protein binding will affect the oral bioavailability of this drug.

8:     T   F   The hepatic clearance of this drug will be smaller than the Cl_{ren}.

9:     T   F   Plasma protein binding will affect the hepatic clearance of this drug.

10:   T   F   Drug B, known to induce enzymes that are also responsible for metabolism of
                    Drug A, will significantly affect the clearance of Drug A.

Question Set III (Matching)

(20 points)

For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a **lipophilic acid (pKa=7.0)**, **protein bound** drug **that is only eliminated through the kidneys** (some answers may be used more than once). The pH of the urine is 7.0

Select the effect on kinetics (this effect should be clinically relevant)

(A) Cl_{REN} ↑ (B) Cl_{ren} ↓ (C) V_D ↓ (D) oral bioavailability F↑ (E) nothing happens or effect is not listed

Physiological change

11: Decrease in plasma protein binding_____

12: Decrease in urine pH _____

13: Increase in liver blood flow _____

14: Doubling in urine flow_____

Question Set IV

Total points 30

A drug is being cleared by the liver and kidneys. The drug is polar, has a molecular weight of 400 Dalton and is neither an acid nor a base. Plasma protein binding is 50% (f_u=0.5). The oral bioavailability is determined by first pass and is 60%. Assume liver blood flow of 80 L/h, a GFR of 130 ml/min and a urine flow of 2 ml/min.

What is the hepatic clearance expressed in L/h. Values between 1 and 80 L/h. Express as full Liters/h (50 not 50.4 L/h). (10 points)

15   Mark A, B, C, or D, if the number in the tens column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case This would be E for **5**0 L/h)*

16:      Mark A, B, C, D, E if the number in the tens column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for **5**0 L/h)*

17:      Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case . You would leave this blank for 5**0** L/h)*

18:      Mark A, B, C, or D, if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0 (E) *Leave blank if this is not the case. This would be E for 5**0** L/h)*

What is the renal clearance expressed in mL/min. Values between 0 and 90 mL/min. Express as full mL/min (50 not 50.4 mL/min). (10 points)

19:     Mark A, B, C, or D, if the number in the tens column is 1 (A), 2(B), 3(C), 4(D), 5(E).
        Leave blank if this is not the case This would be E for 50 L/h)

20:     Mark A, B, C, D, E if the number in the tens column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 50 L/h)*

21:     Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E).
        Leave blank if this is not the case. You would leave this blank for 50 L/h)

22:     Mark A, B, C, or D, if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0 (E)
        Leave blank if this is not the case. This would be E for 50 L/h)

What is the total clearance expressed in L/h. Values between **0 and 90 L/h.** Express as full L/h (50 not 50.4 L/h). (10 points)

23: Mark A, B, C, or D, if the number in the tens column is 1 (A), 2(B), 3(C), 4(D), 5(E).
*Leave blank if this is not the case This would be E for **50** L/h)*

24: Mark A, B, C, D, E if the number in the tens column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for **50** L/h)*

25: Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E).
*Leave blank if this is not the case . You would leave this blank for **50** L/h)*

26: Mark A, B, C, or D, if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0 (E)
*Leave blank if this is not the case. This would be E for **50** L/h)*

Question Set V

(10   points)

A lipophilic acidic drug (pk_a of 7) is eliminated only by the kidney. **Plasma protein binding is 90%**. Glomerular filtration rate is normal (**130 ml/min**). Urine flow is 2ml/min.Urine pH is similar 7.   The volume of distribution is **40L.**

27:    What value best describes the clearance? (5 points)

A: 0.15 mL/min

B: 13   mL/min

C: 130   mL/min

D: 6.6   mL/min

28:    Assume a one compartment body model? What is the renal clearance of a typical polar, (hydrophilic) drug showing 50% plasma protein binding. The patient has a creatinine clearance of 130 ml /min (5 points).

