Managing Phenytoin Serum Levels in the ED
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Case Presentation

A 35-year old otherwise healthy male with a history of a seizure disorder since childhood presents to the emergency department with EMS personnel after having had a seizure. He was postictal upon EMS arrival but in the emergency department he is at his normal baseline mental status. He states that his last seizure was approximately 2 years ago. He ran out of his phenytoin approximately 2 weeks ago and has not picked up the prescription that is waiting for him at a local pharmacy. He has normal vital signs and a normal physical exam. His serum phenytoin level is undetectable.

Questions:

1. What is the most effective phenytoin or fosphenytoin dosing strategy for preventing short-term seizure recurrence in a patient with a pre-existing seizure disorder who presents to the ED with a “subtherapeutic” serum phenytoin level?

2. What are the pharmacokinetic concerns as they relate to achieving a serum phenytoin level ≥ 10 mg/L?

3. What adverse effects are associated with oral, intravenous and intramuscular dosing of phenytoin and fosphenytoin?

4. What is the risk of seizure recurrence in a patient who is discharged from the emergency department?
Managing Phenytoin Serum Levels in the ED

There is much debate among emergency physicians as to the safest, most efficient and cost effective way to treat a patient who has had a recent seizure and has a subtherapeutic serum phenytoin level. Common contemporary dosing strategies include:

1. Administering an intravenous loading dose of phenytoin or fosphenytoin and then starting/restarting daily oral maintenance dosing
2. Administering an oral loading dose of phenytoin and then starting/restarting daily oral maintenance dosing
3. Starting/restarting daily oral maintenance dosing without administering a loading dose

Emergency physicians should understand that the most important measure of a particular antiepileptic drug dosing strategy should be efficacy in preventing seizure recurrence when viewed in conjunction with adverse events and cost.

What is the relationship between a “therapeutic” serum phenytoin level and the prevention of seizures?

Most laboratories report a “therapeutic” serum phenytoin level between 10-20 mg/L. The term “therapeutic” serum phenytoin level is a misleading since many patients remain seizure free at serum levels less than 10 mg/L and some patients may require a serum level greater than 20 mg/L to control their seizures. (Carter, Leppik 1983) Patients are more likely to have adverse effects when their serum phenytoin level rises above 20 mg/dL but many patients will experience adverse effects at “therapeutic” levels. (Ambrosetto, Product information) Most pharmacokinetic studies use achievement of a serum phenytoin level \( \geq 10 \text{ mg/L} \) as the primary outcome variable. Although achieving a serum phenytoin level \( \geq 10 \text{ mg/L} \) may be a measure of pharmacokinetic efficacy, a more relevant measure of clinical efficacy should be prevention of seizure recurrence with an acceptable adverse effects profile.

What are the pharmacokinetic concerns as they relate to achieving a serum phenytoin level \( \geq 10 \text{ mg/L} \)?

A serum phenytoin level \( \geq 10 \text{ mg/L} \) can be achieved by any of the common contemporary dosing strategies. Oral phenytoin dosing at the “appropriate” daily maintenance dose, without a loading dose, can achieve a serum phenytoin level \( \geq 10 \text{ mg/L} \) in 3-7 days. (Buchanan, Gugler, Svensmark). Although many common references recommend that adult dosing be initiated at 300 mg per day, many patients will not achieve a serum phenytoin level \( \geq 10 \text{ mg/L} \) at this daily dose. (Physician’s Desk Reference) Two volunteer studies showed that less than 20% of adult patients taking 300 mg per day achieved a serum level \( \geq 10 \text{ mg/L} \). (Buchanan, Gugler) The reasons for this are multifactorial and include failure to dose the medication based upon a patient’s weight and individual differences in metabolism. Regardless of the initial dosing strategy employed patients require a daily maintenance dosing to maintain their serum level \( \geq 10 \text{ mg/L} \). Patients who are discharged on daily maintenance dosing, even those that receive a loading dose, need follow-up to make sure that they are receiving the appropriate daily maintenance dose of phenytoin.

