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

<table>
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Question

1. _____/10pts
2. _____/15pts
3. _____/10pts
4. _____/15pts
5. _____/15pts
6. _____/10pts
7. _____/15pts
8. _____/10pts

Total _____/100 pts
1. J.K., a 39-year-old, 78 kg male, had been taking 250mg/day of sodium phenytoin; however, his dose had been increased to 350mg/day because his seizures were poorly controlled and because his plasma concentration was only 7mg/L. Now he complains about minor CNS side effects and his measured plasma phenytoin concentration is 21mg/L. Renal and hepatic function are normal. Assume that both of the reported plasma levels represent steady-state levels and that J.K. has complied with the prescribed dosing regimens. Calculate J.K.’s apparent $V_{\text{max}}$ and $K_m$ and a new daily dose of sodium phenytoin that will result in a steady-state concentration of about 15mg/L.

$$K_m = \frac{D_{\text{initial}} - D_{\text{new}}}{C_{ss,\text{initial}} - C_{ss,\text{new}}} = \frac{250 - 350}{250 - 350} = \frac{-5.25}{-5} = 5.25 \text{ mg/L}$$

$$V_{\text{max}} = \frac{F \cdot S \cdot D \cdot (K_m + C_{ss,ave})}{C_{ss,ave} \cdot \tau} = \frac{1 \cdot 0.92 \cdot 250 \cdot (5.25 + 7)}{7 \cdot 1} = 402.5 \text{ mg/day} \approx 403 \text{ mg/day}$$

$$D = \frac{V_{\text{max}} \cdot C_{ss,ave} \cdot \tau}{F \cdot S \cdot (K_m + C_{ss,ave})} = \frac{403 \cdot 15 \cdot 1}{1 \cdot 0.92 \cdot (5.25 + 1)} = 324.48 \text{ mg} \approx 300 \text{ mg/day}$$
2. TL is a 25-year-old male who was admitted for a soft tissue infection in his abdomen. He is 5'10", 175 lbs, WBC = 19, and BUN/SCr = 12/1.1. Wound cultures are positive for Klebsiella pneumoniae. You are asked to review his medication records and initiate gentamicin therapy.

1. Recommend a desirable regimen for this patient
2. List three important physical characteristics you should assess when counseling the patient.
3. How would you write (wording) the order for this drug therapy?

After two days, you review his chart and find that the levels that you requested have been completed and reported as follows:

gentamicin (peak)  6.9 µg/ml
gentamicin (trough) 0.9 µg/ml

Please evaluate (calculate) what his true serum concentrations were using these reported values. Assume that the infusion was 30 minutes, the peak was drawn 30 minutes after the end of the infusion, and that the trough was drawn 30 minutes prior to the next dose (under ideal conditions)

Would you recommend any changes in the regimen based on these recent laboratory data?
1., 3. Dosing regimen design:
Age=25 yr; BW=79.5 kg; SCr=1.1 mg/dl; T=30min; C_{peak}(desired)=8 ug/mL, C_{trough}(desired)=1 ug/mL

First, CrCL:

\[
\text{IBW} = 50 + 2.3 \times 10 = 73 \text{ kg}
\]

\[
CL_{cr} = \frac{(140-25) \times 73}{72 \times 1.1} = 106 \text{ mL/min} = 6.36 L/h
\]

Then V_d and find k:

\[
V_d = 0.25 \times BW = 0.25 \times 79.5 = 19.9 \text{ L}
\]

\[
k = \frac{CL}{V_d} = \frac{6.36}{19.9} = 0.320 \text{ h}^{-1}
\]

Find Dosing Interval and needed dose:

\[
\tau = \frac{\ln(8/1)}{0.320} + 0.5 = 7h \rightarrow 8h
\]

\[
D = 8 \times 0.320 \times 19.9 \times 0.5 \times \frac{1 - e^{-0.320 \times 8}}{1 - e^{-0.320 \times 0.5}} = 25.4 \times \frac{0.923}{0.148} = 160 \text{ mg}
\]

3. Written order: 160 mg q8h gentamicin

2. Patient characteristics:
1) Edema
2) Weight
3) Renal function
4) Age
5) Other meds (penicillin)
Lab data after 2 d therapy: $C_{\text{peak}} = 6.9$ mcg/mL, $C_{\text{trough}}=0.9$ mcg/mL

True $C_{\text{peak}}$ and $C_{\text{trough}}$:

$$C_{\text{max}} = \frac{C^*_\text{max}}{e^{-k\cdot r^*}} = \frac{6.9}{e^{-0.320\cdot 0.5}} = 8.1 \text{ mcg/ml}$$

$$C_{\text{min}} = C^*_\text{min} \cdot e^{-k\cdot r^*} = 0.9 \cdot e^{-0.320\cdot 0.5} = 0.77 \text{ mcg/ml}$$

