

Preventing phenytoin intoxication: Safer use of a familiar anticonvulsant

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Practice recommendations

- To load phenytoin initially or to add a supplemental load, use this formula: for each $\mu\text{g}/\text{mL}$ desired increase in the phenytoin serum level, increase the loading dose by 0.75 mg/kg (C).
- Measure the peak serum level shortly after loading—30 to 60 minutes or more after giving intravenous phenytoin, 2 hours or more after intravenous fosphenytoin, 4 hours or more after intramuscular fosphenytoin, and 16–24 hours after accelerated oral loading (C).
- The daily maintenance dose (mg/kg/d) ordinarily needed to achieve a specified serum level or maintain it after loading is calculated thus: $(8 \times \text{target serum level}) / (6 + \text{target serum level})$ (C).

- Safe practice for initiating or adjusting a maintenance dosage should include patient education and close follow-up (C).

Despite the introduction of new anticonvulsant drugs, phenytoin is still a first-line medication for common types of epileptic seizures, particularly those caused by focal brain lesions.¹⁻⁴ Available in parenteral and oral form, phenytoin (or its pro-drug, fosphenytoin) is widely used. An estimated 873,000 prescriptions for phenytoin were issued during office visits in 2001.⁵

Phenytoin carries a special risk of dose-related toxicity, due to its saturation (zero-order) pharmacokinetics: serum levels often rise much more than would ordinarily be expected after initiating or increasing a maintenance dose. This predicts a vulnerability to toxicity, but does not predict exactly when this will occur in the individual.

The risk of toxicity can be minimized, however, by applying practical dosing and monitoring strategies based on the understanding of phenytoin pharmacokinetics, and by educating patients appropriately.

■ PATIENTS AT RISK: THE SCOPE OF THE PROBLEM

Extrapolating from the more than 5000 hospitals in the US⁶ to our experience in an urban community hospital, we estimate there may be as many

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as 25,000 cases of phenytoin intoxication presenting annually to emergency departments or resulting in hospitalization in the United States. In 1 study, a tertiary hospital recorded phenytoin intoxication from all causes at a rate of 1 inpatient admission per month over a 10-year period.⁷ Another study at a major hospital found 143 instances of phenytoin levels >25 µg/mL in 1 year; 86% of 120 studied cases were toxic, representing 33% of all adverse drug reactions reported.⁸ Thus, evidence points to a substantial problem with patient safety nationwide.

Adverse drug events like phenytoin intoxication increase morbidity, causing such injuries as falls due to ataxia and resulting in expenses of office or emergency department visits and hospitalization. While no prescription strategy, system of monitoring, or “safety net” is likely to eliminate phenytoin mishaps, an informed and active approach to therapeutic management can minimize instances of intoxication.

■ ACTION POINTS AND SAFETY TIPS IN PHENYTOIN THERAPY

Safe therapy with phenytoin depends on observing particular courses of action at 4 stages:

1. Loading
2. Institution of a maintenance regimen
3. Adjustment of the regimen
4. Monitoring, follow-up, and patient education.

Loading

Loading is indicated when the risk of seizures is so great that adequate serum levels of the drug must be reached rapidly. Such situations would include status epilepticus; repeated new seizures (excluding most withdrawal seizures, for example); breakthrough seizures with a low anticonvulsant level; and a first seizure with a high likelihood of repeating, as with a demonstrated focal brain lesion. Depending on the degree of urgency, loading can be accomplished with intravenous phenytoin (at an infusion rate of no more than 50 mg/min), with intravenous or intramuscular fosphenytoin, or with oral phenytoin.

Phenytoin Loading Formula

For each increase of 1 point (1 µg/mL or mg/L) in the phenytoin serum level, increase the loading dose by 0.75 mg/kg.

To load initially, or to add a supplemental load to increase an insufficient phenytoin level, the following formula based on a distribution constant for phenytoin indicates the amount of drug needed to raise the level by a specified amount.⁹

Use the loading formula. The peak serum level of phenytoin after intravenous loading is a function of the drug’s distribution in the body and is independent of the pharmacokinetics of elimination. Subsequent metabolism, which may be affected by other drugs or impairments (eg, liver disease), will affect elimination of the loaded drug but not ordinarily the calculated loading dose. Overloading phenytoin has been documented as a cause of early toxicity.⁷ According to the formula above, a 60-kg patient with no detectable starting level and an (arbitrary) target serum level of 15 µg/mL should need only 675 mg of phenytoin, and not the 1000 mg often administered.

This loading formula is also applicable to *supplementary (“booster”) loading* to reach a higher serum level quickly, either because the initial loading dose did not achieve the intended level or because that level was inadequate to control seizures. In this context, simply increasing the existing or planned daily maintenance dose raises the level too slowly. In addition, the increased maintenance dosage may be inappropriate if the cause of the low level is non-compliance. A higher maintenance dose, under conditions of complete or improved compliance, probably will lead to toxicity.

