PHA 5128

Homework 5 (Answers)

1. R. S. is a 53 kg female patient (47 years) to receive methotrexate therapy. Her serum creatinine is 1.6 mg/dL. She is treated with a loading dose (20 mg) followed by an infusion of 25 mg/h over 36 hours. She will then receive a 10 mg/m2 dose of leucovorin q6h (four doses) followed by eight oral doses (q6h) of 20 mg.

A. Calculate the expected MTX steady-state concentration (in µM).

$$CL_{Cr} = \frac{(140-47)\cdot 53}{85\cdot 1.6} = 36.2 mL/\min \approx 2.2 L/h$$

$$CL_{MTX} = CL_{Cr}\cdot 1.6 = 2.2 L/h \cdot 1.6 = 3.48 L/h$$

$$C_{ss} = \frac{R_0}{CL} = \frac{25 mg/h}{3.48 L/h} = 7.2 mg/L \qquad \Rightarrow$$

$$MTX/\mu M = \frac{MTX/mg/L}{0.454} = \frac{7.2 mg/L}{0.454} = 15.9 \mu M$$

B. Calculate the predicted concentrations at 24, 48 and 60 h after the start of the MTX infusion.

24 h: 15.9 µM

48 h: $Cp = 15.9\mu M \cdot e^{-0.231\cdot 12} = 1.0\mu M$

60 h: $t = \frac{\ln\left(\frac{15.9}{0.5}\right)}{0.231} = 15h \quad \Rightarrow \quad$ 0.5µM at 51 h

$Cp = 0.5\mu M \cdot e^{-0.069\cdot 9} = 0.27\mu M$

C. The reported levels were 14 µM (24h), 1.2 µM (48h) and 0.35 µM (60 h). What recommendation would you make (show calculations)?

$$k_\alpha = \frac{\ln\left(\frac{14}{1.2}\right)}{12} = 0.205h^{-1}$$

$$t_{0.5\mu M} = \frac{\ln\left(\frac{14}{0.5}\right)}{0.205} = 16h \qquad \Rightarrow \qquad \text{0.5 µM at 52 h}$$

$$k_\beta = \frac{\ln\left(\frac{0.5}{0.35}\right)}{8} = 0.045h^{-1}$$

$$t_{0.1\mu M} = \frac{\ln\left(\frac{0.5}{0.1}\right)}{0.045} = 36h \qquad \Rightarrow \qquad \text{0.1 µM = 88 h}$$

Leucovorin covers up to 108 h. No additional leucovorin needed.

2. Camille Carton is a 36-year-old female with newly diagnosed atrial fibrillation with accompanying severe obesity. She is 5'7" tall and weights 338 Ibs. Her cardiologist calls the pharmacy and states that he has had trouble in dosing similar patients in the past and would like some assistance in designing a loading and maintenance IV Lanoxin dosage regimen. She has no other complicating drugs or diseases (serum creatinine = 0.7 mg%) except that she is being continued on Quinidex Extentabs 300 mg Q8H which she has been reliably taking for 3 years. Respond to the physician's request.

$$IBW = 45 + 2.3 \cdot 7 = 61.1kg$$

$$Cl_{creat}(\text{female}) = \frac{(140 - age) \cdot \text{weight}}{85 \cdot \text{SeCr}} = \frac{(140 - 36) \cdot 61.1}{85 \cdot 0.7} = 107mL/\min \approx 6.4L/h$$

$$CL = 0.8mL/kg/\min \cdot weight/kg + CL_{Cr} = 0.8 \cdot 61.1 + 107 = 156mL/\min \approx 9.36L/h$$

with quinidine:

$$CL_{tot} = 0.5 \cdot CL = 4.68L/h \approx 112L/day$$

$$Vd = 3.8 \cdot weight/kg + 3.1 \cdot CL_{Cr} = 3.8 \cdot 61.1 + 3.1 \cdot 107 = 564L$$

with quinidine:

$$Vd = 0.7 \cdot Vd = 0.7 \cdot 564L = 395L$$

Loading Dose:

$$LD = Cp \cdot Vd = 1.5\mu g/L \cdot 395L = 593\mu g \approx 600\mu g$$

Maintenance Dose:

$$MD = Cp,ss \cdot CL \cdot \tau = 1.5\mu g/mL \cdot 112L/day \cdot 1day = 168\mu g/day \approx 175\mu g/day$$

3. Matt is a 40 year old 65 kg intermittent asthmatic who presents to the emergency room with severe dyspnea, coughing, and wheezing. He is treated there with aerosol albuterol (S=0.8), but only partially clears. He is then given 400 mg of IV aminophylline over 30 minutes. Thirty minutes after the loading dose was administered (60 minutes from time zero) the theophylline concentration was 15 µg/ml. He has normal liver, kidney, and cardiac function and is afebrile. He is not receiving any other drugs. After the loading dose, Matt was started on an IV aminophylline constant infusion of 55 mg/hr, Solu-Medrol IV and albuterol nebulization. Eight hours after the first serum level, a second level was 9 µg/ml.

