Phenytoin vs fosphenytoin

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In 1996, Parke-Davis (Division of Warner-Lambert Company, Morris Plains, N.J.), the manufacturer of a phenytoin sodium injection (Dilantin), obtained approval from the Food and Drug Administration (FDA) to market fosphenytoin (Cerebyx) (1, 2). Fosphenytoin, the long-awaited phosphate ester pro-drug of phenytoin, was developed to overcome many of the complications associated with parenteral phenytoin administration and was intended to replace Dilantin (2, 3). To avoid the need to perform molecular weight-based dosage adjustments, the manufacturer has expressed the dose of fosphenytoin as phenytoin sodium equivalents (PE) (2, 4). Along with the benefits of fosphenytoin comes an expensive price tag, forcing clinicians to question whether fosphenytoin is worth the added cost (5, 6). In this review we discuss the 2 agents and present the rationale for Baylor University Medical Center's guidelines for fosphenytoin administration.

Table 1 summarizes the FDA-approved uses for both agents. Although not approved by the FDA for the indication, phenytoin is also effective in the treatment of various atrial and ventricular arrhythmias, including arrhythmias due to digitalis toxicity. It prolongs the effective refractory period and suppresses ventricular pacemaker automaticity (7). Furthermore, phenytoin has been found effective in preventing early onset, posttraumatic seizures (8). Higher doses are also used in the management of trigeminal neuralgia (9).

<table>
<thead>
<tr>
<th>Table 1. Indications (4, 7)</th>
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<tbody>
<tr>
<td><strong>Agent</strong></td>
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<tr>
<td>fosphenytoin</td>
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<td>phenytoin</td>
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PHARMACOKINETICS

Orally, phenytoin is absorbed primarily in the small intestine, with a small amount absorbed in the stomach. The rate and extent of absorption depend upon the product formulation and the physiologic state of the patient. The rapid-release, or prompt, formulation has a dissolution rate that approximates 85% in 30 minutes, producing peak serum concentrations in 1.5 to 3 hours. It must be administered at least twice daily to provide therapeutic serum
concentrations. The slow-dissolution, or extended, formulation (Dilantin Kapseal, Parke-Davis, Division of Warner-Lambert Company, Morris Plains, N.J.) provides peak serum concentrations in 4 to 12 hours, allowing for once-daily dosing (7, 9, 10).

In patients with normal renal function, phenytoin plasma protein binding is 87% to 93%. Binding is lower in neonates and elderly or uremic patients. Concentrations of phenytoin in cerebrospinal fluid are identical to unbound concentrations in plasma, reaching peak values 15 to 60 minutes after intravenous administration. Phenytoin also crosses the placenta and can be found in breast milk (7, 10).

Fosphenytoin converts to phenytoin, formaldehyde, and phosphate rapidly and virtually completely, with negligible amounts of fosphenytoin remaining in plasma 1 hour after administration. The conversion half-life ranges from 8 to 21 minutes, with a mean of 15 minutes. Phosphatases in the liver, red blood cells, and tissue convert the parent agent to phenytoin, independent of the serum concentrations of either the parent or active drug. In patients with hepatic or renal disease, fosphenytoin may have a conversion half-life that is 50% that of healthy patients. This faster conversion rate may be due, in part, to decreased protein binding secondary to hypoalbuminemia (1, 3).

After intramuscular administration, fosphenytoin is 98% to 99% absorbed and is therefore considered bioequivalent to intravenous administration of the same agent. However, the process of absorption appears to be the rate-limiting step in the attainment of therapeutic serum levels. Therapeutic phenytoin concentrations are achieved 30 minutes after intramuscular administration, and peak concentrations occur at 3 hours (1, 2). When injectable phenytoin (pH of 12) is administered intramuscularly, the water solubility of the drug decreases substantially, causing the drug to precipitate at the injection site. This results in slow and erratic absorption (7, 10).

Like phenytoin, fosphenytoin binds extensively to albumin. It displaces any lingering phenytoin from plasma protein binding sites, increasing up to 30% the unbound phenytoin fraction available for antiepileptic activity. This occurs mainly during the conversion of the pro-drug to the active phenytoin compound (30 to 60 minutes after administration). Phenytoin displacement is highest after intravenous administration of a large loading dose of fosphenytoin (~15 mg/kg) infused at a rapid rate (50 to 150 mg PE/min). This displacement phenomenon transiently offsets the delay required for fosphenytoin to convert to active compound after intravenous administration. Phenytoin binding returns to normal as plasma fosphenytoin levels decline. In contrast, little displacement is noted after intramuscular administration of fosphenytoin due to the greater time required for drug absorption from the injection site (1, 3, 4).

