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UFID#: _____

PHA 5127

First Exam
Fall 2009

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

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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 The larger the volume of distribution, the lower the plasma concentration.

2: T F The volume of distribution can not be larger than the actual volume of the patient taking the medicine.

3: T F For a drug that binds to a high affinity-low capacity binding protein in plasma, the f_u and the volume of distribution might depend on the dose of the drug.

4: T F A drug with a large volume of distribution is likely to have a narrow therapeutic window.

5: T F It is likely that drugs in liver disease patients might show a reduced volume of distribution.

6: T F A volume of distribution of 20 L for a lipophilic drug, suggest that the drug's plasma protein binding is more pronounced than the tissue binding.

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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. Consider a lipophilic acidic drug (pka=1, logP=5) and a lipophilic neutral drug B (logP=5). Both do not show any affinity to transporters and show similar tissue and plasma protein binding.*

7: T F Drug B will enter the brain faster.

8: T F Drug A will be unable to enter the interstitial fluid.

9: T F Drug B be is likely to have a larger volume of distribution.

10: T F When the same dose of Drug A and B is given as an iv bolus injection, Drug A's C_o will be higher than Drug's B C_o.

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Question Set III

(15 points)

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

- the fraction ionized and
- the partition coefficient of the unionized form.

	Fraction unionized at pH 7.4	Partition coefficient
Drug A	0.5	2
Drug B	0.2	0.001
Drug C	0	0.0001
Drug D	1	3

Select the drug(s) (A, B, C, or D) that fits best (selection of 1-4 drugs is possible)

11: Drug …….... will cross well built membranes the fastest.

12: Drug ……..…….will cross well built membranes the slowest.

13: In areas of the body were membranes are extremely thin and larger aqueous pores exist, even drug…….. will be taken up at a relative good rate.

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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.*

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

15: T F The rate with which hydrophilic compounds will move across well-built membranes will depend on the concentration gradient between total drug in plasma and total drug in tissue.

16: T F Permeability limited distribution is generally seen for small, lipophilic drugs

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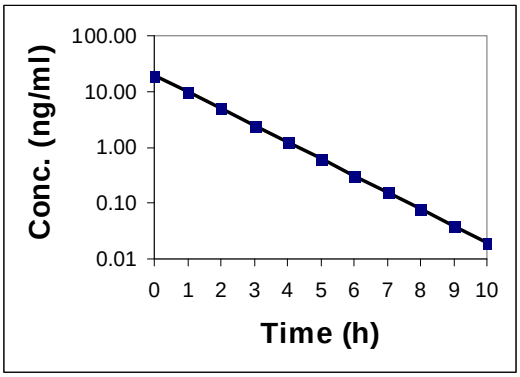
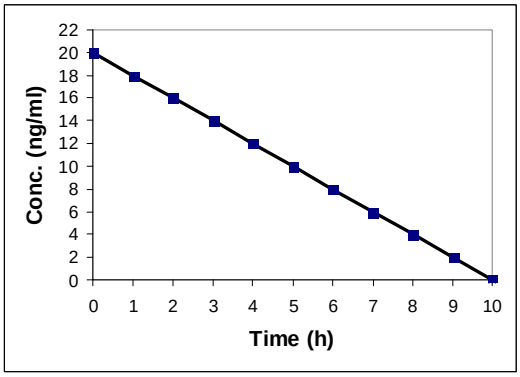
Question Set V (True or False)

(25 points)



Drug A



Drug B

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

17: T F Drug B's rate of elimination is affected by the amount of drug in the body.

18: T F Drug B's elimination rate constant has the unit "ng/ml".

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

20: T F Drug B's concentration-time profile might be explained by saturated metabolic enzymes.

21: T F Drug A's elimination rate constant has the units "ng/ml".

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Question Set VI

(10 points)

Imagine a drug that is given as an intravenous bolus. The dose was 80 mg. The elimination follows first order principles. three hours after administration the drug concentration C1 of 1.48 µg/ml is observed. Four hours after the administration the concentration C2 was 0.37 µg/ml

22: What is the elimination rate constant of this drug?

A) 0.346 h^{-1}

B) 1.386 h

C) 1.386 h^{-1}

D) 0.555 µg/(ml*h)

E) 0.370 h^{-1}

23: What will the concentration be 4.5 hours after injection?

A) 0.185 µg/ml

B) 0.370 mg/ml

C) 0 µg/ml

D) 0.185 µg/ml

E) none of the above

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Question Set VII

(10 points)

24: **A 200 mg dose** of a drug was administered to **patient 1** and **patient 2** by IV bolus injection. For patients 1 and 2, the initial concentrations were 1.25mg/L and 2.5mg/L, respectively. This drug follows a one-compartment body model, crosses membranes easily, distributes well into all tissues, and is around 50% bound to plasma proteins. Why is the initial plasma concentration different for these two patients?

Select the INCORRECT ANSWER

A) Patient 1 has more fat tissue than Patient 2.

B) Fraction unbound in plasma in Patient 1 is higher than that in Patient 2.

C) Tissue unbound fraction in Patient 1 is higher than that in Patient 2.

D) Patient 1 has a smaller volume of distribution than Patient 1.

