PHENYTOIN

DRUGDEX® Evaluations

**DOSING INFORMATION**

**Adult Dosage**

**Normal Dosage**

**Important Note**

Due to the risk of severe hypotension and cardiac arrhythmias, the rate of IV phenytoin administration should not exceed 50 mg/min in adult patients and 1 to 3 mg/kg/min (or 50 mg/min, whichever is slower) in pediatric patients [94][95]

**Phenytoin Intramuscular route**

a) Intramuscular (IM) administration is not generally recommended because of slow and erratic absorption and painful local reactions. If no other route is available, intramuscular doses 50% greater than oral doses will prevent a fall in plasma concentrations [62]

Intramuscular administration should not be used for the treatment of status epilepticus (Prod Info Phenytoin Sodium Injection, USP, 2002). When returned to oral administration, the dose should be reduced by 50% of the original oral dose (one-third of the IM dose) for 1 week to prevent excessive plasma levels due to sustained release of phenytoin from IM sites. If the patient requires more than a week of phenytoin IM, alternative routes should be explored, such as gastric intubation.

b) Seven patients receiving intramuscular phenytoin were noted to have 25 to 50% lower plasma phenytoin levels within 48 to 72 hours after starting intramuscular phenytoin [63]

With the resumption of oral administration of the drug, and plasma levels increased 25 to 100% of the intramuscular levels within 3 to 5 days. The authors postulated that crystallization at the intramuscular injection site of phenytoin with subsequent slow drug release was the mechanism for both initial reduction and later elevation of phenytoin levels. Eleven children received intramuscular doses of 3 to 6 milligrams/kilogram every 6 hours for 8 doses which did not approach even the minimally effective concentration of phenytoin of about 10 micrograms/milliliter [64]

With change to oral administration of the phenytoin the serum levels were noted to be more than tripled those for intramuscular.
Intravenous route

Pre-eclampsia - Seizure

1) Phenytoin 1 gram administered intravenously over one hour, followed by 500 mg orally 10 hours after the initial treatment, was found to provide therapeutic levels in the majority of women with preeclampsia [55]. Only in two patients, weighing greater than 250 pounds, did this regimen provide subtherapeutic levels. The study concluded that a single dosage scheme can be administered to the majority of patients and that routine serum level monitoring is unnecessary.

Oral route

Seizure, During and following neurosurgery; Treatment and Prophylaxis

1) Chewable Tablets (Infatab(R))

a) Adults without previous treatment may be started on 100 milligrams (mg) (2 tablets) 3 times daily and dose should be adjusted to individual needs. The usual maintenance dose is 300 to 400 mg/day. An increased to 600 mg/day (12 tablets) may be made if necessary [39]

Seizure, Generalized Tonic-Clonic and Complex Partial (psychomotor and temporal lobe) Seizures

1) General Information

a) In epilepsy, dosage should be individualized to achieve maximal benefit, including serum level monitoring (optimal control of seizures without clinical signs of toxicity occurs most often with serum levels between 10 to 20 micrograms/milliliter). A period of 7 to 10 days is required to achieve steady-state blood levels; dose adjustments should not be instituted at intervals shorter than 7 to 10 days [28]

b) Guidelines for dosing adjustments based on phenytoin plasma concentrations have been proposed for adults with epilepsy without clinically significant renal or hepatic disease: for plasma phenytoin concentrations less than 7 micrograms/milliliter, a dosage increase of 100 milligrams/day is recommended; for plasma concentrations between 7 and 12 micrograms/milliliter, the dose may be increased by 50 milligrams/day; if the plasma concentration is greater than 12 micrograms/milliliter, the dose may increased by 30 milligrams/day [32].

Dosage increases when the plasma level is above 16 micrograms/milliliter should only be done with caution as even a small increase may result in toxicity. These
recommendations resulted in therapeutic concentrations in the majority of patients followed.

