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

Print:  

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Name  

Total points for exam 100 points (16 questions)
Question #1: (5 points)

What is the general reason that the ultimate desired maintenance dose of Carbamazepine is much higher than the beginning dose?

A) Pharmacodynamic drug tolerance
B) Disease progression
C) Metabolic enzyme autoinduction
D) Renal function increased
E) Carbamazepine is a high hepatic extraction drug
Question #2: (5 points)

M.T., 45-year-old, 65 kg female, is to be started on intravenous phenobarbital sodium (S=0.9). Calculate a loading dose (LD) to yield a phenobarbital concentration of 20 mg/L and the daily maintenance dose (MD) to maintain the phenobarbital concentration of 20 mg/L.

A) LD = 1400 mg, MD = 160 mg
B) LD = 700 mg, MD = 80 mg
C) LD = 1000 mg, MD = 140 mg
D) LD = 1500 mg, MD = 144 mg
E) LD = 900 g, MD = 120 g

\[
LD = \frac{Cp \cdot Vd}{S \cdot F} = \frac{20mg/L \cdot 0.7L/kg \cdot 65kg}{0.9 \cdot 1} = 1011.1mg \approx 1000mg
\]

\[
MD = \frac{Cp \cdot Cl \cdot \tau}{S \cdot F} = \frac{20mg/L \cdot 0.004L/kg/h \cdot 65kg \cdot 24h}{0.9 \cdot 1} = 138.67mg \approx 140mg
\]
**Question #3:** (10 points)

T.X. is a 53 kg female patient (47 years) to receive methotrexate therapy. Her serum creatinine is 1.2 mg/dL. She is treated with a loading dose (20 mg) followed by an infusion of 25 mg/h over 36 hours. She will then receive a 10 mg/m$^2$ dose of leucovorin q6h (four doses) followed by eight oral doses (q6h) of 20 mg. Calculate the expected MTX concentration at 48 hour after the start of the infusion and the expected time that the methotrexate level will fall below 0.1 μM by using the typical half-life parameters? After the drug sampling report [14 μM (24h), 0.40 μM (60 h), and 0.20 μM (75h)], adjust your prediction according to data. (You can assume the plasma concentration already reached steady state after 24 hrs infusion.).

**A**) Expected: $C_{48h}=0.75\, \mu M$, $t_{0.1uM}=73\, \text{hr}$; Adjusted: $C_{48h}=1.74\, \mu M$, $t_{0.1uM}=90\, \text{hr}$

**B**) Expected: $C_{48h}=2.12\, \mu M$, $t_{0.1uM}=85\, \text{hr}$; Adjusted: $C_{48h}=0.75\, \mu M$, $t_{0.1uM}=90\, \text{hr}$

**C**) Expected: $C_{48h}=0.75\, \mu M$, $t_{0.1uM}=90\, \text{hr}$; Adjusted: $C_{48h}=0.82\, \mu M$, $t_{0.1uM}=90\, \text{hr}$

**D**) Expected: $C_{48h}=1.74\, \mu M$, $t_{0.1uM}=80\, \text{hr}$; Adjusted: $C_{48h}=0.74\, \mu M$, $t_{0.1uM}=108\, \text{hr}$

**E**) Expected: $C_{48h}=0.55\, \mu M$, $t_{0.1uM}=68\, \text{hr}$; Adjusted: $C_{48h}=1.74\, \mu M$, $t_{0.1uM}=95\, \text{hr}$

Calculate the expected MTX steady-state concentration (in μM).

$$CL_{Cr} = \frac{140 - 47 \cdot 53}{85 \cdot 1.2} = 48.3\, mL/min \approx 2.9\, L/h$$

$$CL_{MTX} = CL_{Cr} \cdot 1.6 = 2.9\, L/h \cdot 1.6 = 4.64\, L/h$$

$$C_{ss} = \frac{R_0}{CL} = \frac{25\, mg/h}{4.64\, L/h} = \frac{5.39\, mg/L}{0.454} = 11.87\, uM$$
Calculate the predicted concentrations at 24, 48 and 60 h after the start of the MTX infusion.

