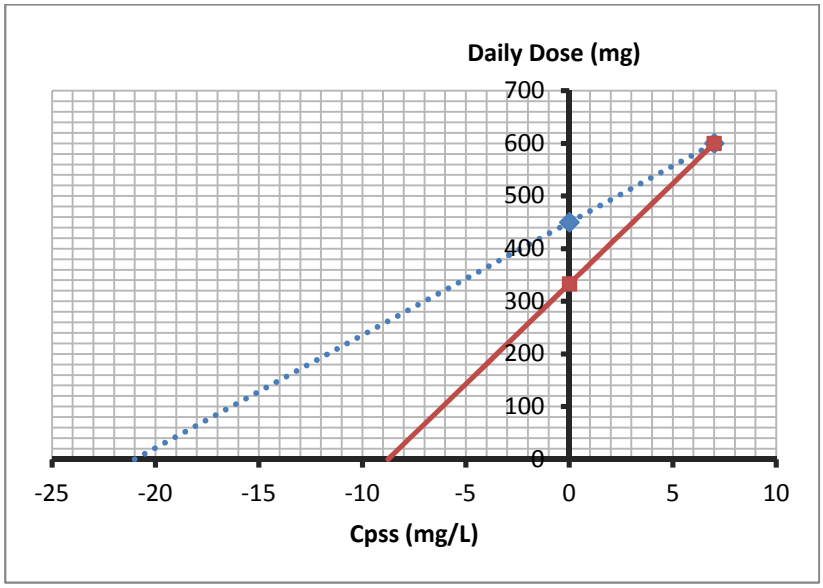
PHA 5128 – Dose Optimization II
Homework 4
Spring 2012

1. A phenytoin patient (75kg) has a plasma concentration of 3.5 mg/L at 200 mg/day and 14 mg/L at 400 mg/day. Using the attached graphy paper determine Km and Vmax as well as the dose needed to produce a concentration of 15 mg/L. Compare the results with the precise calculations(assume S=1 in this case). What is the phenytoin half-life and clearance at 15 mg/L?(2 points)



Answer:

From the graph: Vmax = 600 mg/day; Km = 7 mg/L

Calculated:

$$V_{max} = \frac{(D_1 * S) * (D_2 * S) * (C_2 - C_1)}{C_2 * (D_1 * S) - C_1 * (D_2 * S)} = \frac{D_1 * D_2 * S * (C_2 - C_1)}{C_2 * D_1 - C_1 * D_2}$$

$$= \frac{(200) * (400) * 1 * (14 - 3.5)}{14 * 200 - 3.5 * 400} = 600\ mg/day$$

$$K_m = \frac{C_1 * (V_{max} - D_1 * S)}{D_1 * S} = \frac{3.5 * (600 - 200 * 1)}{200 * 1} = 7\ mg/L$$

$$V_d = 0.65 \frac{L}{kg} * 75\ kg = 48.75\ \mathrm{L}$$

$$t_{1/2} = \frac{0.693 * (K_m + C) * Vd}{V_{max}} = \frac{0.693 * (7 + 15) * 48.75}{600} \approx 1.24 day \approx 30 hr$$

$$CL = \frac{V_{max}}{K_m + C} = \frac{600}{7+15} = 27.3 L/day$$

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2. D.T., a 40 year old male executive with uncontrolled hyperthyroidism with PAT. He has no history of previous illnesses and is not currently receiving any medications. He is 6'1 and weighs 85 kg. Lab: serum potassium = 4.8 mEq/L, serum creatinine = 0.7 mg/dl. Design a loading and maintenance dosage regimen for IV digoxin as you are not sure what the physician will prescribe. Three days after the patient receives your recommended regimen IV, the physician requests a serum digoxin conc. It is reported by the lab to be 0.9 ug/L(1 hour before the next dose). The physician asks 3 questions: 1. What should be the MD dose for IV if the trough need to be 1.2 ug/L at steady-state? 2. What should be the dose if we later switch to PO and keep 1.2 as the target trough for Lanoxicaps or Lanoxin tabs? 3. The patient plans to have surgery next week to control his hyperthyroidism. Will there need to be a change in his digoxin dosage at that time? If so what should be the recommended dosage regimen and a follow-up TDM plan?(3 points)

