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).

\[
C = \frac{K_m \cdot R_0}{V_{\text{max}} - R_0}
\]

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

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

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

The daily dose will be:

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

Or there is a second way to calculate the dose.

Sodium phenytoin:

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

Phenytoin:

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

The daily dose will be:

\[
R_0 = \frac{V_m \cdot C}{(K_m + C)} = \frac{393.75 \times 15}{(2.5 + 15)} = 337.5 \text{mg/day}
\]
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 55 mg/L if the dosing interval is decreased from q12h to q8h?

\[ V_d = 0.14 \text{L/kg} \times 32 \text{kg} = 4.48 \text{L} \]

\[ C_{\text{max}} = C_{\text{min}} + \frac{Dose \cdot F \cdot S}{V_d} = 30 \text{mg/L} + \frac{250 \text{mg} \cdot 1 \cdot 1}{4.48 \text{L}} = 85.8 \text{mg/L} \]

\[ ke = \frac{\ln \left( \frac{C_p_1}{C_p_2} \right)}{t} = \frac{\ln \left( \frac{85.8 \text{mg/L}}{30 \text{mg/L}} \right)}{12 \text{h}} = 0.088 \text{h}^{-1} \]

\[ Dose = \frac{C_{\text{pss}} \cdot V_d \cdot (1 - e^{-ke \cdot \tau})}{F \cdot S \cdot e^{-ke \cdot \tau}} = \frac{55 \text{mg/L} \cdot 4.48 \text{L} \cdot (1 - e^{-0.088 \cdot 8})}{1 \cdot 1 \cdot e^{-0.088 \cdot 8}} = 243 \text{mg} \approx 240 \text{mg} \]
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. Carbamazepine clearance = 0.01 L/h/kg for polytherapy

MD = \( \frac{Cpss \cdot Cl \cdot T}{(S \cdot F)} \)

= \( \frac{7mg/L \cdot 0.1L/hr/kg \cdot 62.5kg \cdot 24hr}{(0.8 \cdot 1)} = 1312.5mg \sim 1300mg \)

10mg/L/7mg/L=1300mg/Xmg \( \Rightarrow X=910mg \sim 900mg \)
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)

\[V_d = (0.7 \text{L/kg})(70 \text{kg}) = 49 \text{L}\]
\[CL = (4 \text{ml/hr/kg})(70 \text{ kg}) = 280 \text{ ml/hr} = 6.72 \text{L/day}\]

phenobarbital sodium \(S = 0.9\)

The loading dose is

\[LD = \frac{V_d \cdot Cp0}{F \cdot S} = \frac{49 \cdot 30 \text{mg/L}}{1 \cdot 0.9} = 1633 \text{mg} \approx 1600 \text{mg}\]

To maintain an average plasma concentration of 20 mg/L

\[MD = \frac{CL \cdot C_{pss} \cdot \tau}{F \cdot S} = \frac{6.72 \text{L/day} \cdot 20 \text{mg/L} \cdot 1 \text{day}}{1 \cdot 0.9} = 149.33 \text{mg} \approx 150 \text{mg}\]