36 h: \[11.87 \mu M\]

48 h: \[C_p = 11.87 \mu M \cdot e^{-0.231 \cdot 12} = 0.75 \mu M\]

\[t_{0.5 \mu M} = \frac{\ln \left( \frac{11.87}{0.5} \right)}{0.231} = 36 + 13.7 = 49.7 h\]

\[t_{0.1 \mu M} = \frac{\ln \left( \frac{0.5}{0.1} \right)}{0.0693} = 49.7 + 72.9 = 122.6 h\]

The reported levels were 14 \(\mu M\) (24h), 0.40 \(\mu M\) (60 h), and 0.20 \(\mu M\) (75h)

\[T_{1/2\beta} = 15 h \Rightarrow t_{0.1 \mu M} = 90 h\]

\[k_\beta = \frac{0.693}{15} = 0.0462 h^{-1}\]

\[t_{0.5 \mu M} = 60 - \frac{\ln \left( \frac{0.5}{0.4} \right)}{0.0462} = 55.2 h\]

\[k_\alpha = \frac{0.174}{55.2 - 36} = 0.174 h^{-1}\]

48 h: \[C_p = 14 \mu M \cdot e^{-0.174 \cdot 12} = 1.74 \mu M\]
Which of the following statements is **FALSE** based on the volume of distribution in obese patients.

A) Hydrophilic drugs display little change in the volume of distribution.

B) The volume of distribution is based on the lipophilicity of the drug.

C) Lipophilic drugs display an increase in the volume of distribution.

D) Hydrophilic drugs display a decrease in the volume of distribution per kilogram.

E) *Lipophilic drugs display a decrease in the volume of distribution per kilogram.*
**Question #5**: (5 points)

D.H. is a male 71kg patient with methicillin-resistant *S. aureus* infection. Which of the following would be a recommended dosing regimen if a gentamicin plasma concentration of 5mg/L 8 hours after the start of the infusion was measured? Please assume average population PK parameters for D.H.

**ODA Nomogram for Gentamicin and Tobramycin at 7 mg/kg**

![Nomogram](image)

A) 500mgQ24h  
B) 500mgQ36h  
C) 500mgQ48h  
D) All of the above  
E) None of the above
Question #6: (5 points)

A 65 year old male (75kg) is admitted to the ER with ventricular tachycardia. He is started on procainamide with a loading dose of 15 mg/kg over 1 hr and a maintenance dose of 120 mg/hr. Serum levels are measured at one hour and twenty-four hours. Concentrations are 6mg/L and 8mg/L. Upon release this patient is to be switched to oral procainamide. Calculate a dosing regimen to give a steady state average concentration of 6 mg/L. Assume the twenty-four hour concentration is at steady state. Hint: use the IV bolus equation for a loading dose to find the Vd. Please calculate ke as ke=Cl/Vd. Do not use any other method.

A) 850 mg BID
B) 800 mg QD
C) 700 mg TID
D) 850 mg TID
E) 700 mg BID

\[ Cl = MD\times S / Cavess = 120 \text{mg/hr}\times 1 \text{hr} \times 0.87 / 8 \text{mg/L} = 13.05 \text{L/hr} \]

\[ Vd = LD \times S / Cp0 = 15 \text{mg/kg}\times 75 \text{kg} \times 0.87 / 6 \text{mg} = 163.13 \text{L} \]

\[ Ke = Cl / Vd = 13.05 \text{L/hr} / 163.13 \text{L} \sim 0.08 \text{hr}^{-1} \]

\[ Tau = \ln(8/4) / 0.08 = 8.66 \text{hr} \sim 8 \text{hr} \]

\[ Dose = Cavess \times Cl \times tau / (0.85 \times 0.87) = 847.1 \sim 850 \text{mg} \]

Dosing Regimen = 850mg TID
**Question #7: (10 points)**

B.D. is a 32 year old 72 kg male. He received a kidney transplant is on cyclosporine 250 mg BID. His trough level is measured and comes back as 80ng/mL. Design a new dosing regimen based on this information with a Cmax of 400ng/mL and a Cmin of 150ng/mL.

Cyclosporine is rapidly absorbed.

- A) 125 mg TID
- B) **250 mg TID**
- C) 200 mg BID
- D) 200 mg TID
- E) 250 mg QD

VD=4.5L/kg * 72kg=324L

Cmax=F*D/Vd+Cmin=0.3*250mg/324L*1000+80ng/mL=311ng/mL

Ke=ln(311ng/mL)/(80ng/mL)/12hours=0.113 hr⁻¹

Tau=ln(400/150)/0.113 hr⁻¹=8.6hours~8hours

Dose=Cmax*(1-e^(-ke*tau))*Vd/F*S=400ng/mL*(1-e^(-0.113 hr⁻¹

*8hours))\*324*1000mL/0.3 = 257.06 \times 10⁶ng = 257mg~250mg

Dosing regimen=250mg TID
**Question #8:** (5 points)

F.W. is a 55-year-old, 75kg male with glomerular nephritis. His creatinine clearance is reasonably good, but he has a serum albumin concentration of 2.2g/dL. F.W. is receiving 350mg/day of phenytoin and has a steady-state phenytoin concentration of 7mg/L. What would be his phenytoin concentration be if his serum albumin concentration was normal? (Normal serum albumin=4.4g/dL).