Measure serum levels. A sound preventive approach¹⁰ is to measure the peak serum level shortly after loading^{11,12}—one-half hour to 1 hour or more after giving intravenous phenytoin, 2 hours or more after intravenous fosphenytoin, 4 hours or more after intramuscular fosphenytoin, and 16 to 24 hours after accelerated oral loading.

While measuring a post-load serum level is not established as a standard of care, the rationale is that a relatively high serum level forewarns of increased risk of early intoxication because of a high starting point for maintenance therapy, and a low level indicates greater vulnerability to seizures (Table 1).

Initial maintenance dosing

A useful maintenance dose formula yields the dose ordinarily needed to achieve a specified serum level or maintain it after loading:⁹

Initial maintenance dosing

The daily maintenance dose in mg/kg/d=
 (8 x target serum level)
 (6 + target serum level)

For a target maintenance level of 15 µg/mL in a 60-kg adult, the dose would be 5.71 mg/kg/d x 60 kg = 343 mg/d (which can guide selection of a practical, starting dosage regimen, such as 300 or 350 mg/d, or 5–6 mg/kg/d, as is often recommended).¹³ This formula is more accurate than guessing at 5 mg/kg vs 6 mg/kg; increasingly, such formulas will be incorporated into computerized dosing protocols, thus putting the advised dose only a click or 2 away.

Even calculated dosages should be subject to modification by individual patient factors, including age, reliability, health status (such as liver function), and potential medication interactions. Computerized protocols will help, but the uncertainty of individual responses¹⁴ simply means that close symptomatic or serum monitoring must be implemented, while not overreacting to isolated variations (Table 2).¹⁵

Important caveat. Phenytoin is typically 90% protein-bound in the serum. Active free phenytoin may be higher than expected if serum albumin is decreased or if bound phenytoin is displaced by other drugs (eg, valproate). Thus, toxicity may be present despite non-elevated total levels of phenytoin, and successive increases in the dosage may

TABLE 1

Preventing phenytoin intoxication at loading
 (independent of pharmacokinetics of elimination)

Toxicity risk	Preventive action
Complications of intravenous infusion	Avoid excessive infusion rate (maximum, 50 mg/min); monitor blood pressure and ECG; assure good IV placement
Overload	Calculate dose by formula, best estimate of prior level Loading formula: to increase the phenytoin serum level by point (1 µg/mL or mg/L), the loading dose should be 0.75 mg/kg. Check post-load level: <ul style="list-style-type: none"> • Intravenous phenytoin: 1/2 hr to 1 hr or more • Intravenous fosphenytoin: 2 hr or more • Intramuscular fosphenytoin: 4 hr or more • Oral phenytoin: 16–24 hr

cause or exacerbate toxicity. Consider obtaining a free phenytoin level, commonly available by specific requisition, if clinical toxicity is suspected despite total levels that do not suggest toxicity. Consultation or careful review of all potential metabolic interactions helps to ensure proper management in such cases.

Adjusting dosage and the maintenance level. Here is a practical guide¹⁶ for incrementally increasing the phenytoin maintenance regimen (at steady state) for an adult:

- serum level <7 µg/mL, increase daily maintenance dose by 100 mg
- serum level of 7–11 µg/mL, increase by 50 mg
- serum level ≥12 µg/mL, increase by only 30 mg.

This guide reflects the fundamental principle of phenytoin’s pharmacokinetics: as the serum level approaches, enters, and increases through the therapeutic range, metabolic elimination

TABLE 2

Preventing phenytoin intoxication at initial maintenance dosing

Toxicity risk	Preventive action
Excessive dose, causing rising level to toxicity	Dose by maintenance-dose formula, adjusting for individual patient factors (eg, liver function). The best safety net is following closely. <i>Maintenance Dose Formula:</i> dose (mg/kg/d) = (8 x target serum level) / (6 + target level).
Incipient side effects going unrecognized	Patient education on early side effects (eg, drowsiness, grogginess, imbalance, vague, dizziness) and need to report promptly; follow-up monitoring by provider for symptoms and serum level.

