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## PHA 5127

### First Exam Fall 2003

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

#### KEY

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Name \_\_\_\_\_

Question/Points

1. \_\_\_\_\_/14 pts

2. \_\_\_\_\_/6 pts

3. \_\_\_\_\_/15 pts

4. \_\_\_\_\_/12 pts

5. \_\_\_\_\_/20 pts

6. \_\_\_\_\_/10pts

7. \_\_\_\_\_/10pts

8. \_\_\_\_\_/12pts

9. \_\_\_\_\_/10pts

10. \_\_\_\_\_/16pts

TOTAL \_\_\_\_\_/125 pts

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1. List the **wrong** statements. A drug shows a plasma protein binding of 50% and a volume of distribution of 100 L. The intrinsic clearance of this drug in the liver is much smaller than the liver blood flow. The oral bioavailability of this drug: (14 points)

- A will be 50%.
- B will **highly** depend on liver blood flow.
- C will be very small (< 10%).
- D will be affected by the GFR.
- E will be significantly increased if the tissue binding is increased.
- F will be significantly increased if the plasma protein binding is increased.
- G will be significantly increased if the intrinsic clearance is increased.

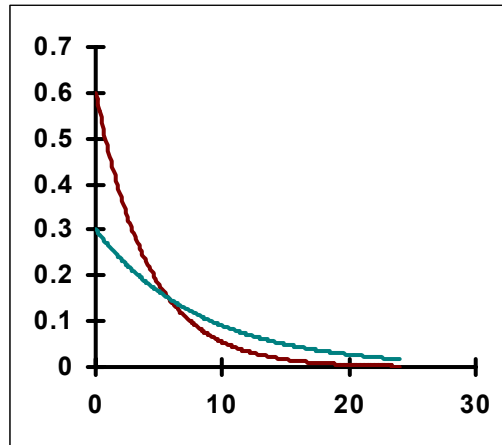
The **wrong** statement(s) is (are):

A, B, C, D, E, F, G

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2. Compare the following two concentration-time profiles after a single bolus injection. The two lines differ in only **one** of the subsequent parameters (Vd, Dose, clearance). Please circle the parameter they differ in (6 points).



The 2 lines differ in

Dose

Vd

Clearance

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3. For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a lipophilic, neutral (no acid or basic group in the molecule), protein bound, **low extraction** drug that is also eliminated by renal elimination (**some answers may be used more than once**). (15 points) Write your selection (a, b, c, d, e, f, or g) on the line behind the physiological change.

Physiological change	Induced changes on kinetic parameters
1.) Increase in metabolic enzymes <u>  b  </u>	a. $Cl_{REN} \downarrow$
2.) Decrease in urine flow <u>  a  </u>	b. $Cl_{HEP} \uparrow$
3.) Increase in liver blood flow <u>  g  </u>	c. oral bioavailability $\downarrow$
4.) Decrease in number of fat cells <u>  f  </u>	d. $V_D \uparrow$
5.) Increase in plasma protein binding <u>  a or f  </u>	e. oral bioavailability $F \uparrow$
	f. $V_D \downarrow$
	g. none of the above

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4. For the following situations, indicate whether the drug is **filtered, reabsorbed or actively secreted** (Assume GFR is  $130 \text{ mL min}^{-1}$ , urine flow is  $1.5 \text{ ml min}^{-1}$ ) (12 points)

- A drug with  $f_u = 0.02$  and a  $Cl_{REN} = 20 \text{ mL min}^{-1}$  is Actively secreted
- A drug with  $f_u = 0.40$  and a  $Cl_{REN} = 52 \text{ mL min}^{-1}$  is filtered
- A drug with  $f_u = 0.30$  and a  $Cl_{REN} = 0.45 \text{ mL min}^{-1}$  is "fully" reabsorbed/reabsorbed

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5. A drug is eliminated through glomerular filtration **and** hepatic metabolism (no other clearance mechanisms are observed). **The drug has a plasma protein binding of 50%**. Glomerular filtration rate in the patient of interest is normal (**130 ml/min**). The drug is highly ionized, but not subject to active transport. The volume of distribution is **50 L**. When given as an i.v. bolus, plasma concentrations **two** hour after administration were **5.2 mg/L**. **Four hours** after administration the concentration was **2.6 mg/L**. (25 pts)

- 5a. What is the  $k_e$ ? Provide full calculations and circle correct answer. Correct answer is only granted if you show calculations?

$$t_{1/2} = 2 \text{ h}$$

$$k_e = \frac{\ln 2}{t_{1/2}} = \frac{\ln 2}{2} = 0.35 \text{ h}^{-1}$$

or

$$k_e = \frac{\ln\left(\frac{5.2}{2.6}\right)}{2 \text{ h}} = 0.35 \text{ h}^{-1}$$

