Name: ________________________
SS#: _________________________

PHA 5128
First Exam
Spring 2002

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

**TYPED KEY**

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
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<tbody>
<tr>
<td>1.</td>
<td>_____/10 pts</td>
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<td>2.</td>
<td>_____/25 pts</td>
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<td>_____/10 pts</td>
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<td>9.</td>
<td>_____/5 pts</td>
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<td>10.</td>
<td>_____/5 pts</td>
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</table>

Total _____/100 pts
1. (10 pts.) Moxifloxacin is a new quinolone anti-infective agent. This class of anti-infective agents can complex with dietary minerals (calcium, iron, etc) and may cause reductions in bioavailability. The following data were obtained after IV bolus administration, oral administration, and oral administration with 100 mg iron(II) sulfate.

<table>
<thead>
<tr>
<th></th>
<th>IV bolus</th>
<th>P.O.</th>
<th>PO+Iron(II) Sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>CMAX (mg/L)</td>
<td>3.62</td>
<td>2.86</td>
<td>1.17</td>
</tr>
<tr>
<td>TMAX (h)</td>
<td>---</td>
<td>1</td>
<td>2.79</td>
</tr>
<tr>
<td>AUC∞ (mg/L h)</td>
<td>34.6</td>
<td>34</td>
<td>20.7</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>11.6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>15.4</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Vc (L/kg)</td>
<td>2.1</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

A) Does iron affect the absolute bioavailability of moxifloxacin?

Yes. AUC∞ is lowered from 34 to 20.7 mg/L · h

B) In one or two sentences explain why the time to maximal concentration (tMAX) changes with the addition of iron (II) sulfate

Iron slows down the absorption rate of moxifloxacin

C) In general, what are the reasons an oral dosage form will <100% (List 3 reasons)?

- Solubility/dissolution rate
- Degradation
- P-glycoprotein
- Incomplete active transport
- First-pass effect
- Poor permeability
2. (25pts) A patient (63 kg, male) was given 120 mg gentamicin bid over 30 minutes (i.v.) from 6:00 to 6:30 am and pm. for five days to obtain measured peaks and troughs of 18 and 1. On day 5, two serum levels were measured:

At 5:30 pm 1.6 µg/mL
At 7:00 pm 10.2 µg/mL

Calculate:

a. The elimination rate constant $k$

$$k = \frac{\ln \left( \frac{10.2}{1.6} \right)}{10.5} = 0.176 h^{-1}$$

b. The elimination half-life

$$t_{1/2} = \frac{0.693}{0.176} = 3.9 h$$

c. The true peak concentration at 6:30 am

$$C_{max} = \frac{10.2}{e^{-0.176 \cdot 0.5}} = 11.1 \mu g / mL$$

d. The true trough concentration at 6:00 pm

$$C_{min} = 1.6 \cdot e^{-0.176 \cdot 0.5} = 1.47 \mu g / mL$$
e. The volume of distribution

\[ V_d = \frac{120 \cdot (1 - e^{-0.176 \cdot 0.5})}{0.176 \cdot 0.5 \cdot (11 - 1.47 \cdot e^{-0.176 \cdot 0.5})} = 11.7L \]

f. The clearance

\[ CL = 0.176 \cdot 11.7 = 2.1 \text{ L/h} \]

g. A revised dosing recommendation

\[ \tau = \frac{\ln \left( \frac{18}{1} \right)}{0.176} + 1.5 = 17.9h \Rightarrow 18h \quad \text{(not compliance-friendly)} \]

\[ C_{\text{max}} = \frac{.8}{e^{-0.176 \cdot 0.5}} = 19.7\mu g / mL \quad \text{better 24 h} \]

\[ D = 19.7 \cdot 0.176 \cdot 11.7 \cdot 0.5 \cdot \frac{(1 - e^{-0.176 \cdot 24})}{(1 - e^{-0.176 \cdot 0.5})} = 237 \Rightarrow 240mg \quad \text{QD} \]
3. (5 pts) What is the difference between a "third compartment" and "third space fluids"?