**c**) Since phenytoin is metabolized in the liver by a saturable enzyme system, serum concentrations are not related linearly to the daily dose and small increases in the dose may produce substantial increases in serum levels, even when the levels are in the therapeutic range, after saturation of metabolizing enzymes occur [33]

2) Chewable Tablets

**a**) Patients who have not received previous treatment may be started on 100 milligrams (2 tablets) orally 3 times daily. The dose should be adjusted to individual patient needs. The usual maintenance dose 300 to 400 mg/day. An increase to 600 mg/day (12 tablets) may be made if necessary [27]

3) Oral Suspension

**a**) For the suspension, the recommended dosage for the treatment of seizures in patients with no previous treatment is 1 teaspoonful or 5 milliliters (125 milligrams) 3 times daily. It is then individualized to the patient. An increase to 5 teaspoonfuls (625 milligrams) divided into 3 doses may be made [26]

**Rectal route**

**a**) Therapeutic serum concentrations of phenytoin have not been achieved by rectal administration in humans. Twenty patients received rectal phenytoin suppositories twice daily at doses escalating from 300 milligrams (mg) to 1200 mg per day over a 10-day period. Even at the highest doses, serum phenytoin concentrations did not exceed 6 to 8 micrograms per milliliter [65]

**b**) Injectable phenytoin solution has been administered rectally to healthy volunteers [66] Volunteers were given 7 milligrams/kilogram rectally. They were required to stay supine for 30 minutes and retain the solution for 1 hour. Absorption began within 30 minutes and bioavailability was 24.4%. Four out of 5 volunteers preferred this route over an intravenous injection.

**c**) Rectally administered phenytoin has not been successful in maintaining appropriate therapeutic levels in patients with seizure activity [67][68] Further studies including more patients and a greater variety of rectal formulations are recommended.
WITHDRAWAL SCHEDULE

a) Summary

1) Risk factors associated with the withdrawal of anticonvulsant therapy in adults have been studied by numerous researchers (Juul-Jensen, 1958) [56][57][58][59][60][61](Calloghan et al, 1988). Seizure type, length of seizure-free period, severity of seizure, and electroencephalogram (EEG) findings have all been related to frequency of seizure recurrence. The successful withdrawal of therapy with the possibility of reversing or eliminating adverse effects must be weighted against the potential harmful effects of an unexpected seizure. Medication should be withdrawn gradually over a period of at least 3 months since sudden withdrawal may precipitate seizures.

Equivalent Doses

a) Dilantin(R) Kapseals(R) are formulated with the phenytoin sodium salt while the Dilantin-125(R) suspension and Infatabs(R) are formulated from the free acid form. The free acid form has an approximately 8% increase in drug content over the sodium salt. When switching from one product to another dosage adjustments and serum level monitoring may be necessary.

Phenytoin Sodium

Intramuscular route

Seizure, During neurosurgery; Treatment and Prophylaxis

1) For prophylaxis of seizures during neurosurgical procedures, 100 to 200 milligrams (2 to 4 milliliters) intramuscularly (IM) is indicated at approximately 4-hour intervals during surgery and continued during the postoperative period [95]

Intravenous route

Seizure, During neurosurgery; Treatment and Prophylaxis

1) Nonemergent loading and maintenance dose

a) Patients who have not received treatment previously may receive injectable phenytoin sodium solution as a nonemergent loading dose of 10 to 15 mg/kg IV loading dose at a rate not exceeding 50 mg/min, although slower administration rates are recommended to minimize potential cardiovascular reactions. The loading dose should be followed by maintenance doses of oral or IV phenytoin every 6 to 8 hours [94]

2) Substitution for oral phenytoin

a) When use of oral phenytoin is not possible, IV phenytoin sodium may be substituted at the same total
daily dose, administered at a rate not to exceed 50 mg/min. Due to differences in bioavailability, plasma phenytoin concentrations may increase when IV phenytoin is substituted for oral phenytoin therapy [94]

**Status epilepticus**

1) For the treatment of status epilepticus, the manufacturer recommends a loading dose of 10 to 15 milligrams/kilogram (mg/kg) administered slowly intravenously at a rate not exceeding 50 mg/minute. The loading dose should be followed by maintenance doses of 100 mg orally or intravenously every 6 to 8 hours. Determination of phenytoin plasma levels is recommended in the subsequent establishment of maintenance dosing [94][95]

2) One author recommends a loading dose of phenytoin for the treatment of status epilepticus of 20 milligrams/kilogram (mg/kg), intravenously at a maximal rate of 50 mg/minute [96]
As much as 30 mg/kg may be required in some patients. Other sources have used an initial loading dose of 18 mg/kg [97]

**Oral route**

**Seizure, During neurosurgery; Treatment and Prophylaxis**

1) Patients who have not received treatment previously may be started on the extended-release capsules at a dose of 100 milligrams (mg) orally 3 times daily with adjustments based on individual requirements. Most adults will be satisfactorily maintained on 100 mg 3 to 4 times daily. If necessary, the dose may be increased to 200 mg 3 times daily. For patients established on 100 mg 3 times a day, therapy may be switched to once daily dosing using one 300 mg extended-release capsule [28]

