1. J. P., (35y, 70 kg, male), had been taking 300mg/day of sodium phenytoin; however, his dose was increased to 400 mg/day because his reported plasma phenytoin concentration was only 8 mg/L. Now his reported plasma phenytoin concentration is 24 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:

\[
V_{\text{max}} = \frac{(D_1 \cdot S) \cdot (D_2 \cdot S) \cdot (C_2 - C_1)}{C_2 \cdot (D_1 \cdot S) - C_2 \cdot (D_2 \cdot S)} = \frac{D_1 \cdot D_2 \cdot S \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 400 \cdot 0.92 \cdot (24 - 8)}{24 \cdot 300 - 8 \cdot 400} = 441.6 \text{ mg/day}
\]

\[
K_m = \frac{C_1 (V_{\text{max}} - D_1 \cdot S)}{D_1 \cdot S} = \frac{8 \times (441.6 - 300 \cdot 0.92)}{300 \cdot 0.92} = 4.8 \text{ mg/L}
\]

The daily dose will be:

\[
R_0 = \frac{V_m \cdot C}{(K_m + C) \cdot S} = \frac{441.6 \times 15}{(4.8 + 15) \cdot 0.92} = 363.64 \text{ mg/day}
\]

Or

Sodium phenytoin:

\[
V_{\text{max}} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 400 \cdot (24 - 8)}{24 \cdot 300 - 8 \cdot 400} = 480 \text{ mg/day}
\]

\[
K_m = \frac{C_1 (V_{\text{max}} - D_1)}{D_1} = \frac{8 \times (480 - 300)}{300} = 4.8 \text{ mg/L}
\]

The daily dose will be:

\[
R_0 = \frac{V_m \cdot C}{(K_m + C)} = \frac{480 \times 15}{(4.8 + 15)} = 363.64 \text{ mg/day}
\]
2. A 105 kg patient is to be treated p.o. with sodium phenytoin capsules. Assuming a phenytoin volume of distribution of 0.7 L/kg, $K_m$ of 4 mg/L and $V_{max}$ of 5 mg/kg/day, calculate the following:

a. Calculate an oral loading dose of sodium phenytoin to produce an initial phenytoin concentration of 15 mg/L.

b. Calculate a daily maintenance dose of sodium phenytoin to produce an average steady state phenytoin concentration of 15 mg/L.

$V_d = 0.7 \text{ L/kg} \cdot 105\text{kg} = 73.5 \text{ L}$

$K_m = 4 \text{ mg/L}$

$V_{max} = 5\text{mg/kg/day} \cdot 105\text{kg} = 525\text{mg/day}$

a. $LD = \frac{V_d \cdot C_p}{S \cdot F} = \frac{73.5L \times 15\text{ mg/L}}{0.92 \times 1} = 1198\text{mg}$ sodium phenytoin $\rightarrow$ around 1200mg

Give 400-400-400mg in 2hr interval to avoid nausea

b. The concentration at steady-state is given by

$$\overline{C}_{pss} = \frac{D \cdot S \cdot F}{Cl \cdot \tau}$$

Since phenytoin exhibits nonlinear clearance:

$$Cl = \frac{V_{max}}{K_m + \overline{C}_{pss}}$$

$$D = \frac{V_{max} \cdot \overline{C}_{pss} \cdot \tau}{(K_m + \overline{C}_{pss}) \cdot S \cdot F} = \frac{525\text{mg/day} \times 15\text{mg/L} \times 1\text{day}}{(4\text{mg/L} + 15\text{mg/L}) \times 1 \times 0.92} = 450.5\text{mg} \approx 450\text{mg}$ sodium phenytoin
3. A female patient will take Depakene Syrup (Valproic Acid) chronically. In a previous trial of a single dose of Depakene (400 mg) in this patient, it was found that an initial concentration of 48 μg/ml had been reduced to 12 μg/ml within 24 hr. Suggest a dosing regimen for chronic treatment to maintain concentration within range from 50 to 100 μg/ml.

\[
k_e = \frac{\ln(C_1 / C_2)}{\Delta t} = \frac{\ln(48/12)}{24} = 0.05776
\]

\[
\tau = \frac{\ln(C_{\text{max}} / C_{\text{min}})}{k_e} = \frac{\ln(100/50)}{0.05776} = 12h
\]

\[
Vd = \frac{Dose}{C_i} = \frac{400}{48} = 8.33L
\]

\[
CL = k_e \cdot Vd = 0.05776 \times \frac{400}{48} = 0.48L/h
\]

\[
C_{\text{max}} = \frac{Dose}{Vd \cdot (1 - e^{-k_e \tau})} \implies Dose = C_{\text{max}} \cdot Vd \cdot (1 - e^{-k_e \tau}) = 100 \times 8.33 \times (1 - e^{-0.05776^{12}}) = 416.5mg
\]

400 mg every 12 hrs (BID)
4. J.T., a 71.5 kg 65 year old male, suffers seizures, and is given phenobarbital of 2 mg/kg twice a day (BID). After one month, his seizures are not controlled and his physician decided to start a concomitant therapy of carbamazepine. Calculate the daily maintenance dose of carbamazepine to produce a target steady state concentration of 7 mg/L using the immediate release formulation. Later the results come back from the lab and the concentration of carbamazepine was 10.5mg/L. In order to achieve the desired serum concentration, what is your suggestion?

For multiple dose, the clearance of carbamazepine is 0.1L/kg/h, and salt factor is 0.8

\[
MD = \frac{C_{pss} \cdot CL \cdot \tau}{S \cdot F} = \frac{7 \text{mg/L} \times 0.1 \text{L/kg/h} \times 71.5 \times 24 \text{h}}{0.8 \times 1} = 1501.5 \text{mg} \approx 1500 \text{mg}
\]

\[
\frac{MD_1}{MD_2} = \frac{C_{pss_2}}{C_{pss_1}} \Rightarrow \frac{1500}{MD_2} = \frac{10.5}{7} \Rightarrow MD_2 = 1000 \text{mg}
\]