Third compartment: Slowly equilibrating tissue where drug will accumulate over time

Third space: Additional body water (edema, ascites)

4. (10 pts) Compare the pharmacokinetic properties of amoxicillin and cloxacillin:

<table>
<thead>
<tr>
<th></th>
<th>amoxicillin</th>
<th>cloxacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL [L/h]</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Vd [L]</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Foral</td>
<td>0.93</td>
<td>0.43</td>
</tr>
<tr>
<td>fb</td>
<td>0.18</td>
<td>0.95</td>
</tr>
<tr>
<td>Fren</td>
<td>0.86</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Calculate and compare for both drugs the total daily oral dose necessary to maintain an average unbound concentration of 10 mg/L in plasma and urine. Assume a urine flow of 2 ml/min.

**Amoxicillin**

Plasma: \( D = \frac{10 \cdot 18 \cdot 24}{0.93 \cdot 0.82} = 5.6g \)

CL\(_R\) = 0.86 \cdot 18 = 15.5 L/h

Excretion Rate = 0.02 mg/min = 1.2 mg/h

\( C = \frac{1.2}{15.5} = 0.077\text{mg} / \text{L} \)

Urine: \( D = \frac{0.077 \cdot 18 \cdot 24}{0.93} = 35.8mg \)

**Cloxacillin**

Plasma: \( D = \frac{10 \cdot 15 \cdot 24}{0.43 \cdot 0.05} = 167g \)

CL\(_R\) = 0.75 \cdot 15 = 11.3 L/h

Excretion Rate = 0.02 mg/min = 1.2 mg/h

\( C = \frac{1.2}{11.3} = 0.106\text{mg} / \text{L} \)

Urine: \( D = \frac{0.106 \cdot 15 \cdot 24}{0.43} = 89mg \)
5. (10 pts) The following data were obtained for 2 generic products (AMP and HHH) and the Brand Drug Product (Y2J).

<table>
<thead>
<tr>
<th></th>
<th>AUC∞ (mg/L h)</th>
<th>AUCt (mg/L h)</th>
<th>Cmax (mg/L)</th>
<th>tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Y2J (reference)</strong></td>
<td>1313</td>
<td>1180</td>
<td>13.1</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>AMP</strong></td>
<td>1090</td>
<td>995</td>
<td>12.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Ratio AMP/Y2J</td>
<td>83.0%</td>
<td>84.3%</td>
<td>95.4%</td>
<td></td>
</tr>
<tr>
<td>90% Confidence</td>
<td>72.1-93.0</td>
<td>79.7-95.5</td>
<td>90.1-101.6</td>
<td></td>
</tr>
<tr>
<td><strong>HHH</strong></td>
<td>1300</td>
<td>1105</td>
<td>12.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Ratio HHH/Y2J</td>
<td>99.0%</td>
<td>93.6%</td>
<td>97.7%</td>
<td></td>
</tr>
<tr>
<td>90% Confidence</td>
<td>93-102.5</td>
<td>91.2-101.4</td>
<td>92.7-103.1</td>
<td></td>
</tr>
</tbody>
</table>

A) What rating is given to bioequivalent products?

AB

B) Is either generic (AMP and HHH) bioequivalent to the brand product (Y2J)? (please give a one or two sentence for your reasoning)

HHH → bioequivalent (90% CI is within 80-125%)

AMP → not bioequivalent

C) Bioequivalence studies, in general, are conducted in:

a. Healthy Volunteers
b. Patient Populations
c. Both of the above
6. (10 pts) L.F., a 28-year-old, 75 kg male, is receiving 100 mg of tobramycin infused IV over 30 minute period q8h. His serum creatinine has increased from 1 mg/dL to 1.8 mg/dL over the past 24 hours. Since his renal function appears to be decreasing, three plasma samples were obtained to monitor serum tobramycin concentrations as follows: just before a dose; one hour after that same dose; and eight hours after that dose (two troughs and one peak level). The serum tobramycin concentrations at these times were 4 mg/L, 8 mg/L, and 5 mg/L, respectively. Calculate the volume of distribution, elimination rate constant, and clearance of tobramycin for L.F. Also, using the pharmacokinetic parameters calculated for L.F. above, develop a dosing regimen that will produce reasonable peak and trough concentrations of tobramycin.