2) Some authorities recommended use of oral loading doses of phenytoin in patients who require rapid steady-state serum levels but intravenous administration is not desirable. In this case, oral loading doses should be reserved for patients in a clinic or hospital setting where serum levels can be closely monitored. Oral loading regimens should not be administered to patients with a history or renal or liver disease. The recommended loading dose regimen is 1 gram divided into 3 doses (400 milligram (mg), 300 mg, 300 mg) administered every 2 hours. Normal maintenance dose should then begin 24 hours after the loading dose with frequent serum level determinations [28]
Seizure, Generalized Tonic-Clonic and Complex Partial (psychomotor and temporal lobe) Seizures

1) In patients receiving no previous therapy, recommended initial doses are 100 milligrams orally 3 times daily; for most adults, satisfactory maintenance doses are 100 milligrams 3 times daily to 4 times daily, but doses of 200 milligrams 3 times daily may be required [28]

2) If seizure control is satisfactory on a divided dose regimen of three 100 milligrams Dilantin Kapseals(R) daily, once-a-day dosing with Dilantin Kapseals(R), 300 milligrams/day, may be considered. Close serum level monitoring is indicated when changing from prompt to extended, or vice versa [28]

3) Loading doses may be utilized to rapidly achieve therapeutic phenytoin levels. This regimen should be reserved for patients in a clinic or hospital setting where phenytoin serum levels can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading regimen. The manufacturer recommends 1 gram divided into 3 doses (400 milligrams, 300 milligrams, and 300 milligrams) administered at two-hourly intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum level determinations [28]

Dosage in Renal Failure

A) Summary: No specific dose adjustment is necessary [74] However, serum phenytoin protein binding is altered in uremia which can affect proper interpretation/evaluation of serum phenytoin concentrations [75][76][77]

The fraction of unbound phenytoin increases as renal function decreased, partially due to decreases in serum albumin [78]

In patients with renal disease, the following equation has been used to relate the measured, or observed, phenytoin concentration to the phenytoin concentration one would expect to measure if there was normal protein binding [79]

\[ C(\text{observed}) = \frac{C(\text{normal})}{0.1 \times \text{albumin} + 0.1} \]

\[ C(\text{normal}) = \text{normal serum phenytoin concentration in nonuremic patients} \]
\[ C(\text{observed}) = \text{observed serum phenytoin concentration in uremic patients} \]
Dosage in Hepatic Insufficiency
A) Phenytoin is primarily metabolized in the liver and patients with hepatic disease may show early signs of toxicity [80]

Dosage in Geriatric Patients
A) Phenytoin

1) Dosage reduction may be required in elderly patients with hypoalbuminemia or renal disease since these patients have been reported to have an increased incidence of neurologic and hematologic toxicity [81][77][82][83][84][85]

In elderly nursing home patients and critically ill trauma patients with hypoalbuminemia, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [86]

\[
\frac{C \text{ (observed)}}{C \text{ (normal)}} = \frac{0.25 \times \text{albumin} + 0.1}{C \text{ (normal)}}
\]

\(C \text{ (normal)} = \text{normal serum phenytoin concentration in non-hypoalbuminemic patients}\)
\(C \text{ (observed)} = \text{observed serum phenytoin concentration in hypoalbuminemic patients}\)

2) The pharmacokinetics of phenytoin in geriatric epileptic patients was evaluated [87]
Their data indicate that in patients 60 to 79 years of age, 21% less phenytoin daily is required to maintain steady-state serum levels of 15 mcg/mL than in patients 20 to 40 years of age. The Michaelis-Menten parameter Vmax declined with age, while the Km appeared to be unaffected. They suggest a reasonable initial dose in elderly patients of 3 milligrams/kilogram/day (approximately 200 milligrams daily) with further doses based on serum concentrations and clinical response.

