PHA 5128 Dose Optimization II, Spring 2013, Homework IV Solution
Total Points: 10

If you any questions regarding this homework assignment, do not hesitate to contact Benjamin Weber (benjaminweber@ufl.edu). Please provide all answers with their **appropriate units** and all graphs with **appropriately labeled axes**. 0.25 points will be deducted for each missing or inappropriate unit or axes label. **Remember to show how you found your answer**. Answers lacking adequate justification may not receive full credit.

Problem 1 (Digoxin; 4 points)

R.J. is a 50-year-old, 70-kg man (non-obese) and has a serum creatinine of 1.2 mg/dL. Calculate a maintenance dose at steady state that will achieve an average digoxin plasma concentration of 750 ng/L. Develop a dosing regimen assuming that digoxin is available in tablets of 125-µg and 250-µg.

$$CL_{Cr} = \frac{(140 - age)(weight\ in\ kg)}{72(SCr_{SS})} = \frac{(140 - 50)(70)}{72(1.2)} = 72.9\frac{mL}{min}$$

$$CL\left[\frac{mL}{min}\right] = 0.8(weight\ in\ kg) + \left(CL_{Cr}\ in\frac{mL}{min}\right) = 0.8 * 70 + 72.9$$

$$\approx 128.9\frac{mL}{min}$$

$$128.9\frac{mL}{min} = 7.73\frac{L}{h} = 185.6\frac{L}{day}$$

$$MD = \frac{CL * C_{ss,avg} * \tau}{F} = \frac{185.6\frac{L}{day} * 0.75\frac{\mu g}{L} * 1day}{0.7} \approx 200\mu g$$

125-µg and 250-µg tablets on alternate days for an average dose of 187.5 µg/day.

You decided to give 125-µg and 250-µg tablets on alternate days for an average dose of 187.5 µg/day. Four weeks later, R.J. is started on long-term medication with quinidine sulfate tablets. Would you have to adjust his dosing regimen? If yes, calculate a new maintenance dose and recommend a new dosing regimen.

$$C_{ss,avg}(old) = \frac{MD * F}{\tau * CL} = \frac{187.5\mu g * 0.7}{1day * 185.6\frac{L}{day}} \approx 700\frac{ng}{L}$$

$$CL(new) = CL(old) * 0.5 = 185.6\frac{L}{day} * 0.5 = 92.8\frac{L}{day}$$

$$MD(new) = \frac{CL(new) * C_{ss,avg}(old) * \tau}{F} = \frac{92.8\frac{L}{day} * 0.7\frac{\mu g}{L} * 1day}{0.7} \approx 90\mu g$$

Change dosing regimen to 125-µg tablets once daily.

<u>Problem 2 (Methotrexate; 3 points)</u>

J.J. is a 25-year-old, 80-kg (non-obese), man with a serum creatinine of 1.0 mg/dL. He has osteonic sarcoma and is to receive 30g IV methotrexate (MTX) infused over 4 h. Calculate the anticipated MTX concentration (in µM) at the end of the 4h infusion, 12h after the start of the infusion, and 48h after the end of the infusion. A sketch of the expected plasma-concentration-time profile may be helpful to answer this problem.

$$CL_{Cr} = \frac{(140 - age)(weight\ in\ kg)}{72(SCr_{SS})} = \frac{(140 - 25)(80)}{72(1.0)} = 127.8\frac{mL}{min}$$

$$127.8\frac{mL}{min} = 7.7\frac{L}{h}$$

$$CL_{MTX} = (1.6)CL_{Cr} = (1.6)7.7\frac{L}{h} = 12.32\frac{L}{h}$$

$$k_e(> 0.5\mu M) = \frac{ln(2)}{3h} = 0.231\frac{1}{h}$$

$$C_4 = \frac{Dose}{(\tau)(CL)}\left(1 - e^{-k_e(>0.5\mu M)*T}\right) = \frac{30000mg}{(4h)\left(12.32\frac{L}{h}\right)}\left(1 - e^{-0.231\frac{1}{h}*4h}\right) = 367\frac{mg}{L}$$

$$367\frac{mg}{L} = 808\mu M$$

$$C_{12} = C_4\left(e^{-0.231\frac{1}{h}*8h}\right) = 808\mu M\left(e^{-0.231\frac{1}{h}*8h}\right) = 127\mu M$$

Let t* be the time (after stop of the infusion) that is required to for MTX concentration to fall to 0.5 µM.

$$t^* = \frac{ln\left(\frac{127\mu M}{0.5\mu M}\right)}{0.231\frac{1}{h}} = 24h$$

$$24h + 12h = 36h$$

Thus, an MTX plasma concentration of 0.5 µM is reached 36 h after the infusion was started

$$k_e(< 0.5\mu M) = \frac{ln(2)}{10h} = 0.0693\frac{1}{h}$$

Note that 48h after the end of the infusion is equivalent to 52h after the start to the infusion

$$\mathbf{52h - 36h = 16h}$$

$$\boldsymbol{C_{52} = 0.5\mu M\left(e^{-0.0693*16h}\right) = 0.16\mu M}$$

<u>Problem 3 (Phenytoin; 3 points)</u>

A male patient of 113 kg in weight was administered sodium phenytoin capsules by oral route. Phenytoin (not the salt form) has a volume of distribution of 0.65 L/kg. This patient exhibited phenytoin K_M of 4.7 mg/L and a V_{max} of 8.2 mg/kg/day. Compute the following:

1. The loading dose required to achieve an initial phenytoin concentration of 20 mg/L
2. The daily maintenance dose to obtain the target average steady-state concentration of 15 mg/L.

(i) To compute the loading dose required to achieve an initial concentration of 20 mg/L

$$V_d = 0.65\,L/kg \times 113kg = 73.45L$$

$$LD = \frac{C_p \cdot V_d}{S \cdot F} = \frac{20\,mg/L \times 73.45\,L}{0.92 \times 1} = 1596.74\,mg \approx 1600\,mg$$

In order to relieve the side effects associated with phenytoin, the loading dose should be given in short intervals, such that the first dose is 400 mg followed by three 400 mg doses at two-hour interval apart.

(ii) The daily maintenance dose needed to obtain the target average steady-state concentration of 15 mg/L is

$$MD = \frac{V_{\max} \cdot Cp_{ss} \cdot \tau}{(K_m + C) \cdot S \cdot F} = \frac{8.2\,mg/kg/day \times 113kg \times 15\,mg/L \cdot 1day}{(4.7\,mg/L + 15) \times 0.92 \times 1} = 766.88 \approx 770\,mg/day$$