Name: _____

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PHA 5127

First Exam
Fall 2007

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

KEY

Name

Question Set/Points

I. 15 pts

II. 10 pts

III. 10 pts

IV 6 pts

V. 15 pts

VI. 15 pts

VII. 10 pts

VIII. 4 pts

IX. 5 pts

TOTAL: 90 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*

1:	T	F	A water-soluble drug will pass across muscle membranes faster than across brain membranes (assume permeability-rate limitations).
2:	T	F	A neutral, lipophilic drug is likely to be absorbed faster in the intestines than in the stomach. Remember that stomach and intestine differ in their properties.
3:	T	F	Lipophilic drugs are generally taken up fast by highly perfused organs.
4:	T	F	Ionized and lipophilic drugs are most likely to cross most membrane barriers.
5:	T	F	Drugs with a high tissue binding always have a large volume of distribution.

A, A, A, B, B

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Question Set II

(10 points)

6: J. Mary was admitted into hospital due to drug intoxication. Her body weight is 60kg. Drug U5127 was used to control the symptoms. U5127 is administered via IV bolus at a dose of 0.25 mg/kg. After drug exposure, they found that U5127 concentration-time profile can be best described by one-compartmental linear model with the equation, $\{C = 0.33 \cdot e^{-0.116 \cdot t}$ (Unit: mg/L)}, where *C* represents U5127 concentration at time t (hr). Calculate U5127 volume of distribution.

A: 45 L

B: 0.76 L

C: 38 L

D: 18 L

E: none of the above

Answer: A

$$Dose: 60 \cdot 0.25 = 15(mg)$$

According to the equation: $C = 0.33 \cdot e^{-0.116 \cdot t}$, and equation for standard one-compartment model: $C = C_0 \cdot e^{-K_e \cdot t}$, then:

$$C_0 = 0.33(mg / L)$$

$$V_d = \frac{Dose}{C_0}$$

$$V_d = \frac{15}{0.33} = 45(L)$$

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Question Set III

(10 points)

7: Quinidine is bound to both of plasma albumin and alpha-1-acid glycoprotein. In patients with chronic liver disease plasma protein binding is decreased by 20%. How will the volume of distribution change in patients? (Assume the fraction unbound in tissue is 70% in both patients and normal subjects, and the fraction bound in plasma is 80% in normal subjects.)

A: Increase to 37.74 L

B: Increase to 22.54 L

C: Stay the same as 13.86 L

D: Stay the same as 46.43 L

E: Decrease to 11.69 L

Answer: B

80% of plasma protein binding is used for calculation of normal people

Vd**=** Vp + Vt ***** Fu/Fu,t

Vd= 3 + 38* 0.2/0.7 = 13.86 L (normal patient)

Vd= 3 + 38* 0.36/0.7 = 22.54 L (in patients with chronic liver disease)

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Question Set IV (True or False)

(6 points)

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

8: T F Compared to skin, liver would have a higher rate of uptake of perfusion-limited lipophilic drugs due to its higher blood flow rate.

9: T F Distribution to a specific tissue for permeability-limited hydrophilic drugs depends on how much and how quickly the blood gets to the specific tissue.

10: T F Perfusion limited distribution is a type of drug distribution into tissue that occurs when the drug is able to cross membranes easily.

Answer: A,B,A

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Question Set V (True or False)

(15 points)

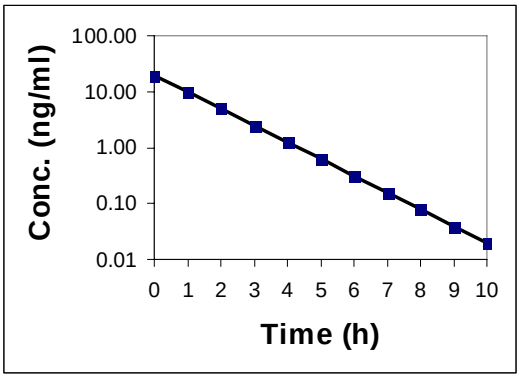

Figure A

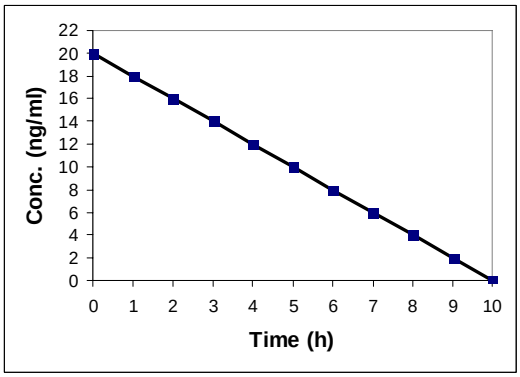

Figure B

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

11: T F Figure A shows a first order elimination process, and ke has a unit of hr^{-1}.

12: T F Figure B shows a zero order elimination process, and ke has a unit of hr^{-1}.

13: T F In Figure B, the fraction of drug eliminated per hour is constant.

14: T F In Figure A, the eliminated drug amount per hour is changing.

15: T F In Figure A, the rate of elimination is dependent of amount of drug in body.

A, B, B, A, A

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Question Set VI

(15 points)

16: A 25 yr old, 70 kg male patient with gram-negative pneumonia, was being treated with gentamicin. Gentamicin had been given as an iv bolus (2 mg/kg). Two samples were taken after dose, and data is shown as following:

Time (h)	Concentration (mg/L)
4	2.5
10	0.5

Calculate the $AUC_{0-\infty}$. (Assume first-order elimination for gentamicin, and please use trapezoidal rule to calculate.)

