

Name: _____

UFID#: _____

PHA 5127

Final Exam Fall 2005

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

Name _____

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

Good LUCK.

Question/Points

TOTAL _____/200 pts

1 _____	10 pts	11 _____	/10 pts	21 _____	/10 pts
2 _____	10 pts	12 _____	/10 pts	22 _____	/10 pts
3 _____	10 pts	13 _____	/5 pts	23 _____	/10 pts
4 _____	10 pts	14 _____	/5 pts		
5 _____	10 pts	15 _____	/5 pts		
6 _____	10 pts	16 _____	/5 pts		
7 _____	10 pts	17 _____	/5 pts		
8 _____	10 pts	18 _____	/10 pts		
9 _____	10 pts	19 _____	/10 pts		
10 _____	10 pts	20 _____	/5 pts		

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Question 1: Select the correct statement(s) concerning a two-compartment body model. (10 pts)

- 1 For a two-compartment-body model drug, the parameter alpha is always larger than the parameter beta.
- 2 The volume of distribution during the beta phase is larger than that of the volume of distribution at steady state.
- 3 We often use one compartment model pharmacokinetics, although a number of drugs show a distinct distribution phase, especially if the higher concentrations during the alpha phase are not related to toxicity.
- 4 Assume that a low extraction drug, showing a two compartment model behavior is metabolized via enzymes that are subject to enzyme induction by other drugs. The volume of distribution during the beta phase might be decreased by such enzyme-inducers

The correct statement(s) is (are):

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

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Question 2: Select from the following statements the **correct** statement(s) (10 pts)

- 1 The time to reach steady state is 4-5 half-lives, **only** when drugs are given as multiple short term infusions or multiple iv bolus injections.
- 2 The time to reach steady state is affected by the clearance and volume of distribution of the drug.
- 3 Drugs showing a high degree of accumulation will also need a long time to reach steady state (no loading dose is given)
- 4 For multiple short term infusions, the time to reach steady state depends on the dose.

A: (1, 2, 3, 4)

B: (1, 2, 4)

C: (1, 3, 4)

D: (2, 3)

E: (2, 4)

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Question 3-6: The following applies to questions 3-6: A 60-kg patient is to be started on a **continuous intravenous infusion**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Assume that none of this drug has been administered this month.

Question 3: If the $C_{p_{ss}}$ is to be 30mg/L, what would be the loading dose (mg) given as intravenous bolus injection? (10 pts)

- A 120 mg
- B 240 mg
- C 1200 mg**
- D 1220 mg
- E 2400 mg

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The following applies to questions 3-6: A 60-kg patient is to be started on a **continuous intravenous infusion**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Assume that none of this drug has been administered this month.

Question 4: What rate of infusion (k_0 for the following constant rate infusion) should result in a $C_{p_{ss}}$ of 30 mg/L (10 pts)

- A: 4.2 hr^{-1}
- B: 42 mg/ 0.5 hours**
- C: 42 mg/hr
- D: 42 mg
- E: none of the above

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The following applies to questions 3-6: A 60-kg patient is to be started on a **continuous intravenous infusion**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Assume that none of this drug has been administered this month.

Question 5: What will be the plasma concentration 2 hours after start of the continuous infusion (remember this patient got a loading dose) (10 pts)

- A: 3.9 mg/L
- B: 4.0 mg/L
- C: 3.6 mg/L
- D: 30 mg/L
- E: None of the above.

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The following applies to questions 3-6: A 60-kg patient is to be started on a **continuous intravenous infusion**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Assume that none of this drug has been administered this month.

Question 6: The infusion is continued for 3 days and the steady state concentration has been maintained at 30 mg/L. The physician wants to change the drug delivery to multiple short term infusions with a C_{max} of 30 mg/L and a trough of 15 mg/L. How many hours after the stop of the continuous infusion should the first short-term infusion be given. (10 points)

- A: 1 h
- B: 2 h
- C: 6 h
- D: 20 h
- E: **None of the above.**

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The following pertains to Questions 7-8

A 60 kg patient is started on 80 mg of gentamycin, every 6 hr given as a one-hour infusion.

Question 7: If this patient is assumed to have an “average” volume of distribution (value of the population mean) of 0.25 L/kg and a normal half-life of 3 hr, what would be the trough plasma concentration at steady state (**C_{\min} value taken 1 hour before the start of the next infusion**)? Please provide calculations. (10 points)

- A: 3.2 mg/L
- B: 2.5 mg/L**
- C: 0.8 mg/L
- D: 1.2 mg/L
- E: None of the above

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A 60 kg patient is started on 80 mg of gentamycin, every 6 hr given as a one-hour infusion.

