NAME: _____
UFID: _____

PHA 5127

First Exam
Fall 2011

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

Name

Question Set/Points

I. 30 pts

II. 20 pts

III. 15 pts

IV 15 pts

V. 25 pts

VI. 10 pts

VII. 10 pts

VIII. 10 pts

IX. 35 pts

TOTAL: 170 pts

Question Set I (True or False)

(30 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false. Assume passive diffusion as the driving force for distribution.*

1: T F Assume a first order absorption process. The rate of absorption of this drug across GI membranes will depend on the dose given.

2: T F A hydrophilic drug cannot have a volume of distribution that is smaller than Vp.

3: T F A drug that shows zero order kinetics when given at a dose of 10 mg bid will continue to show this at higher doses.

4: T F Two drugs show the same $t_{1/2}$. They will show the same Cl and volume of distribution.

5: T F When the same single dose of the drug is given orally either as a solution or in form of a slow release formulation, the AUC estimates for both the formulations are the same. Hence, the dosing regimen should be same for both formulations.

6: T F Plasma can be prepared by removing Ca^{2+} from the blood.

Question Set II (20 points) True (A) or False (B). On the bubble sheet mark *A for true* or *B for false.*

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

A glucocorticoid is given over a long time as an IV infusion to rats. Under these conditions drug concentrations are constant after about 1 hour. Concentrations after 4 and 8 hours are thus the same in the blood. Person X determines after 8 hours how many glucocorticoid receptors are occupied in kidney, the liver and the brain. The number of receptors in these three tissues is about the same and the affinity of the glucocorticoid to the receptors in the three tissues is identical. While the same number of receptors is occupied in kidney and liver after 8 hours, much fewer receptors are occupied in the brain at the same time. Which of the following statements are consistent (True) or not consistent (False) with this observation?

7: T F Glucocorticoids interact with transporters in the brain that pump the drug into the brain cells while this is not the case for kidney and liver

8: T F The blood flow through the brain is lower than that through the kidney and liver.

9: T F Protein binding in liver and kidney is more pronounced, than in the brain, explaining the higher drug concentrations able to interact with the receptors in kidney and liver.

10: T F The brain might metabolize this glucocorticoid efficiently.

Question Set III

(15 points)

Listed in the Table are three properties of acidic drug molecules:

- the fraction ionized at ph=7.4 and
- the partition coefficient of the unionized form.

DRUG	Fraction Unionized at pH=7.4	Partition Coefficient of Unionized form	Molecular Weight (Dalton) Other properties
1	0.5	2.0	240 D
2	0.074	10	120,000 D
3	0.074	10	320 D
4	0.5	2.0	420 D +Very High affinity to pgp

11: Select the correct rank order with which drugs 1-4 will be available to the brain.

A: 1 slower than 2 slower than 3 slower than 4

B: 1 slower than 3 slower than 2 slower than 4

C: 4 slower than 2 slower than 3 slower than 1

D: 4 slower than 2 slower than 1 slower than 3

E: None of the above statements represents the correct answer

Question Set IV (True or False)

(15 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false. Assume no active transport. Assume two unionized, hydrophilic low molecular weight drugs.*

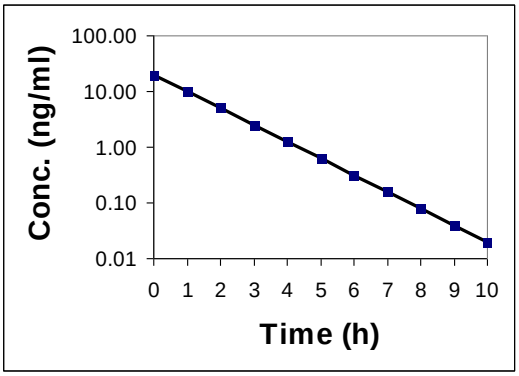
12: T F Compared to fat, the liver is likely to have a higher rate of uptake for such drugs due to its higher blood flow rate.

13: T F Assume the same fu for the two drugs. The drug with the higher tissue binding will enter the tissue faster.