B) Phenytoin Sodium

1) Lower doses or less frequent dosing may be necessary in elderly patients due to reduced phenytoin clearance [94]

Dosage Adjustment During Dialysis
A) Hemodialysis

1) No dosage supplementation is required in patients following hemodialysis or peritoneal dialysis [74]

B) Hemofiltration

1) No dosage supplementation is required in patients undergoing continuous arteriovenous hemofiltration [74]
2) However, phenytoin removal was studied in two patients on continuous arteriovenous hemofiltration and was found to be removed proportionate to the amount of free phenytoin present in the serum. Additionally, when the ultrafiltration flow rate was high, a clinically significant amount of the drug may be removed. Thus, in patients with renal failure in whom the amount of free phenytoin may be increased, continuous arteriovenous hemofiltration at a high ultrafiltration rate may remove a clinically significant amount of the drug. Free and total serum phenytoin levels should be measured; higher daily doses may be needed [88]

**Dosage in Other Disease States**

**A) Phenytoin**

1) Hypoalbuminemia

a) Creatinine Clearance 10 milliliters/minute or greater:

In patients with hypoalbuminemia and a creatinine clearance of 10 milliliters/minute or greater, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [86][79]

\[
\frac{C_{\text{observed}}}{C_{\text{normal}}} = \frac{0.2 \times \text{albumin} + 0.1}{0.2 \times \text{albumin} + 0.1}
\]

C (normal) = normal serum phenytoin concentration in non-hypoalbuminemic patients
C (observed) = observed serum phenytoin concentration in hypoalbuminemic patients

b) Creatinine Clearance less than 10 milliliters/minute:

In patients with hypoalbuminemia and a creatinine clearance of less than 10 milliliters/minute, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [86][79]

\[
\frac{C_{\text{observed}}}{C_{\text{normal}}} = \frac{0.1 \times \text{albumin} + 0.1}{0.1 \times \text{albumin} + 0.1}
\]

C (normal) = normal serum phenytoin concentration in non-hypoalbuminemic patients
C (observed) = observed serum phenytoin concentration in hypoalbuminemic patients

2) Pregnancy

a) The increase in doses required for phenytoin in pregnancy are reportedly related to an increase in metabolic clearance of the drug [89]
b) Progressive decreases in maternal serum phenytoin concentrations occur during pregnancy, with concentrations decreasing greatest towards the end of pregnancy and being lowest at delivery [90]. Approximately 50% of patients required dosing increases of phenytoin to maintain seizure control (average increase 50 milligrams daily). Following delivery, phenytoin concentrations increased dramatically. It appears that phenytoin requirements are greater during pregnancy, requiring increases in doses in some patients; following delivery, the dose should be decreased to avoid the occurrence of toxicity.

3) Obesity

a) The volume of distribution of phenytoin increases with the degree of obesity, and obese individuals will require larger absolute loading doses of phenytoin to achieve therapeutic serum levels rapidly. Distribution of phenytoin into excess body weight (total body weight (TBW) minus ideal body weight (IBW)) is greater than the distribution into ideal body weight by a factor of 1.33. Loading doses may be calculated based on the following equation for volume of distribution (Vd): Vd of phenytoin = assumed Vd in liters/kilogram (kg) x weight in kg; where kg = IBW + 1.33 (TBW - IBW) [91]

4) Trauma Patients

In critically ill trauma patients and elderly nursing home patients with hypoalbuminemia, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [86]

\[
\frac{C \text{ (observed)}}{0.25 \times \text{albumin} + 0.1} = C \text{ (normal)}
\]

C (normal) = normal serum phenytoin concentration in non-hypoalbuminemic patients
C (observed) = observed serum phenytoin concentration in hypoalbuminemic patients

a) An increase in phenytoin metabolism in trauma patients may be explained by a combination of an initial elevation and subsequent fall in cytokine concentration, specifically interleukin-6 (IL-6), plus the administration of high-protein nutrition [92]. Nine patients with severe head injury were given loading doses of phenytoin along with daily maintenance doses. Labs revealed that IL-6 concentration was significantly elevated after the neurotrauma (days 2 to 4) and then fell. The maximum concentration of IL-6 was inversely correlated with a slower rate of phenytoin metabolism. At this time due to a low albumin, the trauma patients were also aggressively receiving protein supplementation (protein induces cytochrome P-450). Both the decrease in IL-6 and the protein supplementation were hypothesized to produce increases in the rate of phenytoin metabolism. A controlled trial should be used to validate these findings.
b) An apparent increase in the clearance of phenytoin occurred in critically ill trauma patients receiving the drug for prophylaxis or treatment of seizures [93]. It is recommended that, in these patients, maintenance of phenytoin plasma levels in the range of 10 to 20 milligrams/milliliter will require incremental increases in the maintenance dose as well as more frequent monitoring of plasma levels for the first 7 to 14 days of therapy. Although the mechanism of the apparently increased clearances are unclear, changes in protein binding, induction of metabolism of phenytoin, or a stress-related transient increase in hepatic metabolic function may be involved.