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Question Set VIII

(10 points)

If we know that the plasma drug concentration 4 hours after a gentamycin dose was given is 4.2 mg/L and the half live is 3 hours, what was the concentration after 1 hours**. Assume that the result will be between 1.0 and 9.9.mg/L.**

25: Mark A, B, C, or D, if the number **before** the decimal point is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case.*

26: Mark A, B, C, or D, if the number **before** the decimal point is 6 (A), 7(B), 8(C), 9(D), *Leave blank if this is not the case.*

27; Mark A, B, C, or D, if the number **after** the decimal point is 1(A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case.*

28: Mark A, B, C, or D, if the number **after** the decimal point is 6 (A), 7(B), 8(C), 9(D), **0 (E**) *Leave blank if this is not the case.*

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Question Set IX

(35 points)

29: T F Free drug concentrations are always the same in plasma and tissues.

30: T F The slower the absorption from the muscle into the blood, the lower the maximum drug concentration observed in the plasma.

31: T F The slower the absorption of a drug from the muscle into the blood, the lower the plasma drug concentration at later time points.

32: T F A slow absorption might allow less frequent dosing.

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

34: T F Plasma is obtained from blood by letting it clot.

35: T F Concentrations in plasma are of relevance for the drug therapy as they are generally identical to concentrations at the target site

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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)

$$\overline{Cp}_{ss} = \frac{D}{CL \cdot \tau}$$

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

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

$$Cl = k_e \cdot V_d$$

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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

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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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Constant rate infusion

Plasma concentration (during infusion)

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

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

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

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Trough (single dose)

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

Peak (multiple dose)

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Calculated volume of distribution

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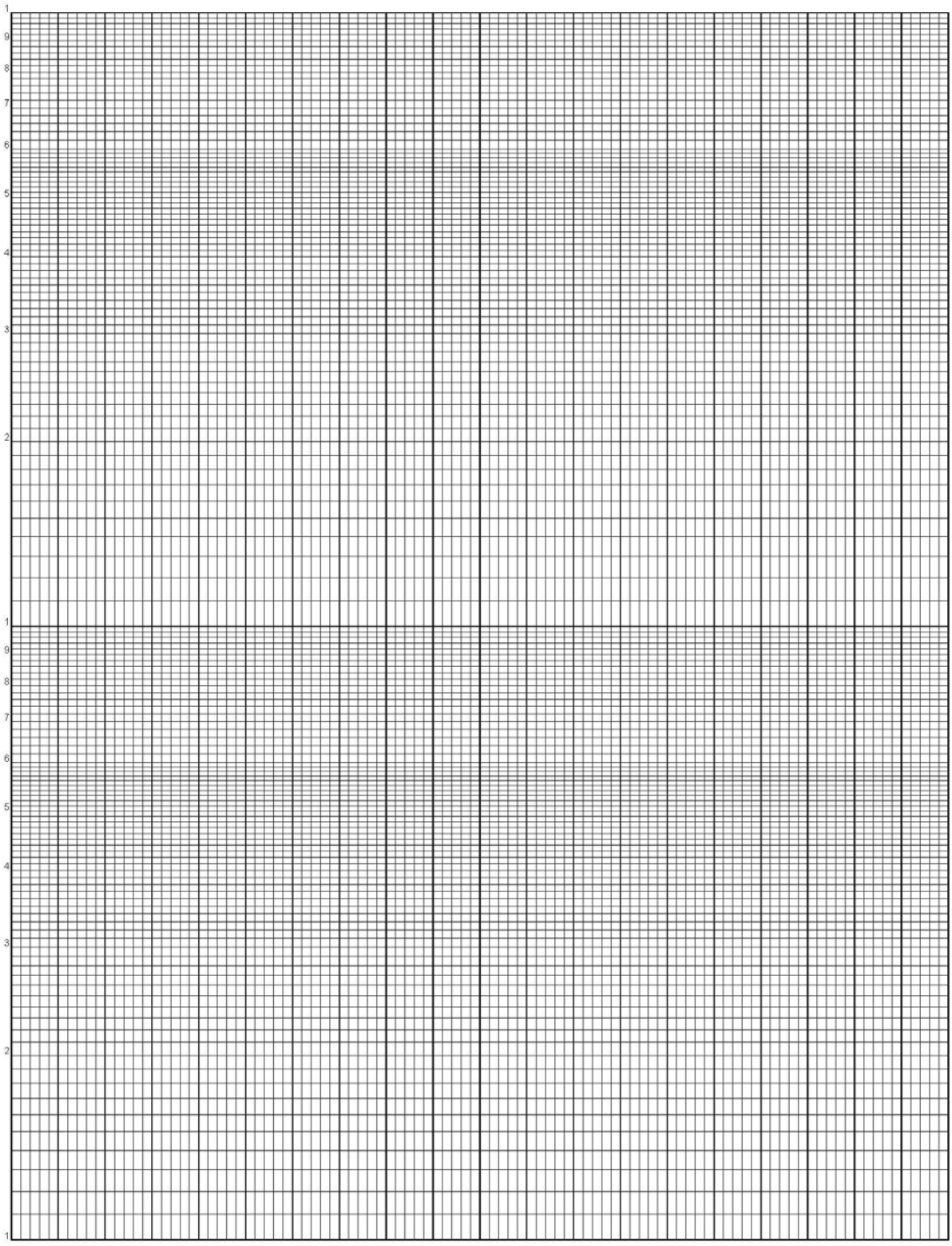

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