Name: KEY

UFID#: ____________

PHA 5127

First Exam
Fall 2012

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. 20 pts

IV 15 pts

V. 25 pts

VI. 20 pts

VII. 15 pts

VIII. 20 pts

IX. 35 pts

TOTAL: 200 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 Assume a drug that is eliminated through metabolism. The drug's plasma concentration decreases by 4 ng/ml every 2 hours. It is likely that the enzymes involved in the metabolism are saturated.

2: T (F) Assume a drug eliminated through enzymatic metabolism. The drug's plasma concentration decreases by 4 ng/ml every 2 hours. The elimination rate constant describing this metabolism will have the unit: 1/hr

3: (T) F The rate at which a lipophilic drug, of low molecular weight that is not an acid nor a base, is taken up by tissues will significantly be related to the blood flow through those tissues.

4: T (F) The rate at which a lipophilic drug that is not an acid nor a base is taken up by fat tissue is likely to be faster than the rate at which it is taken up by the kidney.

5: (T) F The same dose of a drug is given either as a solution or in form of a slow dissolving crystal suspension. The solution will have to be given more often during the day.

6: T (F) Plasma can be prepared by letting the collected patient's blood clot. The resulting supernatant is called plasma.

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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. Consider the lipophilic drug A and a drug B which is even more lipophilic. Both do not show any affinity to transporters (Ficks law applies), show the same tissue and plasma protein binding.*

7: T (F) Drug B will enter the liver faster.

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

9: (T) F Both drugs will have the same volume of distribution.

10: T (F) Drug B is more likely to show permeability limited tissue uptake.

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Question Set III

(20 points)

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

- the fraction unionized 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

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

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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.*

Assume the same dose of penicillin G is given to patients as iv bolus injection (as solution in saline), intramuscular (i.m.) oily injection or orally.

12: (T) F Giving the drug orally will result in a much smaller AUC than after i.m. and iv injection.

13: T (F) Penicillin G is stable in the gastro-intestinal tract.

14: T (F) iv injections allow a less frequent dosing.

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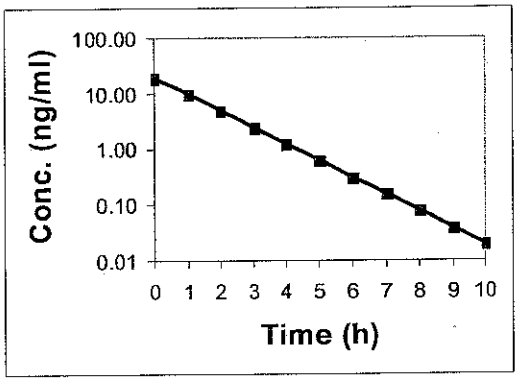
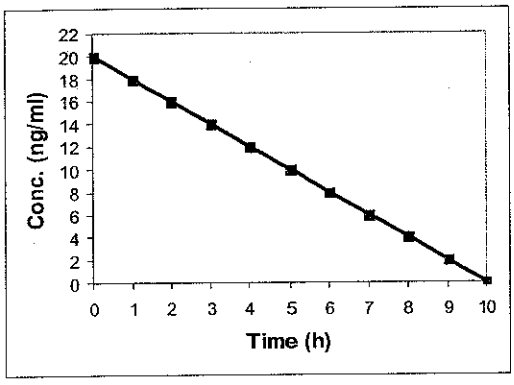
Question Set V (True or False)

(25 points)



Drug A



Drug B

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

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

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

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

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

19: (T) F The half-life of Drug B depends on the concentration that should be cut into half.

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Question Set VI

(20 points)

20: 200 mg of Drug A was administered to a patient through iv bolus injection. A plasma drug concentration of 0.78 mg/L was measured after 2 hours. A plasma drug concentration of 0.16 mg/L was measured after 8 hours. The drug's distribution is instantaneous.

Assuming a **first** order process, calculate the elimination rate constant

A: $0.16\ h^{-1}$

B: 0.16 mg/ (L*h)

C: 0.264 mg/ (L*h)

D: $0.264\ h^{-1}$

E: None of the above

21: 200 mg of Drug A was administered to a patient through i.v bolus injection. A plasma drug concentration of 0.78 mg/L was measured after 2 hours. A plasma drug concentration of 0.16 mg/L was measured after 4 hours. The drug's distribution is instantaneous.

Assuming a **zero** order process, calculate the initial drug concentration

A: 1.32 mg/L

B: 1.32 L

C: 1.4 mg/L

D: None of the above

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Question Set VII

(15 points)

A drug (lipophilic, unionized, low molecular weight) is showing in average a pronounced binding to plasma proteins of 99%. Between-subject variability of protein binding is pronounced. 1000mg of the drug is given as IV bolus injection to two patients. **Patient 1 has a much stronger plasma protein binding** for the drug (99.995%) than the second patient (99.99%). The tissue binding is the same in both patients and is equal to 90%.
Based on the given information please indicate whether **patient 1** will have a larger (↑), smaller (↓) identical (↔) value than patient 2 for:

- total initial total plasma drug concentration ($\mathbf{C_0}$),
- free initial total plasma drug concentration (**free $\mathbf{C_0}$**),
- $\underline{f_u}$
- V_d

22 :

A: $C_0 \uparrow$, free $C_0 \uparrow$, $f_u \downarrow$, $V_d \downarrow$

B: $C_0 \downarrow$, free $C_0 \leftrightarrow$, $f_u \downarrow$, $V_d \uparrow$

C: $C_0 \uparrow$, free $C_0 \downarrow$, $f_u \downarrow$, $V_d \downarrow$

D: $C_0 \uparrow$, free $C_0 \uparrow$, $f_u \uparrow$, $V_d \leftrightarrow$

E: none of above combinations.

