THERAPEUTIC PERSPECTIVE

Fosphenytoin: Current Place in Therapy

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Fosphenytoin is a parenteral phosphate ester prodrug of phenytoin developed to overcome the limitations associated with parenteral administration of phenytoin. Despite potential clinical advantages, pharmacoeconomic concerns have prevented widespread substitution of parenteral phenytoin with fosphenytoin. The purposes of this descriptive review are to (1) highlight recent clinical and pharmacoeconomic data regarding the therapeutic decision to use phenytoin or fosphenytoin for the parenteral management of acute seizures, and (2) discuss the implications of fosphenytoin use in neonatal and pediatric patients. Supporting recent, multidisciplinary, consensus guidelines, it is our opinion that each patient should be evaluated individually to identify those who will benefit most from fosphenytoin. Such patients may include those without intravenous or enteral access, those requiring parenteral therapy with tenuous peripheral intravenous access, and pediatric and neonatal patients. Additionally, institution-specific cost analyses should be done to assure the most appropriate agent is being used, while being sensitive to the potential disparate risk profiles between patient populations. Until the issues of safety relative to cost are objectively ameliorated, individual clinicians will likely use their own experience to dictate the place of fosphenytoin in their respective practices.

KEYWORDS: adverse events, fosphenytoin, pediatric, pharmacoeconomics, phenytoin, seizure

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INTRODUCTION

Fosphenytoin is a parenteral phosphate ester prodrug of phenytoin developed to overcome the limitations associated with parenteral administration of phenytoin. Approved in 1996, fosphenytoin (Cerebyx, Eisai, Teaneck, N.J.) is currently indicated for the control of generalized convulsive status epilepticus (GCSE), and for prevention and treatment of seizures occurring during neurosurgery when conditions preclude the use of intravenous and oral phenytoin. One area of particular interest for fosphenytoin use is in patient populations at risk for adverse events due to parenteral phenytoin administration. In 1999, a multidisciplinary multiinstitutional panel of pharmacy and neurology epilepsy experts published consensus guidelines for the nonemergency use of parenteral phenytoin products.[1] These descriptive guidelines advocate fosphenytoin as the preferred method of parenteral phenytoin delivery in high-risk populations, specifically pediatric patients, elderly patients, hemodynamically unstable patients, and patients without reliable intravenous access. Another area of interest for fosphenytoin use is in the management of GCSE. In a 2003 survey of predominantly U.S. neurologists, 95% (101/106) of respondents agreed that phenytoin was the preferred second-line treatment for GCSE following administration of a rapid-acting benzodiazepine.[2] Sixty-five percent of these respondents chose fosphenytoin over phenytoin as the pre-

ABBREVIATIONS: GCSE, generalized convulsive status epilepticus; PE, phenytoin equivalents; PGS, purple glove syndrome

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ferred method of phenytoin delivery.[2]

Despite potential clinical advantages, pharmacoeconomic concerns have prevented widespread substitution of parenteral phenytoin with fosphenytoin. To be cost-effective, fosphenytoin use must overcome a 16-fold higher average wholesale price (AWP)[3] through cost-avoidance of phenytoin adverse events. This is highly dependent on the patient population as well as the clinical situation being considered, since certain patient populations are at relatively higher-risk for phenytoin-related adverse events and associated sequelae. The purpose of this review is to highlight recent clinical and pharmacoeconomic data regarding the therapeutic decision to use phenytoin or fosphenytoin for the parenteral management of acute seizures. Additionally, discussion of the implications of fosphenytoin use in neonatal and pediatric patients is presented. The pharmacology and clinical trial experience of fosphenytoin have been reviewed extensively elsewhere[4,5]; however, a brief overview of these past data is provided.

ADULT CONSIDERATIONS

Pharmacokinetics, Pharmacodynamics, and Efficacy

Following parenteral (intravenous or intramuscular) administration, fosphenytoin is rapidly converted by endogenous phosphatases to its parent compound phenytoin, 1 mole of phosphate, and 1 mole of formate.[4] Before conversion, fosphenytoin has no antiepileptic activity. Because of the phosphate ester moiety, the molecular weight of fosphenytoin is about 1.5 times that of phenytoin.[4] To help avoid confusion, U.S. Food & Drug Administration (FDA) requires fosphenytoin to be dosed, prescribed, and dispensed in phenytoin equivalents (PE) such that 1 mg PE = 1 mg phenytoin.[4-6] The major advantage of fosphenytoin's phosphate ester moiety is improved water solubility. This property obviates the need for a vehicle consisting of 40% propylene glycol and 10% alcohol at pH 12, such as that required for the formulation of parenteral phenytoin sodium U.S.P. Absence of these diluents allows fosphenytoin to be safely administered intravenously at a maximum infusion rate of 150 mg PE/min, 3-times the maximum rate for intravenous phenytoin. However, therapeutic total phenytoin plasma concentrations are not attained more quickly with fosphenytoin due to a brief delay in conversion of fosphenytoin to phenytoin (mean conversion half-life 15 minutes, range 10–21 minutes).[5,7,8] Nonetheless, central nervous system (CNS) concentrations are essentially equivalent.[9] Although the conversion rate of fosphenytoin to phenytoin is independent of infusion rate, fosphenytoin has greater affinity for phenytoin-specific plasma protein binding sites compared to phenytoin.[10] As such, increasing concentrations of fosphenytoin results in displacement of phenytoin from its protein-binding site, whereby when equivalent doses of each agent are infused at their respective maximum rates (i.e., fosphenytoin 150 mg PE/min; phenytoin 50 mg/min), fosphenytoin results in more rapid attainment of therapeutic unbound phenytoin plasma concentrations.[5,6,11] This pharmacokinetic characteristic partially compensates for the delay in fosphenytoin-to-phenytoin conversion.

