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. ________/15 pts

TOTAL ________/100 pts
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
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 $CL = k_e \cdot V_d$. Therefore, $V_d$ is different. Then Dose is the same.
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)

<table>
<thead>
<tr>
<th>Physiological change</th>
<th>Effect on kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.) Increase in metabolic enzymes</td>
<td>a. Cl_{REN} ↓</td>
</tr>
<tr>
<td>2.) Decrease in urine flow</td>
<td>b. Cl_{HEP} ↓</td>
</tr>
<tr>
<td>3.) Increase in liver blood flow</td>
<td>c. oral bioavailability ↓</td>
</tr>
<tr>
<td>4.) Decrease in number of fat cells</td>
<td>d. V_D ↑</td>
</tr>
<tr>
<td>5.) Decrease in creatinine clearance</td>
<td>e. oral bioavailability F↑</td>
</tr>
<tr>
<td></td>
<td>f. V_D ↓</td>
</tr>
<tr>
<td></td>
<td>g. none of the above</td>
</tr>
</tbody>
</table>

**C, A, E, F, G**
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 \(f_u = 0.02\) and a \(C_{\text{REN}} = 20\) mL min\(^{-1}\) is _______________________
- A drug with \(f_u = 0.40\) and a \(C_{\text{REN}} = 52\) mL min\(^{-1}\) is _______________________
- A drug with \(f_u = 0.30\) and a \(C_{\text{REN}} = 0.45\) mL min\(^{-1}\) is _______________________

\[\text{GRF} \times f_u = 2.6 < C_{\text{REN}}, \text{Secreted}\]
\[\text{GRF} \times f_u = 52 = C_{\text{REN}}, \text{Filtered}\]
\[\text{GRF} \times f_u = 39 > C_{\text{REN}}, \text{Reabsorbed}\]
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. \( k_e = \frac{\ln(5.2) - \ln(2.6)}{3-1} = 0.3465 \text{ hr}^{-1} \)
   b. \( \text{CL}_{\text{tot}} = V_d \cdot k_e = 0.3465 \times 50 = 17.325 \text{ L/hr} \)
   c. \( \text{CL}_{\text{ren}} = 130 \text{ ml/min} = 7.8 \text{ L/hr} \)
   d. \( \text{CL}_{\text{hep}} = 17.325 - 7.8 = 9.525 \text{ L/hr} \)
   e. \( C = 3.67e^{-0.3465 \times 10} = 0.115 \text{ mg/L} \)

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

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.

Greenblatt, 26 September 1998