

Issues Surrounding the Management of Patients Who Present to the ED with Subtherapeutic Phenytoin Levels and a History of Seizures

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Modified from material prepared by
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Key Clinical Questions

- What is the relationship between a “therapeutic” serum phenytoin level and seizure prevention?
- By what route of administration can a serum phenytoin level ≥ 10 mg/L be achieved?
- What adverse events are associated with oral, IV, and intramuscular dosing of phenytoin and fosphenytoin?
- What are the costs of intravenous phenytoin and fosphenytoin and oral phenytoin administration?
- What is the risk of seizure recurrence in a patient that is discharged from the ED?

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Case Presentation

- 35 year-old otherwise healthy male presents to the emergency department after having a seizure
- Past Medical History: seizures since childhood, last seizure 2 years ago
- Medications: ran out of phenytoin 2 weeks ago
- Physical Exam: normal vital signs, normal mental status and normal physical exam
- Serum phenytoin level: undetectable

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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?

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What Common Dosing Strategy Would you Use?

- Administer a loading dose of intravenous phenytoin and start/restart daily oral maintenance doses
- Administer a loading dose of intravenous fosphenytoin and start/restart daily oral maintenance doses
- Administer a loading dose of oral phenytoin and start/restart daily oral maintenance doses
- Start/restart daily oral maintenance doses without administering a loading dose

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What is the Relationship Between a “Therapeutic” Serum Phenytoin Level and Seizure Prevention?

- Many patients remain seizure free at levels less than 10 mg/L and some patients require levels greater than 20 mg/L for seizure control.¹
- At levels greater than 20 mg/L patients are more likely to have adverse events but many patients will experience adverse events at “therapeutic levels”.²

1) Carter: Arch Neurol Psych 1958 and Leppick: Adv Neurol 1983

2) Ambrosetto: Epilepsia 1977 and Product Information

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Although achieving a “therapeutic” serum phenytoin level between 10-20 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.

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By What Route of Administration can a Serum Phenytoin Level ≥ 10 mg/L be Achieved?

- A level ≥ 10 mg/L can be achieved:
 - Immediately following an intravenous loading dose¹
 - Within 3-10 hours in some cases and within 24 hours in most cases following an oral loading dose²
 - Within 3-7 days following daily maintenance dosing without a loading dose³
 - Within 1-2 hours in most cases and within 24 hours in almost all cases following an intramuscular loading dose⁴

1) Carducci, Kugler, Leppick, Salem 2) Osborn, Rantakorn, Record, Wilder

3) Buchanan Gugler Svensmark 4) Boucher, Browne, Kugler, Uthman, Wilder

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Regardless of the initial dosing strategy patients require daily maintenance doses to maintain the serum level ≥ 10 mg/L.

Less than 20% of adult patients taking 300 mg/day will achieve a serum level ≥ 10 mg/L.¹

1) Buchanan, Gugler

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Phenytoin

- Stabilizes membrane Na⁺ channels
- Regulates Ca⁺⁺ channels
- Effective in generalized seizures and status
 - Seizure termination in 40% to 80% of patients
- 18 mg/kg loading dose results in therapeutic (10 μ g/mL) levels up to 24 h

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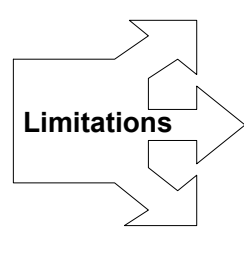
What Adverse Events are Associated with Oral, Intravenous and Intramuscular Dosing of Phenytoin and Fosphenytoin?

- Irrespective of dosing strategy ataxia, nystagmus and somnolence are common.
- Following intravenous dosing:
 - Adverse local effects:
 - phlebitis, purple glove syndrome, tissue necrosis¹
 - Adverse systemic effects:
 - impaired myocardial contractility, dysrhythmias, hypotension, cardiac arrest²

1) Comer, Marchetti, O'Brien, Kilarski
2) Earnst, Russell, York

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Phenytoin Limitations

- 
- Toxic diluents
 - high pH solution
 - Cardiac and soft tissue complications-“purple hand”
 - Hypotension
 - rate/infusion related
 - often requires slowing

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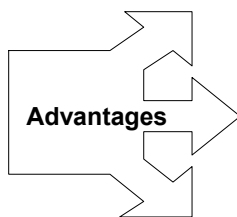


Fosphenytoin: Phosphate-Ester Prodrug

- Water soluble prodrug
- Converted to phenytoin, the active anticonvulsant
- Complete conversion *in vivo* to phenytoin
 - therapeutic free phenytoin levels within 2.7 minutes (IV)
- Rapid infusion rate, enhanced protein binding

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Fosphenytoin Advantages



- No toxic diluents**
 - pH 8.7
 - compatible with IV fluids
- Less pain and fewer infusion site complications**
- Faster IV infusion rates**
 - up to 150 PE/min
 - faster free phenytoin levels

