Phenytoin Pharmacokinetics & Dosing Guide

Basic Phenytoin Pharmacokinetics

Phenytoin is primarily eliminated by hepatic metabolism (>95%) via CYP2C9 with only ~ 5% recovered in the urine as unchanged drug. Phenytoin follows Michaelis-Menten or saturable pharmacokinetics. This is the type of non-linear PK that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug. When this occurs, steady state drug concentrations increase in a disproportionate manner after a dosage increase. In this case the rate of drug removal is described by the Michaelis-Menten relationship that is used for all enzyme systems: Rate of metabolism = (Vmax **X** C)/(Km **+** C), where Vmax = maximum rate of metabolism in mg/d; C = phenytoin concentration in mg/L; Km = substrate concentration in mg/L;. The clinical implication of this PK relationship is that the clearance of phenytoin is not a constant as it is with linear PK, but is concentration or dose dependent. As the dose or concentration of phenytoin increases, the clearance (Cl) decreases at the enzyme approaches saturable conditions. This is the reason concentrations increase disproportionately after a phenytoin dosage increase. As steady state serum concentrations go up the clearance decreases [Cl = Vmax/(km + C)]. Due to this relationship, the t ½ and time to steady state is longer as the dose or concentration is increased for phenytoin.

↓Cl = Vmax/(km + ↑C)

Average PK population values: (much inter-patient variability exists for phenytoin):
Vmax = 500 mg/d (range of 100-1000 mg/d)
Km = 4 mg/L (range of 1-15 mg/L)
Vd = 0.7 L/kg (unaffected by saturable metabolism)

Phenytoin Serum Levels

The usual therapeutic range for total (unbound + bound) phenytoin serum concentrations when the drug is used in the treatment of seizures is 10-20 u/ml. Since phenytoin is highly bound (~90%) to albumin, it is important to take into consideration the patient's albumin level when interpreting total phenytoin levels. In the presence of hypoalbuminemia, a "corrected" phenytoin level should be calculated since the presence of a low albumin may have resulted in a higher than expected percent of unbound phenytoin.

"Corrected" Phenytoin Levels
Corrected concentration = Measured Concentration / [(0.2 x serum albumin) + 0.1] → non ESRD patients
Corrected concentration = Measured Concentration / [(0.1 x serum albumin) + 0.1] → ESRD patients

When to Check Levels
Levels should be checked upon admission (if admitted on phenytoin) to gauge compliance/efficacy and approximately 1 week following a dose adjustment.

Loading Dose Calculation:

mg/kg LD calculation (most commonly used method for determining LD):
15-20 mg/kg (usual dose ~ 1000 mg depending on patient weight)

Pharmacokinetic LD calculation (less commonly used method for determing LD):

$$LD = \frac{Vd \textbf{ X } Css}{S} = \frac{(0.7 \times kg)\ Css}{S}$$

Css = desired steady state concentration
Vd = Phenytoin volume of distribution (0.7 L/kg)
S = fraction of the phenytoin salt form that is active
(0.92 for IV phenytoin, fosphenytoin, capsules; 1 for tablets and suspension)

Maintenance Dose Calculation:

$$MD = \frac{Vmax \textbf{ X } Css}{S(Km + Css)}$$

Vmax = maximum rate of metabolism in milligrams (use 7 mg/kg/day)
Km = substrate concentration in mg/L (use 4 mg/L)
Css = desired steady state concentration

Usual Dosing Intervals

Oral formulations – total maintenance dose usually divided twice daily
IV formulation (fosphenytoin, IV phenytoin) – total maintenance dose divided three times daily

Use of Phenytoin Serum Concnetrations to Alter Doses (*Graves-Cloyd Method)*

$$D_{new} = (D_{old} / Css_{old}) \times Css_{new}^{0.199} \times Css_{old}^{0.804}$$

This dosage adjustment method uses a steady state phenytoin concentration to compute the patient's own phenytoin clearance rate at the dosage being given, then uses the measured concentration and desired concentration to estimate a new dose for the patient.

D_{new} = New Calculated daily dose in milligrams
D_{old} = Daily dose that resulted in current steady state level in milligrams
Css_{old} = Current steady state concentration
Css_{new} = Desired steady state concentration