Name: ______________________

SS#: ______________________

PHA 4123

Second Exam

Spring 1997

**TYPED KEY**

On my honor, I have neither given or received unauthorized aid in doing this assignment.

<table>
<thead>
<tr>
<th>Name</th>
<th>Questions</th>
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<td>_____/20</td>
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<td>TOTAL</td>
<td>_____/100</td>
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1. A 70 yo male patient has recently been experiencing mild side effects to his medications. These side effects were not noted in the past, though the current medications have been in effect for at least the past 5-10 years. Serum levels of the medications are not currently available. Past serum levels >6 months ago may be listed: (10 pts)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Level</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>1.6 meq/Liter</td>
<td>N=0.6-1.2</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>28.0 mcg/ml</td>
<td>N=10-20</td>
</tr>
<tr>
<td>Phenytoin Free</td>
<td>3.2 mcg/ml</td>
<td>N=1-2</td>
</tr>
</tbody>
</table>

A. In this elderly patient, explain by using $V_{\text{max}}$ and $V_d$ possible reasons for an increasing phenytoin CSS with a constant dose.

Age $\uparrow$ → decrease liver mass
Clearance
$V_{\text{max}} \downarrow$

Age $\uparrow$ → decrease protein binding
$V_d \uparrow$

B. Explain by using the fraction excreted ($1-e^{-kt}$), $t_{\frac{1}{2}}$ and $kV_d$ how the renally excreted Lithium may increase in this elderly patient.

Age $\uparrow$ → $CL_{\text{ren}} \downarrow$

$K_e \downarrow$

$T_{\frac{1}{2}} \uparrow$

$(1-e^{kt})\downarrow$

higher Li levels
2. List two treatments that maybe useful in reducing the absorption of an overdosed drug. (5 points)

- Syrup of Ipecac
- Activated Charcoal
- Gastric Lovage

3. A 25 year old female ingested 30 theophylline SR 300 mg tablets approximately 3 hours ago. She weighs 150 pounds. (5 points)

A. Predict the maximum concentration of theophylline in this patient as a result of this overdose.

\[
D = 9 \text{ g} \\
V_d = 0.5 \text{ L/kg} \approx 34 \text{ L} \\
C = \frac{9000}{34} = 260 \mu g / mL
\]

B. Please state the limitations associated with this prediction.

Calculation base on
- population average for \( V_d \)
- instantaneous absorption (unlikely)

Concentration will be lower than calculated.
4. List the possible biological fluids and assay methods for measurement of cyclosporine concentration. Explain why and how the choice of biological fluids and assay methods can affect cyclosporine concentration. Why is it potentially clinically important? [10 pts]

**Fluids**
- Blood
- Serum/plasma

**Assays**
- HPLC - specific
- Monoclonal immunoassay - specific
- Polyclonal immunoassay - non specific

Different assays will give different results

→ different therapeutic ranges

5. You work for the outpatient pharmacy in a major medical center. A recently discharged transplant patient picks up her medicines, including oral cyclosporine capsules. Based on your knowledge concerning the factors that can influence oral cyclosporine bioavailability, list four specific points that you would make as you counsel her regarding her cyclosporine therapy. [10 pts]

- Be consistent with meds
- No other medications without approval
- Contact your MD or RPh if you experience diarrhea
- Avoid grapefruit juice
- Consistent fat intake in meal.
6. CJ is a 18 year old patient with osteosarcoma that was diagnosed in October 1993. She received adjuvant chemotherapy that consisted of doxorubicin and cisplatin for six courses. She is now admitted to your hospital for her first course of high-dose methotrexate (MTX), to be given intravenously at a dosage of 5 gm/m² over 4 hours. On admission, her liver function tests are normal and her serum creatinine was slightly elevated (1.9 mg%).

A. Does the patient have any risk factors for altered MTX pharmacokinetics? If so, list them and explain why they can increase the risk of MTX-related toxicity. [3 pts]

Yes, because of renal impairment and prior cisplatin therapy

B. The physician orders several serum MTX levels at different times after the infusion. Intravenous hydration with urinary alkalinization with sodium bicarbonate. Why is it important to hydrate the patient and alkalinize her urine? [3 pts]

↑ renal elimination of MTX
↑ solubility of MTX and MTX metabolites
↓ risk of nephrotoxicity

C. Her 24 hour MTX level is reported as 2.5 x 10^-6 Moles/Liter. What is your interpretation of this level and your recommendation [4pts]

Please refer to the figure on the next page.

Low risk for MTX toxicity
Continue to monitor MTX levels until < 0.05 µM
Continue leucovorin rescue
7. RW is a 26 YOM receiving chemotherapy for AML who has developed a fever and was placed on vancomycin and ceftazidime empirically. He weighs 80 kg and is 6’ 2” tall. His serum creatinine is 1.2 mg/dL and his WBC is < 100 cells/mm³. What is his estimated creatinine clearance?

\[ CL_{cr} = \frac{(140 - 26) \cdot 80}{1.2 \cdot 72} = 105mL/min \]

RW's vancomycin was begun with a dose of 1 G IV every 12 hours. On the 4th day of therapy, peak and trough serum vancomycin concentrations were done. The "peak" serum vancomycin concentration was drawn 2.5 hours after a 1 hours infusion and was measured as 30.0 µg/ml. The trough, drawn a half an hour before the dose was 11.0 µg/ml.