A. Calculate Matt's actual volume of distribution.

$$Vd = \frac{Dose \cdot F \cdot S}{Cp} = \frac{400mg \cdot 1 \cdot 0.8}{15mg/L} = 21.3L$$

B. Calculate Matt's total body clearance.

$$CL = \frac{2 \cdot R_0}{(C_1 + C_2)} + \frac{2 \cdot Vd \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)} = \frac{2 \cdot 55mg/h}{(9 + 15mg/L)} + \frac{2 \cdot 21.3L \cdot (15 - 9mg/L)}{(15 + 9mg/L) \cdot 8h} = 3.67 + 1.33 = 5L/h$$

C. Calculate the additional IV aminophylline loading dose necessary to increase his level from 9 µg/ml back to 15 µg/ml.

$$LD = \frac{\Delta Cp \cdot Vd}{S \cdot F} = \frac{6mg/L \cdot 21.3L}{0.8 \cdot 1} = \underline{160mg}$$

D. Calculate the IV aminophylline infusion rate necessary to maintain Matt's level at 15 µg/ml after the second loading dose.

$$MD = \frac{Cp,ss \cdot CL}{S \cdot F} \frac{15mg/L \cdot 5L/h}{0.8 \cdot 1} = \underline{94mg/h}$$

4. A. Estimate a digoxin loading dose for tablets that will produce a plasma concentration of 1.5 µg/L for a 70 kg patient being treated for mild to moderate congestive cardiac failure using average pharmacokinetic parameters. How should this loading dose be divided and what would be an appropriate interval between doses?

   B. Assume R.J. is a 50-year-old male with a serum creatinine of 1.0 mg/dL. Calculate a maintenance dose that will achieve an average plasma digoxin concentration of 1.5 µg/L. If the patient had had a serum creatinine of 5 mg/dL, would the estimated loading dose have been different?

A. $Vd = 7.3L/kg \cdot 70kg = 511L$

$$LD = \frac{Vd \cdot Cp_0}{S \cdot F} = \frac{511L \cdot 1.5\mu g/L}{0.7 \cdot 1} = 1095\mu g \approx 1000\mu g = 1mg$$

One-half is given initially, followed by one-fourth every six hours.

B. $$Cl_{creat}(male) = \frac{(140 - age)(weight)}{72 \cdot Scr} = \frac{(140-50) \cdot 70}{72 \cdot 1} = 87.5mL/\min$$

$$CL = 0.33mL/kg/\min \cdot weight/kg + 0.9 \cdot CL_{Cr}(mL/\min)$$

$$= 0.33 \cdot 70 + 0.9 \cdot 87.5 = 101.9mL/\min \approx 146.7L/day$$

$$MD = \frac{Cp,ss \cdot CL \cdot \tau}{S \cdot F} = \frac{1.5\mu g/L \cdot 146.7L/day \cdot 1day}{0.7 \cdot 1} = 314.4\mu g$$

If serum creatinine increases to 5 mg/dL:

$$Cl_{creat}(male) = \frac{(140 - age)(weight)}{72 \cdot Scr} = \frac{(140-50) \cdot 70}{72 \cdot 5} = 17.5mL/\min$$

$$Vd = 3.8 \cdot weight/kg + 3.1 \cdot CL_{Cr} = 3.8 \cdot 70 + 3.1 \cdot 17.5 = 320.3L$$

$$LD = \frac{Vd \cdot Cp_0}{S \cdot F} = \frac{320.3L \cdot 1.5\mu g/L}{0.7 \cdot 1} = 686.4\mu g \approx 700\mu g$$

5. A patient (m, 37y, 74 kg) with a subtherapeutic theophylline (5 µg/mL) is admitted to the ICU. Based on average pharmacokinetics parameters (Vd = 0.5 L/kg, $t_{1/2}$ = 8 h)), calculated an i.v. bolus loading dose and a maintenance dose (i.v. infusion) to increase the level to 15 µg/mL.

$$Vd = 0.5L/kg \cdot 74kg = 37L$$

$$LD = (15 - 5mg/L) \cdot 37L = 370mg$$

$$CL = \frac{0.693}{t_{1/2}} \cdot Vd = \frac{0.693}{8h} \cdot 37L = 3.2L/h$$

$$MD = Cp,ss \cdot CL = 15mg/L \cdot 3.2L/h = 48mg/h \approx 1150mg/day$$