A) 10.9 mg/L

**B) 12.7 mg/L**

C) 15.0 mg/L

D) 20.0 mg/L

E) 9.0 mg/L

\[
C_{p_{normal}} = \frac{C_{p'}}{\left(\alpha \frac{Patient's\ Albu}{Normal\ Albu} \text{ min}\right) + 0.1} = \frac{7\ \text{mg/L}}{\left(\alpha \frac{2.2 \text{ g/dL}}{4.4 \text{ g/dL}}\right) + 0.1} = 12.7\ \text{mg/L}
\]
G.V., a 57-year-old, 55kg woman (5’4”) with congestive heart failure, was admitted to the hospital with for possible digoxin toxicity. Her serum creatinine was 2.8mg/dL, and her dosing regimen at home had been 0.25mg digoxin (tablets) daily for a year. Her digoxin plasma concentration on admission was 3.8μg/L. How long will it take for the digoxin concentration to fall from 3.8 to 2μg/L if no further doses are given?

A) 2.6 days  
B) 5.1 days  
C) 3.7 days  
D) 4.3 days  
E) 7.4 days

\[\text{IBW (female)} = 45.5 + 2.3 \times 4 = 54.7\]

\[\text{Cl}_{cr} (\text{female}) = \frac{(140 - 57) \times 55 \text{kg}}{85 \times 2.8 \frac{\text{mg}}{dL}} = 19.18 \frac{mL}{\text{min}}\]

\[\text{Cl} = \frac{S \times F \times \text{Dose}}{\tau \times \text{Css}} = \frac{1 \times 0.7 \times 250 \text{μg}}{1 \text{day} \times 3.8 \frac{\text{μg}}{L}} = 46.05 \frac{L}{\text{day}}\]

\[\text{V}_d = 3.8 \frac{L}{kg} \times \text{IBW} + 3.1 \times \text{Cl}_{cr} = 3.8 \frac{L}{kg} \times 54.7 \text{kg} + 3.1 \times 19.18 \frac{mL}{\text{min}} = 267.32 L\]

\[k_{es} = \frac{\text{Cl}}{\text{V}_d} = \frac{46.05 \frac{L}{\text{day}}}{267.32 L} = 0.172 \text{day}^{-1}\]

\[t = \frac{\ln \left( \frac{C_1}{C_2} \right)}{k_{es}} = \frac{\ln \left( \frac{3.8 \text{μg}}{2 \text{μg}} \right)}{0.172 \text{day}^{-1}} = 3.73 \text{days}\]
A recent study was performed to evaluate Ritonavir’s effect on Digoxin pharmacokinetics. Six healthy subjects in the treatment group were given Ritonavir for 2 days until steady state of Ritonavir was reached, and the other 6 subjects in the control group were given placebo for 2 days. On day 3, all subjects were given a dose of Digoxin of 0.5 mg. Then blood samples were taken based on designed time points. The quantified digoxin concentrations were plotted with time in the following graph. Table I shows the noncompartmental analysis results. (Ritonavir is a HIV protease inhibitor, and also inhibits metabolism enzymes (CYP450), and P-gp in the renal tubule.) Which of the following statements is FALSE?

**Table I.** Noncompartmental analysis of digoxin kinetic parameters (mean ± SEM) during placebo or ritonavir

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Ritonavir</th>
<th>Wilcoxon test</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-\infty}$ (h·ng/mL)</td>
<td>22 ± 9</td>
<td>41 ± 17</td>
<td>$P &lt; .01$</td>
</tr>
<tr>
<td>$Cl_{0-\infty}$ (mL/min)</td>
<td>409 ± 30</td>
<td>238 ± 29</td>
<td>$P &lt; .001$</td>
</tr>
<tr>
<td>$Cl_{2-\infty}$ (mL/min)</td>
<td>194 ± 23</td>
<td>126 ± 21</td>
<td>$P &lt; .01$</td>
</tr>
<tr>
<td>$Cl_{n,\infty}$ (mL/min)</td>
<td>215 ± 15</td>
<td>112 ± 7</td>
<td>$P &lt; .01$</td>
</tr>
<tr>
<td>$V_d_{ss}$ (L)</td>
<td>255 ± 47</td>
<td>451 ± 60</td>
<td>$P &lt; .001$</td>
</tr>
<tr>
<td>$Ac_{0-\infty}$ (µg)</td>
<td>273 ± 25</td>
<td>295 ± 33</td>
<td>$P = .15$</td>
</tr>
<tr>
<td>$t_{1/2,\infty}$ (h)</td>
<td>16 ± 3</td>
<td>41 ± 9</td>
<td>$P &lt; .01$</td>
</tr>
<tr>
<td>$t_{1/2,\text{EL}}$ (h)</td>
<td>45 ± 3</td>
<td>57 ± 6</td>
<td>$P = .05$</td>
</tr>
<tr>
<td>$t_{1/2,\text{Ex}}$ (h)</td>
<td>52 ± 8</td>
<td>53 ± 6</td>
<td>$P = .79$</td>
</tr>
</tbody>
</table>