Intravenous loading of either phenytoin or fosphenytoin usually achieves a peak serum phenytoin level \( \geq 10 \text{ mg/L} \) within minutes following completion of the infusion. (Carducci, Kugler, Leppik, Salem).
Oral loading of phenytoin as a single dose and in divided doses can produce a serum phenytoin level $\geq 10$ mg/L in some cases within 3-10 hours and in most cases within 24 hours following the initial ingestion. (Osborn, Ratanakorn, Record, Wildner 1973)

Intramuscular loading of fosphenytoin as a single dose and in divided dose can reliably produce serum phenytoin level $\geq 10$ mg/L in most cases within 1-2 hours and in almost all cases within 24 hours following injection. (Boucher, Browne 1989, Kugler, Uthman, Wilder 1996)

**What adverse effects are associated with oral, intravenous and intramuscular dosing of phenytoin and fosphenytoin?**

Irrespective of the dosing strategy, the most common adverse effects associated with phenytoin and fosphenytoin include ataxia, nystagmus, tremor and somnolence. (Wilder 1996)

Fosphenytoin, the disodium phosphate ester of phenytoin, is a parenteral phenytoin pro-drug that is rapidly converted to phenytoin by blood and tissue phosphatases following intravenous and intramuscular injection. (Browne, Leppich) Many of the adverse local effects including phlebitis, purple glove syndrome and tissue necrosis associated with intravenous and intramuscular phenytoin, occur much less frequently when fosphenytoin is administered by these routes. (Comer, Marchetti, O’Brien, Kilarski) Many of the adverse systemic effects including impairment of myocardial contractility, dysrhythmias, hypotension and cardiac arrest associated with intravenous phenytoin administration, have also been reported much less frequently with intravenous fosphenytoin administration. (Earnest, Russell, York). This difference in adverse effects between parenteral phenytoin and fosphenytoin is believed to be in part related to the fact that parenteral phenytoin preparations contain propylene glycol (40%) and ethanol (10%) and are adjusted to a pH of 12. Fosphenytoin, which is more water-soluble, does not contain these same diluents and has a more physiologic pH of 8.6 to 9. (Browne 1996)

Although it is difficult to make comparisons between studies with respect to adverse events since most studies do not report adverse effects in a standardized form and often do not evaluate for their severity, fosphenytoin appears to have a better safety profile than intravenously and intramuscularly administered phenytoin. (Boucher, Jamerson, Henken)

The acquisition costs of fosphenytoin are considerably more than those for either parenteral or oral phenytoin products. In 10/2001 it costs approximately $95.00 for 1000 mg of fosphenytoin, $5.50 for 1000 mg of parenteral phenytoin and $5.00 for 1000 mg of oral phenytoin. (Kuffner). These prices are consistent with those previously published. (Browne 1998)

**What is the risk of seizure recurrence in a patient who is discharged from the ED after received phenytoin?**

Data on the risk of seizure recurrence is commonly reported in years not days. (Hauser) The baseline rate of seizure recurrence within a few days to a few weeks of ED discharge for the patient population of interest is unknown. Without knowing the background prevalence of short-term seizure recurrence, individual studies that address the rate of seizure short-term recurrence are difficult to interpret and compare.

It is difficult to make comparisons between the few studies that did report the rate of seizure recurrence since most of these studies included patients with many different etiologies for their seizures. The underlying cause of seizures is likely an important variable in determining the rate of seizure recurrence. (Cranford)
The rate of seizure recurrence could be estimated in two studies, one involving intravenous phenytoin loading (Cranford, Leppik) and one involving oral phenytoin loading (Osborn).

Cranford et al. administered various doses of intravenous phenytoin, mostly 15-18 mg/kg, to 139 patients on 159 occasions for “repetitive seizures”. Cranford reported that 17/159 (28%) patients had a recurrence of seizures despite a therapeutic phenytoin level and that seizures were controlled in 80% of patients. If there was anoxic or metabolic disturbances seizures were controlled in less than 40% of patients. Leppik et al. reported results from this same group of patients. Interestingly, the rate of seizure recurrence over 24 hours could not be correlated to the serum phenytoin level. Seizure recurrence occurred in 6% of patients with “antiepileptic drug withdrawal”, 11% of patients with “epilepsy cause undetermined” and 18% of patients with “miscellaneous condition”

Osborn et al administered a single 18 mg/kg oral dose of phenytoin capsules or suspension to 44 patients who presented to the emergency department following “one or more recent seizures” who had an undetectable serum phenytoin level, were awake and had the ability to take oral phenytoin. Patients were observed for at least 8 hours. No patient had a seizure recurrence.

Based upon these studies it appears that the rate of seizure recurrence varies from 6-28%, but may be independent of whether or not the patient received an AED.

