Name: _____

UFID#: _____

PHA 5127

First Exam
Fall 2010

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

Name: _____

UFID#: _____

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 If the elimination of a drug is described by a first order process, it will be described by a one compartment model of drug distribution.

2: T F A lipophilic drug can not have a volume of distribution that is smaller than V_T.

3: T F The pka of an acidic drug that shows perfusion limited distribution into tissues is likely to be small.

4: T F Two drugs that have similar elimination half-lives will have similar clearance estimates.

5: T F The same dose of a drug is given orally either as a solution or in form of a slow dissolving crystal suspension. The solution will show higher maximum concentrations in plasma.

6: T F Serum can be prepared by adding heparin to blood.

Name: _____

UFID#: _____

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=14, 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.

Name: _____

UFID#: _____

Question Set III

(15 points)

Listed in the Table are two 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)
1	0.5	2.1	240
2	0.91	0.07	290
3	0.074	10	320
4	0.72	0.005	456

11: Select the correct rank order with which drugs 1-4 will enter brain tissue. Assume that the drugs are not subject to transporters at the blood-brain barrier.

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: 3 slower than 1 slower than 4 slower than 2

Name: _____

UFID#: _____

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.*

12: 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.

13: 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.

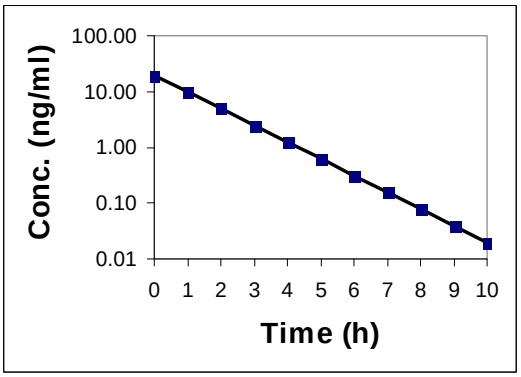
14: T F Permeability limited distribution is generally seen for small, lipophilic drugs

Name: _____

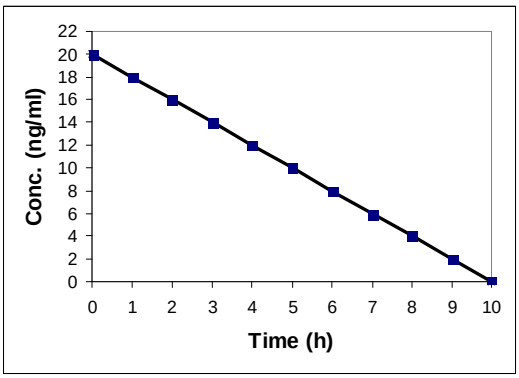
UFID#: _____

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 B's rate of elimination is affected by the amount of drug in the body.

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

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

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

19: T F The half-life of drug B is 5 hours.

Name: _____

UFID#: _____

Question Set VI

(10 points)

20: An investigational new drug is eliminated entirely by hepatic metabolism, with a clearance of 1.40 L/min in subjects with an average liver blood flow of 1.50 L/min. What would be the expected clearance in a congestive heart failure patient with a liver blood flow of 1.10 L/min but no change in hepatic extraction ratio?

A) 1.10 L/min
B) 1.40 L/min
C) 1.18 L/min
D) 1.03 L/min
E) None of the above

21: The lipophilic drug A has a volume of distribution of 100 L. In the presence of drug B, drug A is displaced from plasma albumin sites binding sites only (1.5-fold change in fraction unbound in plasma). Predict the change in volume of distribution for drug A. Assume negligible change in tissue binding

A) 115 L
B) 150 L
C) 200 L
D) 300 L
E) None of the above

Name: _____

UFID#: _____

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), bioavailability (F) for tablet, AUC, and half-life ($t_{1/2}$) of a low-extraction drug? (Please note that ↔ means no change)

A: ↓C_0, ↑ CL, ↓F, AUC↓, ↓ $t_{1/2}$

B: ↔ C_0, ↔ CL, ↑F, AUC ↑, ↔ $t_{1/2}$

C: ↓C_0, ↔CL, ↔ F, AUC↔,↑ $t_{1/2}$

D: ↑C_0, ↓ CL, ↔ F, AUC ↑, ↑ $t_{1/2}$

E: none of above combinations.

Name: _____

UFID#: _____

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

Name: _____

UFID#: _____

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 For a drug that shows permeability controlled uptake into all tissues, total drug concentrations are always higher in the plasma than in tissues.

26: T F When the Vd of a drug is 41L, we can conclude that the drug has no plasma protein binding or tissue binding.

27: T F A fast absorption 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 The Fick's law is: $dQ/dt=D*K*(C_{plasma}-C_{tissue})/h$. The k in the equation denotes the first order elimination rate constant.

