Oral Verses Intravenous Loading of Anticonvulsants

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A 35 year-old otherwise healthy male with a history of a seizure disorder since childhood presents to the emergency department with ambulance personnel after having had a seizure. The patient was postictal upon ambulance personnel arrival but in the emergency department he has a normal mental status. 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.

Key Learning Points:

1. No well designed study has addressed 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 used to treat a patient with who presents to the emergency department after having had a seizure with a “subtherapeutic” phenytoin level. A serum phenytoin level $\geq 10$ mg/L can be achieved by all of the common contemporary dosing strategies including intravenous loading, oral loading and starting/restarting oral maintenance dosing.

2. Fewer adverse local effects (phlebitis, purple glove syndrome and tissue necrosis) and fewer adverse systemic effects (impairment of myocardial contractility, dysrhythmias, hypotension and cardiac arrest) are associated with intravenous fosphenytoin administration when compared to intravenous phenytoin administration.

3. 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.

4. Fosphenytoin is significantly more expensive than intravenous phenytoin.
What does the medical literature say are the options for treatment?

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 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 $\geq 10$ mg/L as the primary outcome variable. Although achieving a serum phenytoin level $\geq 10$ 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 effect profile.

What are the pharmacokinetic concerns as they relate to achieving a serum phenytoin level $\geq 10$ mg/L?

A serum phenytoin level $\geq 10$ 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 $\geq 10$ 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 ≥ 10 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 ≥ 10 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 ≥ 10 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 ≥ 10 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 ≥ 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 ≥ 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 prodrug 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, Henken, Jameson)

**What are the pharmacoeconomic concerns as they relate to phenytoin and fosphenytoin?**

The acquisition costs of fosphenytoin are considerably more than those for either parenteral or oral phenytoin products. In 4/2002 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 emergency department?**

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 emergency department 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) Based upon the available literature it appears that the rate of seizure recurrence following emergency department discharge varies from 6-20%. (Cranford, Huff, Leppick, Osborn).

No well-designed study has compared the rate of seizure recurrence for patients with different etiologies of seizures using any of the common contemporary dosing strategies.

**What guidelines currently exist?**

There are no commonly distributed guidelines that specifically address the issue of 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. This is likely due to the fact that the medical literature does not contain enough information to answer this question.
If no guidelines exist, what would you recommend?

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

When I want to achieve a “therapeutic” serum phenytoin level as soon as possible or prior to emergency department discharge I administer either fosphenytoin or phenytoin intravenously.

Examples:
1. Patient had a prolonged seizure.
2. Patient has a recent history of multiple seizures or status epilepticus.
3. Upon emergency department discharge the patient is likely to be in an environment/situation where another seizure carries an increased risk of morbidity/mortality. Such environments/situations include operating a motor vehicle or dangerous machinery, a hazardous occupational setting, homelessness and suboptimal social situations.
4. Medicolegal concerns

I always want to minimize the risk of adverse local and systemic effects associated with intravenous loading, so, when available, I administer fosphenytoin.

Examples:
1. Patients who have poor intravenous access or small intravenous catheters (children)
2. Patients are agitated.
3. There may be suboptimal supervision during dosing.
4. Medicolegal concerns.

When I want to minimize the amount of time a patient is in the emergency department, when cost is an especially important issue and when the indication for phenytoin therapy is questionable, I administer oral phenytoin.

Examples:
1. Emergency department resources are at a critical level.
2. Alcoholic patients whose seizures are likely secondary to alcohol withdrawal.
Reference List