\[
\ln \left( \frac{8}{5} \right) = \frac{k}{7} = 0.067 h^{-1}
\]

\[
C_{\text{max}} = \frac{8}{e^{-0.067 \cdot 0.5}} = 8.3 \mu g / mL
\]

\[
V_d = \frac{100}{0.067 \cdot 0.5} \cdot \left( \frac{1 - e^{-0.067 \cdot 0.5}}{8.3 - 4 \cdot e^{-0.067 \cdot 0.5}} \right) = 2985 \cdot \frac{0.0329}{4.432} = 22.2 L
\]

\[
CL = 0.067 \cdot 22.2 = 1.49 L/h
\]

\[
\tau = \ln \left( \frac{8}{1} \right) + 0.5 = 31.5 \Rightarrow 24h
\]

\[
D = 8 \cdot 0.067 \cdot 22.2 \cdot 0.5 \cdot \frac{(1 - e^{-0.067 \cdot 24})}{(1 - e^{-0.067 \cdot 0.5})} = 5.95 \cdot \frac{0.8}{0.033} = 144 \Rightarrow 140 mg \text{ Q 24h}
\]

or

\[
D = 8 \cdot 0.067 \cdot 22.2 \cdot 0.5 \cdot \frac{(1 - e^{-0.067 \cdot 36})}{(1 - e^{-0.067 \cdot 0.5})} = 196 mg \Rightarrow 200 mg \text{ Q36h}
\]
7. (10 pts) A drug is administered as a constant rate infusion over 2 days. A plasma concentration profile is obtained which is shown in the two figures below.

a. In the graph below, add the expected curve for a patient with equal clearance but twice the volume of distribution.

b. In the graph below, add the expected curve in a smoker with equal volume of distribution but twice the clearance.
8. (10 pts.) ZV is a 35-year-old, 75-kg, 67" female with gram-negative pneumonia and chronic renal failure. Her serum creatinine is 3.7 mg/dL which has been stable since admission. Determine a gentamicin dose to provide a true steady-state peak of 10 mg/L and a true steady-state trough of 1 mg/mL using conventional dosing.

\[
\text{IBW} = 45 + 2.3 \cdot 7 = 61.1 \text{ kg}
\]

\[
CL_{cr} = \frac{(140 - 35) \cdot 61.1}{85 \cdot 3.7} = 20.4 \text{ mL/min} = 1.22 \text{ L/h}
\]

\[
V_d = 0.25 \cdot [61.1 + 0.4 \cdot 13.9] = 0.25 \cdot 66.7 = 16.7 \text{ L}
\]

\[
k = \frac{1.22}{16.7} = 0.073 \text{ h}^{-1}
\]

\[
\tau = \frac{\ln 10}{0.073} + 0.5 = 32 \text{h} \implies 48 \text{h}
\]

\[
D = 10 \cdot 0.073 \cdot 16.7 \cdot 0.5 \cdot \frac{\left(1 - e^{-0.073 \cdot 48}\right)}{\left(1 - e^{-0.073 \cdot 0.5}\right)} = 6.096 \cdot \frac{0.9699}{0.0358} = 165
\]

\[\implies 160 \text{ mg Q 48 h}\]

or

\[
D = 10 \cdot 0.073 \cdot 16.7 \cdot 0.5 \cdot \frac{\left(1 - e^{-0.073 \cdot 36}\right)}{\left(1 - e^{-0.073 \cdot 0.5}\right)} = 183 \implies 180 \text{ mg Q 36 h}
\]
9. (5 pts) RM is a 75-year-old, 78kg, 5'8" male with Streptococcus viridans endocarditis who is allergic to penicillins and cephalosporins. His serum creatinine is 1.5 mg/dL and stable. Recommend a vancomycin dosing regimen (loading dose and maintenance dose) for this patient.

LD: \(25 \text{ mg/kg} = 2 \text{ g}\)

MD: \(19 \text{ mg/kg} = 1.5 \text{ g} \text{ Q 36h}\)

\[
CL_{cr} = \frac{(140 - 75) \cdot 68.4}{72 \cdot 1.5} = 41 \text{ mL/min}
\]

IBW = 50 + 2.3 \cdot 8 = 68.4 \text{ kg}
10. (5 pts.) Discuss the differences of vancomycin and gentamicin pharmacokinetics and pharmacodynamics.

Vancomycin:  
- time-dependent killing
- Needs constant presence

Glutamicin:  
- concentration dependent killing
- Needs high peaks and low troughs
- Adoptive resistance
- Post-antibiotic effect