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

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

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

$$Cl = k_e \cdot V_d$$

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

<table>
<tr>
<td>If the dosing involves the use of I.V. bolus administration:</td>
<td>
For a single I.V. bolus administration:
$$C_0 = \frac{D}{V}$$
$$C = C_0 \cdot e^{-k_e t}$$
</td>
<td>
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
$$C_{\max ss} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e\tau\tau})}$$
$$C_{\min ss} = C_{\max ss} \cdot e^{-k_e\tau}$$
</td>
</tr>
<tr>
<td>If the dosing involves the use of I.V. infusion:</td>
<td>
For a single short-term I.V. infusion:
Since τ = t for C_{max}
$$C_{\max} = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_eT}\right)$$
$$C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$$
</td>
<td>
For multiple short-term I.V. infusion at steady state:
$$C_{\max} = \frac{D}{Vk_eT} \cdot \frac{\left(1 - e^{-k_eT}\right)}{\left(1 - e^{-k_e\tau}\right)}$$
$$C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$$
</td>
</tr>
</table>

If the dosing involves a I.V. infusion (more equations):

$$C_t = \frac{D}{Vk_eT} \cdot \left(e^{k_eT} - 1\right) \cdot e^{-k_et}$$ (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

$$CL = V \cdot k_e$$

If the dosing involves oral administration:

For a single oral dose:

$$C = \frac{F \cdot D \cdot k_a}{V\left(k_a - k_e\right)} \cdot \left(e^{-k_et} - e^{-k_at}\right)$$

$$t_{\max} = \ln\left[\frac{k_a}{k_e}\right] \cdot \frac{1}{\left(k_a - k_e\right)}$$

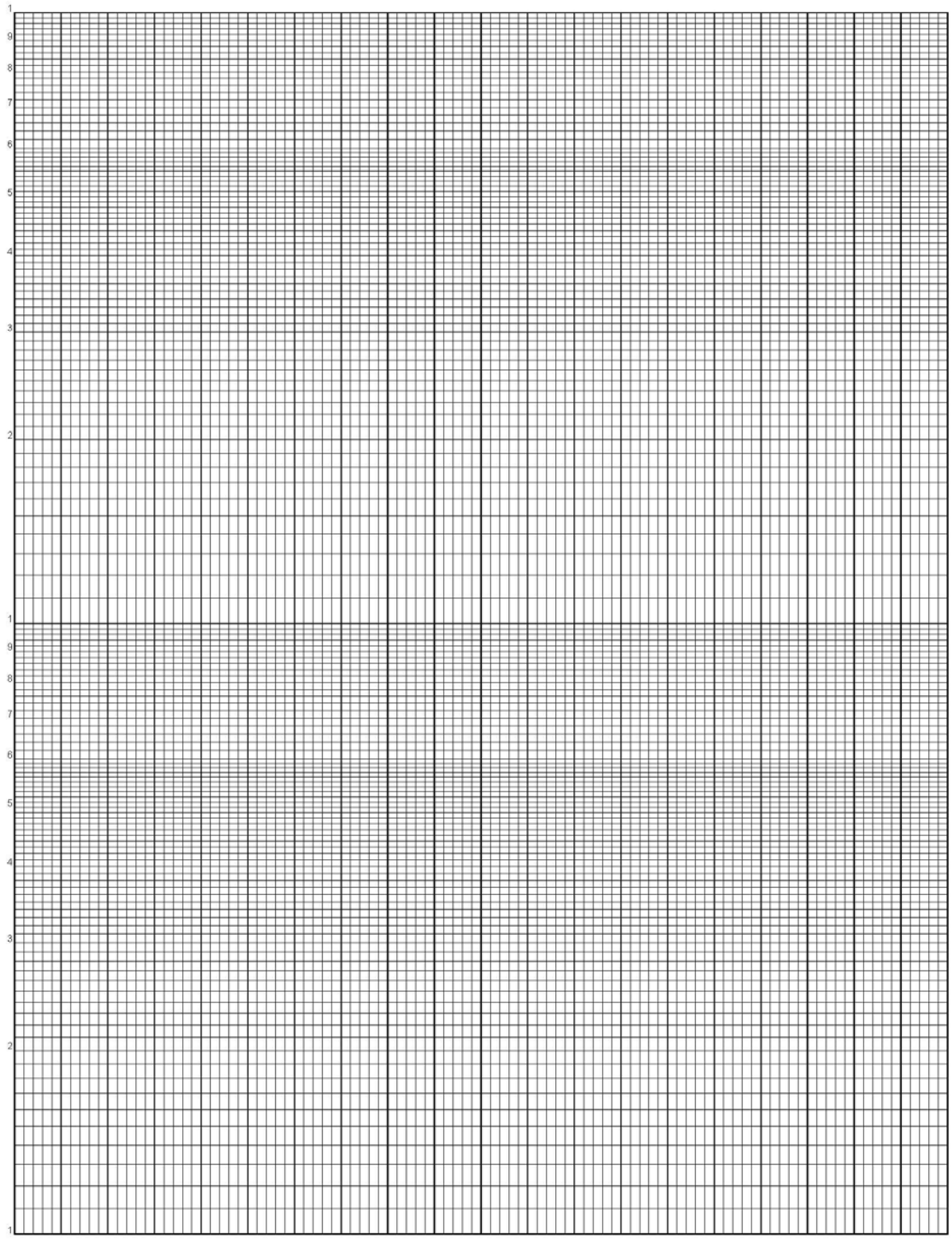
For multiple oral doses:

$$C = \frac{F \cdot D \cdot k_a}{V\left(k_a - k_e\right)} \cdot \left[\frac{e^{-k_et}}{\left(1 - e^{-k_e\tau}\right)} - \frac{e^{-k_at}}{\left(1 - e^{-k_}\right.}\right.$$

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

Name: _____

UFID#: _____



Name: _____

UFID#: _____