

Name: _____

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PHA 5127

Final Exam Key Fall 2003

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 _____ /125 pts

1 _____ /5 pts	11 _____ /5 pts	21 _____ /5 pts
2 _____ /5 pts	12 _____ /5 pts	22 _____ /5 pts
3 _____ /5 pts	13 _____ /5 pts	23 _____ /5 pts
4 _____ /5 pts	14 _____ /5 pts	24 _____ /5 pts
5 _____ /5 pts	15 _____ /5 pts	25 _____ /5 pts
6 _____ /5 pts	16 _____ /5 pts	26 _____ /5 pts
7 _____ /5 pts	17 _____ /5 pts	27 _____ /5 pts
8 _____ /5 pts	18 _____ /5 pts	28 _____ /5 pts
9 _____ /5 pts	19 _____ /5 pts	
10 _____ /5 pts	20 _____ /5 pts	

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Question 1: Select the correct statement(s). The plasma drug concentration versus time curve for a two-compartment model is (5 points)

- 1 biexponential
- 2 monoexponential
- 3 based on second order pharmacokinetic processes
- 4 based on first order pharmacokinetic processes

The correct statement(s) are (is):

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

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

Select from the following statements the **correct** statement(s)
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, as the amount of the drug in the body is decreasing
- 3 is increasing with time after drug administration until it reaches a plateau
- 4 is changing because it takes time for the drug to enter and leave the peripheral compartment.

- A: (1, 2, 3, 4);
- B: (1, 2, 4),
- C: (1, 3, 4),
- D: (2)
- E: (2, 4)

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Question 3-6:

The following applies to questions 3-6: A 60-kg patient is begun on a continuous intravenous infusion of theophylline at 40 mg/hr (based on theophylline, not aminophylline). Forty-eight hours after beginning of the infusion, the plasma concentration is 12 mg/L.

Question 3: If we assume that this concentration is at steady state, what is the theophylline clearance. Please perform calculations on paper, we will check. (5 points)

- A** 3.3 L/hr
- B** 0.3 L/hr
- C** 33 L/hr
- D** 198 L/hr
- E** None of the above

$$CL = \frac{k_0}{C_{p,ss}} = \frac{40mg/h}{12mg/L} = 3.33L/h$$

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Question 4: If the volume of distribution is estimated to be 30 L, what is the half-life? Please perform calculations on paper, we will check. (5 points)

A: 1.7 hr

B: 6.3 hr

C: 13.3 hr

D: 22.1 hr

E: 45.3 hr

$$k_e = \frac{CL}{Vd} = \frac{3.3L/h}{30L} = 0.11h^{-1}$$

$$t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.11} = 6.3h$$

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Question 5: What would the plasma concentration be 10 hr after beginning the infusion. Please perform calculations, we will check. (5 points)

- A: 3.2 mg/L
- B: 4.8 mg/L
- C: 8.1 mg/L
- D: 11.0 mg/L
- E: None of the above.

$$C_p = \frac{k_0}{CL} \cdot (1 - e^{-k_e \cdot t})$$
$$= \frac{40 \text{ mg/h}}{3.3 \text{ L/h}} \cdot (1 - e^{-0.11 \cdot 10}) = 12.12 \text{ mg/L} \cdot 0.67 = 8.12 \text{ mg/L}$$

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Question 6: If the infusion is continued for 3 days and then discontinued, what would the plasma concentration be 12 hours after the stop of the infusion. Please perform calculations, we will check. (5 points)

- A 1.2 mg/L
- B: 3.2 mg/L
- C: 7.6 mg/L
- D: 8.1 mg/L
- E: None of the above

$$C_p(12h) = C_{ss} \cdot e^{-k_e \cdot t}$$
$$= 12 \text{ mg} / \text{L} \cdot e^{-0.11 \cdot 12} = 3.2 \text{ mg} / \text{L}$$

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Question 7: If the infusion is continued for 3 days at 40 mg/hr and the steady state concentration is 12 mg/L what infusion rate would likely result in a steady state concentration of 18 mg/L. Please perform calculations, we will check. (5 points)

- A: 15 mg/L
- B: 30 mg/L
- C: 50 mg/L
- D: 70 mg/L
- E: None of the above.

$$k_0 = C_{p,ss} \cdot CL$$

$$= 18mg / L \cdot 3.3L / h = 59.4mg / h \approx 60mg / h$$

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The following pertains to Questions 8-9

A 60 kg patient is started on 80 mg of gentamycin. Every 6 hr given as 1-hr infusion.