**Answer:**

**Circle the correct answer**

0.15 h<sup>-1</sup>   0.25 h<sup>-1</sup>   0.3 h<sup>-1</sup>   **0.35 h<sup>-1</sup>**   0.4 h<sup>-1</sup>   0.45 h<sup>-1</sup>   0.5 h<sup>-1</sup>   0.55 h<sup>-1</sup>  
0.6h<sup>-1</sup>   0.65 h<sup>-1</sup>   0.7h<sup>-1</sup>   0.85 h<sup>-1</sup>   0.9 h<sup>-1</sup>   1 h<sup>-1</sup>   1.1 h<sup>-1</sup>   1.2 h<sup>-1</sup>  
12h<sup>-1</sup>   120 h<sup>-1</sup>

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5b. What is the total clearance of the drug. Provide full calculations and circle estimate closest to your answer from the list below. Correct answer is only granted if you **show full calculations**.

$$\begin{aligned} CL &= k_e \cdot V_d \\ &= 0.35 \cdot 50 \text{ L/h} \end{aligned}$$

**Answer:**

0.1L/h	0.2L/h	0.4 L/h	0.61L/h	0.8 L/h	1 L/h	3L/h
5L/h	7L/h	9 L/h	11L/h	13L/h	15 L/h	17L/h
21L/h	24L/h	27L/h	30L/h	33L/h	40L/h	45L/h
50L/h	55L/h	60L/h	65L/h	70L/h	80L/h	90L/h
100L/h	150L/h					

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5c. What is the renal clearance of the drug? **Circle the answer closest to your estimate from the list below.**

$$Cl_{\text{ren}} = GFR \cdot f_u = 130 \cdot 0.5 = 65 \text{ ml/min} = 3.9 \text{ L/h}$$

**Answer:**  
**Circle the correct answer**

- |         |         |         |         |         |         |
|---------|---------|---------|---------|---------|---------|
| 0.1 L/h | 0.2 L/h | 0.3 L/h | 0.4 L/h | 0.5 L/h | 0.7 L/h |
| 1L/h    | 2L/h    | 3 L/h   | 4 L/h   | 6L/h    | 9L/h    |
| 12L/h   | 15L/h   | 18L/h   | 21L/h   | 24L/h   | 27L/h   |
| 30L/h   | 33L/h   | 40L/h   | 45L/h   | 50L/h   | 55L/h   |
| 60L/h   | 65L/h   | 70L/h   | 80L/h   | 90L/h   | 100L/h  |
| 150L/h  |         |         |         |         |         |

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5d. What is the hepatic clearance of the drug? ? **Circle the answer closest to your estimate from the list below.**

$$\begin{aligned} Cl_{\text{hep}} &= Cl_{\text{TOT}} - Cl_{\text{ren}} \\ &= 17 - 4 = 13 \text{ L/h} \end{aligned}$$

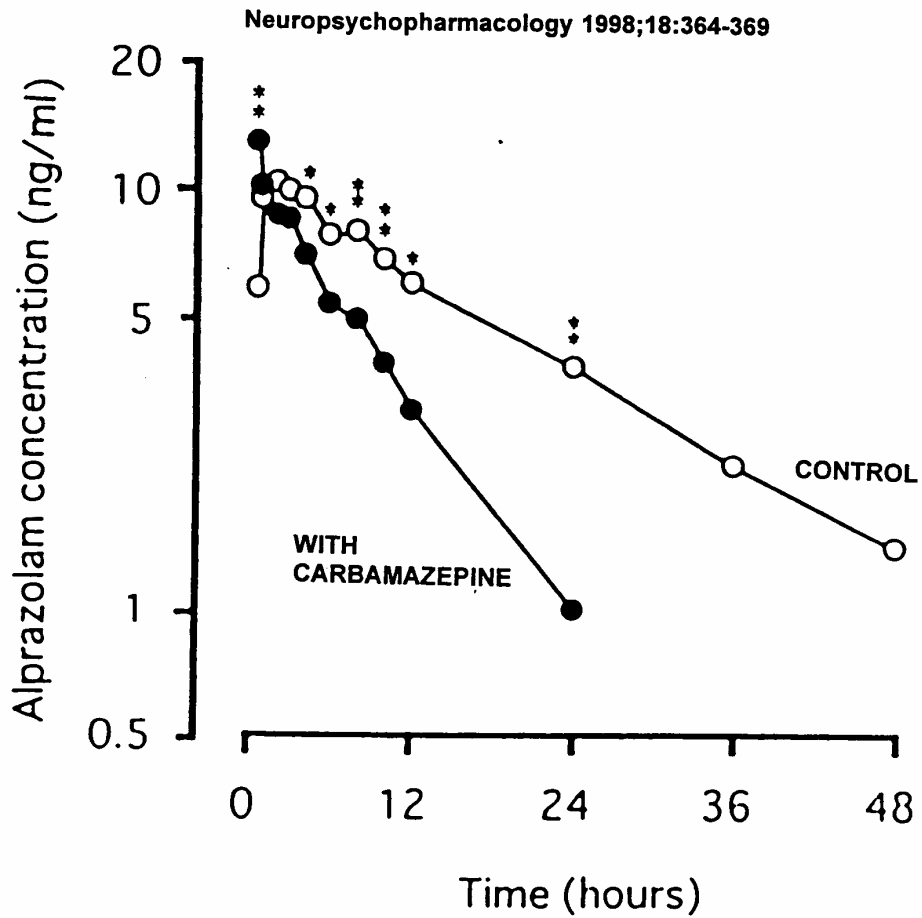
**Answer:**  
**Circle the correct answer**

