Question #1. (2 points)
G.H., 85kg, 55-year-old male, is administrated to the emergency room with asthma that is not responsive to epinephrine. He received a loading dose of aminophylline—a theophylline plasma concentration of 10mg/L was achieved. What aminophylline infusion rate will maintain an average steady-state level of 10mg/L?

Answer:

\[
\text{Maintenance Dose} = \frac{\text{Cl} \times \bar{C}_{ss} \times \tau}{S \times F} = \frac{0.04 \frac{\text{L}}{\text{kg} \times \text{h}} \times 85\text{kg} \times 10 \frac{\text{mg}}{\text{L}} \times 1\text{h}}{0.8 \times 1} = 42.5 \frac{\text{mg}}{\text{h}} \text{ of Aminophylline}
\]

Question #2. (2 points)
H.G. is a 65-year-old, 70kg female with liver cirrhosis that is treated for her arrhythmia with lidocaine. An 80mg i.v. bolus is immediately followed by a 130mg short-term infusion over 15 minutes. The maintenance dose of 120mg/h is started after 1 hour. Please calculate the concentration at the start of the maintenance dose and at steady-state.

Answer:

\[
k_e = \frac{\text{Cl}}{V_d} = \frac{0.36 \frac{\text{L}}{\text{h} \times \text{kg}}}{2.3 \frac{\text{L}}{\text{kg}}} = 0.157 \text{h}^{-1}
\]

\[
C = \frac{S \times \text{LD}}{V_d} e^{-k_e t} + \frac{S \times R_0}{\text{Cl}} \times (1 - e^{-k_e T}) \times e^{-k_e t}
\]

\[
= \frac{0.87 \times 80\text{mg}}{2.3 \frac{\text{L}}{\text{kg}} \times 70\text{kg}} \times e^{-0.157\text{h}^{-1} \times 1\text{h}} + \frac{0.87 \times 130\text{mg}}{0.36 \frac{\text{L}}{\text{h} \times \text{kg}} \times 70\text{kg} \times 0.25\text{h}} \times (1 - e^{-0.157\text{h}^{-1} \times 0.25\text{h}}) \times e^{-0.157\text{h}^{-1} \times 0.75\text{h}}
\]

\[
= 0.37 \frac{\text{mg}}{\text{L}} + 0.69 \frac{\text{mg}}{\text{L}} \times 0.89 = 0.98 \frac{\text{mg}}{\text{L}}
\]
A.L. is a male 55-year-old, 60kg renal transplant patient. His serum creatinine level was determined to be 1.9mg/dL. He was put on 125mg oral cyclosporine Q12h. Please predict his trough value. When the trough concentration was measured, his trough was 80ng/L. Is a dose adjustment necessary? If so, please calculate the new dose ($C_{\text{max}}$=400ng/mL, $C_{\text{min}}$=150ng/mL).

Answer:

$\text{Cl} = 0.5 \frac{L}{h \times \text{kg}} \times \text{TBW} = 0.5 \frac{L}{h \times \text{kg}} \times 60 \text{kg} = 30 \frac{L}{h}$

$V_d = 4.5 \frac{L}{kg} \times \text{TBW} = 4.5 \frac{L}{kg} \times 60 \text{kg} = 270L$

$k_e = \frac{\text{Cl}}{V_d} = \frac{30 \frac{L}{h}}{270L} = 0.111h^{-1}$

$C_{\text{min}} = \frac{\text{F} \times S \times D \times e^{-k_e \times \tau}}{V_d \times (1 - e^{-k_e \times \tau})} = \frac{0.3 \times 1 \times 125\text{mg} \times e^{(-0.111h^{-1} \times 12h)}}{270L \times (1 - e^{(-0.111h^{-1} \times 12h)})} = 0.05 \frac{\text{mg}}{L} = 50 \frac{\text{ng}}{mL}$

The calculated $C_{\text{min}}$ is lower than the measured $C_{\text{min}} \rightarrow$ dose adjustment

Calculate $C_{\text{max}}$ in order to determine the actual $k_e$.

$C_{\text{max}} = \frac{\text{F} \times S \times D}{V_d} + C_{\text{min}}(\text{measured}) = \frac{0.3 \times 1 \times 125\text{mg}}{270L} + 80 \frac{\text{ng}}{mL} = 218.89 \frac{\text{ng}}{mL}$

$k_e = \frac{\ln \left( \frac{C_{\text{max}}}{C_{\text{min}}} \right)}{\tau} = \frac{\ln \left( \frac{218.89}{80} \right)}{12h} = 0.084h^{-1}$

Calculate the dosing interval – use the clinical target values of $C_{\text{max}}$=400ng/mL and $C_{\text{min}}$=150ng/mL.

$\tau = \frac{\ln \left( \frac{400}{150} \right)}{0.084h^{-1}} = 11.68h \sim 12h$
The new dosing regimen is 225mg given orally every 12 hours.

**Question #4.**  (3 points)

M.V., a 53-year-old, 75kg male patient (5’10”, SeCr 1.3mg/dL) received a 30mg i.v. loading dose of methotrexate, followed by a 25mg/h continuous i.v. infusion over 36 hours. At 36h, leucovorin rescue (10mg/m^2 q6h) was started. The following levels were monitored:

- 36h  15µM
- 48h  0.9µM
- 60h  0.25µM

When do you expect the methotrexate levels to fall below 0.1µM?

**Answer:**

\[
k_\alpha = \frac{\ln\left(\frac{15}{0.9}\right)}{12h} = 0.234 h^{-1}
\]

\[
t_{1/2}^{\alpha} = \frac{\ln 2}{k_\alpha} = 2.96 h \sim 3 h
\]

Calculate the time necessary for the concentration to drop to 0.5µM

\[
t(0.5\mu M) = \frac{\ln\left(\frac{15}{0.5}\right)}{0.234 h^{-1}} \sim 14.5 h
\]

A concentration of 0.5µM was reached after 50.5h

\[
k_\beta = \frac{\ln\left(\frac{0.5}{0.25}\right)}{(60 - 50.5)h} = 0.073 h^{-1}
\]

\[
t_{1/2}^{\beta} = \frac{\ln 2}{0.073 h^{-1}} \sim 9.5 h
\]

\[
t(0.1\mu M) = \frac{\ln\left(\frac{0.25}{0.1}\right)}{0.073 h^{-1}} + t(0.25\mu M) \sim 72.6 h
\]