1. L.B., a 50-year-old, 75 kg male (C_{Creat} 1.4mg/dL), has been taking 0.5mg of digoxin tablets orally for his CHF, and at 9:30am on the day of admission, a digoxin plasma concentration of 2.1µg/L was measured. He was continued on his outpatient maintenance dose. On the fourth day, just before his morning dose (three doses of digoxin have been administered each day at 9:30am), a second digoxin sample was obtained. Please predict L.B.’s digoxin concentration in the morning of the fourth day. (3 pts)

Answer:

\[
C_l_{\text{crea}(\text{male})} = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot C_{\text{pCreat}}}
\]

\[
C_{L_{\text{cr}}} = \frac{(140 - 50) \cdot 75}{72 \cdot 1.4} = 67.0mL/\text{min}
\]

\[
C_{l_{\text{Digoxin}}} = 0.33mL/\text{kg/min} \cdot \text{IBW} + 0.9 \cdot C_{l_{\text{crea}}(\text{with-CHF})}
\]

\[
CL = 0.33 \cdot 75 + 0.9 \cdot 67.0 = 85.05mL/\text{min} \approx 5.1L/h \approx 122.5L/day
\]

\[
V_{\text{Digoxin}} = 3.8L/\text{kg} + 3.1 \cdot C_{l_{\text{crea}}}
\]

\[
Vd = 3.8 \cdot 75 + 3.1 \cdot 67.0 = 492.7L
\]

\[
k_e = \frac{CL}{Vd} = \frac{122.5}{492.7} = 0.25\text{days}^{-1}
\]

\[
C_{\text{min(sum)}} = C_{\text{measured}} \cdot e^{-k_e \cdot \tau_1} + \frac{F \cdot D}{Vd} \cdot \left[ e^{-k_e \cdot \tau_2} + e^{-k_e \cdot \tau_3} + e^{-k_e \cdot \tau_1} \right]
\]

\[
= 2.1 \cdot e^{-0.25 \cdot 3\text{days}} + \frac{0.7 \cdot 500}{492.7} \cdot \left[ e^{-0.25 \cdot 3\text{days}} + e^{-0.25 \cdot 2\text{days}} + e^{-0.25 \cdot \text{1day}} \right]
\]

\[
= 0.99(\mu g/ L) + 0.71(\mu g/ L) \cdot [0.47 + 0.61 + 0.77]
\]

\[
= 2.3(\mu g/ L)
\]
2. M.R. is a 60 kg female patient (56 years old, 5'5'') to receive methotrexate therapy. Her serum creatinine is 1.6 mg/dL. She was treated with a loading dose (20 mg) followed by an infusion of 25 mg/h over 36 hours. Then she received leucovorin rescue (10 mg/m² q6h) for 48 hr, and a blood sample was taken at 48 hr, methotrexate concentration was measured. Please predict this methotrexate concentration, and indicate whether leucovorin rescue should continue or not. (3 pts)

**Answer:**

Given Information:
Female, 60kg, 56 yr, 5'5'', C_{pCreat} 1.6 mg/dL
Dose: 20 mg LD + 25 mg/h IV
Time for leucovorin treatment: 48 hr

\[ \text{IBW} = 45.5 \text{kg} + 2.3 \text{kg} \cdot (\text{Height} - 5') \]
\[ \text{IBW} = 45.5 \text{kg} + 2.3 \cdot (5) = 57 \text{ kg} \rightarrow \text{TBW} < 1.2 \text{IBW} \]

\[ C_{l_{\text{creat}}} (\text{female}) = \frac{(140 - \text{age}) \cdot \text{weight}}{(85) \cdot C_{p_{\text{creat}}}} \]

\[ C_{l_{\text{creat}}} (\text{female}) = \frac{(140 - 56) \cdot 60}{(85) \cdot 1.6} = 37.1 \text{ (mL/min)} \] (Use TBW for \( C_{l_{\text{Creat}}} \))

\[ C_{\text{L}} = 1.6 \cdot 37.1 = 59.4 \text{ (mL/min)} = 3.6 \text{ (L/hr)} \]

\[ C_{p_{\text{ss}}} = \frac{R_{0}}{C_{l}} \]

\[ C_{p_{ss}} = 25/3.6 = 6.94 \text{ (mg/L)} = 6.94/0.454 = 15.3 \text{ M} \]

\[ k_{1} = \frac{0.693}{t_{1/2(a)}} = \frac{0.693}{3} = 0.231 h^{-1} \]

\[ \ln \text{ t for 0.5 } \mu\text{M} : \quad t = \frac{0.5}{0.231} = 14.8 h \rightarrow \text{at (14.8 + 36)} = 50.8 h \]

\[ k_{2} = \left\frac{\ln(2)}{t_{1/2(b)}} \right = \frac{\ln(2)}{10} = 0.0693 h^{-1} \]

\[ \ln \frac{C_{p_{1i}}}{C_{p_{2}}} = \ln 0.5 \]

\[ \Delta t = \frac{\ln 0.5}{k_{2}} = \frac{\ln 0.5}{0.0693} = (48 - 14.8) \text{ (stop leucovorin rescue)} \]

\[ C_{p_{2}} = 0.05 \mu\text{M} < < 0.1 \mu\text{M} \]

\[ \text{t for 0.1 } \mu\text{M} : \quad t = \frac{0.1}{0.0693} = 23.2 h \rightarrow \text{at (50.8 + 23.2)} = 74 h \]
A clinical study was performed to assess the effect of Rifampin on the Tacrolimus pharmacokinetics after oral and intravenous administration. The same doses were used in the two phases. A washout period was between two phases. Rifampin is considered to be a first-line agent for the treatment of tuberculosis, and induces CYP3A metabolism and P-gp-mediated transport. The following two PK graphs are from this study. State whether the following statement is TRUE or FALSE? Explain.

3. A clinical study was performed to assess the effect of Rifampin on the Tacrolimus pharmacokinetics after oral and intravenous administration. The same doses were used in the two phases. A washout period was between two phases. Rifampin is considered to be a first-line agent for the treatment of tuberculosis, and induces CYP3A metabolism and P-gp-mediated transport. The following two PK graphs are from this study. State whether the following statement is TRUE or FALSE? Explain.

A: Tacrolimus could be a substrate of P-gp and CYP3A.
B: Tacrolimus is eliminated via renal filtration.
C: Dose regimen needs adjusted for Tacrolimus when co-administration of rifampin.

**Answer:**

A: True, as indicated by the decrease of concentration of Tacrolimus when co-administration of rifampin, and Rifampin induces CYP3A metabolism and P-gp-mediated transport.
B: False, Renal clearance for Tacrolimus is 0% from class slide.
C: True, Rifampin could increase Tacrolimus elimination from body, which could result in no pharmacological/therapeutic effect of Tacrolimus.
4. S.H. is a 78 year old liver transplant patient. In the hospital, he received 450 mg one dose of cyclosporin as an iv infusion which resulted in a trough level of 350 ng/ml. After he is discharged, he will continue with oral cyclosporine treatment. What will be the oral dose regimen in order to achieve the same trough level? (1 pt)

**Answer:**

If 450 mg cyclosporine provides correct plasma levels, dose simply needs to be converted to oral dose ($F = 0.3$)

$$\text{New dose} = \frac{F_{\text{current}}}{F_{\text{NewFormulation}}} \times \text{Current dose}$$

$$= \left( \frac{1}{0.3} \right) \cdot (450 \text{mg}) = 1500 \text{mg / day}$$

Give 500 mg every 8 hours (TID).