B) Phenytoin Sodium

1) Adverse Cardiovascular Reactions

a) If adverse cardiovascular reactions occur during administration, it may be necessary to reduce the rate of administration or discontinue dosing of phenytoin sodium [94]

2) Switching Between Salt and Base

a) There is approximately 8% increase in drug content with the free acid form of phenytoin compared with phenytoin sodium. Serum level monitoring and subsequent dose adjustments may be required when switching between salt and base [94]

3) Switching Between Oral and IM Routes of Administration

a) In a patient currently receiving phenytoin sodium orally, the IM dose should be 50% greater than the oral dose. When returning to oral administration, the oral dose should be 50% of the original oral dose for 1 week due to sustained release from intramuscular tissue sites [94]

PHARMACOKINETICS

Onset and Duration

A) Onset

1) Phenytoin

a) Initial Response

1) Seizure disorder, oral without a loading dose: 7 to 10 days [1126]

a) When administered orally without a loading dose, the onset of phenytoin for seizure disorder is 7 to 10 days [1126]
2) Seizure disorder, oral with a 1 gram loading dose: 8 to 12 hours [1126]

a) When administered orally with a 1 gram loading dose, then onset of phenytoin for seizure disorder is 8 to 12 hours [1126]

2) Phenytoin Sodium

a) Initial Response

1) Seizure disorder, oral, no loading dose: 7 to 10 days [1126]

a) When administered orally without a loading dose, the onset of phenytoin for seizure disorder is 7 to 10 days [1126]

2) Seizure disorder, oral, with 1 gram loading dose: 8 to 12 hours [1126]

a) When administered orally with a 1 gram loading dose, then onset of phenytoin for seizure disorder is 8 to 12 hours [1126]

3) Seizure disorder, IV, with 1 gram loading dose: immediate [1126]

a) When administered intravenously with a 1 gram loading dose, the onset of phenytoin for seizure disorder is immediate [1126]

Drug Concentration Levels

A) Phenytoin

1) Therapeutic Drug Concentration

a) Seizure disorder, 10 to 20 mcg/mL [101][100][1127][1128][1129]

1) Seizure control without clinical signs of phenytoin toxicity most often occurs when serum levels of total phenytoin are maintained between 10 and 20 mcg/mL. Some patients with mild seizure disorders may be able to achieve good control with lower serum levels. Due to differences in metabolism, concomitant illness, or other medications, wide interpatient variability is observed in phenytoin serum concentrations despite equivalent doses [101][100]

2) Total concentrations of 6 to 14 mcg/mL may be more appropriate in the neonate since they have a higher unbound fraction [1130]

3) The clinical effects of phenytoin were reported to correlate better with unbound drug as compared to total plasma concentrations, with usual unbound concentrations associated with optimal therapy being between 1 to 2 mcg/mL[1131][1132]
4) Due to a high incidence of hypoalbuminemia in developing countries, it has been proposed that a corrected phenytoin concentration be used. This would utilize the free phenytoin level and albumin concentration with the Sheiner-Tozer equation to correct for hypoalbuminemia [1133].

5) Phenytoin saliva and plasma concentrations in children have been shown to correlate highly both as total drug concentrations (r=0.92; p less than 0.001) and free concentrations (r=0.97; p less than 0.001) [1134].

2) Time to Peak Concentration

a) Oral, multiple-dose: 1.5 to 3 hours [101][100]

1) Peak plasma levels occur approximately 1.5 to 3 hours following oral administration of phenytoin chewable tablets or oral suspension [101][100]

B) Phenytoin Sodium

1) Therapeutic Drug Concentration

a) Seizure disorder: 10 to 20 mcg/mL [28][94]

1) Seizure control without clinical signs of phenytoin toxicity most often occurs when serum levels of total phenytoin are maintained between 10 and 20 mcg/mL [28][94]

2) The clinical effects of phenytoin were reported to correlate better with unbound drug as compared to total plasma concentrations, with usual unbound concentrations between 1 to 2 mcg/mL being associated with optimal therapy [1131][1132]

3) Increased fraction of free phenytoin is seen in patients with hepatic and renal impairment, as well as in other conditions associated with hypoalbuminemia. Therapeutic monitoring of unbound phenytoin in these patient populations may be clinically appropriate [94]

2) Time to Peak Concentration

a) Oral: 4 to 12 hours [28]

1) Peak phenytoin serum levels occur 4 to 12 hours following oral administration of phenytoin sodium extended-release oral capsule [28]

b) IV: 20 to 25 minutes [1158]
1) When administered intravenously with a loading dose, the Tmax of phenytoin sodium is 20 to 25 minutes [1158]