From the suggested dosing regimen, true steady-state peak and troughs should be

$$C_{\text{max}} = \frac{160}{0.320 \cdot 19.9 \cdot 0.5} \cdot (1-e^{-0.320\cdot 0.5}) = 50.3 \cdot \frac{0.148}{0.923} = 8.1 \text{ mcg/ml}$$

$$C_{\text{min}} = 8.1 \cdot e^{-0.320\cdot 7.5} = 0.74 \text{ mcg/ml}$$

$t_{1/2}$ based of 2 d data = 2h, $t_{1/2}$ based on CrCL = 2.2 h

little difference in predicted and actual blood values…no need to adjust
3. Mr. G.H., a 65-year-old, 76-kilogram male with congestive cardiac failure for the past three years, was admitted on April 18 to the hospital at 15:00 because of her worsening of her congestive cardiac failure symptoms. His admission history indicated that he had taken his digoxin tablet (0.25mg) that morning at the usual time (8:00-9:00), but had failed to take a tablet on Monday (April 17). A plasma sample (blood withdrawn at 17:00) was obtained to see if the symptoms were consistent with non-compliance. A plasma digoxin concentration of 0.8 µg/L and a serum creatinine of 0.7 mg/dL were reported.

a) Based on population parameters, what concentration would you expect? Show calculation.

\[
CL_{cr} = \frac{(140 - 65) \cdot 76}{72 \cdot 0.7} = 113.1 mL/\min
\]

\[
CL = 0.33 \cdot 76 + 0.9 \cdot 113.1 = 126.87 mL/\min = 7.6 L/h = 182.7 L/day
\]

\[
Vd = 3.8 \cdot 76 + 3.1 \cdot 113.1 = 639.4 L
\]

\[
C_{ave} \approx C_{min}
\]

\[
C_{ave} = \frac{F \cdot D}{CL \cdot \tau} = \frac{0.7 \cdot 0.25}{182.7 \cdot 1} = 0.000958 mg/L = 0.96 \mu g/L
\]

b) From the information available, conclude if non-compliance is likely.

- Measured level is a little lower than the expected concentration due to the missed dose on the previous day
- No evidence of non-compliance
4. R. M., a 65-year-old 77 kg male patient, is treated with 400mg q6h quinidine using an immediate-release quinidine sulfate product. A trough level was drawn and was found to be 1.2 µg/mL.

a) What is the expected trough level based on population pharmacokinetic parameters? Show calculation.

\[ V_d = 2.7 \cdot 77 = 207.9L \]
\[ CL = 0.28 \cdot 77 = 21.56L/h \]
\[ k_e = \frac{CL}{V_d} = \frac{21.56}{207.9} = 0.104h^{-1} \]

\[ C_{min} = \frac{F \cdot S \cdot D}{V_d} \cdot \frac{e^{-k_e \tau}}{1 - e^{-k_e \tau}} = \frac{0.7 \cdot 0.82 \cdot 400}{207.9} \cdot \frac{e^{-0.1046}}{1 - e^{-0.1046}} = 1.1 \cdot \frac{0.536}{0.464} = 1.3mg/L = 1.3µg/mL \]

b) Assuming a volume of distribution of 3.1L/kg, what is the clearance and the half-life in this patient?

\[ V_d = 3.1 \cdot 77 = 238.7L \]
\[ C_{max} = 1.2 + \frac{0.7 \cdot 0.82 \cdot 400}{238.7} = 2.2µg/mL \]
\[ k_e = \frac{\ln(\frac{2.2}{1.2})}{6} = 0.101h^{-1} \]
\[ t_{1/2} = \frac{0.693}{0.101} = 6.9h \approx 7h \]
\[ CL = 0.101 \cdot 238.7 = 24.1L/h \]

c) Make a dose recommendation to increase the trough to 1.5µg/mL. Show calculation.

Increase by 25% \[ \Rightarrow 500mg q6h \]

\[ D = \frac{C_{min} \cdot V_d}{F \cdot S} \cdot \frac{1 - e^{-k_e \tau}}{e^{-k_e \tau}} = \frac{1.5 \cdot 238.7 \cdot 1 - e^{-0.1016}}{0.7 \cdot 0.82 \cdot e^{-0.1016}} = 623.78 \cdot \frac{0.454}{0.546} = 518.7mg \]
5. M.W., a 42-year-old, 58 kg female with a serum creatinine of 1.2mg/dL, is to receive 15g i.v. methotrexate infused over four hours. Calculate the methotrexate concentration at the end of the four-hour infusion, 12 hours after the end of the infusion, and 48 hours after the start of the infusion.

\[
CL_{Cr} = \frac{(140 - 42) \cdot 58}{85 \cdot 1.2} = 55.73mL/\text{min} \approx 3.3L/h
\]

\[
CL = 1.6 \cdot 3.3 = 5.28L/h
\]

\[
k_e = \frac{0.693}{3} = 0.231h^{-1}
\]

