

Name: _____

UFID#: _____

PHA 5127

**Final Exam
Fall 2008**

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

Name

Please transfer the answers onto the bubble sheet. Please fill in all the information necessary to identify yourself. The proctors will also collect your exams.

Total points : /185 points

Good LUCK.

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Section 1

Question 1: For the equations describing constant rate infusions. (_5_ pts)

- 1: The drug input is assumed to be a first order process
- 2: The drug input is assumed to be a zero order process
- 3: The elimination is assumed to be a zero order process
- 4: The elimination is assumed to be a first order process
- 5: The drug distribution is modeled as a first order process
- 6: The drug distribution is modeled to be a zero order process

1. The correct statement(s) for question 1 are (is):

- A: 1, 3 and 5
- B: 2, 3 and 6
- C: 1 and 3
- D: 2 and 4
- E: 4 and 6

Question 2: We have defined several volumes of distribution when talking about a 2-compartment model (5 points).

The volume of distribution in a 2 compartment model:

- 1: relates the amount of drug in the body to the plasma concentration.
- 2: is decreasing with time after drug administration.
- 3: depends on clearance during the beta-phase.
- 4: is not constant because it takes time for the drug to enter and leave the peripheral compartment.
- 5: is not constant because $f_u T$ changes.

2. Select the **correct** statement(s)

- A: (1, 2, 3, 4, 5)
- B: (1, 3, 4, 5)
- C: (1, 2, 5)
- D: (1, 4, 5)
- E: (none of the above)

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Section 2:

A 60-kg patient is begun on a continuous intravenous infusion of Drug X at 36 mg/hr. Forty-eight hours after beginning of the infusion, the plasma concentration is 12 mg/L. The elimination rate constant is 0.1155 h^{-1} .

3. How many hours will it take to reach steady state (5 points)

- A: 18 h
- B: Not enough information to provide answer.
- C: 1 days
- D: 2-3 days
- E: 6 days

Question:

If we assume that this concentration is at steady state, what is the clearance? (5 points)

- 4 Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case This would be E for 50 h)*
- 5: Mark A, B, C, D, E if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 50 h)*
- 6: Mark A, B, C, or D, if the number in the first decimal column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case . You would leave this blank for 50 h)*
- 7: Mark A, B, C, or D, if the number in the first decimal column is 6 (A), 7(B), 8(C), 9(D), 0 (E) *Leave blank if this is not the case. This would be E for 50 h)*

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Section 3 :

A 60-kg patient is begun on a continuous intravenous infusion of Drug X at 36 mg/hr. Forty-eight hours after beginning of the infusion, the plasma concentration is 12 mg/L. The elimination rate constant is 0.1155 h^{-1} . Assume a one-compartment model.

Question: What is the volume of distribution in Liters (10 points)

- 8 Mark A, B, C, or D, if the number in the tens column is 1 (A), 2(B), 3(C), 4(D), 5(E).
Leave blank if this is not the case This would be E for 50 l
- 9: Mark A, B, C, D, E if the number in the tens column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 50 l*
- 10: Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E).
Leave blank if this is not the case . You would leave this blank for 50 l
- 11: Mark A, B, C, or D, if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0 (E)
Leave blank if this is not the case. This would be E for 50 l

Section 3 continued:

A 60-kg patient is begun on a continuous intravenous infusion of Drug X at 36 mg/hr. Forty-eight hours after beginning of the infusion, the plasma concentration is 12 mg/L. The elimination rate constant is 0.1155 h^{-1} . The elimination rate constant is 0.1155 h^{-1} . Assume a one-compartment model.

If the infusion is continued for 4 days and then discontinued, what would the plasma concentration be 6 hours after stopping the infusion? Please perform calculations, we might check. (5 points)

- 12 Mark A, B, C, or D, if the number in the tens column is 1 (A), 2(B), 3(C), 4(D), 5(E).
Leave blank if this is not the case This would be E for 50 mg/ l
- 13: Mark A, B, C, D, E if the number in the tens column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 50 mg/ l*
- 14: Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E).
Leave blank if this is not the case . You would leave this blank for 50 m/l
- 15: Mark A, B, C, or D, if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0 (E)
Leave blank if this is not the case. This would be E for 50 m/l

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Question Set 3 continued:

A 60-kg patient is begun on a continuous intravenous infusion of Drug X at 36 mg/hr. Forty-eight hours after beginning of the infusion, the plasma concentration is 12 mg/L. The elimination rate constant is 0.1155 h^{-1} .

