1. E. S., (35y, 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 10 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:

\[
V_{\text{max}} = \left(\frac{D_1 \cdot S}{C_2} \cdot (D_2 \cdot S) \cdot (C_2 - C_1)\right) = \frac{D_1 \cdot D_2 \cdot S \cdot (C_2 - C_1)}{C_2 \cdot (D_1 - C_2 \cdot D_2)} = \frac{300 \cdot 350 \cdot 0.92 \cdot (20 - 10)}{20 \cdot 300 - 10 \cdot 350} = 386.4 \text{mg/day}
\]

\[
K_m = \frac{C_1 (V_{\text{max}} - D_1 \cdot S)}{D_1 \cdot S} = \frac{10 \times (386.4 - 300 \cdot 0.92)}{300 \cdot 0.92} = 4 \text{mg/L}
\]

The daily dose will be:

\[
R_0 = \frac{V_m \cdot C}{(K_m + C) \cdot S} = \frac{386.4 \times 15}{(4 + 15) \cdot 0.92} = 331.6 \text{mg/day}
\]

Or

Sodium phenytoin:

\[
V_{\text{max}} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 350 \cdot (20 - 10)}{20 \cdot 300 - 10 \cdot 350} = 420 \text{mg/day}
\]

Phenytoin:

\[
K_m = \frac{C_1 (V_{\text{max}} - D_1)}{D_1} = \frac{10 \times (420 - 300)}{300} = 4 \text{mg/L}
\]

The daily dose will be:

\[
R_0 = \frac{V_m \cdot C}{(K_m + C)} = \frac{420 \times 15}{(4 + 15)} = 331.6 \text{mg/day}
\]
2. A 100 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 16 mg/L.

\[
V_d = 0.7 \text{ L/kg} \cdot 100 \text{ kg} = 70 \text{ L}
\]
\[
K_m = 4 \text{ mg/L}
\]
\[
V_{max} = 5 \text{ mg/kg/day} \cdot 100 \text{ kg} = 500 \text{ mg/day}
\]

\[
LD = \frac{V_d \cdot C_p}{S \cdot F} = \frac{70L \times 16 \text{ mg/L}}{0.92 \times 1} = 1217 \text{ mg sodium phenytoin} \rightarrow \text{ around 1200 mg}
\]

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

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

\[
\bar{C}_{ps} = \frac{D \cdot S \cdot F}{Cl \cdot \tau}
\]

Since phenytoin exhibits nonlinear clearance:

\[
Cl = \frac{V_m}{K_m + \bar{C}_{ps}}
\]

\[
D = \frac{V_m \cdot \bar{C}_{ps} \cdot \tau}{(K_m + \bar{C}_{ps}) \cdot S \cdot F} = \frac{500 \text{ mg/day} \times 15 \text{ mg/L} \times 1 \text{ day}}{(4 \text{ mg/L} + 15 \text{ mg/L}) \times 1 \times 0.92} \approx 429 \text{ mg} \approx 430 \text{ mg sodium phenytoin}
\]
3. A female patient will take Depakene Syrup (Valproic Acid) chronically. In a previous trial of a single dose of Depakene (500 mg) in this patient, it was found that an initial concentration of 48 µg/ml had been reduced to 14 µg/ml within 24hr. Suggest a dosing regimen for chronic treatment to maintain concentration within range from 50 to 100 µg/ml.

\[
k_e = \frac{\ln(C_1 / C_2)}{\Delta t} = \frac{\ln(48/14)}{24 \text{hr}} = 0.051(1/\text{hr})
\]

\[
\tau = \frac{\ln(C_{\text{max}} / C_{\text{min}})}{k_e} = \frac{\ln(100/50)}{0.051(1/\text{hr})} = 13.6(\text{hr}) \sim 12(\text{hr})
\]

\[
V_d = \frac{\text{Dose}}{C_1} = \frac{500}{48} = 10.4(L)
\]

\[
CL = k_e \cdot V_d = 0.051 \cdot 10.4 = 0.53(L/\text{hr})
\]

\[
C_{\text{max}} = \frac{\text{Dose}}{V_d} \frac{1}{(1-e^{-k_e \tau})} \quad \rightarrow \quad \text{Dose} = C_{\text{max}} \cdot V_d \cdot (1-e^{-k_e \tau}) = 100 \cdot 10.4 \cdot (1-e^{-0.05112}) = 476(mg)
\]

\sim 500 \text{ 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 8.75mg/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

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

\[
\frac{MD_1}{MD_2} = \frac{C_{ps,2}}{C_{ps,1}} > \frac{1500}{MD_2} \Rightarrow \frac{8.75 \text{ mg/L}}{7 \text{ mg/L}} > \Rightarrow MD_2 = 1200 \text{ mg}
\]