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PHENYTOIN

INTRODUCTION

Phenytoin is a hydantoin compound related to the barbiturates that are used for the treatment of seizures. It is an effective anticonvulsant for the chronic treatment of tonic-clonic (grand mal) or partial seizures and the acute treatment of generalized status epilepticus (Table 10-1).^{1,2} After generalized status epilepticus has been controlled with intravenous benzodiazepine therapy and supportive measures have been instituted, phenytoin therapy is usually immediately instituted with the administration of intravenous phenytoin or fosphenytoin. Orally administered phenytoin is used chronically to provide prophylaxis against tonic-clonic or partial seizures. Phenytoin is a type 1B antiarrhythmic and is also used in the treatment of trigeminal neuralgia.

The antiseizure activity of phenytoin is related to its ability to inhibit the repetitive firing of action potentials caused by prolonged depolarization of neurons.^{3,4} Additionally, phenytoin stops the spread of abnormal discharges from epileptic foci thereby decreasing the spread of seizure activity throughout the brain. Posttetanic potentiation at synaptic junctions are blocked which alters synaptic transmission. At the cellular level, the mechanism of action for phenytoin appears related to its ability to prolong the inactivation of voltage-activated sodium ion channels and reduction of the ability of neurons to fire at high frequencies.

THERAPEUTIC AND TOXIC CONCENTRATIONS

The usual therapeutic range for total (unbound + bound) phenytoin serum concentrations when the drug is used in the treatment of seizures is 10–20 μmL . Since phenytoin is highly bound (~90%) to albumin, it is prone to plasma protein binding displacement due to a large variety of factors. Because of this, unbound or “free” phenytoin concentrations are widely available. Although there is clinical data to support the therapeutic range for total phenytoin concentrations, the suggested therapeutic range for unbound phenytoin

TABLE 10-1 International Classification of Epileptic Seizures with Treatment Recommendations

MAJOR CLASS	SUBSET OF CLASS	DRUG TREATMENT FOR SELECTED SEIZURE TYPE
Partial seizures (beginning locally)	1. Simple partial seizures (without impaired consciousness) <ul style="list-style-type: none"> a. With motor symptoms b. With somatosensory or special sensory symptoms c. With autonomic symptoms d. With psychological symptoms 2. Complex partial seizures (with impaired consciousness) <ul style="list-style-type: none"> a. Simple partial onset followed by impaired consciousness b. Impaired consciousness at onset 3. Partial seizures evolving into secondary generalized seizures	<i>Drugs of choice</i> Carbamazepine Phenytoin Lamotrigine Oxcarbazepine <i>Alternatives</i> Valproic acid Gabapentin Topiramate Tiagabine Zonisamide Levetiracetam Primidone Phenobarbital Pregabalin Felbamate
	Generalized seizures (convulsive or nonconvulsive)	1. Absence seizures (typical or atypical; also known as petit mal seizures)
2. Tonic-clonic seizures (also known as grand mal seizures)		<i>Drugs of choice</i> Valproic acid Phenytoin Carbamazepine <i>Alternatives</i> Lamotrigine Topiramate Zonisamide Oxcarbazepine Levetiracetam Primidone Phenobarbital

concentrations is based on the usual unbound fraction (10%) of phenytoin in individuals with normal plasma protein binding. Thus, the generally accepted therapeutic range for unbound phenytoin concentrations is 1–2 $\mu\text{g/mL}$, which is simply 10% of the lower and upper bounds for the total concentration range, respectively.

In the upper end of the therapeutic range ($>15 \mu\text{g/mL}$) some patients will experience minor central nervous system depression side effects such as drowsiness or fatigue.^{3,4} At total phenytoin concentrations above 20 $\mu\text{g/mL}$, nystagmus may occur and can be especially prominent upon lateral gaze. When total concentrations exceed 30 $\mu\text{g/mL}$, ataxia, slurred speech, and/or incoordination similar to ethanol intoxication can be observed. If total phenytoin concentrations are above 40 $\mu\text{g/mL}$, mental status changes, including decreased mentation, severe confusion or lethargy, and coma are possible. Drug-induced seizure activity has been observed at concentrations over 50–60 $\mu\text{g/mL}$. Because phenytoin follows nonlinear or saturable metabolism pharmacokinetics, it is possible to attain excessive drug concentrations much easier than for other compounds that follow linear pharmacokinetics. Clinicians should understand that all patients with “toxic” phenytoin serum concentrations in the listed ranges will not exhibit signs or symptoms of phenytoin toxicity. Rather, phenytoin concentrations in the ranges given increase the likelihood that an adverse drug effect will occur.

