1. 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:

Vc=0.65L/kg*60kg=39L

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

sodium phenytion

$$C = \frac{K_m \cdot D}{V_m - D} --> K_m = \frac{C(V_m - D)}{D} = \frac{21(390-350)}{350} = 2.4 mg/L$$

phenytion

$$t = \frac{(K_m \cdot \ln\left(\frac{C_1}{C_2}\right) + C_1 - C_2) \cdot Vd}{V_m \cdot S} = \frac{(2.4 \cdot \ln\left(\frac{21}{8}\right) + 21 - 8) \cdot 39}{390 \cdot 0.92} = 1.66 day \approx 40 hours$$

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)

$$V_{\max} = \frac{F \cdot S \cdot Dose / \tau \cdot (K_m + Cpss)}{Cpss} = \frac{1 \cdot 0.92 \cdot 300 mg / day \cdot (5 mg / L + 7 mg / L)}{7 mg / L} = 473 mg / day$$

$$Dose = \frac{V_m \cdot Cpss \cdot \tau}{F \cdot S \cdot (K_m + Cpss)} = \frac{473 mg / day \cdot 15 mg / L \cdot 1 day}{1 \cdot 0.92 \cdot (5 mg / L + 15 mg / L)} = 385.6 mg \approx 400 mg$$

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)

$$Cp_{normal} = \frac{Cp'}{\left((1-\alpha)\cdot\frac{Patient'sAlbu\min}{NormalAlbu\min}\right)+0.1} = \frac{6mg/L}{\left((1-0.1)\cdot\frac{2.2g/dL}{4.4g/dL}\right)+0.1} = 10.9mg/L$$

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. $$LD = \frac{Vd \cdot Cp0}{F \cdot S} = \frac{0.7L/kg \cdot 55kg \cdot 30mg/L}{1 \cdot 0.9} = 1.3g$$

b. $$MD = \frac{CL \cdot Cpss \cdot \tau}{F \cdot S} = \frac{0.004L/h/kg \cdot 55kg \cdot 22mg/L \cdot 24h}{1 \cdot 0.9} = 129.07mg \approx 130mg$$

c. $$MD = \frac{CL \cdot Cpss \cdot \tau}{F \cdot S} = \frac{0.1L/h/kg \cdot 55kg \cdot 6mg/L \cdot 24h}{1 \cdot 0.8} = 990mgQD \approx 500mgBID$$

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= 0.004L/h/kg * 70kg = 0.28L/h

Vd= 0.7 * 70 = 49 L

Ke=CL/Vd= (0.28L/h)/49L=0.0057h-1= 0.137 day -1

T1/2=0.693/0.137=5.05 day, so so after 25 days (about 5 half-life), the steady state should be achieved.

Tau = 12h =0.5day

$$Cpss\min = \frac{D \cdot S \cdot F \cdot e^{-ke \cdot Tau}}{Vd \cdot (1 - e^{-ke \cdot Tau})} = \frac{100mg \cdot 1 \cdot 1 \cdot e^{-0.137 \cdot 0.5}}{49L \cdot (1 - e^{-0.137 \cdot 0.5})} = 28.78mg / L \approx 29mg / L$$