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

Name

Questions Points
1. _______/15
2. _______/15
3. _______/15
4. _______/15
5. _______/10
6. _______/10
7. _______/10
8. _______/10
Total _______/100
1. M.N., a 45-year-old, 60 kg female with a serum creatinine of 0.9 mg/dL is to be given tobramycin. (15 points)

a) Calculate a maintenance dose which will produce a “peak” concentration of 8 mg/L one hour after the infusion has been started, and a trough concentration at the end of the dosing interval of 1 mg/L. Assume that tobramycin will be administered as a one-half hour infusion.

\[
CL_{cr} = \frac{(140 - 45) \cdot 60}{85 \cdot 0.9} = 74.5mL/min = 4.5L/h
\]

\[
V_d = 0.25 \cdot 60 = 15L
\]

\[
k = \frac{4.5}{15} = 0.3h^{-1}
\]

\[
\tau = \frac{\ln 8}{0.3} + 1 = 7.9h \Rightarrow 8h
\]

\[
C_{max} = \frac{8}{e^{-0.3 \cdot 0.5}} = 9.3\mu g/mL
\]

\[
D = 9.3 \cdot 0.3 \cdot 1.5 \cdot 0.5 \cdot \left(1 - e^{-0.3 \cdot 0.5}\right) = 20.93 \cdot 0.91 \cdot 0.14 = 136 \Rightarrow 140mg
\]

b) If M.N. was to be given tobramycin 5 mg/kg QD, what would be the calculated steady-state peak concentration one hour after starting the half-hour infusion? Also predict subsequent steady-state plasma concentrations 12 hours after starting the infusion and at the trough.

\[
D = 5 \cdot 60 = 300
\]

\[
C_{max} = \frac{300}{4.5 \cdot 0.5} \cdot \left(1 - e^{-0.3 \cdot 0.5}\right) = 133.3 \cdot 0.14 \cdot 0.99 = 18.9\mu g/mL
\]

\[
C^*_{max} = 18.9 \cdot e^{-0.3 \cdot 0.5} = 16.3\mu g/mL
\]

\[
C_{12h} = 18.9 \cdot e^{-0.3 \cdot 1.5} = 0.6\mu g/mL
\]

\[
C_{24h} = 18.9 \cdot e^{-0.3 \cdot 2.5} = 0.02\mu g/mL
\]
2. Z.C., a 75 kg, 34-year-old patient with a serum creatinine of 1.6 mg/dL has been receiving IV tobramycin, 100 mg over one half-hour Q 8 hr, for several days. A peak plasma concentration obtained one hour after the start of the infusion was 8 mg/L, and a trough concentration obtained just before the initiation of a dose was 3.0 mg/L. Estimate the apparent elimination rate constant, clearance and volume of distribution for tobramycin in Z.C. Also, calculate a dosing regimen for Z.C. that will achieve a peak concentration of 7 mg/L and trough concentrations of approximately 1 mg/L. (15 points)

\[
\ln \left( \frac{8}{3} \right) \quad k = \frac{7}{0.14} = 0.14 h^{-1}
\]

\[
V_d = 0.25 \cdot 75 = 18.8 L
\]

\[
CL = 0.14 \cdot 18.8 = 2.6 L/h
\]

\[
\tau = \frac{\ln 7}{0.14} + 1 = 14.9 h \Rightarrow 12 h
\]

\[
C_{max} = \frac{7}{e^{-0.140.5}} = 7.5
\]

\[
D = 7.5 \cdot 0.14 \cdot 18.8 \cdot 0.5 \cdot \frac{(1 - e^{-0.1412})}{(1 - e^{-0.140.5})} = 9.9 \cdot \frac{0.81}{0.07} = 115 \Rightarrow 120 mg
\]

Better:

\[
V_d = \frac{100}{0.14 \cdot 0.5} \cdot \frac{(1 - e^{-0.140.5})}{(8 - 3 \cdot e^{0.140.5})} = 18.6 L
\]
3. A.K., a 64-year-old, 53 kg female, was admitted to the hospital for possible digoxin toxicity. Her serum creatinine was 3.4 mg/dL and her dosing regimen at home had been 0.25 mg of digoxin daily for many months. The digoxin plasma concentration on admission was reported to be 3.5 ng/mL. If no more doses are given how long will it take for the digoxin concentration to fall from 3.5 to 2.0 ng/mL? Calculate the daily dose which will maintain A.K.’s average digoxin plasma concentration at 1.5 ng/mL. (15 points)

\[ CL = \frac{F \cdot D}{C \cdot \tau} = \frac{0.7 \cdot 0.25}{3.5 \cdot 24} = 2.1 \, L/h \quad \text{or} \]

\[ CL_{cr} = \frac{(140 - 64) \cdot 53}{85 \cdot 3.4} = 13.9 \, mL/min = 0.84 \, L/h \]

estimated \( CL = 0.33 \cdot 53 + 0.9 \cdot 13.9 = 17.5 + 12.5 = 30 \, mL/min = 1.8 \, L/h \)
(with CHF)

\[ V_d = 3.8 \cdot 53 + 3.1 \cdot 13.9 = 201.4 + 43.1 = 244.5 \, L \]