COMPARATIVE SAFETY

Intravenous fosphenytoin vs intravenous phenytoin

Jamerson et al reviewed the frequency, severity, and time course of venous irritation after administration of a single intravenous dose of phenytoin compared with an equimolar dose
of fosphenytoin. Twelve volunteers were randomly given a 30-minute peripheral infusion of either undiluted phenytoin (250 mg) or fosphenytoin (375 mg). They returned 14 to 21 days later and received an infusion of the crossover agent in the other forearm. The subjects were then asked to assess any venous irritation (pain, burning, or itching) on a 10-point ordinal scale, while the investigators evaluated the injection site for phlebitis, induration, exudation, and cording in a blind manner. Follow-up continued for 120 hours after the infusion. All 12 patients reported pain at the infusion site during the phenytoin infusion, while only 2 reported pain in this area during the fosphenytoin administration. Eight subjects experienced phlebitis with phenytoin, but the investigators found only 1 case of phlebitis with fosphenytoin ($P < 0.05$). Six patients had cording with phenytoin; no cording was found with fosphenytoin (11).

In a study partially funded by Parke-Davis, Boucher et al randomly assigned 116 neurosurgical patients who required anticonvulsant prophylaxis or treatment to receive either intravenous fosphenytoin ($n = 88$) or intravenous phenytoin ($n = 28$) in a double-blind trial. Those patients assigned to the intravenous fosphenytoin group received a mean loading dose of 1082 mg PE, followed by a mean maintenance dose of 411 mg PE. The 28 patients assigned to the phenytoin group received a mean loading dose of 1082 mg, followed by a mean maintenance dose of 422 mg. Treatment was continued for 3 to 14 days. Seizures were reported in 3% of the intravenous fosphenytoin and 7% of the intravenous phenytoin patients, which was not statistically significant (NS). Sixty-six percent of the fosphenytoin patients and 61% of the phenytoin patients experienced a decrease in their systolic blood pressure $>20$ mm Hg (NS). Adverse events necessitated reduced infusion rates in 14% of the intravenous fosphenytoin and 36% of the intravenous phenytoin recipients (NS). Six percent of those patients receiving fosphenytoin and 25% of those receiving intravenous phenytoin reported mild injection site irritation ($P < 0.05$). The authors concluded that intravenous fosphenytoin was better tolerated than intravenous phenytoin in this patient population (12).

**Intravenous fosphenytoin vs intramuscular fosphenytoin**

Leppik and colleagues administered maintenance doses of fosphenytoin (range, 150 to 450 mg PE) to 43 patients at 4 centers during an open-label, crossover study of patients with well-controlled seizures. A total of 32 patients received fosphenytoin intramuscularly, and 37 patients were given the agent intravenously. There were no statistically significant changes in heart rate, respiration, or diastolic blood pressure in either group. However, patients did experience a significant decrease in systolic blood pressure 15 minutes to 2 hours after intravenous administration and 30 minutes to 4 hours after intramuscular administration ($P < 0.05$). Forty-four percent of the patients receiving intravenous fosphenytoin and 25% of the patients receiving intramuscular fosphenytoin had $>1$ episode of nystagmus. In addition, 21% of patients receiving intravenous fosphenytoin had paresthesias, and 17% of those patients receiving intramuscular fosphenytoin reported pain at the injection site. The significance of these events was not addressed (13).

**COMPARATIVE EFFICACY**
Phenytoin has been used in the treatment of seizures since its anticonvulsant activity was first discovered about 50 years ago. Although no placebo-controlled trial has been performed to prove phenytoin anticonvulsant efficacy, extensive clinical experience has provided the basis for its acceptance as an antiepileptic agent. In fact, many efficacy studies, including fosphenytoin trials, have used phenytoin as the comparison drug (14).

**Phenytoin: status epilepticus**

Treiman and colleagues performed a multicenter, randomized, double-blind trial comparing the efficacy of lorazepam, 0.1 mg/kg; phenytoin, 18 mg/kg; diazepam, 0.15 mg/kg, plus phenytoin, 18 mg/kg; and phenobarbital, 15 mg/kg, in 518 patients with generalized status epilepticus. Treatment success was defined as no motor or electroencephalographic seizure 20 to 60 minutes from the start of treatment. The authors reported that each treatment was equally effective; however, lorazepam alone was superior to phenytoin alone when seizures were assessed 20 minutes after initial drug administration. Unfortunately, this study did not examine the current preferred treatment of status epilepticus, lorazepam followed by phenytoin (15).