CLINICAL USEFULNESS OF UNBOUND PHENYTOIN CONCENTRATIONS

Unbound phenytoin concentrations are an extremely useful monitoring tool when used correctly. The relationship between total concentration (C), unbound or “free” concentration (C_f), and unbound or “free” fraction (f_B) is $C_f = f_B C$. For routine therapeutic drug monitoring purposes, total phenytoin serum concentrations are still the mainstream way to gauge therapy with the anticonvulsant. In most patients without known or identifiable plasma protein binding abnormalities, the unbound fraction of phenytoin will be normal (~10%) and unbound drug concentration measurement is unnecessary. At present, unbound drug concentrations are 50–100% more expensive than total concentrations, take longer to conduct by the laboratory and have results returned to clinicians, and are not available at all laboratories. Generally, unbound phenytoin serum concentration monitoring should be restricted to those patients with known reasons to have altered drug plasma protein binding. Exceptions to this approach are patients with an augmented or excessive pharmacologic response compared to their total phenytoin concentration. For example, if a patient has a satisfactory anticonvulsant response to a low total phenytoin concentration, one possible reason would be abnormal plasma protein binding ($f_B = 20\%$) for some unidentified reason, so that even though the total concentration was low (5 $\mu\text{g/mL}$), a therapeutic unbound concentration was present in the patient ($C_f = f_B C = 0.2 \cdot 5 \mu\text{g/mL} = 1 \mu\text{g/mL}$). Conversely, if a patient has a possible phenytoin-related adverse drug reaction and the total phenytoin concentration is within the therapeutic range, a possible reason could be abnormal protein binding (20%) for an unidentified reason, so that even though the total concentration appeared to be appropriate (15 $\mu\text{g/mL}$), a toxic unbound concentration was present in the patient ($C_f = f_B C = 0.2 \cdot 15 \mu\text{g/mL} = 3 \mu\text{g/mL}$).

Unbound phenytoin serum concentrations should be measured in patients with factors known to alter phenytoin plasma protein binding. These factors fall into three broad categories:

TABLE 10-2 Disease States and Conditions that Alter Phenytoin Plasma Protein Binding

INSUFFICIENT ALBUMIN CONCENTRATION (HYPOALBUMINEMIA)	DISPLACEMENT BY ENDOGENOUS COMPOUNDS	DISPLACEMENT BY EXOGENOUS COMPOUNDS
Liver disease Nephrotic syndrome Pregnancy Cystic fibrosis Burns Trauma Malnourishment Elderly	Hyperbilirubinemia Jaundice Liver disease Renal dysfunction	Drug interactions Warfarin Valproic acid Aspirin (>2 g/d) NSAIDs with high albumin binding

(1) lack of binding protein where there are insufficient plasma concentrations of albumin, (2) displacement of phenytoin from albumin binding sites by endogenous compounds, and (3) displacement of phenytoin from albumin binding sites by exogenous compounds (Table 10-2).⁵⁻²³ When multiple factors that decrease phenytoin plasma protein binding are present in a patient, the free fraction can be as high as 30–40%.²⁴

Low albumin concentrations, known as hypoalbuminemia, can be found in patients with liver disease or the nephrotic syndrome, pregnant women, cystic fibrosis patients, burn patients, trauma patients, malnourished individuals, and the elderly. Albumin concentrations below 3 g/dL are associated with high phenytoin unbound fractions in the plasma. Patients with albumin concentrations between 2.5–3 g/dL typically have phenytoin unbound fractions of 15–20%, while patients with albumin concentrations between 2.0–2.5 g/dL often have unbound phenytoin fractions >20%. Albumin is manufactured by the liver so patients with hepatic disease may have difficulty synthesizing the protein. Patients with nephrotic syndrome waste albumin by eliminating it in the urine. Malnourished patients can be so nutritionally deprived that albumin production is impeded. Malnourishment is the reason for hypoalbuminemia in some elderly patients, although there is a general downtrend in albumin concentrations in older patients. While recovering from their injuries, burn and trauma patients can become hypermetabolic and albumin concentrations decrease if enough calories are not supplied during this phase of their disease state. Albumin concentrations may decline during pregnancy as maternal reserves are shifted to the developing fetus and are especially prevalent during the third trimester.