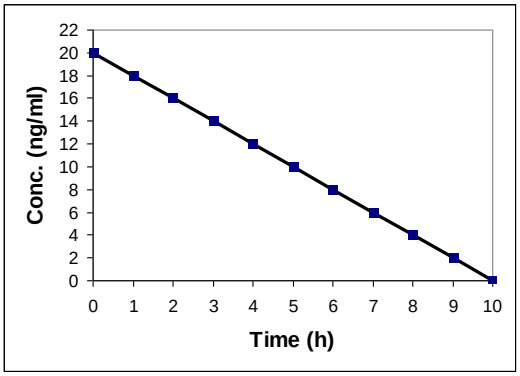
14: T F Assume the same fuT for the two drugs. The drug with the higher plasma protein binding will enter the tissue faster.

Question Set V (True or False)

(25 points)



Drug A



Drug B

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

15: T F Drug A's rate of elimination is not affected by the amount of drug in the body.

16: T F Drug A's elimination rate constant has the unit "1/ml".

17: T F For Drug A and B, the fraction of drug eliminated per hour is constant.

18: T F Drug A is only eliminated through transporters in the kidney. No metabolism occurs. Drug A's concentration-time profile might look very similar to that of Drug B, when given at much lower doses.

19: T F There is not one $t_{1/2}$ for drug B.

Question Set VI

(10 points)

20: The drug concentrations after iv bolus injection of a drug with first order elimination (one compartment body model) was 2ng/ml after 1 hour and 0.8 ng/ml after 3.5 hours post injection. What is the half-life of this drug?

A 1.44 h
B 1.89 h
C 4.36 h
D 0.37 h
E None of the above

21: A drug has a half-life of 3hours. A dose of 2000 **µ**g was given as an iv bolus injection. Vd is 100L. Three hours post injection (assume one compartment body model, first order elimination), the concentration was 5 µg/L. What is the $AUC_{0-\infty}$?

A 115 µg*h/L
B 86.5 µg*h/L
C 60.0 µg*h/L
D 90.0 µg*h/L
E None of the above

Question Set VII

(10 points)

22: How will the increase in both tissue binding and liver blood flow affect the initial concentration (C_0), clearance (CL), AUC, and half-life ($t_{1/2}$) of drug A. Assume E is constant.

A: $\downarrow C_0, \uparrow$ CL, $\downarrow$AUC

B: $\leftrightarrow C_0, \leftrightarrow$ CL, $\uparrow$AUC

C: $\downarrow C_0, \leftrightarrow$CL, $\leftrightarrow$AUC

D: $\uparrow C_0, \downarrow$ CL, $\uparrow$AUC

E: none of above combinations.

Question Set VIII

(10 points)

23: Chronic liver disease causes a 20% decrease in verapamil clearance. However, half-life of verapamil increases 4 fold. Clearly the volume of distribution has also changed due to the chronic liver disease. What is the volume of distribution of verapamil in a patient with chronic liver disease? (Healthy population values: CL= 60L/h; Vd= 300 L)

A: 300L

B: 1200L

C: 960L

D: 240L

E: None of above

Question Set IX

(35 points)

24: T F Free drug concentrations are always the same in plasma and tissues, when the distribution occurs instantaneously.

25: T F Enzyme induction can result in a faster onset of action when a prodrug is metabolized by this enzyme, assuming the prodrug is given by iv bolus.

26: T F Drugs that are subject to pgp transport in the GI membranes, might show higher oral bioavailability when given with a drug that blocks pgp activity.

27: T F Giving a drug in the form of a slow dissolving salt might allow less frequent dosing.

28: T F A slower absorption might be advantageous for a drug with a narrow therapeutic window.

29: T F D/AUC=CL as CL=ke*Vd and D/AUC=ke*Vd and Vd=(D/AUC*ke), AUC depends on ke.

30: T F PK is important as doubling of the plasma concentrations will generally result in a doubling of the effect.

