Name: _____

UFID #: _____

PHA 5127

Second Exam

Fall 2007

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

Name

Put all answers on the bubble sheet

TOTAL _____/130 pts

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Question Set I (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 as true (A) or false (B). Drug A is cleared only by hepatic metabolism and has an intrinsic clearance of 80,000 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 if given together.

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Question Set II
(18 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 a peak concentration of 0.18 μg is observed (C_o). When given orally, the oral bioavailability is 99.9 %. Plasma Protein Binding is 50% (f_u=0.5).

Peak [ug/ml]	**0.18**
V [L]	**108**
F (%)	**99.9**
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 also responsible for metabolism of Drug A will significantly affect the clearance of Drug A

11: T F Drug B, known to induce enzymes that are also responsible for metabolism of Drug A is likely to decrease the clearance of A

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Question Set III (Matching)
(20 points)

For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a **hydrophilic strong acid**, **protein bound** drug **that is only eliminated through the kidneys** (some answers may be used more than once).

Select the effect on kinetics
(A) Oral Bioavailability F↓ *(B)* Cl_{ren} ↓ *(C)* V_D ↑ (D) oral bioavailability F↑
(E) nothing happens or effect is not listed

Physiological change
12: Decrease in plasma protein binding____

13: Decrease in tissue binding ____

14: Decrease in GFR ____

15: Increase in urine flow_____

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Question Set IV
(20 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 to that of blood (about 7). The volume of distribution is **40L.**

16: What value describes best the clearance? (10 points)

A: 0.15 mL/min
B: 13 mL/min
C: 130 mL/min
D: 6.6 mL/min
E: none of the above

17: Assume a one compartment body model? What is the renal clearance of a typical aminoglycoside in a patient showing a creatinine clearance of 65 ml /min (10 points). The plasma protein binding for this aminoglycoside is 90 %.

A: 58.5 ml/min

B: 130 ml/min

C: 65 ml/min

D: 6.5 ml/min

E: 35.8 ml/min

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Question Set V
(10 points)

18: 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?

A: 72 ml/min

B: 84 ml/min

C: 70 ml/min

D: 103 ml/min

E: none of the above

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Question Set VI

(5 points)

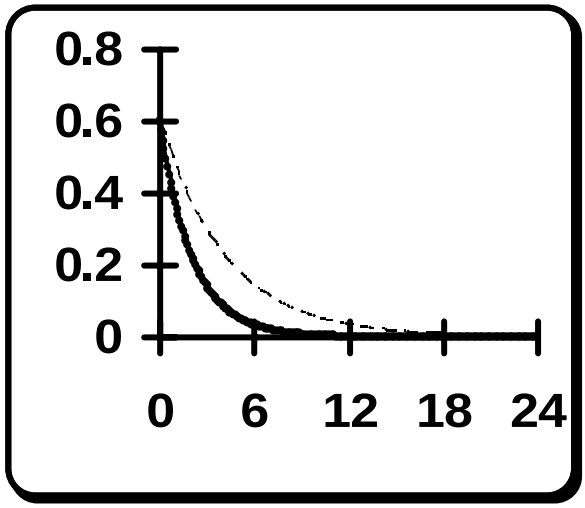
19: The following patients differ in the

(A) dose received

(B) clearance

(C) volume of distribution

Peak (mg/L)	0.60	**0.60**
Ke (1/h)	0.2	**0.5**
t1/2 (h)	2.9	**1.4**
AUC (mg/L*h)	2.50	**1.25**



Name: _____

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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)

20:	T	F	The renal clearance of a drug (as determined by filtration and reabsorbtion) always depends on the tissue binding of the drug.
21:	T	F	To determine the clearance of a drug, one needs to know whether the drug is a one or two compartment drug.
22:	T	F	Drinking a lot of water (urine flow is doubled) will increase significantly the renal clearance of aminoglycocsides
23:	T	F	For an acidic drug with a pk_a of 1.0, adjustment of the urine pH within physiological ranges will significantly change the renal clearance.
24:	T	F	Hepatic clearance depends on the drug plasma concentration, as the rate of metabolism increases with increasing drug concentrations in the blood.

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Question Set VIII (True or False)

(12 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) for a drug that is mainly eliminated through hepatic metabolism.

25: T F The larger the volume of distribution, the smaller the AUC of a given drug..

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

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

28: T F An increase in plasma protein binding will under no circumstances result in a decrease of the drug's hepatic clearance

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Question Set IX (5 points)

29. Which of the following statements 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.

3) Genetic variability in metabolizing enzymes always alters hepatic clearance.

4) In general, we should always use IBW for drug recommendations for calculating creatinine clearance (CL_{cr})

A) 2, 3, 4

B) 1, 3 & 4

C) 2, 3

D) 3, 4

E) None of the above

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Question Set X (10 points)

30. An investigational new drug is eliminated entirely by liver (hepatic) metabolism, with a clearance of 1.35L/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

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

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)

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

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

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

$$Cl = k_e \cdot V_d$$

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:

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

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