Displacement of phenytoin from plasma protein binding sites by endogenous substances can occur in patients with hepatic or renal dysfunction. The mechanism is competition for albumin plasma protein binding sites between the exogenous substances and phenytoin. Bilirubin (a byproduct of heme metabolism) is broken down by the liver, so patients with hepatic disease can have excessive bilirubin concentrations. Total bilirubin concentrations in excess of 2 mg/dL are associated with abnormal phenytoin plasma protein binding. End-stage renal disease patients (creatinine clearance <10–15 mL/min) with uremia (blood urea nitrogen concentrations >80–100 mg/dL) accumulate unidentified compound(s) in their blood that displace phenytoin from plasma protein binding sites. Abnormal phenytoin binding persists in these patients even when dialysis procedures are instituted.

Phenytoin plasma protein binding displacement can also occur due to exogenously administered compounds such as drugs. In this case, the mechanism is competition for albumin binding sites between phenytoin and other agents. Other drugs that are highly bound to albumin and cause plasma protein binding displacement drug interactions with phenytoin include warfarin, valproic acid, aspirin (>2 g/d), and some highly bound nonsteroidal antiinflammatory agents.

Once the free fraction (f_B) has been determined for a patient with altered phenytoin plasma protein binding ($f_B = C_f/C$, where C is the total concentration and C_f is the unbound concentration), it is often not necessary to obtain additional unbound drug concentrations. If the situations that caused altered plasma protein binding are stable (albumin or bilirubin concentration, hepatic or renal function, other drug doses, etc.), total phenytoin concentrations can be converted to concurrent unbound values and used for therapeutic drug monitoring purposes. For example, an end-stage renal failure patient is receiving phenytoin therapy as well as valproic acid and warfarin. The concurrently measured total and unbound phenytoin concentrations are 5 $\mu\text{g/mL}$ and 1.5 $\mu\text{g/mL}$, respectively, yielding an unbound fraction of 30% [$f_B = C_f/C = (1.5 \mu\text{g/mL} / 5 \mu\text{g/mL}) = 0.30$]. The next day, a total phenytoin concentration is measured and equals 6 $\mu\text{g/mL}$. The estimated unbound concentration using this information would be 1.8 $\mu\text{g/mL}$: $C_f = f_B C = 0.30 \cdot 6 \mu\text{g/mL} = 1.8 \mu\text{g/mL}$. Of course, if the disease state status or drug therapy changes, a new unbound phenytoin fraction will be present and need to be remeasured using an unbound/total phenytoin concentration pair.

