L.J., a 60 kg male, was admitted to the hospital for the seizures. A loading dose of sodium phenytoin was given to achieve 15 mg/L, and then maintenance dose was given 300mg daily. After a week, a steady-state concentration was measured at 8 mg/L. The physician decided to increase maintenance dose to 350 mg daily. After another week, the concentration of phenytoin at steady-state was at 21mg/L, which is too high. The following dose was discontinued until concentration drops to 15 mg/L. How long will it take to achieve this drop from 24 mg/L to 15 mg/L? (2 points)

Answer:

\[ V_c = 0.65 \text{L/kg} \times 60 \text{kg} = 39 \text{L} \]

\[ V_{\text{max}} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 350 \cdot (21 - 8)}{21 \cdot 300 - 8 \cdot 350} = 390 \text{mg/day} \]

\[ C = \frac{K_m \cdot D}{V_m - D} \quad \Rightarrow \quad K_m = \frac{C (V_m - D)}{D} = \frac{21(390 - 350)}{350} = 2.4 \text{mg/L} \]

\[ t = \frac{(K_m \cdot \ln \left( \frac{C_1}{C_2} \right) + C_1 - C_2) \cdot V_d}{V_m \cdot S} = \frac{(2.4 \cdot \ln \left( \frac{21}{8} \right) + 21 - 8) \cdot 39}{390 \cdot 0.92} = 1.66 \text{day} \approx 40 \text{hours} \]
2. M.W. is a 33-year-old, 65 kg male with a seizure disorder that has only partially been controlled with 300 mg/day of sodium phenytoin. His plasma phenytoin concentration has been measured twice over the past year and both times it was reported to be 7 mg/L. His Km value is 5 mg/L. Calculate a dose which will achieve a steady-state concentration of 15 mg/L. (2 points)

\[
V_{\text{max}} = \frac{F \cdot S \cdot \text{Dose}}{\tau \cdot (K_m + C_{pss})} = \frac{1 \cdot 0.92\cdot 300 \text{ mg/day} \cdot (5 \text{ mg/L} + 7 \text{ mg/L})}{7 \text{ mg/L}} = 473 \text{ mg/day}
\]

\[
\text{Dose} = \frac{V_m \cdot C_{\text{pss}} \cdot \tau}{F \cdot S \cdot (K_m + C_{\text{pss}})} = \frac{473 \text{ mg/day} \cdot 15 \text{ mg/L} \cdot 1 \text{ day}}{1 \cdot 0.92 \cdot (5 \text{ mg/L} + 15 \text{ mg/L})} = 385.6 \text{ mg} \approx 400 \text{ mg}
\]
3. M.W. is a 50-year-old, 70kg male with glomerular nephritis. His creatinine clearance is reasonably good, but he has a serum albumin concentration of 2.2g/dL. M.W. is receiving 350mg/day of phenytoin and has a steady-state phenytoin concentration of 6mg/L. What would be his phenytoin concentration be if his serum albumin concentration were normal? (normal serum albumin=4.4g/dL). (1 pts)

\[
C_{P_{normal}} = \frac{C_p'}{(1 - \alpha) \cdot \frac{\text{Patient's Albu min}}{\text{Normal Albu min}}} + 0.1 = \frac{6 \text{mg/L}}{(1 - 0.1) \cdot \frac{2.2 \text{g/dL}}{4.4 \text{g/dL}}} + 0.1 = 10.9 \text{mg/L}
\]
4. A patient (35 years old, 55 kg) is to be started on phenobarbital sodium. (3 points)
   a. Calculate a loading dose to yield a $C_{p0}$ of 30 mg/L
   b. Calculate a daily maintenance dose to produce an average steady state concentration of 22 mg/L.
   c. The same patient is to be treated simultaneously with carbamazepine. Propose an oral maintenance
dosing regimen for carbamazepine for this patient to achieve a carbamazepine level of 6 μg/mL.

   a. $LD = \frac{Vd \cdot Cp0}{F \cdot S} = \frac{0.7 L/kg \cdot 55 kg \cdot 30 mg/L}{1.0} = 1.3g$

   b. $MD = \frac{CL \cdot Cpss \cdot \tau}{F \cdot S} = \frac{0.004 L/h/kg \cdot 55 kg \cdot 22 mg/L \cdot 24 h}{1.0} = 129.07 mg \approx 130 mg$

   c. $MD = \frac{CL \cdot Cpss \cdot \tau}{F \cdot S} = \frac{0.1 L/h/kg \cdot 55 kg \cdot 6 mg/L \cdot 24 h}{1.0} = 990 mg QD \approx 500 mg BID$
5. 50 year old, 70 kg male has been receiving 200mg/day (100 mg BID) of phenobarbital (S=1) for the past 25 days. Please calculate the phenobarbital plasma concentration just before the morning dose on Day 26. For phenobarbital Vd = 0.7 L/kg, CL = 0.004L/h/kg for adults. (2 points)

\[ Cl = 0.004 \text{L/h/kg} \times 70 \text{kg} = 0.28 \text{L/h} \]
\[ Vd = 0.7 \times 70 = 49 \text{L} \]

\[ Ke = \frac{CL}{Vd} = \frac{0.28 \text{L/h}}{49 \text{L}} = 0.0057 \text{h}^{-1} = 0.137 \text{day}^{-1} \]

\[ \frac{T1/2}{2} = \frac{0.693}{0.137} = 5.05 \text{ day}, \text{ so so after 25 days (about 5 half-life), the steady state should be achieved.} \]
\[ Tau = 12 \text{h} = 0.5 \text{day} \]

\[ Cpss \min = \frac{D \cdot S \cdot F \cdot e^{-ke\cdot Tau}}{Vd \cdot (1 - e^{-ke\cdot Tau})} = \frac{100 \text{mg} \cdot 1 \cdot 1 \cdot e^{-0.137\cdot0.5}}{49 \text{L} \cdot (1 - e^{-0.137\cdot0.5})} = 28.78 \text{mg} / \text{L} \approx 29 \text{mg} / \text{L} \]