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

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

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)

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

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)

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

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)

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

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

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

$$Cl = k_e \cdot V_d$$

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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} $C_{\max} = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_eT}\right)$ $C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$	**For multiple short-term I.V. infusion at steady state:** $C_{\max} = \frac{D}{Vk_eT} \cdot \frac{\left(1 - e^{-k_eT}\right)}{\left(1 - e^{-k_e\tau}\right)}$ $C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$

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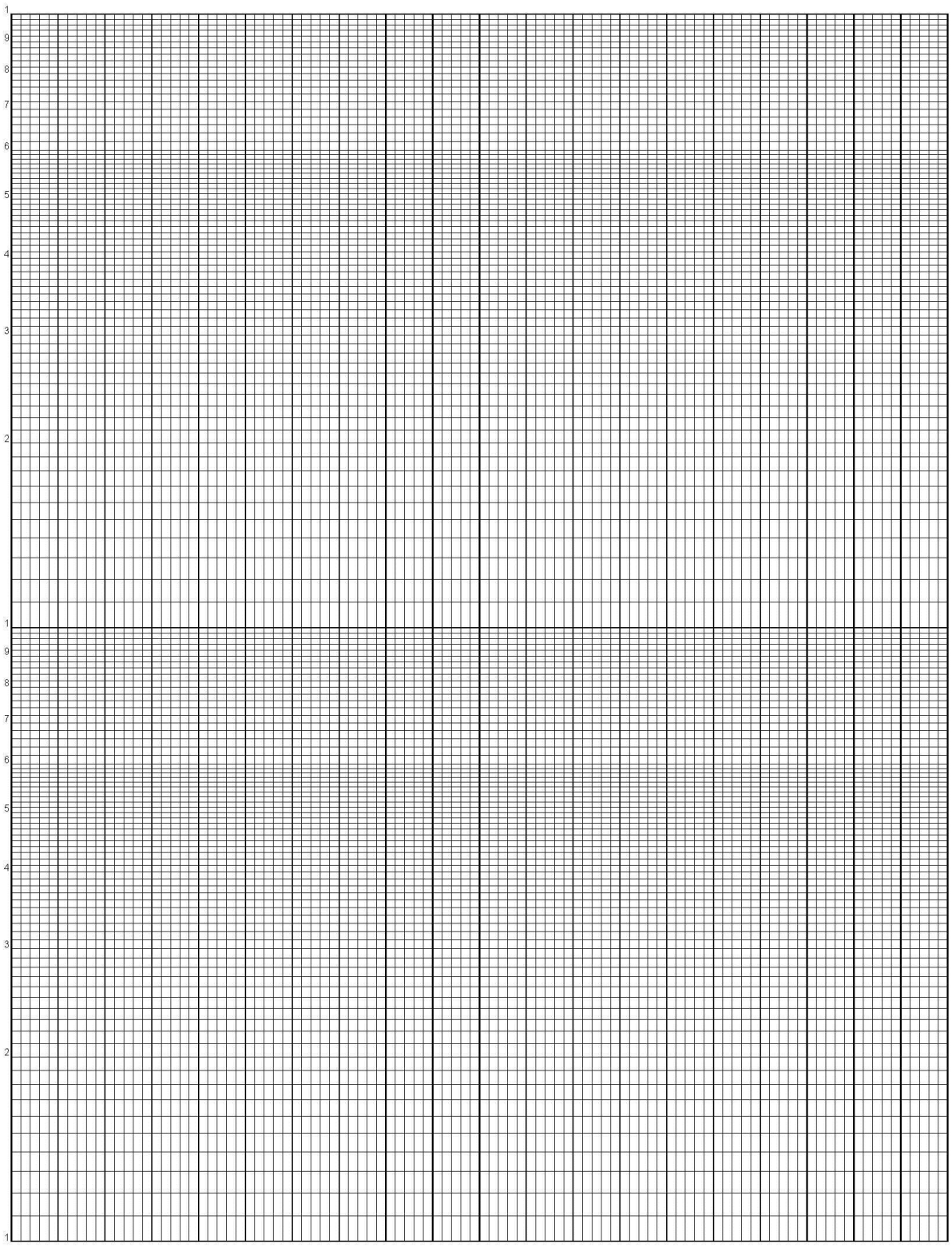

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