When unbound phenytoin concentrations are unavailable, several methods have been suggested to estimate the value or a surrogate measure of the value. The most common surrogate is an estimation of the equivalent total phenytoin concentration that would provide the same unbound phenytoin concentration if the patient had a normal unbound fraction value of 10%. These calculations "normalize" the total phenytoin concentration so that it can be compared to the usual phenytoin therapeutic range of 10–20 $\mu\text{g/mL}$ and used for dosage adjustment purposes. The equation for hypoalbuminemia is: $C_{\text{Normal Binding}} = C/(X \cdot \text{Alb} + 0.1)$, where $C_{\text{Normal Binding}}$ is the normalized total phenytoin concentration in $\mu\text{g/mL}$, C is the actual measured phenytoin concentration in $\mu\text{g/mL}$, X is a constant equal to 0.2 if protein binding measurements were conducted at 37°C or 0.25 if conducted at 25°C, and Alb is the albumin concentration in g/dL .^{25,26} If the patient has end-stage renal disease (creatinine clearance <10–15 mL/min), the same equation is used with a different constant value ($X = 0.1$).²⁵ [Note: In most experimental laboratories protein binding is determined at normal body temperature (37°C), in most clinical laboratories protein binding is determined at room temperature (25°C)]. Because these methods assume that the normal unbound fraction of phenytoin is 10%, the estimated unbound phenytoin concentration ($C_{f_{\text{EST}}}$) is computed using the following formula: $(C_{f_{\text{EST}}}) = 0.1 C_{\text{Normal Binding}}$. A different approach is taken by the equations used for patients with concurrent valproic acid administration. In this case, the unbound phenytoin concentration ($C_{f_{\text{EST}}}$) is estimated using simultaneously measured total phenytoin (PHT in $\mu\text{g/mL}$) and valproic acid (VPA in $\mu\text{g/mL}$) concentrations: $C_{f_{\text{EST}}} = (0.095 + 0.001 \cdot \text{VPA})\text{PHT}$.^{27,28} This value is compared to the usual therapeutic range for unbound phenytoin concentrations (1–2 $\mu\text{g/mL}$) and used for dosage adjustment purposes. It should be noted that these equations only provide estimates of their respective concentrations, and actual unbound phenytoin concentrations should be measured whenever possible in patients with suspected abnormal phenytoin plasma protein binding.

Example 1 JM is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.2 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His total phenytoin concentration is 7.5 µg/mL. Assuming that any unbound concentrations performed by the clinical laboratory will be conducted at 25°C, compute an estimated normalized phenytoin concentration for this patient.

1. Choose appropriate equation to estimate normalized total phenytoin concentration at the appropriate temperature.

$$C_{\text{Normal Binding}} = C / (0.25 \cdot \text{Alb} + 0.1) = (7.5 \text{ µg/mL}) / (0.25 \cdot 2.2 \text{ g/dL} + 0.1) = 11.5 \text{ µg/mL}$$

$$C_{\text{f}_{\text{EST}}} = 0.1 C_{\text{Normal Binding}} = 0.1 \cdot 11.5 \text{ µg/mL} = 1.2 \text{ µg/mL}$$

This patient's estimated normalized total phenytoin concentration is expected to provide an unbound concentration equivalent to a total phenytoin concentration of 11.5 µg/mL for a patient with normal drug protein binding ($C_{\text{f}_{\text{EST}}} = 1.2 \text{ µg/mL}$). Because the estimated total value is within the therapeutic range of 10–20 µg/mL, it is likely that the patient has an unbound phenytoin concentration within the therapeutic range. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

Example 2 LM is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.2 g/dL) and poor renal function (creatinine clearance = 10 mL/min). His total phenytoin concentration is 7.5 µg/mL. Compute an estimated normalized phenytoin concentration for this patient.

1. Choose appropriate equation to estimate normalized total phenytoin concentration.

$$C_{\text{Normal Binding}} = C / (0.1 \cdot \text{Alb} + 0.1) = (7.5 \text{ µg/mL}) / (0.1 \cdot 2.2 \text{ g/dL} + 0.1) = 23.4 \text{ µg/mL}$$

$$C_{\text{f}_{\text{EST}}} = 0.1 C_{\text{Normal Binding}} = 0.1 \cdot 23.4 \text{ µg/mL} = 2.3 \text{ µg/mL}$$

This patient's estimated normalized total phenytoin concentration is expected to provide an unbound concentration equivalent to a total phenytoin concentration of 23.4 µg/mL for a patient with normal drug protein binding ($C_{\text{f}_{\text{EST}}} = 2.3 \text{ µg/mL}$). Because the estimated total value is above the therapeutic range of 10–20 µg/mL, it is likely that the patient has an unbound phenytoin concentration above the therapeutic range. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

Example 3 PM is an epileptic patient being treated with phenytoin and valproic acid. He has a normal albumin concentration (albumin = 4.2 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His steady-state total phenytoin and valproic acid concentrations are 7.5 µg/mL and 100 µg/mL, respectively. Compute an estimated unbound phenytoin concentration for this patient.