0.1 L/h	0.2 L/h	0.3 L/h	0.4 L/h	0.5L/h	0.6L/h	0.7 L/h
0.8L/h	0.9L/h	1.0L/h	1.0 L/h	1.2 L/h	1.4 L/h	1.6 L/h
1.8L	2.0L/h	2.2 L/h	2.4L/h	2.8L/h	3.0L/h	3.1 L/h
3.3 L/h	3.5 L/h	3.7 L/h	3.9 L/h	4.1 L/h	4.3 L/h	4.5 L/h
4.7 L/h	5 L/h	7 L/h	9 L/h	10 L/h	12L/h	14L/h
18 L/h	22L/h	26 L/h	30L/h	40L/h		

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6. The same dose of Alprazolam was given either with placebo or with carbamazepine. Briefly explain what is going on, in 5 words or less. (10 points)



Please answer in 2 words or less.

Enzyme induction

Or

Similar statement

Increase in clearance and shorter half-life, more metabolism was not sufficient.

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7.) Which of the following statements about renal clearance is (are) **wrong**? (10 points)

- A) The degree of tubular reabsorption might be affected by the pH of the urine.
- B) Highly ionized drugs with no affinity to transporters tend to stay in the urine.
- C) Tubular reabsorption can only be an active process.
- D) The renal clearance of serum creatinine is identical the GFR.
- E) Creatine clearance can only be used to estimate the renal clearance of drugs that are similar to creatine, which does not show plasma albumin binding.

List **wrong** statement(s):

C, E

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8.) Which of the following statements concerning volume of distribution is (are) **correct**? Consider that the amount of drug in the body is constant. (12 points)

- A) The higher the volume of distribution, the more drug is in the tissue.
- B) The lower the volume of distribution, the lower the drug concentration in plasma.
- C) The volume of distribution relates the amount of drug in the body to the plasma concentration.
- D) The volume of distribution relates the plasma concentration to the actual tissue concentration.
- E) The volume of distribution increases with increasing blood flow.
- F) For a lipophilic drug, a large volume of distribution can only be observed if the plasma protein binding is less than the tissue binding.

List the **correct** statements:

A, C, F

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- 9) What of the following statements concerning a drug distributed according to perfusion limitations are **correct**? Assume no active transport. (10 points)
- A) The drug can not be a strong acid.
  - B) The drug can not be a strong base.
  - C) The drug can be a weak base
  - D) The drug can be a weak acid.
  - E) Such a drug will generally enter tissues faster than a drug showing permeability limited uptake.

**Correct** answer(s):

A, B, C, D, E

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- 10) **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. (16 points)

**TABLE 1: INPUT PARAMETERS**

	<b>Patient 1</b>
D [mg]	<b>40</b>
fu	<b>1</b>
fuT	<b>0.3</b>
CLi [L/h]	<b>3</b>
Q [L/h]	<b>90</b>
Vp [L]	<b>3</b>
VTW [L]	<b>38</b>

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.

Please mark 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** (—), **will be larger** (↑), or **will be smaller** (↓) than those estimates observed in **Patient 1**.

**Table 2: OUTPUT PARAMETERS**

	<b>Patient 1</b>	<b>Patient 2</b>
Peak [ug/ml]	<b>0.3</b>	↑
Ke [1/h]	<b>0.02</b>	—
V [L]	<b>130</b>	↓
CL [L/h]	<b>2.9</b>	↓
$t_{1/2}$ [h]	<b>31.0</b>	—
E	<b>0.03</b>	↓
F [%]	<b>96.8</b>	—
AUC [ug/ml*h]	<b>13.8</b>	↑