PHA 5128
CASE STUDY 4

Spring 2011

(Phenobarbital/Carbamazepine/Valproic Acid, Phenytoin)

1. R. F., (30y, 70 kg, male), had been taking 300mg/day of sodium phenytoin; however, his dose was increased to 350 mg/day because his reported plasma phenytoin concentration was only 8 mg/L. Now his reported plasma phenytoin concentration is 20 mg/L. Both of the reported plasma concentrations represent steady-state level. Calculate a new daily dose of sodium phenytoin that will result in a steady state level of 15 mg/L (Salt factor = 0.92).

$$C = \frac{K_m \cdot R_0}{V_{\max} - R_0}$$

We have two concentration of Phenytoin resulting from two different daily dose, so we use:

$$V_{\max} = \frac{(D_1 \cdot S)\cdot(D_2 \cdot S)\cdot(C_2 - C_1)}{C_2 \cdot (D_1 \cdot S) - C_2 \cdot (D_2 \cdot S)} = \frac{D_1 \cdot D_2 \cdot S \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 350 \cdot 0.92 \cdot (20-8)}{20 \cdot 300 - 8 \cdot 350} = 362.25 mg/day$$

$$K_m = \frac{C_1(V_{\max} - D_1 \cdot S)}{D_1 \cdot S} = \frac{8 \times (362.25 - 300 \cdot 0.92)}{300 \cdot 0.92} = 2.5 mg/L$$

The daily dose will be:

$$R_0 = \frac{V_m \cdot C}{(K_m + C)\cdot S} = \frac{362.25 \times 15}{(2.5+15)\cdot 0.92} = 337.5 mg/day$$

Or there is a second way to calculate the dose.

Sodium phenytoin:

$$V_{\max} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 350 \cdot (20-8)}{20 \cdot 300 - 8 \cdot 350} = 393.75 mg/day$$

Phenytoin:

$$K_m = \frac{C_1(V_{\max} - D_1)}{D_1} = \frac{8 \times (393.75 - 300)}{300} = 2.5 mg/L$$

The daily dose will be:

$$R_0 = \frac{V_m \cdot C}{(K_m + C)} = \frac{393.75 \times 15}{(2.5+15)} = 337.5 mg/day$$

2. V.W., a 15-year-old, 32 kg male, is receiving 250 mg of valproic acid q12h for absence seizures. His steady-state trough concentration was 30 mg/L. Because of inadequate seizure control and the lack of apparent side effects, it is decided to increase the trough concentration to 55 mg/L. What dose will be required to achieve the target trough concentration of 55mg/L if the dosing interval is decreased from q12h to q8h?

Vd=0.14L/kg*32kg=4.48L

$$C\max = C\min + \frac{Dose \cdot F \cdot S}{Vd} = 30mg/L + \frac{250mg \cdot 1 \cdot 1}{4.48L} = 85.8mg/L$$

$$ke = \frac{\ln\left(\frac{Cp1}{Cp2}\right)}{t} = \frac{\ln\left(\frac{85.8mg/L}{30mg/L}\right)}{12h} = 0.088h^{-1}$$

$$Dose = \frac{Cpss \cdot Vd \cdot (1 - e^{-ke \cdot \tau})}{F \cdot S \cdot e^{-ke \cdot \tau}} = \frac{55mg/L \cdot 4.48L \cdot (1 - e^{-0.088 \cdot 8})}{1 \cdot 1 \cdot e^{-0.088 \cdot 8}} = 243mg \approx 240mg$$

3. Thirty two year old, 62.5 kg female will receive IR carbamazepine regimen.

   a. please calculate a daily oral dose to achieve average steady plasma concentration of 7mg/L for monotherapy (Please use the key parameters available in the slides).

   b. if the patient has been receiving 1.5 mg/kg Phenobarbital every 12 hours for the past 2 months. However this patient's seizures are not controlled and it was decided to start this patient on a concomitant therapy of carbamazepine. Calculate the daily maintenance dose to produce a target steady state concentration of 7mg/L using the immediate release formulation. Later the results come back from the lab and the level of carbamazepine was 10mg/L. What dose should be given to get the desired serum concentration?

   a. Carbamazepine is an anticonvulsant agent, its clearance = 0.064 L/h/kg for monotherapy

   For IR Carbamazepine, S=0.8

$$Dose = \frac{Cpss \cdot CL \cdot \tau}{F \cdot S} = \frac{(7mg/L) \cdot (0.064L/h/kg \cdot 62.5) \cdot 24h}{1 \cdot 0.8} = 840mg$$

   b.Carbamazepin clearance = 0.01 L/h/kg for polytherapy

   MD=Cpss*Cl*T/(S*F)

   =7mg/L*0.1L/hr/kg*62.5kg*24hr /(0.8*1)=1312.5mg~1300mg

   10mg/L/7mg/L=1300mg/Xmg → X=910mg~900mg

4. A patient (35 years old, 70 kg) is to be started on intravenous phenobarbital sodium. The therapeutic range is 10-30 mg/L. A loading dose is given so as to yield a Cp0 of 30 mg/L. Calculate this loading dose and the daily maintenance dose to produce an average steady state phenobarbital concentration of 20 mg/L. (Dose in phenobarbital sodium)

   Vd = (0.7L/kg)(70kg) = 49L
   CL = (4 ml/hr/kg)(70 kg) = 280 ml/hr = 6.72L/day

   phenobarbital sodium S=0.9

   The loading dose is

$$LD = \frac{Vd \cdot Cp0}{F \cdot S} = \frac{49L \cdot 30mg/L}{1 \cdot 0.9} = 1633mg \approx 1600mg$$

   To maintain an average plasma concentration of 20 mg/L

$$MD = \frac{CL \cdot Cpss \cdot \tau}{F \cdot S} = \frac{6.72L/day \cdot 20mg/L \cdot 1day}{1 \cdot 0.9} = 149.33mg \approx 150mg$$