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

**Typed Key**

Name

1. _______ / 8 points (Children & Elderly)
2. _______ / 10 points (Theophylline)
3. _______ / 20 points (Phenytoin)
4. _______ / 20 points (Methotrexate)
5. _______ / 7 points (Digoxin)
6. _______ / 10 points (Aminoglycoside)
7. _______ / 5 points (Hepatic Disease)
8. _______ / 5 points (Renal Disease)
9. _______ / 15 points (Miscellaneous)

_________ / 100 points
1. Special Populations: Children and Elderly (8 points)

A) Drug X is given PO to an infant and an adult. The oral bioavailability of Drug X is 80% in infants and 50% in adults. Which statement(s) best explain this situation?

a. Drug X is a weak base. Infants have a more alkaline stomach pH and therefore more drug will be unionized and diffuse into systemic circulation easier.

b. Drug X is a weak acid. Infants have a more alkaline stomach pH and therefore more drug will be unionized and diffuse into systemic circulation easier.

c. Drug X is subject to first-pass metabolism. Infants have lower hepatic metabolism than adults and therefore more drug will enter systemic circulation.

d. Infants have a higher volume of distribution and therefore will have a higher bioavailability.

Answer: __________ a, c __________
B) Young and elderly volunteers were given 100 mg of Drug Y via IV bolus. Which statement(s) accurately relate to the following graph? (Assume therapeutic plasma concentrations are the same in both age groups)

![Graph showing different Vd and t1/2 for young and elderly]

- Different V_d
- Elderly ↑ V_d ⇒ longer t1/2

**a.** When dosing Drug Y, the dosing interval (τ) would be **longer** in the elderly than in the young.

**b.** When dosing Drug Y, the dosing interval (τ) would be **shorter** in the elderly than in the young.

**c.** An IV bolus loading dose would be **lower** in the elderly than in the young.

**d.** An IV bolus loading dose would be **higher** in the elderly than in the young.

Answer: ______ a, d _________
2. *Theophylline*. CH is a 25 year old 46 kg female admitted to the ER for the exacerbation of her asthma caused by excessive exercise. Estimate an IV loading dose and IV infusion rate of aminophylline (85% theophylline) to achieve plasma levels of 15 mg/L. (assume $V_D$ and CL are normal). (10 points)

\[ LD = \bar{C}_{ss} \cdot V_d \]

\[ V_d = (0.5 \text{ L/kg})(46 \text{ kg}) = 23 \text{ L} \]

\[ LD = \frac{15 \text{ mg}}{L} \cdot 23L = 345 \text{ mg } \text{ theophylline} \]

LD = 430 mg aminophylline

\[ \bar{C}_{ss} = \frac{D \cdot 8 \cdot F}{CL \cdot \tau} \]

\[ CL = (0.4 \text{ L/h/kg})(46) = 1.84 \text{ L/h} \]

\[ \frac{D}{\tau} = \frac{\bar{C}_{ss} \cdot CL}{S \cdot F} = \frac{15 \text{ mg}}{2} \cdot \frac{1.84 \text{ L/h}}{(0.80)(1)} \]

\[ M \frac{D}{\tau} = \frac{35 \text{ mg}}{h} \text{ aminophylline} \]
3. **Phenytoin.** AD is 26 year old 50 kg female with a recent diagnosis of a seizure disorder. She needs to be started on phenytoin. (20 points)

A) Phenytoin follows non-linear pharmacokinetics. Draw a line that best describes non-linear pharmacokinetics.

![Graph showing AUC vs Dose]

B) Recommend a loading dose with a target of $C_{\text{peak}} = 20 \text{ mg/L}$

$$LD = V_d \cdot \frac{C_{\text{peak}}}{S}$$

$$V_d = (0.654 \text{ L/kg})(50 \text{ kg})$$

$$= 32.5 \text{ L}$$

$$LD = \frac{2.5L \times 20 \text{ mg/L}}{0.92} = 700 \text{ mg}$$

LD = 700 mg Na phenytoin
AD has also been calibrated with 2 doses of phenytoin:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Resulting Plasma Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
<td>5 mg/L</td>
</tr>
<tr>
<td>350 mg</td>
<td>20 mg/L</td>
</tr>
</tbody>
</table>

Using a Mullen Plot below,

C) What is the $V_{MAX}$ and $K_M$ for AD? (ranges are acceptable)

$V_{max} \approx 475 \text{ mg/d}$

$K_m \approx 6 \text{ mg/L}$

D) What is the recommended daily dose with a target of 15 mg/L?

