Name: _____

SS#: _____

PHA 5127

First Exam
Fall 2002

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

Name

Question/Points

1. _____/15 pts
2. _____/15 pts
3. _____/15 pts
4. _____/15 pts
5. _____/25 pts
6. _____/15pts

TOTAL _____/100 pts

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1. True or False The oral bioavailability of a drug whose clearance is close to the liver blood flow (15 points)

T F will be small

T F will depend on liver blood flow

T F will depend on plasma protein binding

T F will be close to 100%.

T F will be affected by the GFR

T, T, T, F, F

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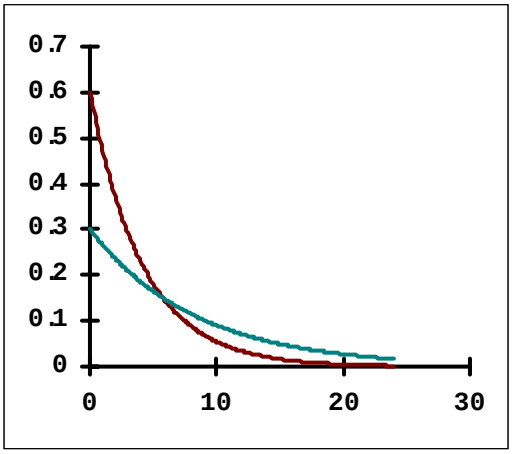
2. Compare the following two concentration time profiles (15 points).



The 2 graphs differ in either

Dose,
Vd
Clearance

Give the reasons for your decision

The question is: there is ONLY one parameter that is different between the two drugs. We need to find out which one it is and explain why.

The plot showed that C_0 is different; hence either Dose or V_d must be different. As a result, clearance is the same. Since $t_{1/2}$ is different, k_e is different. We know $CL=k_e*V_d$. Therefore, Vd is different. Then Dose is the same.

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3. For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a lipophilic, unionizable (no acid or basic group in the molecule), protein bound drug that shows **extensive liver** metabolism (E=1) and renal elimination. (some answers may be used more than once). (15 points)

Physiological change		Effect on kinetics
1.)	Increase in metabolic enzymes_____	a. Cl_{REN} ↓
2.)	Decrease in urine flow____	b. Cl_{HEP} ↓
3.)	Increase in liver blood flow____	c. oral bioavailability ↓
4.)	Decrease in number of fat cells_____	d. V_D ↑
5.)	Decrease in creatinine clearance_____	e. oral bioavailability F↑
		f. V_D ↓
		g. none of the above

C, A, E, F, G

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4. For the following situations, indicate whether the drug is *filtered, reabsorbed or actively secreted* (Assume GFR is 130 mL min^{-1}, urine flow is 1.5 ml min^{-1}) (15 points)

    - A drug with f_u = 0.02and a Cl_{REN} = 20 mL min^{-1} is _____
    - A drug with f_u = 0.40 and a Cl_{REN} = 52 mL min^{-1} is _____
    - A drug with f_u = 0.30 and a Cl_{REN} = 0.45 mL min^{-1} is _____

GRF*fu=2.6 < Clren, Secreted

GFR*fu=52 = Clren, Filtered

GFR*fu=39 > Clren, Reabsorbed

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5. A drug is eliminated through glomerular filtration and hepatic metabolism (no other clearance mechanisms are observed). **It does not bind to plasma proteins**. Glomerular filtration rate is normal (**130 ml/min**). No active renal secretion and passive or active reabsorption after renal filtration is observed. The volume of distribution is **50 L.** When given as an i.v. bolus, plasma concentrations **one** hour after administration were **5.2 mg**/L. **3 hours** after administration the concentration was **2.6 mg/L**. (25 pts)

    a. k_e=(ln5.2-ln2.6)/(3-1)=0.3465 hr^{-1}
    b. CLtot=V_d*k_e=0.3465*50=17.325 L/hr
    c. CLren=130 ml/min=7.8 L/hr
    d. CLhep=17.325-7.8=9.525 L/hr
    e. C=$3.67e^{-0.3465*10}$=0.115 mg/L

5a. What is k_e?

5b. What is the total clearance of the drug.

5c. What is the renal clearance of the drug?

5d. What is the hepatic clearance of the drug?

5e. After 10 doses of this drug (given once a day) the concentration two hours after the last dose is 3.67 mg/L. What will be the concentration 10 hours later (12 hours after the last injection)

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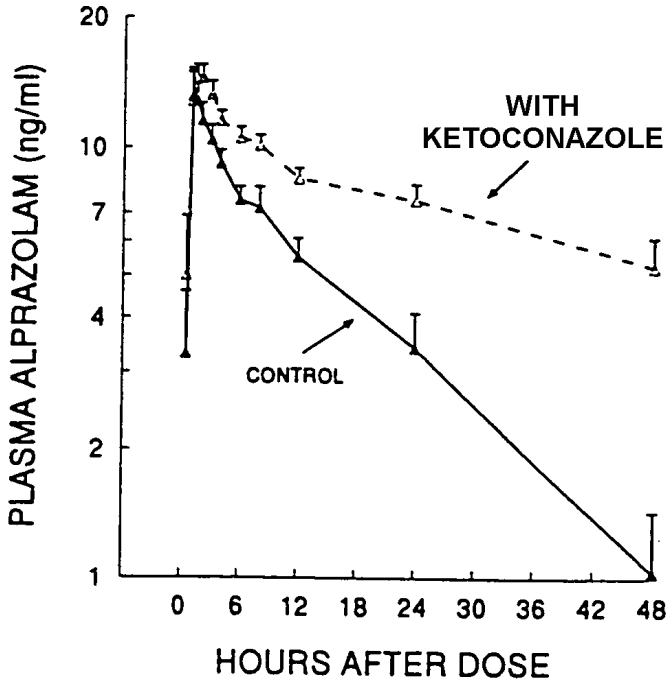
6. The same dose of Alprazolam was given either alone or with ketocozanole. Explain what is going on. (15 points)



Greenblatt, 26 September 1998

Ketoconazole is an enzyme inhibitor. Therefore, Ketoconazole inhibited the enzyme that is responsible for the metabolism of Alprazolam and increased the half-life of Alprazolam. There has to be a difference in clearance, since a change in Vd would not explain the difference in AUC.,