Question: What infusion rate would likely result in a steady state concentration of 24 mg/L. (10 points) **Round appropriately.**

- 16: Mark A, B, C, or D, if the number in the tens column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case This would be E for 50 mg/h*
- 17: Mark A, B, C, D, E if the number in the tens column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 50 mg/h*
- 18: Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case . You would leave this blank for 50 mg/h*
- 19: Mark A, B, C, or D, if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0 (E) *Leave blank if this is not the case. This would be E for 50 mg/h*

Section 4:

A 60 kg patient is started on 80 mg of gentamycin given every 6 hr as 1-hr infusion. This patient is assumed to have an “average” volume of distribution (value of the population mean) of 0.25 L/kg and a half-life of 3 hr.

Question : What would be the plasma concentration after the first infusion (**one hour after the stop of the infusion**). Please provide calculations (5 points). Round appropriately.

- 20: Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case This would be E for 5.0 mg/L*
- 21: Mark A, B, C, D, E if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 5.0 mg/L*
- 22: Mark A, B, C, or D, if the number in the first decimal column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case . You would leave this blank for 5.0 mg/L*
- 23: Mark A, B, C, or D, if the number in the first decimal column is 6 (A), 7(B), 8(C), 9(D), 0 (E) *Leave blank if this is not the case. This would be E for 5.0 mg/L*

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Section 4 continued :

A 60 kg patient receives 80 mg of gentamycin given every 6 hr as 1-hr infusion. This patient is assumed to have an “average” volume of distribution (value of the population mean) of 0.25 L/kg and a half-life of 3 hr.

Question: Based on above information, what is the fluctuation at steady state that you can expect? Please provide calculations. Round appropriately (5 points)

24: Mark A, B, C, or D, if the number in the ones column is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case. This would be E for 5*

25: Mark A, B, C, D, E if the number in the ones column is 6 (A), 7(B), 8(C), 9(D), 0(E) *Leave blank if this is not the case. You would leave this blank for 5.0 mg/L*

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Section 4 (5 points each)

The following questions are related to parts (blocks) of equations that are shown in the equation blocks A, B, C, D, E

A: $(1 - e^{-k_e T})$

B: $\frac{k_o}{CL}$

C: $\frac{k_o}{CL} (1 - e^{-k_e T})$

D: $\frac{1}{1 - e^{-k_e \tau}}$

E: $e^{-k_e t'}$

26. What form of administration is captured when blocks A, B, D and E are multiplied together (C is not included for this question)? Mark answer in 26: (5 points)

- A: single iv bolus injection
- B: multiple oral absorption
- C: multiple bolus injections
- D: multiple short term infusions
- E: single constant rate infusion

Question : Identify the block that best describes to following. (20 points)

27: A factor suitable to quantify how much a single short term infusion is away from the steady state level that would be observed if a patient receives one infusion for a long time.

28: This block can be used to calculate the trough concentration at steady state from C_{max} values, when given either as multiple short term infusions or multiple iv bolus injections.

29: This block provides the C_{max} after a drug is given as a single short term infusion

30: this block provides the accumulation (at steady state) when a dose is given at defined dosing intervals

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Section 5:

What of the following statements are true (A) or false (B) (25 points)

- 31: T F If the terminal slope after oral administration is less steep than after iv injection, drug particles might dissolve very slowly.
- 32: T F If the first pass effect is saturable for a given drug, the faster oral absorption, the higher will be the oral bioavailability
- 33: T F For bioequivalence, the area of the concentration time profiles is not important as bioequivalence is only interested in the equivalence of biological effects
- 34: T F A two compartment body model is useful to describe the plasma concentrations time profiles of drugs that enter parts of the body slowly.
- 35: T F The smaller CL and the larger the volume of distribution, the larger the accumulation of multiple short term infusions.