**What is the most effective phenytoin or fosphenytoin dosing strategy for preventing short term seizure recurrence in a patient with a pre-existing seizure disorder who presents to the emergency department within 24 hours of having had a seizure without status epilepticus and who is determined to have a “subtherapeutic” serum phenytoin level?**

There are three potential strategies for managing subtherapeutic phenytoin levels in a patient on phenytoin who presents to the ED having had a seizure:

1. Administering an intravenous loading dose of phenytoin or fosphenytoin and then starting/restarting daily oral maintenance dosing
2. Administering an oral loading dose of phenytoin and then starting/restarting daily oral maintenance dosing
3. Starting/restarting daily oral maintenance dosing without administering a loading dose

The medical literature does not contain enough information to determine which of the three strategies is best. There are no well-designed studies that address the short-term rate of seizure recurrence and the short-term rate and severity of adverse events by directly comparing any of the common contemporary dosing strategies. A serum phenytoin level ≥10 mg/L can be achieved by all of the common contemporary dosing strategies and by intramuscular administration of fosphenytoin. Fewer adverse events are associated with fosphenytoin administration when compared to parenteral phenytoin administration but fosphenytoin is significantly more expensive.

Emergency physicians need to understand the pharmacokinetic, pharmacoeconomic and adverse event profiles of phenytoin and fosphenytoin as well as the limitations of the available medical literature. Emergency physicians who understand these issues are best suited to help their patients make informed decisions regarding the different dosing strategies.
References


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Annotated Bibliography


A prospective study administering 18 mg/kg of oral phenytoin at one time to 44 patients with a recent seizure and no detectable serum phenytoin. Only approximately 50% of patients had therapeutic serum levels at 10 hours post administration. No patient had a recurrent seizure during the 8-hour observation period regardless of serum level.


Two-part study of the pharmacokinetics of oral phenytoin loading. In part I, 19 healthy volunteers received 15 mg/kg; serum levels were in the therapeutic range within 2-3 hours. Authors concluded that the appropriate dosing for males was 19 mg/kg, and for females, 25 mg/kg. In part II, phenytoin loading was performed on seizure patients with therapeutic levels within 2-3 hours. Concluded that single oral loading was safe and effective.


Prospective study of the complications from intravenous phenytoin loading in an ED. 200 patients had a total of 72 complications: 29 with burning at infusion site, 36 with drug intoxication, 7 with hypotension or arrhythmias. Authors recommend infusions at 40 mg/min or less and provide excellent guidelines for safe administration.


Prospective study of 42 adults receiving intravenous phenytoin, 15 mg/kg. Concluded that infusions can be safely given at 50 mg/min to patients with no cardiovascular disease and 25 mg/min to those with cardiovascular disease.


This was one of the first publications on the pharmacokinetics of fosphenytoin demonstrating its safety of administration and its low side effect profile. In an open label component of the study, 25 volunteers received intravenous fosphenytoin, one experienced significant hypotension that was easily corrected.


This is an excellent overview of phenytoin; its indications, its pharmacokinetics, and its administration.

Retrospective review of 179 consecutive patients who received intravenous phenytoin; 6% developed the purple glove syndrome. One patient required surgical therapy while the others resolved with conservative therapy.
Questions:

1) Which of the following is a reported side effect of intravenous loading of phenytoin?
   a) Vein sclerosis
   b) Hypotension
   c) Ataxia
   d) Purple glove syndrome
   e) All

2) The oral loading dose for phenytoin is:
   a) 5 mg / kg
   b) 10 mg / kg
   c) 20 mg / kg
   d) 30 mg / kg
   e) 40 mg / kg

3) Which of the following is a correct statement:
   a) Fosphenytoin is will precipitate in dextrose solutions and must only be administered in normal saline.
   b) Fosphenytoin can be administered intramuscular but absorption is erratic and therapeutic levels are not reached for at least 4 hours
   c) Fosphenytoin does not cause hypotension and does not require cardiac monitoring when administered intravenously
   d) Fosphenytoin requires a propylene glycol vehicle which limits its infusion rate
   e) Fosphenytoin is over 98% bioavailable when given intravenously

4) In patients who are loaded orally with single dose phenytoin, when is it estimated that their serum level will be in the therapeutic range?
   a) 1 hour
   b) 3 hour
   c) 5 hour
   d) 7 hour
   e) 9 hour

Answers:
1 – e, 2 – c, 3 – e, 4 - c