1. Methotrexate can be given intrathecally as a chemotherapy. List some basic factors to consider prior to giving methotrexate intrathecally.

1. CL: Renal dysfunction
2. DDI: Other drugs that alter methotrexate clearance
3. Disease state: Defects in cerebrospinal flow (meningeal leukemia)
4. CNS methotrexate level not to exceed 10-8 molar, therefore monitoring required prior to second dose

2. X.Y., 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

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

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

\[
C_{36} = \frac{30}{5.2} = 5.8\text{mg/L} = 12.8\mu\text{M}
\]

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

Time for 0.5 μM:

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

\[
C_{60} = 0.5 \cdot e^{0.0693} \cdot 10 = 0.25\mu\text{M}
\]
3. M.C. is admitted with an acute theophylline overdose. A serum level is measured at 53 μg/mL. Assuming an 8 hour half-life and no further drug absorption, how long does it take for the serum level to drop to the upper limit of the therapeutic range (20 μg/mL)?

\[ t_{1/2} = 8 \text{ h} \]

\[ k = \frac{0.693}{t_{1/2}} = 0.0866 \text{ h}^{-1} \]

\[ C = C_0 \cdot e^{-k \cdot t} \]

\[ 20 = 53 \cdot e^{-0.0866 \cdot t} \]

\[ \frac{20}{53} = e^{-0.0866 \cdot t} \]

\[ \ln \left( \frac{20}{53} \right) = -0.0866 \cdot t \]

\[ t = \frac{\ln \left( \frac{20}{53} \right)}{-0.0866} = 11.3 \text{ h} \]

4. F.Q. is 53-year-old, 82-kilogram patient with congestive cardiac failure for the past three years. She was admitted on Feb 20 to the hospital at 16:00 because of a worsening of her congestive cardiac failure symptoms. Her admission history indicated that she had taken her digoxin tablet (0.25 mg) that morning at the usual time (8:00-9:00), but had failed to take a tablet the day before (Feb 19). A plasma sample (blood withdrawn at 17:00) was obtained to see if the symptoms were consistent with noncompliance. A plasma digoxin concentration of 0.9 μg/L and a serum creatinine of 0.9 mg/dL were reported.

a) What would plasma sample conclude in terms of patient compliance?

b) What is the expected plasma concentration at steady state (Cp,ss)?

a) Not likely, the expected and measured concentrations will be comparable

b) CLcr = 0.85*(140-53)*82/(72*0.9) – 93.6 mL/min

CL=0.33*82+0.9-93.6 = 111 mL/min or 6.7 L/hr

Cp,ss = F*Dose/(CL*tou) = 0.7*0.25/(6.7*24) = 1.1 ng/mL
5. J.C., 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 the loading dose and the maintenance infusion rate that will achieve a steady-state lidocaine level of 3 mg/L.

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

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

additional LD of 70 mg after 20 and 40 min

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