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Question Set VIII

(20 points)

Assume a drug is substrate of a specific transport protein. What of the following statements are **True (A) or False (B). On the bubble sheet mark *A for true* or *B for false***

23: T (F) Transporters do not use energy.

24: T (F) Transporters only eliminate drugs from the body.

25: T (F) Transporters are only present in liver and kidney.

26: (T) F Transporters are saturable.

27: (T) F Transporters work often in conjunction with enzymes.

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Question Set IX

(35 points)

28: (T) F Free drug concentrations are assumed to be the same in plasma and tissues, when the distribution is assumed to be instantaneous.

29: 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.

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

31: T (F) A fast absorption might allow less frequent dosing.

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

33: T (F) The Fick's law is: $dq/dt = D * K * (Cplasma - Ctissue)/h$. The k in the equation denotes the first order elimination rate constant.

34: 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)

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

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)

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

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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Plasma concentration (during infusion)

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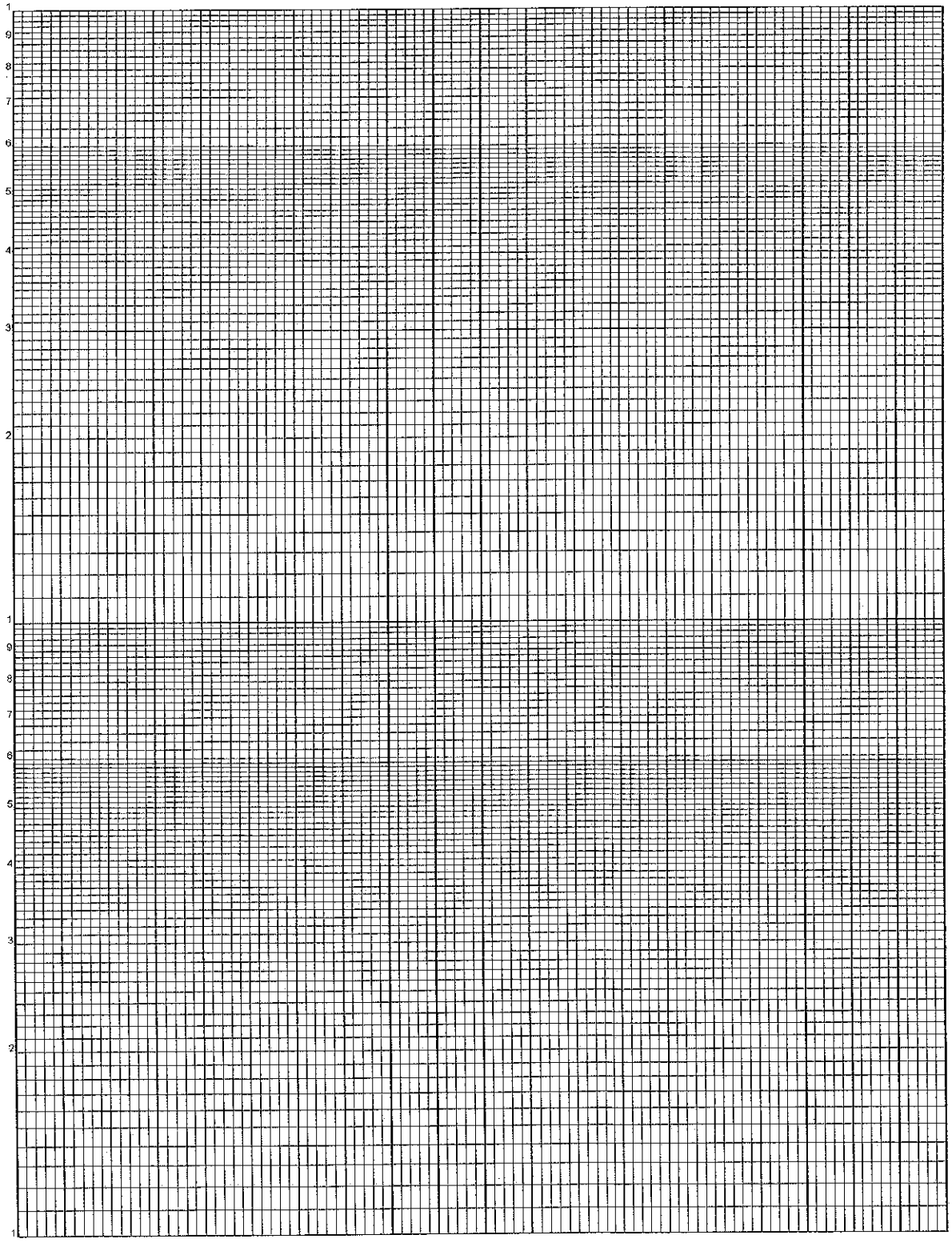

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