

Very Brief Notes on

The Clinical Pharmacokinetics of

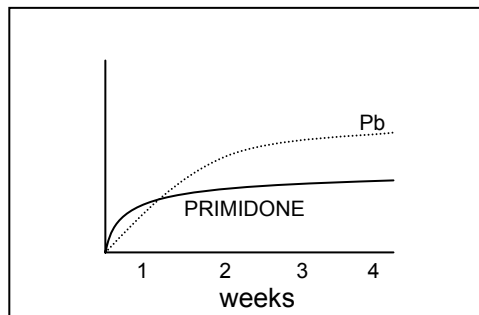
PRIMIDONE

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PRIMIDONE

- Generalized Complex partial seizures.
 - Primidone metabolism Phenobarbital (approx. $\frac{1}{5}$ converted) ^{20%} to pb
 - Available: 50 and 250 mg Tablets
250mg/5ml suspension
 - Daily dose: 10-20 mg/kg adults
15-30 mg/kg children
 - C_p (therapeutic) = 5-12 mg/L
if \uparrow 15 mg/L \rightarrow side effects
 - $F = 1.0$, $S = 1.0$
 - $V_d = 0.6$ L/kg
 - $CL_T = 0.06$ L/kg/hr
 - $CL_R = 0.015$ L/kg/hr
 - CL (To Pb) = 0.012 L/kg/hr
 - $t_{1/2} \approx 8$ hr
- } 20% metabolized
25% excreted unchanged
- $\therefore \tau = 6 - 12$ hr

- several weeks



Question #1:

Pt. (56 kg), D = 250 mg \square 6 hr for 3 months.
Calculate trough conc. of primidone.

Solution:

$$CL = 0.06 \text{ L/kg/hr} \times 65 \text{ kg} = 3.9 \text{ L/hr}$$

$$V_d = 0.6 \text{ L/kg} \times 65 \text{ kg} = 39 \text{ L}$$

$$\therefore k_d = \frac{CL}{V_d} = \frac{3.9 \text{ L/hr}}{39 \text{ L}} = 0.1 \text{ hr}^{-1}$$

$$\therefore t_{1/2} = \frac{0.693}{k_d} = \frac{0.693}{0.1} = 6.93 \text{ hr}$$

$$\tau = 6 \text{ hr}$$

$$\begin{aligned} \text{(Trough Level)} = C_{ss}^{\min} &= \frac{S.F.D}{V_d(1 - e^{-k_d\tau})} \cdot e^{-k_d\tau} \\ &= \frac{(1)(1)(250)}{39(1 - e^{-5.1 \times 6})} \cdot e^{-5.1 \times 6} = 7.8 \text{ mg/L} \approx 8 \text{ mg/L} \end{aligned}$$

Question #2

What would be \bar{C}_{ss} ?

$$\bar{C}_{ss} = \frac{(S)(F)(D/\tau)}{CL} = \frac{(1)(1)(250/6)}{3.9} = 10.7 \text{ mg/L}$$

- Calculate the rate at which primidone is converted to Pb?

$$CL = 0.012 \times 65 \text{ kg} = 0.78 \text{ L/hr} \quad \boxed{} \rightarrow$$

$$\begin{aligned} \text{Rate} = R_A &= CL \cdot \bar{C}_{ss} \\ &= 0.78 \text{ L/hr} \times 10.7 \text{ mg/L} = 8.3 \text{ mg/hr} \\ &\approx 200 \text{ mg daily} \\ &\quad (8.3 \times 24) \end{aligned}$$

- What is the expected \bar{C}_{ss} for Pb as a result of administration of primidone?

$$\begin{aligned} CL_{Pb} &= 0.1 \text{ L/kg/day} \times 65 \text{ kg} = 6.5 \text{ L/day} \\ \bar{C}_{ss} &= \frac{S.F \cdot (D/\tau)}{CL} = \frac{200 \text{ mg/day}}{6.5 \text{ L/day}} = 31 \text{ mg/L} \end{aligned}$$

Which is 3 times the expected average primidone level, and 4 times the trough level of primidone.