A. Are these therapeutic?

Yes, Peak seems low, need to extrapolate \( \rightarrow C_{max} = 41 \)

B. Estimate the patient's half-life and the "peak".

\[ k = \frac{30}{8} = 0.125h^{-1} \]

\[ t_{1/2} = 5.5hr \]

\[ C_{max} = \frac{30}{e^{-0.125 \cdot 2.5}} = 41 \]

C. Are these levels reasonable?

Yes

D. What would you do if the patient complained of intermittent hearing loss?

\( \rightarrow \) Possible adverse effects
\( \rightarrow \) Increase dosing interval to Q12
8. In many textbooks the term “biological half-life” is used to describe the duration of pharmacological effects.

Show that this terminology is not useful for a drug that has the following properties: (10 pts)

a. Pharmacokinetics follows a one-compartment body model and is linear.
b. Pharmacodynamics follows an Emax-model (range 20-80% of maximum effect)

PK: \[ C = C_0 e^{-kt} \] or \[ \ln C = \ln C_0 -kt \]

PD: \[ E = m \cdot \ln C + b \]

PK-PD: \[ E = m \cdot (\ln C_0 -kt) + b \]

= \[ m \cdot \ln C_0 + b - m \cdot k \cdot t \] zero order

= \[ A - B \cdot t \] no constant half-life

\[ t_{\text{tEA max}} \cdot = \frac{4}{k} \]

Compare the time that it takes for the concentration to drop from 80% to 20% of \( C_{\text{max}} \) with the time it takes for the effect to drop from 80% to 20% of \( E_{\text{max}} \). (10 pts)

PK: 2 half-lives: \[ \frac{2 \cdot 0.693}{k} = \frac{1.4}{k} \]

PD: \[ E_{80\%} = 0.8 \cdot E_{\text{max}} = A - \frac{e_{\text{max}} \cdot k}{4} \cdot t_{80} \]

\[ E_{20\%} = 0.8 \cdot E_{\text{max}} = A - \frac{e_{\text{max}} \cdot k}{4} \cdot t_{20} \]

\[ \Delta t = \frac{0.6 \cdot 4}{k} = \frac{2.4}{k} \Rightarrow 3.5 \text{ half-lives} \]
9. Describe the changes in the maturation process for the premature infant through adolescent, to normal adults for the pharmacokinetic parameters of distribution and elimination. Assume in this example the drug is primarily water soluble, and is 5% metabolized by the liver, and 90% eliminated unchanged in the urine. (Suggestion: put your answer in the form of a table to make it easier) (10 points)

<table>
<thead>
<tr>
<th></th>
<th>Distribution (Vd)</th>
<th>Elimination (CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature + term neonate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Infants</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Toddlers/school age</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Adolescence</td>
<td>—</td>
<td>↑</td>
</tr>
<tr>
<td>Adults</td>
<td>—</td>
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</tbody>
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10. A 2 week old, 30 week gestational age, 1.3kg, infant has been hospitalized since birth for prematurity. The infant now appears to be septic, and has some chest X-ray changes possible indicating pneumonia. A previous trach culture from 5 days ago was growing enterobacter cloacae sensitive to tobramycin, and is now felt this organism may be causing the infants current problems.

Tobramycin is started at 3.6mg iv q 12hr on 4/14/97 at 0800, and remains on a 0800 and 2000 schedule when serum samples on 4/17/97. The following tobramycin serum samples are drawn:

Tobramycin peak concentration 6.3 mcg/ml drawn on 4/17/97 at 0930.
Tobramycin trough concentration 1.4 mcg/ml drawn on 4/17/97 at 1930

The tobramycin is sent to the floor in syringes, with 3.6mg in a volume of 0.36ml.

   A. What intravenous delivery factors are important in the delivery of this small volume of Tobramycin? (3 pts)

- low volume tubing
- low iv flow rates
- syring pumps for accurate delivery
- small volume delivered
B. Determine the $k_e$ and $t_{1/2}$ of tobramycin in this patient. You need to show work to receive full credit. (3 pts)

\[
\ln\left(\frac{6.3}{1.4}\right)\frac{10}{10} = 0.15 h^{-1}
\]

\[t_{1/2} = 4.6 h\]

C. Calculate the tobramycin "post-distribution" peak which would have occurred at 0900. (3 pts)

\[
C = \frac{6.5}{e^{-0.15 \times 0.5}} = 7.0 \mu g / mL
\]

D. Calculate the dose and dosage schedule to achieve a peak serum tobramycin concentration of at least 8 mcg/ml, using your answer in C above for this determination. (1 pt)

\[
C_{\text{max}} = \frac{6.5}{e^{-0.15 \times 4}} = 7.6
\]

↑ dose by 6% ⇒ 3.8 mg Q12 or 4 mg Q12 (not much change)