Question 8: 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 peak plasma concentration at steady state (the true C_{\max} value). Please provide calculations. (5 points)

- A: 3.2 mg/L
- B: 8.9 mg/L
- C: 12.2 mg/L
- D: 15.4 mg/L
- E: None of the above

$$Vd = 0.25L / kg \cdot 60kg = 15L$$

$$k_e = \frac{0.693}{t_{1/2}} = \frac{0.693}{3h} = 0.231h^{-1}$$

$$CL = k_e \cdot Vd = 0.231h^{-1} \cdot 15L = 3.5L / h$$

$$\begin{aligned} C_{\max} &= \frac{Dose}{CL \cdot T} \cdot \frac{(1 - e^{-k_e \cdot T})}{(1 - e^{-k_e \cdot \tau})} \\ &= \frac{80mg}{3.5L / h \cdot 1h} \cdot \frac{(1 - e^{-0.231 \cdot 1})}{(1 - e^{-0.231 \cdot 6})} = 22.86mg / L \cdot \frac{0.206}{0.75} = 6.28mg / L \end{aligned}$$

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Question 9: Based on above volume of distribution and $t_{1/2}$ estimates, is the 6 hr dosing interval sufficient to achieve a fluctuation of not more than 6. Please provide calculations. (5 points)

- A:** yes
- B:** no
- C:** Don't have enough information to make this conclusion.

$$F = e^{k_e \cdot \tau} = e^{0.231 \cdot 6} = 4$$

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Questions 10 -13

The following questions 10-13 are related to the equation shown below. Explain the meaning of the blocked parts of the equation in the following questions 10-13.

$$C_{p_{\min}} = \boxed{\frac{D}{V_d}} \cdot \boxed{\frac{1}{1 - e^{-k_e \cdot \tau}}} \cdot \boxed{e^{-k_e \cdot \tau}}$$

Question 10: What information does D/V_d provide (5 points)

$$\frac{D}{V_d}$$

- A: C_{\max} after the first dose when given as iv infusion
- B: Trough concentration at steady state when given as infusion
- C: C_{\max} after the first dose when given as iv bolus
- D: Degree of accumulation
- E: Allows the calculation of the trough concentration, without this part of the equation , one would obtain C_{\max} .

Question 11: What does this part of the equation tells us (5 points)

$$\frac{1}{1 - e^{-k_e \cdot \tau}}$$

- A: Gives us the degree steady state has been reached during a constant rate infusion
- B: Trough concentration at steady state when given as infusion
- C: C_{\max} after the first dose when given as iv bolus
- D: Degree of accumulation during multiple iv bolus injections
- E: Allows the calculation of the trough concentration, without this part of the equation , one would obtain C_{\max} .

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Question 12: What does this part of the equation provide (5 points)

$$e^{-k_e \cdot \tau}$$

- A: C_{\max} after the first dose when given as iv infusion
- B: Trough concentration at steady state when drug is given as infusion
- C: C_{\max} after the first dose when given as iv bolus
- D: Degree of accumulation
- E: Allows the calculation of the trough concentration after multiple iv bolus injections, without this part of the equation, one would obtain C_{\max} .

Question 13

Select the correct statement(s) The oral bioavailability of a drug whose hepatic clearance is much smaller than the liver blood flow (5 points)

- 1 will be small
- 2 will depend on liver blood flow
- 3 will depend on plasma protein binding
- 4 will be close to 100%.
- 5 will be affected by the GFR

Select the correct statements:

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

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Question 13-18: **Patient 1** 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 this patient are shown below.

TABLE 1: INPUT PARAMETERS

	Patient 1
D [mg]	40
fu	1
fuT	0.3
CLi [L/h]	3
Q [L/h]	90
Vp [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 **only** in the plasma protein binding to this drug. As you can see from the INPUT parameters, 100% of the drug in plasma is free for **Patient 1**. Contrary to this, in **Patient 2**, 33% of the drug present in plasma is free.