A: 30.5 mg/L*hr

B: 34.1 mg/L*hr

C: 19.6 mg/L*hr

D: 9.0 mg/L*hr

E: none of the above

Answer: A

First, need to find out the drug concentration at time zero (C_0),

$$k_e = \frac{\ln(C_2/C_1)}{(t_1 - t_2)} = \frac{\ln(0.5/2.5)}{(4-10)} = 0.268\ h^{-1}$$

$$C_t = C_0 \cdot e^{-ke \cdot t}$$

$$C_0 = C_t \cdot e^{ke \cdot t} = 2.5 \cdot e^{0.268 \times 4} = 7.303\ \textbf{mg/L}$$

Then, using trapezoidal rule: $AUC_{t1\text{-}t2} = \frac{(C_1 + C_2)}{2} \cdot (t_2 - t_1)$

Time (h)	Conc(mg/L)	$AUC_{t1\text{-}t2}$
0	**7.303**	
4	2.5	19.606
10	0.5	9
$AUC_{0\text{-}10}$		**28.606**

$$AUC_{10-\infty} = \frac{C_x}{k_e} = \frac{0.5}{0.268} = 1.866\ \text{mg*h/L.}$$

$AUC_{0-\infty} = AUC_{0-10} + AUC_{10-\infty} = 28.606 + 1.866 =$ **30.5 mg*h/L.**

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Question Set VII

(10 points)

17: A 100 mg dose of a drug was administered to two patients by IV bolus injection. For patients A and B, the initial concentrations (C_0) were 1.25mg/L and 2.5mg/L, respectively. This drug follows a one-compartment body model, crosses membranes easily, distributes well into all tissues, and is around 50% bound to plasma proteins. Why is the initial plasma concentration different for these two patients? Select the correct answer from below.

A: Patient B has more fat tissue than Patient A.

B: Plasma unbound fraction in Patient B is higher than that in Patient A.

C: **Tissue unbound fraction in Patient B is higher than that in Patient A.**

D: Patient B has larger volume of distribution than Patient A.

E: None of Above

Answer: C

For a dose administered IV bolus, $Cp(0) = \frac{D}{V_d}$

Since both patients received the same dose and achieved different initial concentrations, V_d must be different for these two patients. V_d may be calculated by rearranging the equation above to give $V_d = \frac{D}{Cp(0)}$

For patient A, $V_d = \frac{100mg}{1.25mg/L} = 80L$

For patient B, $V_d = \frac{100mg}{2.5mg/L} = 40L$

For a drug that distributes well into all tissues and crosses membranes easily, the tissue volume into which a drug may distribute is 38 L (total tissue water). Plasma volume is 3 L. The volume of distribution may be related to these plasma and tissue volumes by $V_d = V_p + V_T \cdot \frac{fu}{fu_T}$

fu is given as 0.5. If we assume a tissue water volume of 38L for both patients, fu_T must be different in these patients. The expression above may be rearranged to give.

$$fu_T = \frac{V_T \cdot fu}{(V_d - V_p)}$$

For patient A, $fu_T = \frac{(38L)(0.5)}{(80L - 3L)} = 0.25$

For patient B, $fu_T = \frac{(38L)(0.5)}{(40L - 3L)} = 0.51$

Thus, the difference in V_d 's may be explained by the 2-fold difference in tissue binding of the drug. (An alternative hypothesis is that patient A has more fat tissue leading to more binding of the drug. If more drug is bound, the free fraction decreases.)

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Question Set VIII

(4 points)

18: Given a lipophilic drug that can enter all tissues easily , state how the volume of distribution will change under the following condition. If not mentioned, other parameters are assumed to be fixed.

Both f_u and $f_{u,T}$ double

A: Increase;

B: Decrease

C: No change

D: Not enough information given to answer question

Answer: C

$$V_p(\leftrightarrow) + V_t(\leftrightarrow)\frac{F_u(\uparrow)}{F_{u,T}(\uparrow)} = V(\leftrightarrow)$$

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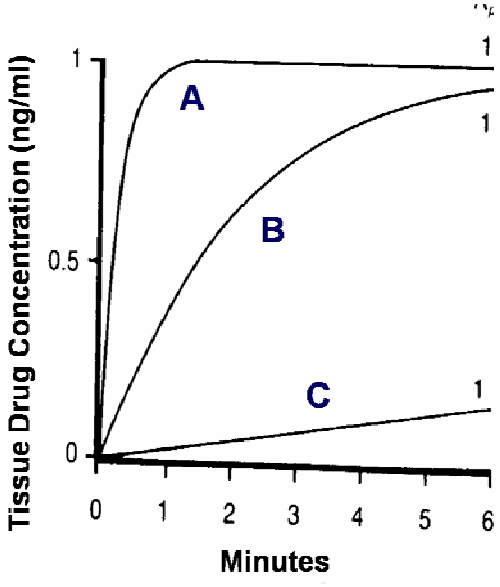
Question Set IX

(5 points)

19: Drug A follows a perfusion-limited distribution. Drug concentration-time profiles from several tissues (A, B, and C) were plotted as below. Which of following answer is correct?



A: Tissue A: Brain; Tissue B: Skin; Tissue C: Liver

B: Tissue A: Skin; Tissue B: Kidneys; Tissue C: Fat

C: **Tissue A: Lungs; Tissue B: Muscle; Tissue C: Fat**

D: Tissue A: Kidneys; Tissue B: Fat; Tissue C: Liver

E: Tissue A: Skin; Tissue B: Muscle; Tissue C: Fat

Answer: C

Blood flow through organs

- Lungs 5000 ml/min
- Liver 1350 ml/min
- Kidneys 1100 ml/min
- Muscle 750 ml/min
- Brain 700 ml/min
- Skin 300 ml/min
- Fat 200 ml/min