MD = 325 mg/d
4. Methotrexate. FP a 62 year old, 5'8", 110 kg male is being treated for non-Hodgkins lymphoma with methotrexate (MTX) (CrCl 74 mL/min). He will also receive 20 mg of IV leucovorin q6h for the first four doses followed by 8 doses PO q6h. The leucovorin regimen will begin immediately after the MTX infusion has been discontinued. (20 points)

A) Determine an infusion rate of MTX to reach steady-state plasma levels of 10 μM (10x10^{-6} M) (infusion time is 36 h).

\[
\bar{C}_{ss} = \frac{Ro}{CL}
\]

\[
CL = 6 \times \frac{4 \text{ mL/min}}{1000 \text{ mL}} = 7.1 \text{ L/h}
\]

\[
(0.454) \cdot 10 \mu \text{M} \cdot 7.1 \text{ L/h} = Ro
\]

Ro = 32 mg/h

B) What is the MTX concentration at 48 h after start of the infusion?

\[
C_{36} = 10 \mu \text{M}
\]

\[
C_2 = C_1 \cdot e^{-k_e t}
\]

\[
C_{48} = 10 \mu \text{M} \cdot e^{\left(\frac{0.693}{3}\right) \cdot 8 - 36} = 0.63 \mu \text{M}
\]
C) What is the MTX concentration at 60 h (Use 0.5 \( \mu \text{M} \) as the cutoff point)?

\[
\ln \left( \frac{10}{0.5} \right) = 13h
\]

\[
C_2 = C_1 \cdot e^{ke \cdot t}
\]

\[
C_{w0} = 0.5\mu\text{M} \cdot e^{\left( \frac{0.693}{10} \right) \cdot 13} = 0.23\mu\text{M}
\]

D) How long after the start of the infusion will plasma concentrations be < 0.1 \( \mu\text{M} \)?

\[
\ln \left( \frac{0.5}{0.1} \right) = 23h
\]

\[
t = \frac{\ln \left( \frac{0.5}{0.1} \right)}{0.693} = 23h
\]

\[
36 + 13 + 23 = 72\text{ h}
\]
5. *Digoxin*. CG is a 60 year old male with congestive heart failure (CHF) (50 kg, 67 inches, CrCl 18.5 mL/min) admitted to the hospital for digoxin toxicity. Regular at home dosing was 0.25 mg QD of Lanoxin ($F_{ORAL}=0.70$). At admission, his plasma digoxin was 4.0 μg/L. (7 points). Assume CHF

A) How long will it take for the digoxin concentration to fall from 4.0 to 2.0 μg/L?

**IBW = 50 + 2.3 (7)=66 kg**

V_d = 3.8(66) + 3.1(18.5) = 308L

CL = (0.33)(66) + (0.9)(18.5) = 38.4 mL/min = 2.3 L/h

$k_e = \frac{2.3}{308} = 0.075L/h$

\[ t = \frac{\ln\left(\frac{4}{2}\right)}{0.0072} = 97h \]

**V_d = 308L**

\[ CL = \frac{DFS}{C_{ss} \cdot \tau} \]

\[ (250)(0.7) \]
\[ (4.0)(24h) \]

\[ t=100h \]

B) Calculate a daily dose which will maintain CG's average digoxin concentration at 2 μg/L.

\[ D = \frac{C_{ss} \cdot CL}{\tau} = \frac{(2)(2.0)}{(0.7)} = 0.140mg \]
6. Aminoglycosides. AB, a 42 kg, 21 year old female patient (CrCl=110 mL/min) is started on IV of tobramycin 100 mg q8h at 8:00am. Infusion time is half an hour (0.5 h). Plasma levels during the first infusion were taken at 9:00am and 4:00pm and the values can be found in the following table. What concentrations would you expect to see based on population values? (10 points)

<table>
<thead>
<tr>
<th>Time</th>
<th>Measured Level (mg/L)</th>
<th>Expected Level (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 am</td>
<td>6.1</td>
<td>5.98 mg/L</td>
</tr>
<tr>
<td>4:00 pm</td>
<td>0.069</td>
<td>0.07 mg/L</td>
</tr>
</tbody>
</table>