1. Choose appropriate equation to estimate unbound phenytoin concentration.

$$C_{\text{f}_{\text{EST}}} = (0.095 + 0.001 \cdot \text{VPA})\text{PHT} = (0.095 + 0.001 \cdot 100 \text{ µg/mL})7.5 \text{ µg/mL} = 1.5 \text{ µg/mL}$$

This patient's estimated unbound phenytoin concentration is expected to be within the therapeutic range for unbound concentrations. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

CLINICAL MONITORING PARAMETERS

The goal of therapy with anticonvulsants is to reduce seizure frequency and maximize quality of life with a minimum of adverse drug effects.³ While it is desirable to entirely abolish all seizure episodes, it may not be possible to accomplish this in many patients. Patients should be monitored for concentration-related side effects (drowsiness, fatigue, nystagmus, ataxia, slurred speech, incoordination, mental status changes, decreased mentation, confusion, lethargy, coma) as well as adverse reactions associated with long-term use (behavioral changes, cerebellar syndrome, connective tissue changes, coarse facies, skin thickening, folate deficiency, gingival hyperplasia, lymphadenopathy, hirsutism, osteomalacia). Idiosyncratic side effects include skin rash, Stevens-Johnson syndrome, bone marrow suppression, systemic lupus-like reactions, and hepatitis.

Phenytoin serum concentrations should be measured in most patients. Because epilepsy is an episodic disease state, patients do not experience seizures on a continuous basis. Thus, during dosage titration it is difficult to tell if the patient is responding to drug therapy or simply is not experiencing any abnormal central nervous system discharges at that time. Phenytoin serum concentrations are also valuable tools to avoid adverse drug effects. Patients are more likely to accept drug therapy if adverse reactions are held to the absolute minimum. Because phenytoin follows nonlinear or saturable pharmacokinetics, it is fairly easy to attain toxic concentrations with modest changes in drug dose.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Phenytoin is primarily eliminated by hepatic metabolism (>95%). Hepatic metabolism is mainly via the CYP2C9 enzyme system with a smaller amount metabolized by CYP2C19. About 5% of a phenytoin dose is recovered in the urine as unchanged drug. Phenytoin follows Michaelis-Menten or saturable pharmacokinetics.^{29,30} This is the type of nonlinear pharmacokinetics 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 serum concentrations increase in a disproportionate manner after a dosage increase (Figure 10-1). In this case the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems: rate of metabolism = $(V_{\max} \cdot C) / (K_m + C)$, where V_{\max} is the maximum rate of metabolism in mg/d, C is the phenytoin concentration in mg/L, K_m is the substrate concentration in mg/L, and where the rate of metabolism = $V_{\max} / 2$.

The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of phenytoin is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent. As the dose or concentration of phenytoin increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions: $Cl = V_{\max} / (K_m + C)$. This is the reason concentrations increase disproportionately after a phenytoin dosage increase. For example, phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants of $V_{\max} = 500$ mg/d and $K_m = 4$ mg/L. The therapeutic range of phenytoin is 10–20 $\mu\text{g/mL}$. As the steady-state concentration of phenytoin increases from 10 $\mu\text{g/mL}$ to 20 $\mu\text{g/mL}$, clearance decreases from 36 L/d to 21 L/d: $Cl = V_{\max} / (K_m + C)$; $Cl = (500 \text{ mg/d}) / (4 \text{ mg/L} + 10 \text{ mg/L}) = 36 \text{ L/d}$; $Cl = (500 \text{ mg/d}) / (4 \text{ mg/L}$

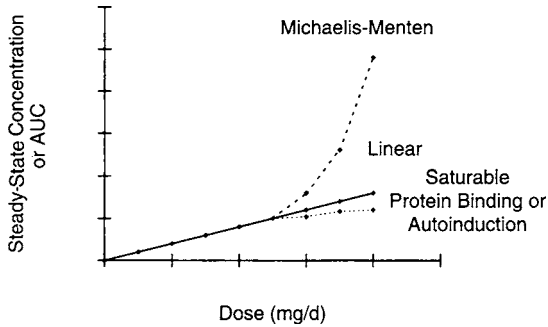


FIGURE 10-1 If a drug follows linear pharmacokinetics, C_{ss} or AUC increases proportionally with dose resulting in a straight line on the plot. Nonlinear pharmacokinetics occurs when the C_{ss} or AUC versus dose plot results in something other than a straight line. If a drug follows Michaelis-Menten pharmacokinetics (e.g., phenytoin, aspirin), as steady-state drug concentrations approach K_m serum concentrations increase more than expected due to dose increases. If a drug follows nonlinear protein binding (e.g., valproic acid, disopyramide), total steady-state drug concentrations increase less than expected as dose increases.

