1. An elderly patient, 75 kg male, was received sodium phenobarbital at 100 mg twice a day (rapidly absorbed). After a month, a morning blood sample was taken before dosing, and the phenobarbital plasma concentration was reported to be 28 mg/L. What would be the predicted concentration at that time? (Assume all the pharmacokinetic parameters are population values in the slide)

**Answer:**

Half-life of Phenobarbital is around 120 hrs for adults; therefore, after a month, steady-state has been achieved.

\[
K_e = \frac{C_l}{V_d} = \frac{0.004}{0.7} \text{ for adults}
\]

\[
C_{min,ss} = \frac{Dose \cdot S \cdot F}{V_d} \cdot \frac{e^{-k \tau}}{1 - e^{-k \tau}} = \frac{100 \text{mg} \cdot 1 \cdot 0.9 \cdot e^{-0.004/0.7 \cdot 12}}{0.7 \text{L/kg} \cdot 75 \text{kg} \cdot (1 - e^{-0.004/0.7 \cdot 12})} = 24.3 (\text{mg/L})
\]
2. B.J, a 10 year old boy (35kg), suffers seizures, and is given valporic acid spinkles 250mg three times a day. Calculate the fluctuation of valporic acid at steady state. Assume rapid absorption. The trough concentration was 38.0 mg/L. Please calculate a new dosing regimen in order to achieve target concentration between 40 mg/L and 80 mg/L.

**Answer:**

Calculate $C_{\text{max}}$ from the measured trough concentration:

$$C_{\text{max}} = \frac{\text{Dose}}{V_d} + C_{\text{min}} = \frac{250\text{mg}}{0.14L/kg \cdot 35kg} + 38\text{mg} / \text{L} = 89.02(\text{mg} / \text{L})$$

$$F = \frac{C_{\text{max}}}{C_{\text{min}}} = \frac{89.02}{38} = 2.3$$

$$k_e = \frac{\ln(C_{\text{max}} / C_{\text{min}})}{\tau} = \frac{\ln(89.02 / 38)}{8\text{hr}} = 0.106(1/\text{hr})$$

$$\tau = \frac{\ln(C_{\text{max}} / C_{\text{min}})}{k_e} = \frac{\ln(80 / 40)}{0.106(1/\text{hr})} = 6.5(\text{hr}) \sim 6(\text{hr})$$

$$C_{\text{max\_target}} = \frac{\text{Dose}}{V_d} \cdot \frac{1}{(1 - e^{-k_e \tau})} \quad \rightarrow \quad \text{Dose} = C_{\text{max\_target}} \cdot V_d \cdot (1 - e^{-k_e \tau}) = 80 \cdot 0.14 \cdot 35 \cdot (1 - e^{-0.106 \cdot 6}) = 184(\text{mg})$$

Dose Regimen:

~200 mg every 6 hrs (QID)
3. S.A. a 35 year-old, 75 kg female, had been taking 300 mg of sodium phenytoin daily. Due to the low plasma concentration of phenytoin (7 mg/L) and poorly controlled seizures, her dose was increased to 400 mg/day. After a couple of weeks, she experienced CNS side effects, and another blood sample was taken. Plasma phenytoin concentration is 23 mg/L. (Assume that both of the reported plasma concentrations represent steady-state levels.)

A: Calculate a new daily dose of phenytoin that will result in a steady-state level of about 15 mg/L.

Answer:

\[ V_{\text{max}} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_1 \cdot D_2} = \frac{300 \cdot 400 \cdot (23 - 7)}{23 \cdot 300 - 7 \cdot 400} = 468 \text{ (mg) (Sodium Phenytoin)} \]

\[ \rightarrow 430 \text{ (mg) (Phenytoin)} \]

\[ C = \frac{K_m \cdot D}{V_{\text{max}} - D} \rightarrow K_m = \frac{C \cdot (V_{\text{max}} - D)}{D} = \frac{23 \cdot (468 - 400)}{400} = 3.91 \text{ (mg / L)} \]

\[ D = \frac{V_{\text{max}} \cdot C}{K_m + C} = \frac{468 \cdot 15}{3.91 + 15} = 371 \text{ (mg) -375 mg (Sodium Phenytoin)} \]

B: Estimate the phenytoin volume of distribution, and clearance after new dose regimen.

Answer:

\[ V_d = 0.65 (L/kg) \cdot 75 \text{ (kg)} = 48.75 \text{ (L)} \]

\[ CL = \frac{V_{\text{max}}}{K_m + C} = \frac{430}{3.91 + 15} = 22.7 \text{ (L)} \]
4. A clinical study was conducted to assess the effect of carbamazepine on the pharmacokinetics of drug X after a single oral dose. The mean drug X concentration-time profile is shown in the Figure. It is known that drug X is metabolized mainly by CYP3A4.

**Describe the graph and make a conclusion.**

![Drug X concentration-time profile](image)

**Answer:**

1) The peak plasma concentrations of Drug X without carbamazepine coadministration are higher than that with carbamazepine coadministration.

2) Conclusion: Carbamazepine is a potent inducer of CYP3A4 which influenced the concentrations of Drug X significantly. This study provided an in vivo evidence of involvement of CYP3A4 in the metabolism of Drug X.