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IM Fosphenytoin Use

- Single site injections >20 cc possible
- Therapeutic levels achieved by 30 min
- No difference in pain
 - placebo vs fosphenytoin
 - single vs multiple site injection
- Only mild irritation noted, regardless of volume

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Fosphenytoin Dosing: Phenytoin Equivalents

- Dosing is equivalent to phenytoin dosing
- Phenytoin solution is 50 mg/mL
- Fosphenytoin solution is 50 PE/mL
- 1 g fosphenytoin PEs = 1 g phenytoin
- Include PE and infusion rate in ordering fosphenytoin

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Both local and systemic adverse effects are reported much less common with fosphenytoin than with intravenous phenytoin.¹


1) Boucher, Jameson, Henken

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What are the Costs of Intravenous Phenytoin, Fosphenytoin and Oral Phenytoin?

It costs approximately:


- \$95.00 for 1000 mg of fosphenytoin
- \$5.50 for 1000 mg of parenteral phenytoin
- \$5.00 for 1000 mg of oral phenytoin

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What is the Risk of Seizure Recurrence in a Discharged ED Patient?

- Data on the risk of seizure recurrence is commonly reported in years not days or weeks.
- It is difficult to compare studies because:
 - The background incidence of short term seizure recurrence is unknown.
 - Most studies included patients with many different etiologies for their seizures.
- 6-20% is a rough estimate

Cranford, Huff, Leppick, Osborn

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What the Literature Can Tell Us

- A serum phenytoin level ≥ 10 mg/L can be achieved by all of the common contemporary dosing strategies and by intramuscular fosphenytoin administration.
- Fewer adverse effects are associated with administration of fosphenytoin than parenteral phenytoin preparations.
- Fosphenytoin remains considerably more expensive than parenteral phenytoin.

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What the Literature Cannot Yet Tell Us

Whether there is a difference in the short term rate of seizure recurrence between the different common dosing strategies


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

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Practical Recommendations

- When I want to achieve a “therapeutic serum phenytoin level” prior to ED discharge, I* administer fosphenytoin or phenytoin IV
- Examples
 - Prolonged seizure
 - History of multiple seizures or status epilepticus
 - Following emergency department discharge the patient is likely to be in an environment/situation where another seizure carries an increased risk of morbidity or mortality
 - Medicolegal concerns

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Practical Recommendations

- In order to minimize the adverse local and systemic effects associated with intravenous dosing, when available, administer fosphenytoin
- Examples
 - Poor intravenous access or small intravenous catheters
 - Agitated patients
 - Suboptimal supervision during dosing
 - Medicolegal concerns

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Practical Recommendations

- In order to minimize the time a patient is in the emergency department, when cost is especially an important issue and when the indication for phenytoin therapy is questionable administer oral phenytoin
- Examples
 - Emergency department resources are at a critical level
 - Alcohol withdrawal patient whose seizures are likely partially due to alcohol withdrawal

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Key Learning Points

- What is the relationship between a “therapeutic” serum phenytoin level and seizure prevention?
- By what route of administration can a serum phenytoin level ≥ 10 mg/L be achieved?
- What adverse events are associated with oral, IV, and intramuscular dosing of phenytoin and fosphenytoin?
- What are the costs of intravenous phenytoin and fosphenytoin and oral phenytoin administration?
- What is the risk of seizure recurrence in a patient that is discharged from the ED?

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Key Learning Points

- What is the relationship between a “therapeutic” serum phenytoin level and seizure prevention?
- Variable between individuals....

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Key Learning Points

- By what route of administration can a serum phenytoin level ≥ 10 mg/L be achieved?
- Oral phenytoin loading, intravenous phenytoin or fosphenytoin administration, or IM phenytoin administration will all yield levels \geq over variable times

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Key Learning Points

- What adverse events are associated with oral, IV, and intramuscular dosing of phenytoin and fosphenytoin?
- All routes will have dizziness or nystagmus with high levels
- Too rapid intravenous administration of phenytoin or fosphenytoin may yield cardiac arrhythmias or hypotension, perhaps more with phenytoin
- Soft tissue necrosis may follow extravasation of phenytoin

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Key Learning Points

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Key Learning Points

- What is the risk of seizure recurrence in a patient that is discharged from the ED?
- UNKNOWN

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What Common Dosing Strategy Would you Use NOW?

- A. Administer a loading dose of intravenous phenytoin and start/restart daily oral maintenance doses
- B. Administer a loading dose of intravenous fosphenytoin and start/restart daily oral maintenance doses
- C. Administer loading dose of oral phenytoin and start/restart daily oral maintenance doses
- D. Start/restart daily oral maintenance doses without administering a loading dose

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