+ 20 mg/L) = 21 L/d. (Note: $\mu\text{g/mL} = \text{mg/L}$ and this substitution was directly made to avoid unnecessary unit conversion.) Unfortunately, there is so much interpatient variability in Michaelis-Menten pharmacokinetic parameters for phenytoin (typically $V_{\max} = 100\text{--}1000 \text{ mg/d}$ and $K_m = 1\text{--}15 \mu\text{g/mL}$) that dosing the drug is extremely difficult.

Phenytoin volume of distribution ($V = 0.7 \text{ L/kg}$) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) as well as the unbound concentration of drug in the blood (f_B) and tissues (f_T): $V = V_B + (f_B/f_T)V_T$. Also, half-life ($t_{1/2}$) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics: $t_{1/2} = (0.693 \cdot V)/Cl$. However, since clearance is dose- or concentration-dependent, half-life also changes with phenytoin dosage or concentration changes. As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug: $\uparrow t_{1/2} = (0.693 \cdot V) / \downarrow Cl$. Using the above example for clearance and the volume of distribution for a 70-kg person ($V = 0.7 \text{ L/kg} \cdot 70 \text{ kg} \approx 50 \text{ L}$), half-life changes from 1 d ($t_{1/2} = [0.693 \cdot V] / Cl = [0.693 \cdot 50 \text{ L}] / 36 \text{ L/d} = 1 \text{ d}$) to 1.7 d ($t_{1/2} = [0.693 \cdot 50 \text{ L}] / 21 \text{ L/d} = 1.7 \text{ d}$) as phenytoin serum concentrations increase from 10 $\mu\text{g/mL}$ to 20 $\mu\text{g/mL}$. The clinical implication of this finding is that the time to steady state (3–5 $t_{1/2}$) is longer as the dose or concentration is increased for phenytoin. On average, the time to steady-state serum concentrations is approximately 5 days at a dosage rate of 300 mg/d and 15 days at a dosage rate of 400 mg/d.²⁹

Under steady-state conditions the rate of drug administration equals the rate of drug removal.³¹ Therefore, the Michaelis-Menten equation can be used to compute the maintenance dose (MD in mg/d) required to achieve a target steady-state phenytoin serum concentration (C_{ss} in $\mu\text{g/mL}$ or mg/L):

$$MD = \frac{V_{\max} \cdot C_{ss}}{K_m + C_{ss}}$$

Or, solved for C_{ss} :

$$C_{ss} = \frac{K_m \cdot MD}{V_{max} - MD}$$

When phenytoin steady-state concentrations are far below the K_m value for a patient, this equation simplifies to: $MD = (V_{max}/K_m)C_{ss}$ or, since V_{max}/K_m is a constant, $MD = Cl \cdot C_{ss}$. Therefore, when $K_m \gg C_{ss}$, phenytoin follows linear pharmacokinetics. When phenytoin steady-state concentrations are far above the K_m value for a patient, the rate of metabolism becomes a constant equal to V_{max} . Under these conditions only a fixed amount of phenytoin is metabolized per day because the enzyme system is completely saturated and cannot increase its metabolic capacity. This situation is also known as zero-order pharmacokinetics. First-order pharmacokinetics is another name for linear pharmacokinetics.

