PHA 5128 – Dose Optimization II
Case Study 3
Spring 2012

A.J., a 50 yr old male, 200 lbs in weight, had been taking 300 mg/day sodium phenytoin. Upon examination of his plasma phenytoin level, his reported concentration was only 9 mg/L. So the doctor increased his dose to 350 mg/day. The new plasma phenytoin concentration, after the dose adjustment, was 19 mg/L. Assume that both of the reported plasma phenytoin concentrations were at steady state. Compute the new daily dose of sodium phenytoin that will result in a steady state level of 15 mg/L (salt factor is 0.92).

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

We use the equations below to estimate V_{max} and K_m, since phenytoin follows non-linear pharmacokinetics.

$$V_{\max} = \frac{(D_1 \cdot S)\cdot(D_2 \cdot S)\cdot(C_2 - C_1)}{C_2 \cdot (D_1 \cdot S) - C_2 \cdot (D_2 \cdot S)} = \frac{D_1 \cdot D_2 \cdot S \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 350 \cdot 0.92 \cdot (19-9)}{19 \cdot 300 - 9 \cdot 350} = 378.82 mg/day$$

$$K_m = \frac{C_1 (V_{\max} - D_1 \cdot S)}{D_1 \cdot S} = \frac{9 \times (378.82 - 300 \cdot 0.92)}{300 \cdot 0.92} = 3.35 mg/L$$

The daily dose is

$$R_0 = \frac{V_m \cdot C}{(K_m + C)\cdot S} = \frac{378.82 \times 15}{(3.35+15)\cdot 0.92} = 336.59 mg/day$$

Alternately, one can compute using the following equations:

For sodium phenytoin,

$$V_{\max} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 350 \cdot (19-9)}{19 \cdot 300 - 9 \cdot 350} = 411.76 mg/day$$

For phenytoin,

$$K_m = \frac{C_1 (V_{\max} - D_1)}{D_1} = \frac{9 \times (411.76 - 300)}{300} = 3.35 mg/L$$

The daily dose is

$$R_0 = \frac{V_m \cdot C}{(K_m + C)} = \frac{411.76 \times 15}{(3.35+15)} = 336.59 mg/day$$

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A 48 year old female patient of 67 kg is to receive carbamazepine regimen. (a) Compute the daily oral dose (for immediate release formulation) to achieve an average steady state plasma concentration of 7.5 mg/L, assuming monotherapy (i.e. no concomitant medication). (b) This patient had received 1.5 mg/kg phenobarbital q12h for the past 12 months without any success in controlling her seizures. The medical practitioner decided to start this patient on a concomitant therapy with carbamazepine. Compute the daily maintenance dose to achieve a target steady state concentration of 7.5 mg/L using the immediate release formulation. Her blood samples after being on a maintenance regimen of carbamazepine showed a level of 10 mg/L carbamazepine. Compute the dose adjustment so that she gets to the desired plasma concentration of 7.5 mg/L.

(A) Carbamazepine CL in monotherapy is 0.064 L/h/kg

$$Dose = \frac{Cp_{ss} \times CL \times \tau}{F \times S} = \frac{7.5 mg/L \times 0.064 L/h/kg \times 67 kg}{1 \times 0.8} = 40.2 mg$$

(B) Carbamazepine CL in the presence of phenobarbital is 0.1 L/h/kg.

Maintenance dose is computed such that

$$MD = \frac{Cp_{ss} \times CL \times \tau}{S \times F} = \frac{7.5 mg/L \times 0.1 L/h/kg \times 67 kg \times 24 h}{1 \times 0.8} = 1507.5 mg \approx 1500 mg$$

Using proportionality and assuming linear pharmacokinetics,

$$\frac{10 mg/L}{7.5 mg/L} = \frac{1500 mg}{x} \Rightarrow x = 1125 mg \approx 1100 mg$$

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A 19 year old, 80 kg male patient received 200 mg valproic acid once every 12 hours to control absence seizures. His steady-state trough concentration was estimated to be 21 mg/L. Due to ineffective seizure control, his doctor decided to increase the dose such that the target trough concentration is 50 mg/L. Compute the dose required to achieve this target trough concentration based on q8h regimen.

First we compute the volume of distribution, assuming that this 19 year old patient is an adult

$$V_d = 0.14 L/kg \times 80\,kg = 11.2\,L$$

$$C_{\max} = C_{\min} + \frac{Dose \cdot F \cdot S}{V_d} = 21 + \frac{200 \cdot 1 \cdot 1}{6.4} = 52.25\,mg/L$$

$$ke = \frac{\ln\left(\frac{Cp_1}{Cp_2}\right)}{t} = \frac{\ln\left(\frac{52.25 mg/L}{21 mg/L}\right)}{12h} = 0.076 h^{-1}$$

$$Dose = \frac{Cp_{ss} \times V_d \times (1 - e^{-ke \cdot \tau})}{F \times S \times e^{-ke \cdot \tau}} = \frac{50 mg/L \times 11.2\,L \times (1 - e^{-0.076 \bullet 8})}{1 \times 1 \times e^{-0.076 \bullet 8}} = 468.58\,mg \approx 470\,mg$$

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A male patient, 35 years of age, 87 kg, is started on intravenous phenobarbital sodium. The normal therapeutic range for this medication is 10 – 30 mg/L. A loading dose was administered to achieve a Cp(t=0) of 30 mg/L. Calculate what the loading dose should be and the daily maintenance dose to produce an average steady state phenobarbital concentration of 25 mg/L. Note that the dose should be in phenobarbital sodium.

$$V_d = 0.7\,L/kg \times 87\,kg = 60.9\,L$$
$$CL = 4\,mL/h/kg \times 87\,kg = 348\,mL/h = 8.35\,L/day$$

The salt factor for phenobarbital sodium is 0.9.

The loading dose can be computed:

$$LD = \frac{V_d \times Cp(t=0) \times \tau}{F \times S} = \frac{60.9\,L \times 30\,mg/L}{1 \times 0.9} = 2030\,mg \approx 2000\,mg$$

The maintenance dose required to achieve a steady state average concentration of 25 mg/L is

$$MD = \frac{CL \times Cp_{ss}}{F \times S} = \frac{8.35\,L/day \times 25\,mg/L}{1 \times 0.9} = 231.94\,mg/day \approx 230\,mg/day$$

Note that the maintenance dose should be based on dose per day.