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Section 6:

Patient 1 and 2 received a drug as **an iv bolus injection**. Pharmacokinetic and physiological characteristics, such as dose, fraction of the drug unbound in plasma and tissue, intrinsic clearance, liver blood flow, and volume of plasma and volume of the tissue water in these patient are shown below. Assume drug is cleared through liver metabolism.

TABLE 1: INPUT PARAMETERS

	Patient 1	Patient 2
D [mg]	40	40
fu	1	1
fuT	0.3	0.3
CLi [L/h]	3000	0.1
Q [L/h]	90	90
Vp [L]	3	3
VTW [L]	38	38

The next table shows the resulting pharmacokinetic parameters in **Patient 1**.

Please circle in the free column of the Table 2 for each parameter whether the parameter (Peak concentration, Ke, V_d, Cl, t_{1/2}, E, F, AUC) will be **will be larger (A)**, about **the same (B)**, or **will be smaller (C)** than those estimates observed in **Patient 1**.

Mark on the bubble sheet the appropriate A, B, C (40 points)

Table 2: OUTPUT PARAMETERS

Question:		Patient 1	Patient 2
36 (5 points)	Peak [µg/ml]	1.0	Larger (A), about the same (B), Smaller (C)
37 (5 points)	Ke [1/h]	2.0	Larger (A), about the same (B), Smaller (C)
38 (5 points)	V_d [L]	41	Larger (A), about the same (B), Smaller (C)
39 (5 points)	CL [L/h]	81.8	Larger (A), about the same (B), Smaller (C)
40 (5 points)	t_{1/2} [h]	0.35	Larger (A), about the same (B), Smaller (C)
41 (5 points)	E	0.91	Larger (A), about the same (B), Smaller (C)
42 (5 points)	F [%] for tablet	9.1	Larger (A), about the same (B), Smaller (C)
43 (5 points)	AUC [µg/ml*h]	0.5	Larger (A), about the same (B), Smaller (C)

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Section 7: (40 points)

44. Which of the following factors **might** significantly affect the renal clearance of an acidic drug ($pK_a = 7$) that has a molecular weight of 200 Dalton? Assume urine pH of 7 (5 pts).

1. plasma protein binding
2. volume of distribution.
3. Oral bioavailability
4. pH of urine
5. liver blood flow

A: 1, 2, 3

B: 1, 4

C: 1, 2, 4

D: 1, 3, 5

E: none of the above combinations

Mark whether the following statements are **true** (A) or **false** (B). (35 points)

- 45 T F Loading doses are mainly given for drugs with small volume of distribution and/or high clearance
- 46 T F Assume that the oral bioavailability of a drug is 50%. If the oral absorption of this drug is very fast, C_{max} after oral absorption will be about half of that after iv administration.
- 47 T F Assume that the oral bioavailability of a drug is 50%. If the oral absorption of this drug is slow, C_{max} after oral absorption will be about half of that after iv administration
- 48 T F After iv bolus injections, 200 mg given every 12 hours will result in the same average C_{pss} than 400 mg given once a day.
- 49 T F 200 mg given every 12 hours will result in the same AUC than 400 mg given once a day.
- 50 T F Drug A shows at steady state an accumulation after multiple short term infusions of 4, Drug B shows one of 2. Drug B will achieve steady state fast.
- 51 T F Assume the half life of a drug to be 8 hours. The drug should be given every 8 hours to achieve a fluctuation of 2.

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)

$$C = \frac{C_0 \cdot e^{-k_e \cdot t}}{(1 - e^{-k_e \cdot \tau})}$$

Peak (multiple dose)

$$C_{\max} = \frac{C_0}{(1 - e^{-k_e \cdot \tau})}$$

Trough (multiple dose)

$$C_{\min} = \frac{C_0 \cdot e^{-k_e \cdot \tau}}{(1 - e^{-k_e \cdot \tau})}$$

Average concentration (steady state)

$$\bar{C}_{p_{ss}} = \frac{D}{CL \cdot \tau}$$

Oral administration

Plasma concentration (single dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t})$$