\[ k = \frac{CL}{V_d} = \frac{2.1}{245} = 0.0086 h^{-1} \quad \text{(0.0073 h\textsuperscript{-1})} \]

\[ t = \frac{\ln\left(\frac{3.5}{2}\right)}{0.0086} = 65h \quad \text{(77 h)} \]

\[ \frac{D}{24} = \frac{C \cdot CL}{F} = \frac{1.5 \cdot 2.1}{0.7} = 4.5 \]

\[ D = 4.5 \cdot 24 = 108 \, \mu g \Rightarrow 100 \, \mu g \quad \Leftarrow (93 \, \mu g) \]
4. R.S., a 65-year-old, 68-kg male (SeCr 1.3 mg/dL) is to receive a course of methotrexate therapy. His regimen will consist of a 30 mg methotrexate loading dose to be administered over 10 minutes, followed by an IV infusion of 30 mg/hr for the next 36 hours. He will then receive a 20 mg dose of leucovorin every six hours intravenously for the first four doses followed by eight doses orally at six-hour intervals. The leucovorin regimen will begin immediately after the 36-hour methotrexate infusion has been discontinued and is scheduled to continue for the next 72 hours, ending 108 hours after initiation of the methotrexate therapy. Methotrexate levels are scheduled to be obtained 24 hours after the beginning of the 30 mg/hr infusion, at 48 hours (12 hours after the end of the 36-hour infusion), and at 60 hours (24 hours after the end of the methotrexate infusion). Calculate the anticipated methotrexate concentrations at the scheduled sampling times. (15 points)

\[
CL_{cr} = \frac{(140 - 65) \cdot 68}{72 \cdot 1.3} = 54.5 \text{ mL / min}
\]

\[
CL_{MTX} = 1.6 \cdot 54.5 = 87.2 \text{ mL/min} = 5.2 \text{ L/h}
\]

\[
C_{24} = \frac{30}{5.2} = 5.8 \text{ mg / L} = 12.8 \mu M
\]

\[
C_{48} = 12.8 \cdot e^{-0.2312} = 0.8 \mu M
\]

Time for 0.5 \mu M:

\[
t = \frac{\ln\left(\frac{12.8}{0.5}\right)}{0.231} = 14 \text{ h after end of infusion} \Rightarrow C_{50}
\]

\[
C_{60} = 0.5 \cdot e^{-0.0693 \cdot 10} = 0.25 \mu M
\]
5. P.T., a 35-yea-old, 74 kg male, had been taking 300 mg/day of phenytoin; however, his dose was increased to 350 mg/day because his seizures were poorly controlled and because his plasma concentration was only 7 mg/L. Now he complains of minor CNS side effects and his reported plasma phenytoin concentration is 22 mg/L. Renal and hepatic function are normal. Assume that both of the reported plasma concentrations represent steady state levels and that P.T. has complied with the prescribed dosing regimens. Calculate P.T.’s apparent Vm and Km and a new daily dose of phenytoin that will result in a steady-state level of about 15 mg/L. (10 points)

\[
\frac{7}{300} \cdot Vm - 7 = \frac{22}{350} \cdot Vm - 22
\]

\[
15 = 0.0395 \cdot Vm
\]

Vm = 380 mg

Km = 1.9 µg/mL

\[
D = \frac{380 \cdot 15}{1.9 + 15} = 337mg
\]
6. A.R., a 62-year-old, 65 kg male, was admitted with a diagnosis of hepatic encephalopathy and cirrhosis. On the fourth hospital day, he developed ventricular arrhythmias and lidocaine was ordered. Calculate a bolus dose (be specific) and a maintenance infusion rate that will achieve a steady-state lidocaine level of 3 mg/L. (10 points)

\[ V_c = 0.6 \times 65 = 39 \text{ L} \]

\[ LD = \frac{3 \times 39}{0.87} = 134 \text{ mg} \Rightarrow 140 \text{ mg} \]

additional LD of 70 mg after 20 and 40 min

\[ MD = \frac{3 \times 0.36 \times 65}{0.87} = 81 \text{ mg/h} \Rightarrow 80 \text{ mg/h} \]

7. S.R., a 70 kg, 40-year-old male, has been receiving an IV aminophylline infusion at a rate of 35 mg aminophylline/hr. At the beginning of the therapy, an IV loading bolus dose of 750 mg has been administered. The reported plasma theophylline concentrations at 1 hr and 8 hr after the start of the infusion are 19 and 15 mg/L. Calculate the expected steady-state theophylline concentration in this patient. Is a dosing adjustment needed? (10 points)

\[ CL = \frac{2 \times 35 \times 0.85}{(19 + 15)} + \frac{2 \times 0.5 \times 70 \times (19 - 15)}{(19 + 15) - (8 - 1)} \]

\[ = 1.75 + 1.18 = 2.93 \text{ L/h} \]

\[ C = \frac{35 \times 0.85}{2.93} = 10.2 \mu g/\text{mL} \]

To increase dose for \( C = 15 \Rightarrow 50 \text{ mg/h} \)

8. Explain why digoxin has a much longer half-life than gentamicin. (10 points)

Digoxin has a much larger volume of distribution

(7-8 L/kg vs 0.25 L/kg)