



1.11. Phenytoin/Fosphenytoin

Pharmacokinetic Parameters

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Table 1.11-1. Volume of Distribution

Age	Volume (Mean ± SD)
Neonates and infants (<1 year)	1 ± 0.3 L/kg
Children (≥1 year), adults, and geriatrics ^a	0.65 ± 0.2 L/kg

^aThe geriatric population is more likely to have decreased serum albumin and therefore a larger apparent volume of distribution. The altered binding that results in a larger volume of distribution will be offset by a lower observed total phenytoin concentration and, therefore, no change in the usual loading dose is required.

Since phenytoin is a relatively lipid-soluble drug, obese patients have a larger volume of distribution (in liters) equal to:

$$V_{(\text{obese in L})} = 0.65 \frac{\text{L}}{\text{kg}} [(\text{IBW}) + 1.33(\text{ABW} - \text{IBW})]$$

where ABW is actual body weight in kg and IBW is ideal body weight in kg.

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Table 1.11-2. Reported Values of V_{max} and K_m

Age	K_m (Mean ± SD)	V_{max} (Mean ± SD) ^a
Children		
6 months – < 4 years	6.6 ± 4.2 mg/L	14 ± 4.2 mg/kg/day
4 – < 7 years	6.8 ± 3.5 mg/L	10.9 ± 3.0 mg/kg/day
7 – < 10 years	6.5 ± 3.0 mg/L	10.1 ± 2.6 mg/kg/day
Adolescents (10 – 16 years) ^b	5.7 ± 2.7 mg/L	8.3 ± 2.8 mg/kg/day
Adults (18 – ≤ 59 years)	4.3 ± 3.5 mg/L	7.0 ± 3.0 mg/kg/day
Geriatrics (> 59 years) ^c	5.8 ± 2.3 mg/L	7.0 ± 3.0 mg/kg/day

^aFor obese patients, the maximum velocity of drug elimination (V_{max}) for phenytoin probably should be based on ideal body weight (IBW).

^bData unavailable for the 17-year-old.

^cThe limited data available suggest that K_m and V_{max} are similar to adults.

Key Equations

- For low albumin and creatinine clearance greater than 25 mL/min:

$$C_{\text{normal binding}} = \frac{C_{\text{reported}}}{\left[(0.9) \left(\frac{\text{albumin}}{4.4} \right) \right] + 0.1}$$

- The following equation can be used to estimate the time necessary to achieve 90% of the steady state concentration:

$$t_{90\%} = \left\{ \frac{(K_m)(V)}{\left[V_{\text{max}} - \left(\frac{(S)(F)(D)}{\tau} \right) \right]^2} \right\} \left[(2.3 \times V_{\text{max}}) - (0.9) \left(\frac{(S)(F)(D)}{\tau} \right) \right]$$

where the following units apply:

V in L,

K_m in mg/L,

V_{max} in mg/day,

and dose/ τ in mg/day.

The accuracy of this equation and the calculated time to steady state depends on the values used for V_{max} , K_m , and V.

- The time required for a phenytoin concentration to decline from an initial concentration (C_i) to a lower concentration (C) may be estimated by the following equation, which assumes that no absorption occurs in the time between C_i and C:

$$t = \frac{\left[(K_m) \left(\ln \left(\frac{C_i}{C} \right) \right) \right] + (C_i - C)}{\left(\frac{V_{\text{max}}}{V} \right)}$$

where the following units apply:

K_m , C, and C_i in mg/L;

V_{max} in mg/day;

V in L; and

t in days.

Self-Assessment Problems

- A 70-kg, 5'9", 25-year-old male is admitted after a motor vehicle accident. After open head surgery, he develops tonic-clonic seizure activity. His albumin is normal (4.4 g/dL or 44 g/L).

A. Determine a maintenance dose (mg every 12 hours) of fosphenytoin for this patient to achieve a predicted concentration ($C_{\text{ss}_{\text{avg}}}$) of between 12 and 18 mg/L. Use a dose that can then be converted to phenytoin capsules once he is able to manage oral intake.

B. Determine a loading dose (mg) of fosphenytoin to achieve the concentration predicted for the maintenance dose.

- A 75-year-old, 80-kg, male patient has been receiving phenytoin sodium capsules at a rate of 500 mg/day. His laboratory tests on admission reveal a serum creatinine of 1 mg/dL and an albumin of 2.8 g/dL. He has been admitted to rule out phenytoin toxicity due to severe ataxia, nystagmus, and diplopia. A phenytoin concentration on admission is 16 mg/L.

A. Predict the concentration that might be expected if he had a normal serum albumin.

B. Does the result from Part A potentially explain his apparent phenytoin toxicity?

- Determine an IV loading dose (in mg) of fosphenytoin for a desired post-load concentration of 18 mg/L to be given to a 30-year-old, 75-kg female patient who is 5'2" tall.
- A 7-month-old, 8-kg child is admitted with seizures. You are asked to determine loading and maintenance doses of phenytoin (IV for load and suspension for maintenance) to produce concentrations of 15 mg/L for post-load and $C_{\text{ss}_{\text{avg}}}$.
 - Determine the loading dose (in mg).
 - Determine the maintenance dose to be given every 12 hours (in mg).