Question 8: If the infusion is given the first time, how much lower is the first peak when compared to the C_{\max} at steady state ($C_{\max,ss}$). (10 points)

- A:** 25% of $C_{\max,ss}$
- B:** 50% of $C_{\max,ss}$
- C** 75% of $C_{\max,ss}$
- D:** 99% of
- E:** Don't have enough information to provide this information.

Question 9:

$$C_{p \min} = \frac{k_o}{CL} \cdot \frac{1 - e^{-k_e * T}}{1 - e^{-k_e * \tau}} \cdot e^{-k_e * (t')}$$

Select the true statements concerning the following part of the equation: **(10 points)**

$$1 - e^{-k_e * T}$$

- 1 Provides information on how much the first C_{\max} (after the first short term infusion) is away from the steady level of a continuous infusion using the same k_o .
- 2: Allows the calculation of the trough concentration after the stop of the infusion, as it converts the peak levels into the trough value
- 3: Makes sure that the resulting plasma concentrations will increase with increasing infusion time T.
- 4: Provides information on how much higher the C_{\max} values will be at steady state compared to the C_{\max} after the first dose..
- 5: Will give, when multiplied with the k_o/CL term, the peak concentration after the first dose.

The correct answers are:

A: 1, 2, 3, 4

B: 1, 3, 5

C: 1, 4, 5

D: ... 2, 3, 5

E: None of the above combinations

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Question 10: The term below is used for the design of dosing regimens. Select the correct statements (10 pts).

$$\frac{\ln F}{k_e}$$

- 1: It tells us, that the shorter the half-life of a drug the shorter the dosing interval will be for a given F value.
- 2: This term can be used under certain circumstances to calculate tau for multiple short term infusions if one adds the infusion time T to the above expression.
- 3: It only allows calculation of the dosing interval for multiple short term infusions if one knows the “true” peak and trough level at steady state.
- 4: This term should only be used for a drug after oral administration, as it relates the oral bioavailability of a drug to the dosing interval.

The correct answers are:

A: 1, 2, 3

B: 1, 2

C: 1, 3

D: ... 4

E: None of the above combinations

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Question 11: Assume you are a researcher who has to determine the pharmacokinetics of a very lipophilic drug after oral administration. The drug has been shown to bind to plasma proteins extensively. It can not be given intravenously. In dissolution studies (in-vitro) the drug showed a very slow dissolution rate. The drug was extensively metabolized in vitro by P-450 (very high Cl_{int}) Select the correct statements (10 points).

- 1: The drug is likely to show a low oral bioavailability.
- 2: The half-life of the drug can be determined from the terminal phase of the concentration time profile (drug concentrations after C_{max}).
- 3: During multiple dosing, the fluctuation between peak and trough will not be as pronounced as for a similar drug in development that shows a fast dissolution behavior but similar enzymatic metabolism.
- 4: Enzyme induction will affect the oral bioavailability of the drug.

The correct answers are:

- A: 1, 2, 3, 4
B: 1, 3, 4
C: 1, 4
D: 2, 3
E: None of the above combinations

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Question 12 For multiple iv bolus injection one can state (10 points)

- 1 that the average steady state concentration depends on the volume of distribution.
- 2 that cutting the dosing interval from 24 to 12 hours but **maintaining the daily dose** will double the average steady state concentration.
- 3 that an increase in the patient's volume of distribution might necessitate a reduction of the patient's dosing interval in order to maintain the same degree of fluctuation.
- 4 that for a drug with predominantly renal elimination the dosing interval should increase with decreasing creatinine clearance
- 5 that a reduction in the dosing interval (individual dose stays the same) will not change the peak levels observed at steady state.

Select the correct statements:

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

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Question 13-20: Patient 1 received a **low extraction drug** as an iv bolus injection. Pharmacokinetic and physiological characteristics, such as dose, fraction of the drug unbound in plasma (f_u) and tissue (f_{uT}), volume of plasma (V_p) and volume of the tissue water (VTW) in this patient are shown below.