TABLE 3

Preventing phenytoin intoxication at dosage adjustment

Toxicity risk	Preventive action
Mistaken change in maintenance dosage, leading to toxicity (eg, dosage is appropriate, but patient has been noncompliant)	Determine whether need for change is urgent; if so, give supplemental load to achieve target, by loading dose formula. Do not increase maintenance dose for acute response but only for sustained response if prior maintenance dosage shown to be inadequate. <i>Maintenance dose adjustment guideline:</i> Serum level <7 µg/mL, increase daily dose by 100 mg Serum level 7–11 µg/mL, increase daily dose by 50 mg Serum level ≥12 µg/mL, increase daily dose by 30 mg.
Increasing maintenance dose by too large an increment at one time (eg, 100 mg/d with a level of 14 µg/mL)	Focus on the patient, not the serum level in isolation. Only if clinically indicated, increase the maintenance dose according to guideline based on current serum level. Close follow-up, monitoring, and patient education as above.
Unnecessary increase in dose in patient who has long been optimally controlled with a “low” level (eg, 9 µg/mL, therapeutic range 10–20 µg/mL)	Use “therapeutic range” as a general guide, but individualize dose according to each patient’s seizure control, any particular risks (eg, driving, job safety), and any side effects.

does not rise proportionately, as it would in the more usual, first-order pharmacokinetics. In zero-order, saturation kinetics, an absolute amount of drug is eliminated per unit of time (as in the case of ethanol). The higher the phenytoin level, the more likely a seemingly reasonable increment in daily dosage, such as 100 mg (as from 300 mg to 400 mg per day) will turn out to be a prescription for toxicity (**Table 3**).

Monitoring for “dose-related” (concentration-related) toxicity

After starting or adjusting a phenytoin regimen, a common practice—but an inadequate one from a preventive point of view—is to order a serum drug level 2 or more weeks hence, to determine the steady-state level. If toxicity is to occur, however, it will happen before a steady state is reached, which is normally expected in 5 to 7 half-

lives (or in 5–14 days at a typical phenytoin “half-life” of 24–48 hours).

Phenytoin toxicity may occur earlier than this because of its zero-order, saturation kinetics, which progressively increases the time required for 50% elimination as the level rises. Arrangements should be made to monitor the patient for toxic symptoms and consider a serum level several days (eg, 3–7 days) after dosage adjustment. Even if this level is not excessively elevated, a rise from a post-load level portends heightened risk of toxicity.

Follow-up management: educate patients

Patient safety during therapy depends not only on adhering to rational pharmacologic principles, but also on patient education and active safeguards. A patient’s awareness of toxic symptoms functions as an early-warning system. Inform patients not only about “allergic” side effects, but about incipient, dose-related side effects, including drowsiness and impaired balance, and drug-drug and drug-disease interactions. Follow-up cannot follow a cookbook approach, and slowly developing symptoms, such as drowsiness, may be minimized by the patient.

As they are developed, computer-based protocols can facilitate dosing orders and can prompt patient education, provision of hand-outs, and appropriate follow-up appointments or other monitoring contacts.

Follow-up intervals depend upon the condition of the patient, including the ability to recognize and report symptoms. Ideally, a weekly phone call or other contact—initiated by the patient, family, other caregivers, or clinician—should be made until the patient appears to be well controlled with an acceptable serum level and without side effects. Subsequently, patient and caregiver attention to monitoring symptoms and potential interactions remains the best, practicable safeguard against clinical toxicity.¹⁴

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Intervention at a community teaching hospital reduces phenytoin intoxication and costs

Our 140-bed, urban community teaching hospital logs 30,000 emergency visits each year. We retrospectively documented an average of 5 cases of inadvertent, symptomatic phenytoin intoxication per year in our emergency department over a 4-year period. The range of phenytoin levels was 22.2–59.4 µg/mL (therapeutic range 10–20 µg/mL), and the median was 39 µg/mL.

Of the 15 patients seen in the first 3 years, 12 were admitted to the hospital, generating an average charge of \$4119. During the fourth year, we implemented a didactic and case-based program to educate house officers and attending physicians about phenytoin pharmacokinetics, the risks of dose-related toxicity, and ways to prevent it.

Over the subsequent 3 years (without any major change in overall patterns of drug choice), prospective surveillance revealed only 1 to 2 cases of phenytoin intoxication per year, 2 of which occurred in difficult-to-control patients with repeated emergency visits.

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STUDY QUALITY

- 1—Good-quality, patient-oriented evidence (eg, validated clinical decision rules, systematic reviews and meta-analyses of randomized controlled trials [RCTs] with consistent results, high-quality RCTs, or diagnostic cohort studies)
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DRUG BRAND NAMES

- Bupropion • Zyban
- Carbamazepine • Atretol, Depitol, Epitol, Tegretol
- Gabapentin • Neurontin
- Lamotrigine • Lamictal
- Nortriptyline • Aventyl, Pamelor
- Oxcarbazepine • Trileptal
- Phenytoin • Dilantin, Phenytek
- Tiagabine • Gabitril
- Topiramate • Topamax
- Valproic acid • Depakene, Depakote
- Vigabatrin • Sabril (available only in Canada)