- at the end of the infusion:

\[
C_{\text{max}} = \frac{D}{CL \cdot T} \cdot (1 - e^{-k_e \cdot T}) = \frac{15000}{5.28 \cdot 4} \cdot (1 - e^{-0.231 \cdot 4}) = 710.23 \cdot 0.6 = 426.14mg/L
\]

conversion into molar concentration:

\[
C_{\text{max}} = \frac{426.14}{0.454} = 938.6\mu M
\]

- 12 hours after the end of the infusion:

\[
C_{12h} = C_{\text{max}} \cdot e^{-k_e \cdot t} = 426.14 \cdot e^{-0.231 \cdot 12} = 26.65mg/L
\]

conversion into molar concentration:

\[
C_{12h} = \frac{26.65}{0.454} = 58.7\mu M
\]
• 48 hours after the start of the infusion (44 hours after the end of the infusion):

\[
t = \frac{\ln \left( \frac{C_{12h}}{0.5} \right)}{k_e} = \frac{\ln \left( \frac{58.7}{0.5} \right)}{0.231} = 20.6h \approx 20h \quad \Rightarrow 12h + 20h = 32h \text{ after the end of infusion}
\]

\[
\Rightarrow 44h - 32h = 12h
\]

\[
k_e = \frac{0.693}{10} = 0.0693h^{-1}
\]

\[
C_{44h} = 0.5 \cdot e^{-k_e \cdot t} = 0.5 \cdot e^{-0.0693 \cdot 12} = 0.22 \mu M
\]
6. H.D, an 81 kg male, became nauseated after receiving i.v. aminophylline 90mg/h for several days. A plasma sample for theophylline was obtained and the infusion was discontinued. Twelve hours later a second plasma sample was obtained. The reported plasma theophylline concentrations were 36mg/L and 17mg/L, respectively. Estimate the hourly dose of aminophylline required to maintain the plasma theophylline concentration at 15mg/L. Show all calculations.

\[
k_t = \frac{\ln\left(\frac{36}{17}\right)}{12} = 0.063h^{-1}
\]

\[
Vd = 0.5 \cdot 81 = 40.5L \\
CL = 0.063 \cdot 40.5 = 2.55L/h
\]

\[
MD = \frac{C_{ss,ave} \cdot CL \cdot \tau}{F \cdot S} = \frac{15 \cdot 2.55 \cdot 1}{1 \cdot 0.85} = 45mg
\]
7. S.K., is a 64-year-old, 66kg female with clinical class II heart failure. She was started on lidocaine for ventricular arrhythmias which occurred on postoperative Day 1 following her cardiac surgery. She received an initial 65mg i.v. bolus dose of lidocaine at 9.30a.m. followed by 140mg over the next 15min. (9mg/min). At 10.30 a.m. she was to be placed on a 1.5mg/min constant infusion. Calculate her lidocaine concentration at the start of the maintenance infusion and at steady state.

\[ V_d = 0.9 \cdot 66 = 59.4L \]
\[ CL = 0.36 \cdot 66 = 23.76L/h = 0.4L/min \]

\[ k_e = \frac{CL}{V_d} = \frac{23.76}{59.4} = 0.4h^{-1} = 0.0067\min^{-1} \]

at the start of the maintenance infusion:
\[ C_{\text{max}} = \frac{F \cdot S \cdot D}{V_d} \cdot e^{-k_e \cdot \frac{T}{2}} + \frac{F \cdot S \cdot D}{CL \cdot T} \cdot (1 - e^{-k_e \cdot \frac{T}{2}}) \cdot e^{-k_e \cdot \frac{T}{2}} \]

\[ = \frac{1 \cdot 0.87 \cdot 65}{59.4} \cdot e^{-0.0067 \cdot 60} + \frac{1 \cdot 0.87 \cdot 140}{0.4 \cdot 15} \cdot (1 - e^{-0.0067 \cdot 15}) \cdot e^{-0.0067 \cdot 45} \]

\[ = 0.952 \cdot 0.67 + 20.3 \cdot 0.096 \cdot 0.74 = 2.1mg/L \]

at steady-state:
\[ C_{ss,ave} = \frac{F \cdot S \cdot D}{CL \cdot \tau} = \frac{1 \cdot 0.87 \cdot 1.5}{0.4} = 3.26mg/L \]
8. G.H., a 65kg liver transplant patient, is receiving 475mg of cyclosporine QD as an i.v. infusion. Currently, her hepatic function tests appear to be stable, and for the past four days she has been improving clinically with steady-state trough cyclosporine concentrations of approximately 170µg/L. What would be an appropriate oral cyclosporine dose for G.H. to achieve a new steady-state concentration of approximately 200µg/L? Show calculations.

\[
NewDose = \frac{C_{ss,desired}}{C_{ss, current}} \cdot \frac{F_{current}}{F_{newdosageform}} \cdot Dose_{current}
\]

\[
= \frac{200}{170} \cdot \frac{1.0}{0.3} \cdot 475 = 1863mg \approx 1900mg
\]