Another accepted answer would be:

\[ \text{Vd} = S \times F \times \text{Loading Dose/C1} = (0.8 \times 1 \times 750 \text{mg}) / 19 \text{mg/L} = 31.6 \text{L} \]
NAME: _________________________
SS#: _________________________

$$Cl = \frac{2 \times R_0}{(C_1 + C_2)} + \frac{2 \times V_d \times (C_1 - C_2)}{(C_1 + C_2) \times (t_2 - t_1)} = \frac{2 \times 0.8 \times 35}{(19 + 15)} + \frac{2 \times 31.6 \times (19 - 15)}{(19 + 15) \times (7 - 1)} = 2.88L/h$$

$$R_0 = \frac{C_{\text{max}} \times Cl}{S \times F} = \frac{15 \times 2.88}{0.8 \times 1} = 54mg/h \approx 56mg/h$$
7. *Hepatic Disease.* Chronic liver disease causes a 50% decrease in verapamil clearance. However, half-life of verapamil increases 4 fold in chronic liver disease. Clearly the volume of distribution has changed due to the chronic liver disease. (5 points)

A) What is the volume of distribution of verapamil in a patient with chronic liver disease? (Healthy population values: \( CL = 60 \text{L/h}; V_D = 350 \text{L} \))

**Healthy**

\[ CL = k_e \cdot V_d \]
\[ 60 = k_e \cdot 350 \text{L} \]
\[ k_e = 0.171 \text{L/h} \]
\[ t_{1/2} = 4\text{h} \]

**Hepatic**

\( CL \downarrow 50\% = 30 \text{L/h} \)

If \( t_{1/2} = 16 \)
\[ 690 \text{L} = V_d \]

B) Why would volume of distribution change with chronic liver disease (one or two words should suffice)?

**Hypoalbumenia**

(\( \downarrow f_b \))
8. Renal Disease. Cefditoren pivoxil is newly approved third-generation cephalosporin antibiotic. Cefditoren has an oral bioavailability of 14% and is primarily eliminated via renal excretion (CL= 5 L/h, $F_{REN}=0.95$). Treatment of bronchitis caused by *S. pneumoniae* for adults with normal renal function is 400 mg q12h for 10 days. However, it is recommended that a dosage of 200 mg q24h be used in patients with severe renal impairment. What would be the average steady-state concentrations ($\bar{C}_{ss}$) in a patient with normal renal function and a patient with severe renal impairment (75% reduction in renal function). (5 points)

Normal

$$\bar{C}_{ss} = \frac{D \cdot F}{CL \cdot \tau} = \frac{(400)(0.14)}{(5)(12)} = 0.93 \text{ mg/L}$$

Renal

$$CL = CL_{NR} + CL_{ren}$$

$$CL = (0.05)CL + (0.95)CL$$

$$C_{disease} = (0.05)CL + (0.95)(0.25)CL$$

$$CL^* = 0.29CL = (0.29)(5)$$

$$CL^* = 0.29 \times 5$$

$$= (0.29)(5)$$

$$CL = 1.43 \text{ L/h}$$

$$\bar{C}_{ss} = \frac{D \cdot F}{CL \cdot \tau} = \frac{(200)(0.14)}{(1.43)(24)}$$

$$\bar{C}_{ss} = 0.82 \text{ mg}$$
NAME: _________________________  
SS#: __________________________

9. Miscellaneous. Fill in the blank (15 points, 3 points each).

A) Carbamazepine’s clearance increases with repeated doses due to a phenomenon called _____ autoinduction________________________.

B) The antiepileptic drug, _____ phenobarbital_____________, has an age-dependent clearance and can take almost 1 month to reach steady-state.

C) β-blockers can decrease liver blood flow and affect the clearance of a high extraction drug like lidocaine. The average steady state levels (C_{SS}) of lidocaine when taken with β-blockers would increase / decrease / not change and the time it takes to achieve steady-state would increase / decrease / not change.

D) Part of the therapeutic effect of procainamide is may be due the formation of the active metabolite, _____ NAPA__________, which is formed by the processes of __ acetylation __.

E) JJ (25 yr, female, 50 kg) is hospitalized after an aerobics class with premature ventricular contractions (PVCs). A slow IV push loading dose of _____86_______ mg lidocaine should be given to achieve a peak level of 3 mg/L.

\[ LD = \frac{V \cdot C_{SS}}{s} = \frac{(0.57 \text{ng})(50)(3)}{(0.87)} \]