TABLE 1: INPUT PARAMETERS

	Patient 1
D [mg]	40
f_u	1
f_{uT}	1
V_p [L]	3
VTW [L]	38

The next table shows the resulting pharmacokinetic parameters in **Patient 1**. Let's assume a second patient receives the same dose of this drug, given as an iv bolus injection. Both patients **differ in the tissue and plasma protein binding** to this drug. As you can see from the INPUT parameters, 100% of the drug in plasma and tissue is free for **Patient 1**. **Contrary to this, in Patient 2, 50% of the drug present in tissue is free ($f_{uT}= 0.5$) and 50% of the drug in plasma is free ($f_u=0.5$)**

Please circle in the free column of the Table 2 (and indicate on your Scantron) for each parameter whether the parameter (Peak concentration, V_d , Cl , $t_{1/2}$, AUC) **will be larger (A), be ABOUT the same (B), or will be smaller (C)** than those estimates observed in **Patient 1**.

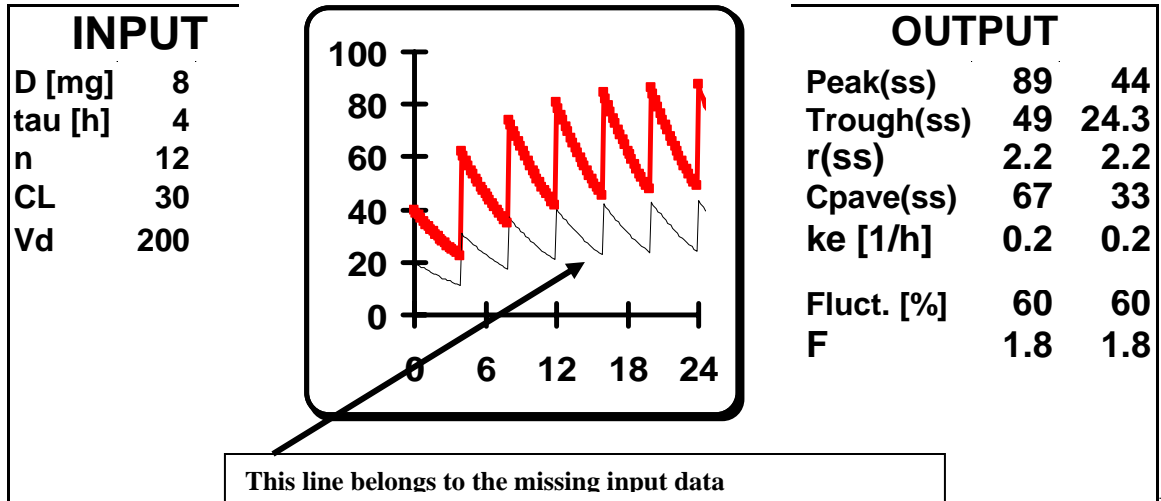
Table 2: OUTPUT PARAMETERS

Question:		Patient 1	Patient 2
13 (5 points)	V_d [L]	41	Larger (A), same (B) , Smaller (C)
14 (5 points)	CL [L/h]	9	Larger (A), same (B), Smaller (C)
15 (5 points)	$t_{1/2}$ [h]	3	Larger (A) , same (B), Smaller (C)
16 (5 points)	Peak [$\mu\text{g/ml}$]	1.1	Larger (A), same (B) , Smaller (C)
17 (5 points)	AUC [$\mu\text{g/ml}\cdot\text{h}$]	4.4	Larger (A) , same (B), Smaller (C)

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Question 18: The following concentration time profiles were observed after multiple iv bolus injections of a drug. The two curves differ in one of the input parameters (Dose, tau, CL or Vd). (10 points).



Identify the one input parameter that differs

- A: Dose
- B: Clearance
- C: Volume of distribution
- D: tau
- E: none of the above

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Question 19: Which of the following factors significantly affect(s) the renal clearance of a very strong acid ($pK_a=0.1$) that has no affinity to active transporters: (10 pts)

1. plasma protein binding.
2. activity of cationic transporters in the tubuli.
3. urine flow.
4. pH of urine.
5. GFR.

A: 1, 2, 3

B: 1, 2

C: 1, 5

D: 1, 3, 5

E: none of the above combinations

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Questions 20- 23

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

Question 20 (5 points)

T (A) F (B) Loading doses are mainly given for drugs with a long half-life.

Question 21 (10 points)

T (A) F (B) Two compartment body model drugs are likely to show pronounced permeability controlled distribution into at least some tissue components.

Question 22 (10 points)

T (A) F (B) “Linear pharmacokinetics” means that the plasma drug concentration versus time plots are directly related to the dose of the drug.

Question 23 (10 points)

T (A) F (B) The concentration time profiles of an oral tablet will be very similar to an iv bolus injection of the same dose if the absorption is very fast and the oral bioavailability will be close to 100 %.