$AUC_{0-\infty}$ Area under plasma concentration–time curve from time 0 to infinity; $Cl_{0-\infty}$ total clearance; $Cl_{2-\infty}$ renal clearance; $Cl_{n,\infty}$ nonrenal clearance; $V_d_{ss}$ volume of distribution at steady state; $Ac_{0-\infty}$ amount excreted into urine from time 0 to infinity; $t_{1/2,\infty}$ terminal elimination half-life in plasma; $t_{1/2,\text{EL}}$ terminal urinary excretion half-life determined by excretion rate versus time plot; $t_{1/2,\text{Ex}}$ terminal urinary excretion half-life determined by amount remaining to be excreted versus time plot.

A) Digoxin is metabolized by cytochrome P-450 enzymes.
B) Ritonavir had a profound impact on volume of distribution of digoxin.
C) Digoxin could be partially eliminated by P-gp mediated renal tubular secretion.
D) Similar to ritonavir, quinidine increases the volume of distribution of digoxin when co-administrated.
E) Toxicity could be an issue when digoxin and ritonavir are co-administered.
Ritonavir inhibits P-gp in renal tubule, and Digoxin could be also eliminated by P-gp mediated renal tubular secretion as the renal clearance for digoxin decreases when Ritonavir is co-administered and Digoxin is a P-gp substrate.

Based on the graph and table, it is clearly shown that Ritonavir could decrease Digoxin Total clearance, renal clearance, and increase volume of distribution, but Quinidine decreases the volume of distribution of Digoxin.

Digoxin concentration could exceed its therapeutic window, resulting in toxicity when total clearance of Digoxin decreases.
**Question #11: (5 points)**

Moxifloxacin is a new quinolone anti-infective agent. This class of antiinfective 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>C_{MAX} (mg/L)</td>
<td>3.62</td>
<td>2.86</td>
<td>1.17</td>
</tr>
<tr>
<td>T_{MAX} (h)</td>
<td>---</td>
<td>1</td>
<td>2.79</td>
</tr>
<tr>
<td>AUC_{0} (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>T_{1/2} (h)</td>
<td>15.4</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>V_{c} (L/kg)</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Which of the following statement is **FALSE**?

A) Iron slows down the absorption rate of moxifloxacin as indicated by the change of the time to maximal concentration after the addition of iron (II) sulfate.

B) Iron has effects on the absolute bioavailability of moxifloxacin.

C) The oral bioavailability of moxifloxacin is relatively high (>95%).

D) **Co-administration of TUMS® (antacid, calcium carbonate) results in the increase of moxifloxacin exposure.**

E) The reason that bioavailability of an oral dosage form is less than 100% could be numerous, such as degradation, solubility/dissolution rate, and first-pass effect.
Question #12: (5 points)

Select all TRUE statements.

1) Clearance can be thought of as a volume of plasma from which the drug is removed in a specific time period.

2) If elimination from the central/body compartment is first order we can assume that a one compartment pharmacokinetic model is applicable.

3) Given \( C_p = C_{p0} e^{-k_{et}} \), and two data points \((t_1, C_{p1})\) and \((t_2, C_{p2})\), the elimination rate constant can be calculated as the slope \[= \left( \ln C_{p2} - \ln C_{p1} \right) / (t_2 - t_1) \] multiplied by -1.

4) If the infusion rate constant \( k_0 \) is doubled the steady state plasma concentration \( (C_{pss}) \) will be doubled, assuming the other parameters are unchanged.

5) Appropriate unit for AUC is mg·hr·L.

A) 1, 2, 3
B) 2, 3, 4
C) 2, 3, 5
D) 1, 3, 4
E) 1, 2, 5
Question #13: (10 points)

I.M. is a 50 year old male, 75 kg, 5’10”, intermittent asthmatic who presents to the emergency room with severe dyspnea, coughing, and wheezing. He is treated there with aerosol albuterol, but only partially clears. He is then given 400 mg of IV aminophylline (S = 0.8) over 30 minutes. Thirty minutes after the loading dose was administered (60 minutes from time zero) the theophylline concentration was 14μg/ml. He has normal liver, kidney, and cardiac function and is afebrile. He is not receiving any other drugs. After the loading dose, M.P. was immediately started on an IV theophylline constant infusion of 55 mg/hr, Solu-Medrol IV and albuterol nebulization. Eight hours after the first serum level, a second level was 8μg/ml.