**Fosphenytoin: status epilepticus**

The use of intravenous fosphenytoin for the treatment of status epilepticus was studied in an open-label, single-dose trial of patients having >=2 generalized seizures without regaining consciousness between seizures (16). Fifty patients (93%) who received fosphenytoin at a mean dose of 1450 mg (range, 324 to 3000 mg) delivered at a mean infusion rate of 182 mg/min (range, 55 to 327 mg/min) had seizures terminate within 30 minutes of receiving the drug. In 27 of 28 patients, total phenytoin concentrations >=10 ?g/mL and free phenytoin concentrations >=1 ?g/mL were achieved within 10 to 20 minutes of fosphenytoin initiation. Some patients experienced a decline in their blood pressure, but this was not considered clinically significant (16, 17).

**Fosphenytoin: substitution for oral phenytoin**

Two hundred forty patients who were receiving oral phenytoin for either a seizure disorder or postoperative seizure prophylaxis were enrolled in a multicenter, randomized, double-blind, placebo-controlled study. Patients were randomized to receive either 5 days of treatment with their regular oral phenytoin dose plus an intramuscular placebo (n = 61) or an equimolar dose of intramuscular fosphenytoin plus an oral placebo (n = 179). The incidence of adverse events in the 2 groups was similar (fosphenytoin, 68%; phenytoin, 62%; NS), but there were differences in the types of adverse events reported: nystagmus (15% vs 8%), tremor (10% vs 13%), headache (9% vs 5%), incoordination (8% vs 5%), ecchymosis (7% vs 5%), somnolence (7% vs 10%), and dizziness (5% vs 3%), in fosphenytoin and phenytoin, respectively. In 13 patients who underwent a more in-depth pharmacokinetic evaluation, intramuscular fosphenytoin was found to produce plasma phenytoin concentrations equal to or greater than those produced with an equimolar dose of oral phenytoin. Fosphenytoin-treated patients experienced 0.13 seizures per day compared with the phenytoin-treated patients who had a mean of 0.18 seizures per day (NS). Over the
5 days of therapy, the mean trough phenytoin concentrations in the fosphenytoin group rose slightly, which the authors felt was consistent with the differences in bioavailability between intramuscular fosphenytoin (99%) and oral therapy (90%). As a result, the investigators suggested that it might be prudent to measure serum phenytoin concentrations after 3 to 4 days of the intramuscular substitution (18).

ADVERSE REACTIONS

Adverse effects of phenytoin include gingival hyperplasia, hirsutism, and, in some patients, behavioral changes and cognitive dysfunction. In addition, nausea, emesis, nystagmus, ataxia, lethargy, and seizures can occur at toxic concentrations. Phenytoin can also cause a mild increase in liver enzymes that does not require discontinuation of therapy. More serious adverse effects include thrombocytopenia, anemia, leukemia, and lymphadenopathy. Phenytoin may also cause Stevens-Johnson syndrome or toxic epidermal necrolysis. If a rash appears during phenytoin therapy, it is recommended that the drug be discontinued immediately. An exfoliative, bullous, or purpuric rash is suggestive of Stevens-Johnson syndrome. However, if the rash is morbilliform or scarlatiniform, therapy may be resumed after the rash has resolved (7, 10, 19).

Injectable phenytoin can cause local or injection site reactions such as pain, burning, or itching; however, the frequency of such complaints is poorly described. Depressed atrial and ventricular conduction and ventricular fibrillation have also been associated with the intravenous use of phenytoin. These complications are more commonly encountered in elderly or debilitated patients. As a result, cardiac monitoring is recommended during administration of intravenous loading doses. In addition, intravenous phenytoin may cause hypotension if it is administered at rates exceeding 50 mg/min (2, 11).

Adverse effects specific to fosphenytoin include burning, itching, and paresthesias that may last up to 14 hours in some patients. Although the area of discomfort varies, several reports localize these areas of discomfort to the groin, back, lower abdomen, head, and neck. These paresthesias usually occur during intravenous administration of larger doses at rapid infusion rates. Hypotension may also occur after intravenous infusions of high doses at rapid rates. Cardiac monitoring is recommended during administration and for 10 to 20 minutes after completion of intravenous loading doses. Also, fosphenytoin contains 0.0037 mMol phosphate/mg PE and has the potential to contribute to phosphate accumulation in patients with renal dysfunction (3, 4, 10).

DOISING AND ADMINISTRATION

Since phenytoin and fosphenytoin are both highly protein bound, dosage adjustments may be required in patients with renal/hepatic disease or in those who have hypoalbuminemia. As the unbound drug concentration correlates better with phenytoin's efficacy and toxicity, it may be prudent to make these dosage adjustments based on free phenytoin or adjusted phenytoin serum concentrations (4, 20).
Loading doses of both phenytoin and fosphenytoin require dilution prior to intravenous administration (4, 7). Injectable phenytoin is compatible only with 0.9% saline and should be infused through an in-line filter because of its potential to precipitate at physiologic pH. Also, as a result of the hypotension and bradycardia associated with intravenous phenytoin administration, a maximum rate of 50 mg/min is recommended (25 mg/min in the elderly and patients with cardiac disease) (7).

