PHA 5128 Dose Optimization II, Spring 2011, Homework V 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. Please provide all answers on separate sheets (does not apply to TRUE/FALSE questions). **Remember to show how you found your answer**. Answers lacking adequate justification may not receive full credit.

Problem 1 (Digoxin)

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)</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

$$52h - 36h = 16h$$

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

<u>Problem 3 (Theophylline)</u>

J.P., a 126-kg (total body weight), 6'1'' tall, 56-year-old man, is seen in the emergency department with asthma that is unresponsive to inhaled bronchodilators and epinephrine. Estimate an IV loading dose and maintenance dose (expressed as dosing rate) of theophylline that will produce a theophylline concentration of 10 mg/L. J.P. suffers from CHF and smokes 2 packs of cigarettes a day.

$$IBW_{male} = 50kg + 13(2.3kg) = 79.9$$

$$79.9kg * 1.2 \approx 96kg$$

Thus, J.P. is obese. Use IBW to calculate CL and VD.

$$CL = \left(0.04\frac{L}{h * kg}\right)(79.9kg)(1.6)(0.4) = 2.05\frac{L}{h}$$

$$VD = \left(0.5\frac{L}{kg}\right)(79.9kg) = 39.95L$$

$$LD = (VD)(C_{desired}) = (39.95L)\left(10\frac{mg}{L}\right) \approx 400mg$$

$$MD = (C_{ss,avg})(CL) = \left(10\frac{mg}{L}\right)\left(2.05\frac{L}{h}\right) = 20.5\frac{mg}{h}$$

J.P. could finally be convinced to stop smoking and lost 30kg. How would you have to adjust his loading dose and maintenance dose (expressed as dosing rate)?

Patient is non-obese. Use TBW.

$$CL_{new} = \left(0.04\frac{L}{h * kg}\right)(96kg)(0.4) = 1.54\frac{L}{h}$$

$$VD_{new} = \left(0.5\frac{L}{kg}\right)(96kg) = 48L$$

$$LD_{new} = (VD)(C_{desired}) = (48L)\left(10\frac{mg}{L}\right) = 480mg$$

$$MD_{new} = MD = (C_{ss,avg})(CL_{new}) = \left(10\frac{mg}{L}\right)\left(1.54\frac{L}{h}\right) = 15.4\frac{mg}{h}$$

Problem 4 (Theophylline)

J.D. is a 2-year-old, 9 kg male child in the hospital who is placed on a theophylline drip at 1 g/kg/hr after first receiving a 5 mg/kg bolus at 1 pm. The infusion is discontinued at 7pm. Plasma concentration samples were obtained at 2pm and 8pm. Could you use the Chiou-equation to estimate his clearance? Explain why or why not.

It is not possible to use the Chiou-equation to estimate his clearance because the last sample was not obtained during the infusion.

Problem 5 (Lidocaine)

R.I., a 65-year-old, 70-kg man (non-obese), was admitted with a diagnosis of cirrhosis. On the fourth day, he developed ventricular arrhythmias, and lidocaine was ordered. He received an initial 60-mg bolus dose at 10am followed by 120-mg administered over the next 15 minutes (8 mg/min). At 11am he was to be given a 2 mg/min constant infusion. Calculate his anticipated lidocaine concentration at the start of his maintenance infusion and at steady state. Evaluate this dosing regimen based on therapy recommendations for lidocaine. (Hint: A graph of the anticipated concentration time profile might be helpful to answer this problem)

$$VD = \left(2.3\frac{L}{kg}\right)70kg = 161L$$

$$CL = 0.36\frac{L}{h(kg)}70kg = 25.2\frac{L}{h}$$

$$k_e = \frac{CL}{VD} = \frac{25.2\frac{L}{h}}{161L} = 0.157\frac{1}{h}$$

Use VD in to calculate plasma concentration at the beginning of the maintenance infusion because the distribution should be complete 45 minutes after the end of the infusion.

$$C_{11} = \frac{(S)(Dose)}{VD}e^{-k_e*1h} + \frac{(S)(Dose)}{(CL)(T)}\left(1 - e^{-k_e*T}\right)\left(e^{-k_e*0.75h}\right) =$$

$$\frac{(0.87)(60)}{161L}e^{-0.157\frac{1}{h}*1h} + \frac{(0.87)(120)}{\left(25.2\frac{L}{h}\right)(0.25h)}\left(1 - e^{-0.157\frac{1}{h}*0.25h}\right)\left(e^{-0.157\frac{1}{h}*0.75h}\right) =$$

$$0.28\frac{mg}{L} + 0.57\frac{mg}{L} = 0.85\frac{mg}{L}$$

$$C_{ss,avg} = \frac{(Dose)S}{\tau * CL} = \frac{(120mg)0.87}{1h * 25.2\frac{L}{h}} = 4.14mg/L$$

Lidocaine plasma concentrations of 1-5 mg/mL are usually associated with therapeutic control of ventricular arrhythmias. Thus, anticipated plasma levels are in the therapeutic range.