Please calculate I.M.'s total body clearance, a second IV loading dose to increase his level from 8 μg/ml to 15 μg/ml, and a IV aminophylline infusion rate to maintain the concentration at 15 μg/ml.

A) Cl: 3.65L/h; LD: 185mg; MD: 150mg/h
B) Cl: 2.99L/h; LD: 220mg; MD: 50mg/h
C) Cl: 3.65L/h; LD: 185mg; MD: 70mg/h
D) Cl: 6.56L/h; LD: 200mg; MD: 120mg/h
E) Cl: 3.44L/h; LD: 200mg; MD: 80mg/h

\[ V_d = \frac{Dose \times F \times S}{C_p} = \frac{400 \text{ mg} \times 1 \times 0.8}{14 \text{ mg/L}} = 22.86 \text{ L} \]
\[
Cl = \frac{2 \times R_0}{(C_1 + C_2)} + \frac{2 \times V_d \times (C_1 - C_2)}{(C_1 + C_2) \times (t_2 - t_1)} = \frac{2 \times 55 \, \text{mg}}{h} + \frac{2 \times 22.86 \, \text{L} \times (14 - 8) \, \text{mg}}{L \times 8h} = \frac{5 \, L}{h} + 1.56 \frac{L}{h} = 6.56 \frac{L}{h}
\]

\[
LD = \frac{\Delta C_p \times V_d}{S \times F} = \frac{7 \, \text{mg}}{L} \times \frac{22.86 \, \text{L}}{0.8 \times 1} = 200 \, \text{mg}
\]

\[
MD = \frac{C_{\text{ps}} \times Cl}{S \times F} = \frac{15 \, \text{mg}}{L} \times \frac{6.56 \, \text{L}}{0.8 \times 1} = 123 \, \text{mg} \frac{L}{h}
\]
**Question #14:** (5 points)

B.D. is a 72 year old 64 kg female with cirrhosis. She was started on lidocaine for ventricular arrhythmias. She received an initial IV bolus dose of 100 mg at 930AM followed by a 220 mg IV infusion over the next 15 minutes. At 1030AM a maintenance infusion will be started. What will the lidocaine concentration be at this time?

A) 1.64 mg/L  

B) 2.54 mg/L  

C) 0.99 mg/L  

D) 0.58 mg/L  

E) 3.02 mg/L

\[ V_d = 2.3 \text{L/kg} \times 64 \text{ kg} = 147.2 \text{L} \]

\[ C_l = 0.36 \text{L/hr/kg} \times 64 \text{ kg} = 23.04 \text{ L/hr} \]

\[ K_e = 23.04 \text{L/hr} / 147.2 \text{ L} = 0.157 \text{ hr}^{-1} \]

\[ C = F*S*Dose*e^{(-k_e*t)} / V_d + Dose*F*S/ (C_l*T) * (1-e^{(-k_e*T)}) *e^{(-k_e*t')} \]

\[ C = 1*0.87*100\text{mg} * e^{(-0.157\text{hr}^{-1} * 1\text{hr})} / 147.2\text{L} + 220\text{mg} * 0.87 * 1/(23.04\text{L/hr} * 0.25 \text{hr}) * (1-e^{(-0.157 \text{hr}^{-1} * 0.25 \text{hr})}) * e^{(-0.157*0.75)} = 1.64 \text{mg/L} \]
Question #15: (5 points)

In the following Mullen-plot of phenytoin, identify x1, y1 and x2.

A) x1=Vmax, y1=Km, x2=Css_3

B) x1=Km, y1=Vmax, x2=Css_3

C) x1=Vmax, y1=Css_3, x2=Km

D) x1=Css_3, y1=km, x2=Vmax

E) none of above
**Question #16:** (5 points)

Which combination of the following factors makes the serum creatinine level a good choice to estimate renal function?

1) Creatinine is endogenous
2) Creatinine is only eliminated by the kidneys
3) Creatinine shows no plasma protein binding
4) Creatinine urinary excretion rate is not affected by the disease state
5) Creatinine is constantly formed in muscles

A) 1, 2 & 4  
**B) 1, 2, 3 & 5**  
C) 1, 3, 4 & 5  
D) 2, 3, 4 & 5  
E) All of the above