A: 58.5 ml/min

B: 130 ml/min

C: 65 ml/min

D: 6.5 ml/min

E: 35.8 ml/min

Question Set VI

(10 points)

> Robert is very sick and needs treatment with an aminoglycoside. In order to start him on the aminoglycoside an iv bolus loading dose shall be given. Your responsibility is to give him the first dose. In order to do so, you have to estimate Robert's creatinine clearance. Robert is 5 ft 10 inches tall, 34 years old, male, and weights 280 pounds. His serum creatinine is 1.5 mg/dl.

What creatinine clearance do you come up with? (Creatinine clearance between 1 and 99 mL/min. Use full numbers 51, not 50.7 mL/min)

29:    Mark A, B, C, or D, if the number in the tens column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case This would be E for 50 L/h)*

30:    Mark A, B, C, D, E if the number in the tens column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 50 L/h)*

31:    Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case . You would leave this blank for 50 L/h)*

32:    Mark A, B, C, or D, if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0 (E) *Leave blank if this is not the case. This would be E for 50 L/h)*

Question Set VII (True or False)

(15 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

Mark whether the following statements are true (A) or False (B)

33: T F The renal clearance of a drug (as determined by filtration and reabsorbtion) always depends on the tissue binding of the drug.

34: T F The hepatic clearance of a drug is dependent on the plasma concentration of the drug in the body, as more drug can be metabolized when the plasma concentration of the drug is high.

35: T F For an acidic, lipophilic drug with a pk_a of 7.5, adjustment of the urine pH within physiological ranges will significantly change the renal clearance.

Question Set VIII (True or False)

(25 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

Mark whether the following statements are true (A) or false (B)

36: T F   The larger the clearance of a drug, the smaller the AUC of a given drug.

37: T F   Doubling the dose will generally double the AUC of a drug after iv bolus injection

38: T F   An increase in plasma protein binding will always result in a decrease of the drug's hepatic clearance

39: T F   The highest renal clearance will be similar to the kidney blood flow

40: T F   Drugs with a renal clearance that is larger than GFR*fu are candidates for drug/drug interactions.

Question Set IX (5 points)

41:     Which of the following statements is/are correct?

1)   We can roughly assume that a change in clearance will result in a change in volume of distribution.

2)   Drug A is 40% protein bound, drug B 98% protein bound. A two percent decrease in plasma protein binding will be most significant for drug A with respect to the clearance.

3)   Genetic variability in metabolizing enzymes does always alter hepatic clearance.

4)   In general, we should always use IBW for calculating creatinine clearance.

A)   2, 3, 4

B)   1, 3 & 4

C)   2, 3

D)   3, 4

E)   None of the above

Question Set X (5 points)

42: An investigational new drug is eliminated entirely by liver (hepatic) metabolism, with a clearance of 1.35 L/min in subjects with an average liver blood flow of 1.50L/min. What would be its expected clearance in a congestive heart failure patient with a liver blood flow of 1.10L/min but no change in hepatic extraction ratio?

A) 1.10L/min

B) 1.50L/min

C) 1.18L/min

D) 0.99L/min

E) Cannot be determined because the dose is not given.

Useful Pharmacokinetic Equations

Symbols

D = dose
τ = dosing interval
CL = clearance
Vd = volume of distribution
k_e = elimination rate constant
k_a = absorption rate constant
F = fraction absorbed (bioavailability)
K_0 = infusion rate
T = duration of infusion
C = plasma concentration

General

Elimination rate constant

$$k_e = \frac{CL}{Vd} = \frac{\ln\left(\dfrac{C_1}{C_2}\right)}{(t_2 - t_1)} = \frac{\ln C_1 - \ln C_2}{(t_2 - t_1)}$$

Half-life

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL} = \frac{\ln(2)}{k_e} = \frac{0.693}{k_e}$$

Intravenous bolus

Initial concentration

$$C_0 = \frac{D}{Vd}$$

Plasma concentration (single dose)

$$C = C_0 \cdot e^{-k_e \cdot t}$$

Plasma concentration (multiple dose)

$$C = \frac{C_0 \cdot e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Peak (multiple dose)

$$C_{max} = \frac{C_0}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = \frac{C_0 \cdot e^{-k_e \cdot \tau}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Average concentration (steady state)

$$\overline{C}p_{ss} = \frac{D}{CL \cdot \tau}$$

Oral administration

Plasma concentration (single dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(e^{-k_e \cdot t} - e^{-k_a \cdot t}\right)$$