Because fosphenytoin exhibits a relative decrease in protein binding with higher doses administered at higher rates of infusion, it is recommended that loading doses of fosphenytoin be administered at 150 mg PE/min when rapid achievement of therapeutic plasma concentrations is critical. In nonemergent situations, administration at lower infusion rates (50 to 100 mg PE/min) will produce a slightly lower and delayed maximum free phenytoin concentration. Fosphenytoin is compatible with both dextrose and saline solutions at concentrations ranging from 1.5 to 25 mg PE/mL. Intramuscular fosphenytoin injection volumes of up to 30 mL at a single site have been used and were well tolerated, but, as a rule, many patients will not tolerate this injection volume; a maximum of 5 mL per site is recommended (3, 4, 21).

A comparison of additional dosing recommendations is provided in Table 2.

<table>
<thead>
<tr>
<th>Dosing parameter</th>
<th>Fosphenytoin</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial adult dose</td>
<td>not available</td>
<td>100 mg, 3 times a day</td>
</tr>
<tr>
<td>Initial pediatric dose</td>
<td>not available</td>
<td>5 mg/kg/day</td>
</tr>
<tr>
<td><strong>Intravenous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading dose</td>
<td>15-20 mg PE/day</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>4-6 mg PE/kg/day</td>
<td>100 mg every 3-8 hours</td>
</tr>
<tr>
<td>Maintenance (oral substitute)</td>
<td>same as oral phenytoin dose</td>
<td>same as oral dose</td>
</tr>
<tr>
<td>Maximum infusion rate</td>
<td>150 mg PE/min</td>
<td>50 mg/min</td>
</tr>
<tr>
<td>Minimum time for 1-gram load</td>
<td>0.7 minutes</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Compatible with saline</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Compatible with 5% dextrose</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Intramuscular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necessity loading dose</td>
<td>10-20 mg PE/kg</td>
<td>not recommended*</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>4-6 mg PE/kg</td>
<td>not recommended*</td>
</tr>
<tr>
<td>Maintenance (oral substitute)</td>
<td>same as oral phenytoin dose</td>
<td>dose may need to be increased 50%</td>
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</table>

* can be given 100 mg every 6-8 hours for up to 1 week

**RECOMMENDED MONITORING**

Serum phenytoin determinations should be obtained at least 1 hour after completion of a loading dose infusion. Follow-up phenytoin concentrations are recommended at least 5 to 7 half-lives after treatment initiation, dose change, or drug change (i.e., when any drug known to interact with phenytoin is added or deleted from the patient's regimen). Samples are typically collected in a serum (red-top) tube that does not contain an anticoagulant (1, 7).

Cardiac and respiratory monitoring recommendations for fosphenytoin are the same as those for phenytoin. In order to allow time for fosphenytoin to convert to phenytoin, serum phenytoin concentrations should be obtained at least 2 hours after completion of an
intravenous loading dose of fosphenytoin or 4 hours after an intramuscular dose (1, 3). However, unlike patients receiving phenytoin, patients receiving fosphenytoin should have their blood samples collected in tubes containing EDTA as an anticoagulant (lavender top) to minimize ex vivo conversion of fosphenytoin to phenytoin (1).

DISCUSSION

Due to the disparity in acquisition costs between injectable phenytoin and injectable fosphenytoin, some institutions have reservations about adding fosphenytoin to their formularies. A single study addressing the potential pharmacoeconomic impact of fosphenytoin was conducted by Marchetti and colleagues. The study, conducted in 1994, employed an activity-based, cost-accounting model and was funded by Parke-Davis. The conclusions of the study were in favor of fosphenytoin; however, many published criticisms question the study's design, cost-accounting methods, and bias potential (22).

Fosphenytoin's better tolerability and more rapid intravenous administration rate make it attractive for loading doses. However, given the time course required for its conversion by tissue phosphatases, it does not deliver therapeutic levels of phenytoin at a more rapid rate than injectable phenytoin. To date, fosphenytoin has not shown a statistically (or clinically) significant reduction in cardiovascular side effects over injectable phenytoin. In addition, the product's storage requirement of refrigeration and the potential for medication errors with multiple forms of intravenous phenytoin make it a less desirable product.

Baylor University Medical Center has made both phenytoin and fosphenytoin available as formulary choices. However, guidelines for the use of fosphenytoin injection have been developed for its use at the institution. These guidelines are presented in the Appendix.

References