**ADME**

**Absorption**

**A) Phenytoin**

1) Bioavailability

a) Oral: 20% to 90% [1127]

1) The bioavailability of phenytoin varies from the different manufacturers from 20% to 90% [1127]

2) In neonates, oral and intravenous phenytoin doses resulted in similar serum concentrations [1130]

2) Effects of Food

a) increases the absorption of phenytoin [1135]

1) The increased absorption is most pronounced in infants, and less so in older children and adults [1135]

2) Enteral feedings may impair the absorption of phenytoin [1135][1136]

3) Phenytoin administered via a jejunostomy tube has resulted in non-detectable serum levels [1137]

**B) Phenytoin Sodium**

1) Bioavailability

a) Oral, phenytoin sodium capsules: 70% to 100% [1150]

1) The bioavailability of oral phenytoin sodium capsules ranges from 70% to 100% [1150]

2) The bioavailability of phenytoin varies from the different manufacturers from 20% to 90% [1127]

3) In neonates, oral and intravenous phenytoin doses resulted in similar serum concentrations [1130]

b) Rectal, phenytoin sodium injection: 24.4% [1159]
1) The bioavailability of phenytoin is 24.4% following rectal administration of phenytoin sodium injection [1159]

2) Effects of Food

a) increases the absorption of phenytoin [1135]

1) The increased absorption is most pronounced in infants, and less so in older children and adults [1135]

2) Enteral feedings may impair the absorption of phenytoin [1135][1136]

3) Phenytoin administered via a jejunostomy tube has resulted in non-detectable serum levels [1137]

Distribution

A) Distribution Sites

1) Phenytoin

a) Protein Binding

1) highly protein-bound [101][100]

88 to 93% [1138][1139][1140]

a) Phenytoin is highly bound to plasma proteins [101][100]

b) Impairment of protein binding of phenytoin may occur with neonatal or elderly patients, late pregnancy, hyperbilirubinemia, hepatic disease, uremia, nephrotic syndrome, burns, surgery, diabetes, malnutrition, or other conditions associated with hypoalbuminemia as well as combination therapy with valproic acid, phenylbutazone, aspirin, tolbutamide and sulfonamides [1141][1142]

In neonates the unbound fraction may be as high as 20% [1130]

c) In patients with renal disease, the following equation has been used to relate the measured, or observed, phenytoin concentration to the phenytoin concentration one would expect to measure if there was normal protein binding [1143]

\[
C_{\text{normal}} = \frac{C_{\text{observed}}}{0.1 \times \text{albumin} + 0.1}
\]

d) \(C_{\text{normal}}\) = normal serum phenytoin concentration in nonuremic patients

e) \(C_{\text{observed}}\) = observed serum phenytoin concentration in uremic patients

f) In patients with hypoalbuminemia, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [1144][1143]
g) C (normal) = normal serum phenytoin concentration in non-hypoalbuminemic patients

h) C (observed) = observed serum phenytoin concentration in hypoalbuminemic patients

i) In elderly nursing home patients and critically ill trauma patients with hypoalbuminemia, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [1144]

\[
C(\text{normal}) = \frac{C(\text{observed})}{0.2 \times \text{albumin} + 0.1}
\]

j) C (normal) = normal serum phenytoin concentration in non-hypoalbuminemic patients

k) C (observed) = observed serum phenytoin concentration in hypoalbuminemic patients

l) In neonates the unbound fraction may be as high as 20% [1130]

m) A 68% increase in free phenytoin concentration was observed in the sera of patients with HIV [1145]

b) Other distribution sites

1) Brain, good [1135]

a) The concentration in the brain is reported to be 89% to 128% of the plasma concentration [1135]

2) Placenta, good [1146][1147]

a) Plasma phenytoin concentrations of the mother's vein at term were similar to those seen for the umbilical vein and artery [1146][1147]

3) Saliva, unquantified [1148][1149]

a) Phenytoin concentration in saliva reflects the unbound, active circulating drug in plasma [1148][1149]
2) Phenytoin Sodium

a) Protein Binding

1) highly protein-bound [28] 88 to 93% [1138][1139][1140]

a) Phenytoin is highly bound to plasma proteins [28]

b) Impairment of protein binding of phenytoin may occur with neonatal or elderly patients, late pregnancy, hyperbilirubinemia, hepatic disease, uremia, nephrotic syndrome, burns, surgery, diabetes, malnutrition, or other conditions associated with hypoalbuminemia as well as combination therapy with valproic acid, phenylbutazone, aspirin, tolbutamide and sulfonamides [1141][1142]