Time of maximum concentration (single dose)

$$t_{max} = \frac{\ln\left(\dfrac{k_a}{k_e}\right)}{(k_a - k_e)}$$

Plasma concentration (multiple dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(\frac{e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)} - \frac{e^{-k_a \cdot t}}{\left(1 - e^{-k_a \cdot \tau}\right)}\right)$$

Time of maximum concentration (multiple dose)

$$t_{max} = \frac{\ln\left(\dfrac{k_a \cdot \left(1 - e^{-k_e \cdot \tau}\right)}{k_e \cdot \left(1 - e^{-k_a \cdot \tau}\right)}\right)}{(k_a - k_e)}$$

Average concentration (steady state)

$$\overline{C} = \frac{F \cdot D}{CL \cdot \tau}$$

Clearance

$$Cl = \frac{Dose \cdot F}{AUC}$$

$$Cl = k_e \cdot V_d$$

Constant rate infusion

Plasma concentration (during infusion)

$$C = \frac{k_0}{CL} \cdot \left(1 - e^{-k_e \cdot t}\right)$$

Plasma concentration (steady state)

$$C = \frac{k_0}{CL}$$

Calculated clearance (Chiou equation)

$$CL = \frac{2 \cdot k_0}{(C_1 + C_2)} + \frac{2 \cdot Vd \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)}$$

Short-term infusion

Peak (single dose)

$$C_{max(1)} = \frac{D}{CL \cdot T} \cdot \left(1 - e^{-k_e \cdot T}\right)$$

Trough (single dose)

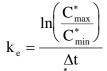$$C_{min(1)} = C_{max(1)} \cdot e^{-k_e \cdot (\tau - T)}$$

Peak (multiple dose)

$$C_{max} = \frac{D}{CL \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = C_{max} \cdot e^{-k_e \cdot (\tau - T)}$$

Calculated elimination rate constant

$$k_e = \frac{\ln\left(\frac{C_{max}^*}{C_{min}^*}\right)}{\Delta t}$$

with C_{max}^* = measured peak and C_{min}^* = measured trough,
measured over the time interval Δt

Calculated peak

$$C_{max} = \frac{C_{max}^*}{e^{-k_e \cdot t^*}}$$

with C_{max}^* = measured peak, measured at time t^* after the end of the infusion

Calculated trough

$$C_{min} = C_{min}^* \cdot e^{-k_e \cdot t^*}$$

with C_{min}^* = measured trough, measured at time t^* before the start of the next infusion

Calculated volume of distribution

$$Vd = \frac{D}{k_e \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{[C_{max} - (C_{min} \cdot e^{-k_e \cdot T})]}$$

Calculated recommended dosing interval

$$\tau = \frac{\ln\left(\frac{C_{max(desired)}}{C_{min(desired)}}\right)}{k_e} + T$$

Calculated recommended dose

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

Two-Compartment-Body Model

$$C = a \bullet e^{-\alpha t} + b \bullet e^{-\beta t}$$

$$AUC_\infty = a / \alpha + b / \beta$$

$$Vd_{area} > Vd_{ss} > Vc$$

Creatinine Clearance

$$CL_{creat}(male) = \frac{(140 - age) \bullet weight}{72 \bullet Cp_{creat}}$$

$$CL_{creat}(female) = \frac{(140 - age) \bullet weight}{85 \bullet Cp_{creat}}$$