For parenteral use, phenytoin is available in two different dosage forms. Phenytoin sodium, the sodium salt of phenytoin, contains 92% phenytoin by weight. Even though it is a salt of phenytoin, the drug is still relatively insoluble in water. To facilitate dissolution, ethanol and propylene glycol are added to the vehicle, and the pH of the solution is adjusted to between 10–12. When given intramuscularly, phenytoin sodium injections are very painful.³² Some of the drug probably precipitates in the muscle injection site, and this results in prolonged absorption of drug over several days. When given intravenously, injection rates should not exceed 50 mg/min to avoid hypotension. Even at lower infusion rates, profound hypotension can result in patients with unstable blood pressure or shock. Phenytoin sodium injection can be given by slow intravenous push of undiluted drug, or added to normal saline at a concentration of 10 mg/mL or less and infused <50 mg/min. When added to normal saline, the drug should be given as soon as possible after being mixed to avoid precipitation, and a 0.22- μ m in-line filter should be used to remove any drug crystals before they reach the patient.

To avoid many of the problems associated with phenytoin sodium injection, a water-soluble phosphate ester prodrug of phenytoin, fosphenytoin, has been developed. Conversion of fosphenytoin to phenytoin is rapid, with a fosphenytoin half-life of approximately 15 minutes. To avoid confusion, fosphenytoin is prescribed in terms of phenytoin sodium equivalents (PE). Thus, 100 mg PE of fosphenytoin is equivalent to 100 mg of phenytoin sodium. Hypotension during intravenous administration fosphenytoin is much less of a problem than with phenytoin sodium. The maximal intravenous infusion rate is 150 mg PE/min. Transient pruritus and paresthesia are associated with this route of administration. Intramuscular absorption is rapid with a peak concentration about 30 minutes after injection, and bioavailability via this route of administration is 100%. However, fosphenytoin is much more expensive than phenytoin sodium injection, and this has limited its widespread use. Because of this, most clinicians have reserved fosphenytoin use to patients requiring intramuscular phenytoin, or to patients with unstable or low blood pressure requiring intravenous phenytoin therapy.

For oral use, capsules contain phenytoin sodium (92% phenytoin, by weight) while tablets and suspension contain phenytoin. Phenytoin sodium capsules are labeled as extended phenytoin sodium capsules or prompt phenytoin capsules. Extended phenytoin capsules release phenytoin slowly from the gastrointestinal tract into the systemic circulation. The extended-release characteristics of this dosage form are due to the slow dissolution

of the drug in gastric juices and not the result of extended-release dosage form technology. Prompt phenytoin sodium capsules are absorbed fairly quickly from the gastrointestinal tract because they contain microcrystalline phenytoin sodium which dissolves quicker in gastric juices. As a result of their sustained-release properties, phenytoin doses given as extended phenytoin sodium capsules can be given every once or twice daily, but prompt phenytoin sodium capsules must be given multiple times daily. Extended phenytoin sodium capsules are available in 30 mg, 100 mg, 200 mg, and 300 mg strengths.

Phenytoin tablets (50 mg, chewable) and suspension (125 mg/5 mL) for oral use are available as the acid form of the drug. Both the tablet and suspension dosage forms are absorbed more rapidly than extended phenytoin sodium capsules, and once daily dosing with these may not be possible in some patients. The suspension is thick, and the drug is difficult to disperse evenly throughout the liquid. If not shaken well before dispensing a dose, the drug can flocculate out into the bottom of the bottle. When this occurs, phenytoin concentrations near the top of the bottle will be less than average, and doses given when the bottle is $\frac{2}{3}$ or more full will contain less phenytoin. Conversely, phenytoin concentrations near the bottom of the bottle will be greater than average, and doses given when the bottle is $\frac{1}{3}$ or less full will contain more phenytoin. This problem can be avoided to a large extent if the dispensing pharmacist shakes the bottle very well (several minutes) before giving to the patient.

