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 $K_m$ and $V_{max}$ 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: $V_{max} = 600 \text{ mg/day}$; $K_m = 7 \text{ mg/L}$

Calculated:

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

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

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

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

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

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

\[
IBW = 50 kg + 2.3 kg \times (Height - 5') = 50 + 2.3 \times 13 = 79.9 kg
\]

\[
1.2 \times IBW = 79.9 \times 1.2 = 95.9 kg
\]

\[
TBW = 85 kg < 1.2 \times IBW \quad \text{So use TBW}
\]

\[
Cl_{\text{creat(male)}} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times Cl_{\text{pcreat}}} = \frac{(140 - 40) \times 85}{72 \times 0.7} = 168.65 \text{ ml/min}
\]

\[
Cl_{\text{Digoxin}} = 0.8 \times \text{IBW} + \frac{Cl_{\text{creat(without CHF)}}}{CL_{\text{Digoxin}}} = 0.8 \times 79.9 + 168.65 = 232.57 \text{ ml/min} \quad \text{without Heperthyroidism}
\]

\[
Cl_{\text{Digoxin}} = Cl_{\text{Digoxin}} \times 1.3 = 302.34 \text{ ml/min}
\]

\[
= 302.34 \text{ ml/min} \times 1440 \text{ min/day} \times 1 \text{L/1000ml}
\]

\[
= 435.37 \text{ L/day} \quad \text{with Heperthyroidism}
\]

To calculate Vd:

\[
Vd_{\text{Digoxin}} = 3.8 \times \text{IBW} + 3.1 \times Cl_{\text{pcreat}}
\]

\[
= 3.8 \times 79.9 + 3.1 \times 168.65 = 826.4 \text{ L} \quad \text{without Heperthyroidism}
\]

\[
Vd = Vd_{\text{Digoxin}} \times 1.3 = 1074.4 \text{ (L)} \quad \text{with Heperthyroidism}
\]

Therefore:

\[
LD = C_{p0} \times Vd/F = 1.5 \times 1074.4 = 1611.5 \text{ ug}
\]
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\[ MD = Cl \times C_{pss} \times \tau / F = 435.37 \times 1.5 \times 1 = 653.1 \text{ ug} \]

1) dose proportional:
\[ 653.1 \times \frac{1.2}{0.9} = 870.8 \text{ ug/day} \]

2) oral dose:
\[ 870.8 / 0.7 = 1244 \text{ ug/day} \]

3) decrease IV dose to \( 870.8 / 1.3 = 670 \text{ ug} \) or Tablet dose to \( 1244 / 1.3 = 957 \text{ ug} \)
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:**

\[
C_{\text{Cl\_creat\_male}} = \frac{(140 - \text{age}) \times \text{weight}}{85 \times C_{\text{p\_creat}}} = \frac{(140 - 40) \times 52}{85 \times 1.4} = 43.7 \text{ ml/min} \approx 2.62 \text{ L/hr}
\]

\[
C_L = 1.6 \times C_{\text{Cl\_creat}} = 1.6 \times 2.62 \text{ L/hr} = 4.19 \text{ L/hr}
\]

\[
k_e = \frac{0.693}{3} = 0.231 \text{ hr}^{-1}
\]

\[
C_p(12\text{hr}) = \frac{Dose}{C_L \times T} \times \left(1 - e^{-k_e T}\right) \times e^{-k_e t} = \frac{1000}{4.19 \times 4} \times \left(1 - e^{-0.231 \times 4}\right) \times e^{-0.231 \times 12} = 2.25 \text{ mg/L}
\]

\[
C_p(12\text{hr})\mu M = \frac{2.25 \text{ mg/L}}{0.454} = 4.96 \text{ \mu M}
\]
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. (3 points)

**Answer:**

\[ Cl_{\text{creat(male)}} = \frac{(140 - \text{age}) \times \text{weight}}{85 \times C_p^{\text{creat}}} = \frac{(140 - 47) \times 63}{85 \times 1.3} = 53.0 \text{ ml/min} \approx 3.18 \text{ L/hr} \]

\[ CL = 1.6 \times CL_{\text{creat}} = 1.6 \times 3.18 \text{ L/hr} = 5.09 \text{ L/hr} \]

\[ C_{ss} = \frac{R_0}{CL} = \frac{36}{5.09} = 7.07 \text{ mg/L} \]

\[ C_{ss}(\mu M) = \frac{7.07}{0.454} = 15.6 \mu M \]

24 h: \hspace{1cm} 15.6 \mu M

48 h: \hspace{1cm} \[ C_p(48hr) = C_p(24hr) \times e^{-ke^{t}} = 15.6 \times e^{-0.231 \times 12} = 0.98 \mu M \]

60 h: \hspace{1cm} \[ t = \frac{\ln(0.5)}{0.231} = 15hr \quad \rightarrow 0.5 \mu M \text{ at 51hr} \]

So \[ C_p(60hr) = C_p(51hr) \times e^{-ke^{t}} = 0.5 \times e^{-0.069 \times 9} = 0.27 \mu M \]