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL_{creat} in ml/min

K_e for aminoglycosides

$$K_e = 0.00293(CrCL) + 0.014$$

Metabolic and Renal Clearance

$$E_H = \frac{Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_H = E_H \cdot Q_H = \frac{Q_H \cdot Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_{ren} = RBF \cdot E = GFR \cdot \frac{C_{in} - C_{out}}{C_{in}}$$

$$Cl_{ren} = \frac{\text{rate of excretion}}{\text{plasma concentration}}$$

$$Cl_{ren} = fu \cdot GFR + \left[\frac{\text{Rate of secretion - Rate of reabsorption}}{\text{Plasma concentration}} \right]$$

$$Cl_{ren} = \frac{\text{Urine flow} \cdot \text{urine concentration}}{\text{Plasma concentration}}$$

Ideal Body Weight

Male
IBW = 50 kg + 2.3 kg for each inch over 5ft in height

Female
IBW = 45.5 kg + 2.3 kg for each inch over 5ft in height

Obese
ABW = IBW + 0.4*(TBW-IBW)

Volume of Distribution

$$V = V_P + V_T \cdot K_P$$

$$V = V_P + V_T \cdot \frac{fu}{fu_T}$$

Clearance

$$Cl = \frac{Dose}{AUC}$$

$$Cl = k_e \cdot V_d$$

For One Compartment Body Model

If the dosing involves the use of I.V. bolus administration:	**For a single I.V. bolus administration:** $$C_0 = \frac{D}{V}$$ $$C = C_0 \cdot e^{-k_e t}$$	**For multiple I.V. bolus administration:** $$Cn(t) = \frac{D}{V} \cdot \frac{\left(1 - e^{-nk_e \tau}\right)}{\left(1 - e^{-k_e \tau}\right)} \cdot e^{-k_e t}$$ at peak: t = 0; at steady state n→∞ at trough: t = τ $$C_{\max ss} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e \tau})}$$ $$C_{\min ss} = C_{\max ss} \cdot e^{-k_e \tau}$$
If the dosing involves the use of I.V. infusion:	**For a single short-term I.V. infusion:** Since τ = t for C$_{max}$ $$C_{\max} = \frac{D}{V k_e T} \cdot \left(1 - e^{-k_e T}\right)$$ $$C_{\min} = C_{\max} \cdot e^{-k_e (\tau - T)}$$	**For multiple short-term I.V. infusion at steady state:** $$C_{\max} = \frac{D}{V k_e T} \cdot \frac{\left(1 - e^{-k_e T}\right)}{\left(1 - e^{-k_e \tau}\right)}$$ $$C_{\min} = C_{\max} \cdot e^{-k_e (\tau - T)}$$

If the dosing involves a I.V. infusion (more equations):	$C_t = \dfrac{D}{Vk_eT} \cdot \left(e^{k_eT} - 1\right) \cdot e^{-k_et}$ (most general eq.) during infusion t = T so, $C_t = \dfrac{D}{Vk_eT} \cdot \left(1 - e^{-k_et}\right)$ (during infusion) at steady state t → ∞, e^{-k_et}, t → 0 so, $Cpss = \dfrac{D}{Vk_eT} = \dfrac{k_0}{Vk_e} = \dfrac{k_0}{CL}$ (steady state) remembering $k_0 = \dfrac{D}{T}$ and $CL = V \cdot k_e$
If the dosing involves oral administration:	**For a single oral dose:** **For multiple oral doses:** $C = \dfrac{F \cdot D \cdot k_a}{V(k_a - k_e)} \cdot \left(e^{-k_et} - e^{-k_at}\right)$ $C = \dfrac{F \cdot D \cdot k_a}{V(k_a - k_e)} \cdot \left[\dfrac{e^{-k_et}}{\left(1 - e^{-k_e\tau}\right)} - \dfrac{e^{-k_at}}{\left(1 - e^{-k_a\tau}\right)}\right]$ $t_{\max} = \ln\left[\dfrac{k_a}{k_e}\right] \cdot \dfrac{1}{(k_a - k_e)}$ $t_{\max} = \ln\left[\dfrac{k_a \cdot \left(1 - e^{-k_e\tau}\right)}{k_e \cdot \left(1 - e^{-k_a\tau}\right)}\right] \cdot \dfrac{1}{(k_a - k_e)}$