Answer:
To calculate CL:

$$IBW = 50\ kg + 2.3\ kg * (Height - 5') = 50 + 2.3 * 13 = 79.9kg$$

$$1.2 * IBW = 79.9 * 1.2 = 95.9\ kg$$

$TBW = 85$ kg < 1.2 IBW So use TBW

$$Cl_{creat}(male) = \frac{(140 - age) * weight}{72 * C_{pcreat}} = \frac{(140 - 40) * 85}{72 * 0.7} = 168.65\ ml/min$$

$$Cl_{Digoxin} = 0.8\ ml/kg/min * IBW + Cl_{creat(without-CHF)}$$

$= 0.8 * 79.9 + 168.65 = 232.57\ ml/min$← without Heperthyroidism

$$Cl_{Digoxin} = Cl_{Digoxin} * 1.3 = 302.34\ ml/min$$

=302.34 ml/min*1440 min/day *1L/1000ml

=435.37 L/day← with Heperthyroidism

To calculate Vd:

$$Vd_{Digoxin} = 3.8\ L/kg * IBW + 3.1 * Cl_{creat}$$

$= 3.8 *$79.9+3.1*168.65=826.4 L← without Heperthyroidism

$Vd = Vd_{Digoxin} \cdot 1.3 = 1074.4$ (L) ← with Heperthyroidism

Therefore:

$$LD = C_{p0} * Vd/F = 1.5 * 1074.4 = 1611.5\ ug$$

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$MD = Cl * C_{pss} * \tau/F = 435.37 * 1.5 * 1 = 653.1\ ug$

1) dose proportional:

$$653.1 * \frac{1.2}{0.9} = 870.8\ ug/day$$

2) oral dose;

$$870.8/0.7 = 1244\ ug/day$$

3) decrease IV dose to 870.8 / 1.3 = 670 ug or Tablet dose to 1244 / 1.3 = 957 ug

3. K.E., a 40-year-old, 52 kg female with a serum creatinine of 1.4 mg/dL, is to receive 1 g IV methotrexate infused over four hours. Calculate the methotrexate concentration 12 hours after the end of the infusion. (2pts.)

Answer:

$$Cl_{creat}(male) = \frac{(140 - age) * weight}{85 * C_{pcreat}} = \frac{(140 - 40) * 52}{85 * 1.4} = 43.7\ ml/min \approx 2.62 L/hr$$

$$CL = 1.6 * CL_{creat} = 1.6 * 2.62\ L/hr = 4.19\ L/hr$$

$$k_e = \frac{0.693}{3} = 0.231\ hr^{-1}$$

$$C_p(12hr) = \frac{Dose}{CL * T} * \left(1 - e^{-k_e * T}\right) * e^{-k_e * t} = \frac{1000}{4.19 * 4} * \left(1 - e^{-0.231 * 4}\right) * e^{-0.231 * 12}$$
$$= 2.25\ mg/L$$

$$C_p(12hr) uM = \frac{2.25\ mg/L}{0.454} = 4.96\ uM$$

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4. E.R. is a 63 kg female patient (47 years old) on methotrexate therapy. Her serum creatinine is 1.3 mg/dL. She is treated with a loading dose (20 mg) followed by an infusion of 36 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. Calculate the expected MTX concentrations at 24, 48 and 60 hours after the start of the infusion. (3points)

Answer:

$$Cl_{creat}(male) = \frac{(140 - age) * weight}{85 * C_{pcreat}} = \frac{(140 - 47) * 63}{85 * 1.3} = 53.0\ ml/min \approx 3.18\ L/hr$$

$$CL = 1.6 * CL_{creat} = 1.6 * 3.18\ L/hr = 5.09\ L/hr$$

$$C_{ss} = \frac{R_0}{CL} = \frac{36}{5.09} = 7.07\ mg/L$$

$$C_{ss}(uM) = \frac{7.07}{0.454} = 15.6uM$$

24 h: 15.6 µM

48 h: $C_p(48hr) = Cp(24hr) * e^{-k_e * t} = 15.6 * e^{-0.231*12} = 0.98uM$

60 h: $t = \frac{\ln\left(\frac{15.06}{0.5}\right)}{0.231} = 15hr$ →0.5uM at 51hr

So $C_p(60hr) = Cp(51hr) * e^{-k_e * t} = 0.5 * e^{-0.069*9} = 0.27uM$