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)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(\frac{e^{-k_e \cdot t}}{(1 - e^{-k_e \cdot \tau})} - \frac{e^{-k_a \cdot t}}{(1 - e^{-k_a \cdot \tau})} \right)$$

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

$$\bar{C} = \frac{F \cdot D}{CL \cdot \tau}$$

Clearance

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

$$Cl = k_e \cdot V_d$$

Constant rate infusion

Plasma concentration (during infusion)

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

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)

$$C_{\max(1)} = \frac{D}{CL \cdot T} \cdot (1 - e^{-k_e \cdot T})$$

Trough (single dose)

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

Peak (multiple dose)

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

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

$$Vd = \frac{D}{k_e \cdot T} \cdot \frac{(1 - e^{-k_e \cdot T})}{[C_{\max} - (C_{\min} \cdot e^{-k_e \cdot T})]}$$

Calculated recommended dosing interval

$$\tau = \frac{\ln\left(\frac{C_{\max(\text{desired})}}{C_{\min(\text{desired})}}\right)}{k_e} + T$$

Calculated recommended dose

$$D = C_{\max(\text{desired})} \cdot k_e \cdot V \cdot T \cdot \frac{(1 - e^{-k_e \cdot \tau})}{(1 - e^{-k_e \cdot T})}$$

Two-Compartment-Body Model

$$C = a \cdot e^{-\alpha t} + b \cdot e^{-\beta t}$$

$$AUC_{\infty} = a / \alpha + b / \beta$$

$$Vd_{\text{area}} > Vd_{\text{ss}} > Vc$$

Creatinine Clearance

$$CL_{\text{creat}} (\text{male}) = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot Cp_{\text{creat}}}$$

$$CL_{\text{creat}} (\text{female}) = \frac{(140 - \text{age}) \cdot \text{weight}}{85 \cdot Cp_{\text{creat}}}$$

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL_{creat} in ml/min

K_e for aminoglycosides

$$K_e = 0.00293(\text{CrCL}) + 0.014$$

Metabolic and Renal Clearance

$$E_H = \frac{Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_H = E_H \cdot Q_H = \frac{Q_H \cdot Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_{ren} = \text{RBF} \cdot E = \text{GFR} \cdot \frac{C_{in} - C_{out}}{C_{in}}$$

$$Cl_{ren} = \frac{\text{rate of excretion}}{\text{plasma concentration}}$$

$$Cl_{ren} = fu \cdot \text{GFR} + \left[\frac{\text{Rate of secretion} - \text{Rate of reabsorption}}{\text{Plasma concentration}} \right]$$

$$Cl_{ren} = \frac{\text{Urine flow} \cdot \text{urine concentration}}{\text{Plasma concentration}}$$

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

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

$$Cl = k_e \cdot V_d$$

For One Compartment Body Model

<p>If the dosing involves the use of I.V. bolus administration:</p>	<p>For a single I.V. bolus administration:</p> $C_0 = \frac{D}{V}$ $C = C_0 \cdot e^{-k_e t}$	<p>For multiple I.V. bolus administration:</p> $C_n(t) = \frac{D}{V} \cdot \frac{(1 - e^{-nk_e \tau})}{(1 - e^{-k_e \tau})} \cdot e^{-k_e t}$ <p>at peak: $t = 0$; at steady state $n \rightarrow \infty$ at trough: $t = \tau$</p> $C_{\max ss} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e \tau})}$ $C_{\min ss} = C_{\max ss} \cdot e^{-k_e \tau}$
<p>If the dosing involves the use of I.V. infusion:</p>	<p>For a single short-term I.V. infusion: Since $\tau = t$ for C_{\max}</p> $C_{\max} = \frac{D}{Vk_e T} \cdot (1 - e^{-k_e T})$ $C_{\min} = C_{\max} \cdot e^{-k_e (\tau - T)}$	<p>For multiple short-term I.V. infusion at steady state:</p> $C_{\max} = \frac{D}{Vk_e T} \cdot \frac{(1 - e^{-k_e T})}{(1 - e^{-k_e \tau})}$ $C_{\min} = C_{\max} \cdot e^{-k_e (\tau - T)}$

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