In neonates the unbound fraction may be as high as 20% [1130]

c) In patients with renal disease, the following equation has been used to relate the measured, or observed, phenytoin concentration to the phenytoin concentration one would expect to measure if there was normal protein binding [1143]

\[
C_{(\text{normal})} = \frac{C_{(\text{observed})}}{0.1 \times \text{albumin} + 0.1}
\]

d) \( C_{(\text{normal})} \) = normal serum phenytoin concentration in nonuremic patients

e) \( C_{(\text{observed})} \) = observed serum phenytoin concentration in uremic patients

f) In patients with hypoalbuminemia, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [1144][1143]

\[
C_{(\text{normal})} = \frac{C_{(\text{observed})}}{0.2 \times \text{albumin} + 0.1}
\]

g) \( C_{(\text{normal})} \) = normal serum phenytoin concentration in non-hypoalbuminemic patients

h) \( C_{(\text{observed})} \) = observed serum phenytoin concentration in hypoalbuminemic patients

i) In elderly nursing home patients and critically ill trauma patients with hypoalbuminemia, the following equation has been useful in predicting normalized phenytoin concentration in institutions where assays are performed at 25 degrees Celsius [1144]

\[
C_{(\text{normal})} = \frac{C_{(\text{observed})}}{0.25 \times \text{albumin} + 0.1}
\]
j) $C_{\text{normal}}$ = normal serum phenytoin concentration in non-hypoalbuminemic patients

k) $C_{\text{observed}}$ = observed serum phenytoin concentration in hypoalbuminemic patients

l) In neonates the unbound fraction may be as high as 20% [1130]

m) A 68% increase in free phenytoin concentration was observed in the sera of patients with HIV [1145]

b) Other distribution sites

1) Placenta, good [1146][1147]

a) Plasma phenytoin concentrations of the mother's vein at term were similar to those seen for the umbilical vein and artery [1146][1147]

2) Saliva, unquantified [1148][1149]

a) Phenytoin concentration in saliva reflects the unbound, active circulating drug in plasma [1148][1149]

B) Distribution Kinetics

1) Phenytoin

a) Volume of Distribution

1) 0.5 to 1.0 L/kg [1127][1150][1140]

a) The Vd for the unbound fraction is about 0.5 to 0.64 L/kg and is altered in uremic patients [1139]

b) The volume of distribution of phenytoin increases with the degree of obesity, and obese individuals will require larger absolute loading doses of phenytoin to achieve therapeutic serum levels rapidly. Distribution of phenytoin into excess body weight (total body weight (TBW) minus ideal body weight (IBW)) is greater than the distribution into ideal body weight by a factor of 1.33 [91]
2) Phenytoin Sodium

a) Volume of Distribution

1) Vd, IV: 0.95 L/kg [1161]

a) The volume of distribution following single IV doses in children (9.4 to 21.3 mg/kg) was 0.95 L/kg and declined with age, with a range of 1 to 1.5 L/kg below the age of 5 years to 0.6 to 0.8 L/kg above the age of 8 years [1161]

b) The volume of distribution of phenytoin increases with the degree of obesity, and obese individuals will require larger absolute loading doses of phenytoin to achieve therapeutic serum levels rapidly. Distribution of phenytoin into excess body weight (total body weight (TBW) minus ideal body weight (IBW)) is greater than the distribution into ideal body weight by a factor of 1.33 [91]

Metabolism

A) Metabolism Sites and Kinetics

1) Phenytoin

a) Liver, extent unknown [101][100][1135]

1) Phenytoin is hydroxylated in the liver by a saturable enzyme system [101][100][1135]

2) There is some evidence that phenytoin enhances its own elimination through enzyme induction [1151]

2) Phenytoin Sodium

a) Liver: via CYP2C9 and CYP2C19 [94]

1) Phenytoin sodium is metabolized by a saturable hepatic process via CYP2C9 and CYP2C19 [94]

2) Phenytoin is hydroxylated in the liver by a saturable enzyme system, although the extent to which this occurs is unknown [28]

B) Metabolites

1) Phenytoin Sodium

a) 5-(para-hydroxyphenyl)-5-phenylhydantoin: unknown [94]
1) The principal metabolite of phenytoin is 5-(para-hydroxyphenyl)-5-phenylhydantoin. The activity of 5-(para-hydroxyphenyl)-5-phenylhydantoin is unknown [94]