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

Table 2: OUTPUT PARAMETERS

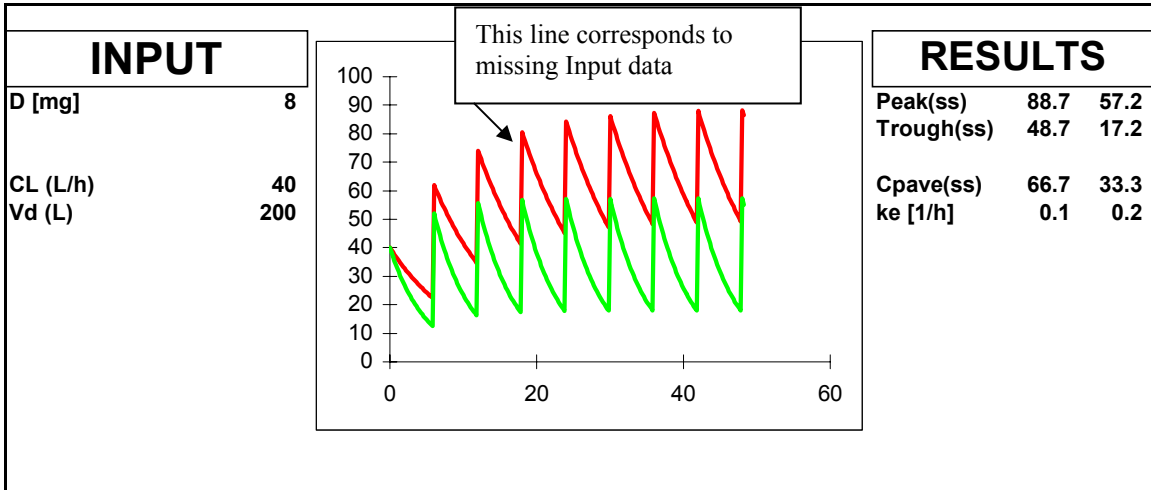
Question:		Patient 1	Patient 2
14 (5 points)	Peak [ug/ml]	0.3	Larger (A) , same (B), Smaller (C)
15 (5 points)	Ke [1/h]	0.02	Larger (A), same (B) , Smaller (C)
16 (5 points)	V [L]	130	Larger (A), same (B), Smaller (C)
17 (5 points)	CL [L/h]	2.9	Larger (A), same (B), Smaller (C)
18 (5 points)	$t_{1/2}$ [h]	31.0	Larger (A), same (B) , Smaller (C)
19 (5 points)	E	0.03	Larger (A), same (B), Smaller (C)
20 (5 points)	F [%]	96.8	Larger (A), same (B) , Smaller (C)
21 (5 points)	AUC [ug/ml*h]	13.8	Larger (A) , same (B), Smaller (C)

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Question 22 :

The following concentration time profiles were observed after multiple bolus injections of a drug. The two curves differ in one of the input parameters (Dose, CL or Vd). (5 pts).



Identify the one input parameter that differs

- A: Dose
- B: Clearance
- C: Volume of distribution

peak after first dose is the same:

$$C_0 = \frac{Dose}{Vd} \quad \Rightarrow \quad \text{same Dose, same Vd}$$

⇒ Clearance must be different

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Question 23:

Which of the following factors significantly affect the renal clearance of a unionized drug that shows complete passive renal reabsorption from the "urine" back into the blood: (5 pts)

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

A: 1, 2, 3

B: 1, 3

C: 1, 3, 4, 5

D: 1, 3, 5

E: 3

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Questions 24- 28

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

Question 24 (5 points)

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

Question 25 (5 points)

T (A) F (B) A high volume of distribution will result in a high clearance

Question 26 (5 points)

T (A) F (B) If Drug A is excreted by glomerular filtration as well as by hepatic metabolism and Drug B is cleared only by hepatic clearance, then in a patient with total renal failure, total body clearance of drug A and B will be affected.

Question 27 (5 points)

T (A) F (B) The oral bioavailability of a drug is determined significantly by the extraction ratio E.

Question 28 (5 points)

T (A) F (B) The distribution of highly lipophilic small drug molecule is perfusion rate limited.