PHA 5128 – Spring 2008

Dose Optimization II

Homework V

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:

$$\text{Maintenance Dose} = \frac{\text{Cl} \times \overline{\text{Css}} \times \tau}{\text{S} \times \text{F}} = \frac{0.04\frac{\text{L}}{\text{kg} \times \text{h}} \times 85\text{kg} \times 10\frac{\text{mg}}{\text{L}} \times 1\text{h}}{0.8 \times 1} = 42.5\frac{\text{mg}}{\text{h}} \text{ of Aminophylline}$$

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 15minutes. 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:

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

$$\text{C} = \frac{\text{S} \times \text{LD}}{\text{V}_\text{d}} \times \text{e}^{-\text{k}_\text{e}\text{t}} + \frac{\text{S} \times \text{R}_0}{\text{Cl}} \times \left(1 - \text{e}^{-\text{k}_\text{e} \times \text{T}}\right) \times \text{e}^{-\text{k}_\text{e} \times \text{t}}$$

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

$$= 0.37\frac{\text{mg}}{\text{L}} + 0.69\frac{\text{mg}}{\text{L}} \times 0.89 = 0.98\frac{\text{mg}}{\text{L}}$$

$$C_{ss} = \frac{S \times R_0}{Cl} = \frac{0.87 \times 120\frac{mg}{h}}{0.36\frac{L}{h \times kg} \times 70kg} = 4.14\frac{mg}{L}$$

Question #3. (3 points)

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 through concentration was measured, his trough was 80ng/L. Is a dose adjustment necessary? If so, please calculate the new dose (C_{max}=400ng/mL, C_{min}=150ng/mL).

Answer:

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

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

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

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

The calculated C_{min} is lower than the measured C_{min} → dose adjustment

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

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

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

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

$$\tau = \frac{\ln\left(\frac{400}{150}\right)}{0.084h^{-1}} = 11.68h \sim 12h$$

$$D = \frac{C_{max} \times V_d \times (1 - e^{(-k_e \times \tau)})}{F \times S} = \frac{400\frac{ng}{mL} \times 270000mL \times (1 - e^{(-0.084h^{-1} \times 12h)})}{0.3 \times 1} = 228.6mg$$

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 36hours. 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:

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

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

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

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

A concentration of 0.5µM was reached after 50.5h

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

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

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