Excretion

A) Kidney

1) Phenytoin

a) Renal Excretion (%)

1) Extent unknown; excreted following intestinal reabsorption [101][100]

a) After administration, most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestine and excreted in the urine [101][100]

2) Phenytoin Sodium

a) Renal Excretion (%)

1) Extent unknown; excreted following intestinal reabsorption [28]

a) After administration, most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestine and excreted in the urine [28]

B) Bile

1) Phenytoin

a) Extensive [101][100]

1) After administration, most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestine and excreted in the urine [101][100]

2) Phenytoin Sodium

a) Extensive [28]

1) After administration, most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestine and excreted in the urine [28]
C) Total Body Clearance

1) Phenytoin Sodium

a) Decreased in elderly [94]

1) Phenytoin clearance decreased by 20% in patients age 70 and older compared with patients age 20 to 30 years old [94]

Elimination Half-life

A) Parent Compound

1) Phenytoin

a) 14 hours (chewable tablets) [101] 22 hours (oral suspension) [100]

1) The mean plasma half-life is 14 hours (range 7 to 29 hours) following administration of phenytoin chewable tablets [101]

2) The mean plasma half-life after administration of the oral suspension is 22 hours (range 7 to 42 hours) [100]

3) Small dose increases (eg, 10% or more) may increase the half-life of phenytoin and produce marked increases in serum levels [101]

4) During the first 7 days of life, the half-life ranged from 6 to 140 hours in predominantly full-term newborns [1156]

2) Phenytoin Sodium

a) 22 hours (extended-release capsule) [28]10 to 15 hours (IV) [94]

1) The mean plasma half-life is 22 hours (range 7 to 42 hours) following administration of phenytoin sodium extended-release oral capsules; variability is due to the saturation kinetics [28]

2) Following IV administration of phenytoin sodium, the elimination half-life ranges from 10 to 15 hours [94]

3) During the first 7 days of life, the half-life ranged from 6 to 140 hours in predominantly full-term newborns [1156]
Extracorporeal Elimination

A) Hemodialysis

1) Phenytoin
   a) Dialyzable: Yes, 41.3% [1152]

   1) Results reported by an institution utilizing a CT-190G high flux dialyser indicated that phenytoin is removed by hemodialysis. Pre- and post-hemodialysis serum phenytoin levels were measured on 10 occasions in 4 men. A mean pre-dialysis phenytoin level was 19.2 mg/L with a post-dialysis mean level of 11.7 mg/L. This is a 41.3% reduction in serum phenytoin level. The authors warn that with a significant amount of phenytoin removed along with the removal of uremic toxins resulting in enhanced protein binding, free phenytoin levels could be low at the end of a dialysis session necessitating an extra post-dialysis phenytoin dose [1152]

2) Phenytoin Sodium
   a) Dialyzable: Yes, 41.3% [1152]

   1) Phenytoin is not entirely bound to plasma proteins, and could potentially be removed via hemodialysis [94]

   2) Results reported by an institution utilizing a CT-190G high flux dialyser indicated that phenytoin is removed by hemodialysis. Pre- and post-hemodialysis serum phenytoin levels were measured on 10 occasions in 4 men. A mean pre-dialysis phenytoin level was 19.2 mg/L with a post-dialysis mean level of 11.7 mg/L. This is a 41.3% reduction in serum phenytoin level. The authors warn that with a significant amount of phenytoin removed along with the removal of uremic toxins resulting in enhanced protein binding, free phenytoin levels could be low at the end of a dialysis session necessitating an extra post-dialysis phenytoin dose [1152]

B) Peritoneal

1) Phenytoin
   a) Dialyzable: No [1153][1154]

   1) Phenytoin not removed via peritoneal dialysis [1153][1154]

2) Phenytoin Sodium
   a) Dialyzable: No [1153][1154]
1) Phenytoin not removed via peritoneal dialysis

C) Plasmapheresis

1) Phenytoin

a) Dialyzable: Yes, 10% [1155]

1) A two plasma volume (4.4 hours) exchange removes 10 +/- 7% of total body phenytoin stores [1155]

2) Phenytoin Sodium

a) Dialyzable: Yes, 10% [1155]

1) A two plasma volume (4.4 hours) exchange removes 10 +/- 7% of total body phenytoin stores [1155]

Last Modified: March 13, 2012

COPYRIGHT © 1974- 2012 Thomson Reuters. All rights reserved.