For most drugs, the 8% difference in dose between dosage forms containing phenytoin (suspension and tablets, 100 mg = 100 mg phenytoin) and phenytoin sodium (capsules and injection, 100 mg = 92 mg phenytoin) would be trivial and could easily be ignored. However, because phenytoin follows nonlinear pharmacokinetics, an 8% difference in dose can result in major changes in phenytoin serum concentrations. For example, if a patient is stabilized on a dose of intravenous phenytoin sodium 300 mg/d (300 mg/d phenytoin sodium \times 0.92 = 276 mg phenytoin) with a steady-state concentration of 17 μ g/mL, switching the patient to phenytoin suspension 300 mg/d could result in steady-state phenytoin concentrations exceeding 20 μ g/mL (15–30% increase or more) and result in toxicity. Conversely, if a different patient is stabilized on a dose of phenytoin suspension 300 mg/d with a steady-state concentration of 12 μ g/mL, switching the patient to intravenous phenytoin sodium 300 mg/d (300 mg/d phenytoin sodium \times 0.92 = 276 mg phenytoin) could result in steady-state phenytoin concentrations below 10 μ g/mL (15–30% decrease or more) and result in loss of efficacy. Usually, phenytoin doses are not fine-tuned to the point of directly accounting for the difference in phenytoin content (i.e., 276 mg of phenytoin suspension would not be prescribed for the patient receiving 300 mg of phenytoin sodium injection). Rather, clinicians are aware that when phenytoin dosage forms are changed, phenytoin content may change and anticipate that the drug concentration may increase or decrease because of this. Because of this, most individuals recheck phenytoin serum concentrations after a dosage form change is instituted.

The oral bioavailability of phenytoin is very good for capsule, tablet, and suspension dosage forms and approximates 100%.^{33–36} At larger amounts, there is some dose-dependency on absorption characteristics.³⁷ Single oral doses of 800 mg or more produce longer times for maximal concentrations to occur (T_{\max}) and decreased bioavailability. Since larger oral doses also produce a higher incidence of gastrointestinal side effects (primarily nausea and vomiting due to local irritation), it is prudent to break maintenance doses larger than 800 mg/d into multiple doses. If oral phenytoin loading doses are given,

a common total dose is 1000 mg given as 400 mg, 300 mg, and 300 mg separated by 2- to 6-hour time intervals. Enteral feedings given by nasogastric tube interfere with phenytoin absorption.³⁸⁻⁴¹ Possible mechanisms include decreased gastrointestinal transit time which reduces absorption contact time, binding of phenytoin to proteins contained in the feedings, and adherence of phenytoin to the lumen of the feeding tube. The solution to this problem is to stop the feedings, when possible, for 1-2 hours before and after phenytoin administration, and increase the oral phenytoin dose.⁴⁰ It is not unusual for phenytoin oral dosage requirements to double or triple while the patient receives concurrent nasogastric feedings (e.g., usual dose of 300-400 mg/d increasing to 600-1200 mg/d while receiving nasogastric feedings). Of course, intravenous or intramuscular phenytoin or fosphenytoin doses could also be substituted while nasogastric feedings were being administered. Although poorly documented, phenytoin oral malabsorption may also occur in patients with severe diarrhea, malabsorption syndromes, or gastric resection.

The typical recommended loading dose for phenytoin is 15-20 mg/kg resulting in 1000 mg for most adult patients. Usual initial maintenance doses are 5-10 mg/kg/d for children (6 months-16 years old) and 4-6 mg/kg/d for adults. For adults the most prescribed dose is 300-400 mg/d of phenytoin. Because of an increased incidence of adverse effects in older patients (>65 years old), many clinicians prescribe a maximum of 200 mg/d as an initial dose for these individuals.^{42,43}

IMPACT OF ALTERED PLASMA PROTEIN BINDING ON PHENYTOIN PHARMACOKINETICS

The pharmacokinetic alterations that occur with altered plasma protein binding result in complex changes for total and unbound steady-state phenytoin concentrations and drug response. As previously discussed (please see Chapter 3), hepatic drug metabolism is described by the following equation:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance. For drugs such as phenytoin with a low hepatic extraction ratio ($\leq 30\%$), the numeric value of liver blood flow is much greater than the product of unbound fraction of drug in the blood and the intrinsic clearance of the compound ($LBF \gg f_B \cdot Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [$LBF \approx LBF + (f_B \cdot Cl'_{int})$]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug for a drug with a low hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF} = f_B \cdot Cl'_{int}$$

In order to illustrate the differences that may occur in steady-state drug concentrations and pharmacologic effects for patients with altered phenytoin plasma protein binding, a graphical technique will be used (Figure 10-2A). The example assumes that phenytoin is