Because of its poor aqueous solubility and risk of intramuscular precipitation, intramuscular administration of phenytoin is relatively contraindicated, although officially approved for dosing via this route. Conversely, fosphenytoin is extremely soluble in aqueous solutions. As such, therapeutic doses of fosphenytoin can be safely administered intramuscularly with virtually little to no evidence of local irritation.[12] Following intramuscular injection, fosphenytoin is completely absorbed and converted to phenytoin (i.e., 100% bioavailability) with peak fosphenytoin plasma concentrations attained in about 30 minutes and peak phenytoin concentrations in 3 hours.[12] Because of the delay in absorption and conversion time to phenytoin, intramuscular fosphenytoin results in a pharmacokinetic profile more similar to oral phenytoin than intravenous phenytoin or fosphenytoin. However, intramuscular fosphenytoin has greater bioavailability and results in transiently higher unbound phenytoin concentrations compared to oral phenytoin.[5,12] Therefore, this FDA-approved route of administration is a distinct advantage of fosphenytoin over phenytoin, particularly in patients that require nonemergent parenteral phenytoin therapy (i.e., maintenance therapy), but in whom intravenous access is limited or absent.

The primary reason for the development of fosphenytoin was to improve on the tolerability and delivery of parenteral phenytoin, as discussed above. Because of the similar pharma-

cokinetic and pharmacodynamic properties (i.e., time to achievement of therapeutic phenytoin concentrations) between fosphenytoin and phenytoin, the comparative efficacy of these agents has been shown to be equivalent, as previously reviewed.[4,5]

Safety

From a safety perspective, intravenous administration of fosphenytoin has been associated with significantly fewer infusion site reactions compared to phenytoin.[4,5,13] The main factors responsible for the improved administration safety of fosphenytoin are the differences in the respective parenteral formulations discussed above. Due to the propylene glycol and pH, intravenous administration of phenytoin can cause mild to severe injection site pain, venous irritation, and phlebitis.[7,14-18] Cases of soft tissue necrosis[19,20] and purple glove syndrome (PGS; discussed in more detail later)[21-26] have also been reported. Clinical comparison trials in adults have demonstrated infusion site reactions (i.e., pain, phlebitis, or irritation) to occur in 40–70% of patients receiving phenytoin versus 3–10% of patients receiving fosphenytoin. Reported rates of mild to moderate infusion site pain range from 1–7% for fosphenytoin compared to 3–20% for phenytoin. In a double blind, multicenter study comparing maximum rate of intravenous fosphenytoin administration (150 mg PE/minute) with the maximum rate of intravenous phenytoin administration (50 mg/minute) in 112 adult patients, infusion site irritation occurred in 11% and 86% of patients, respectively.[27] Although there was no difference in efficacy, the results of this trial are a testament to the improved local tolerability of fosphenytoin infusion.

In addition to local infusion site reactions, phenytoin is associated with concentration-dependent, CNS-specific adverse effects (e.g., nystagmus, dizziness, ataxia, somnolence). Since fosphenytoin is converted completely to phenytoin, these effects are also observed with fosphenytoin. In clinical comparison trials, the only adverse events unique to patients receiving fosphenytoin were infusion-related, nonallergic paresthesias and pruritus.[4,5,7,8] These infusion rate-related effects were transient and localized to the groin, buttocks, and face. All cases resolved completely within 5–10 minutes after the end of the fosphenytoin infusion.[4,5] Furthermore, these adverse events have not been observed with the intramuscular administration of fosphenytoin. It has been suggested that the phosphate ester moiety of fosphenytoin is responsible.[5] In a recent prospective, observational study of 256 emergency department patients (202 of which received fosphenytoin and 77 received phenytoin), fosphenytoin-specific pruritus occurred in 13 (6.4%) patients while 5 (2.5%) patients reported paresthesias.[7] Both paresthesias and pruritus were transient, occurring only during fosphenytoin infusion and lasting 5–30 minutes. No patient receiving phenytoin reported these effects. Mean infusion rates for each agent were 89 $\pm$ 26 mg PE/min and 19 $\pm$ 4 mg/min, respectively. Although fosphenytoin-related paresthesias and pruritus are generally benign, moderate to severe discomfort may require a decrease in infusion rate or, rarely, cessation of infusion in lucid patients. Nevertheless, due to their transient nature, the overall clinical significance of these effects is modest when compared to phenytoin-specific infusion site reactions.

Historically, adverse cardiovascular effects have also been associated with rapid intravenous administration of phenytoin.[14,28,29] Reports of hypotension are likely due to the rapid administration of propylene glycol[30] whereas electrocardiogram (ECG) changes are a result of phenytoin-induced cardiac depression.[4,31] These effects are uncommon, however, when infusions rates are at or below 50 mg/min.[1] Although concerns of adverse cardiovascular effects have generally eluded fosphenytoin, postmarketing surveillance suggests that these effects may occur, particularly in elderly patients and those with preexisting cardiac disease.[1] In comparative trials, the occurrence of cardiovascular compromise was similar and uncommon for both phenytoin and fosphenytoin.[5] However, recent reports have also found administration of fosphenytoin to result in untoward cardiovascular effects including hypocalcemic-like ECG changes[32] as well as hypotension, bradycardia, and heart block.[33] Although many of these reports followed rapid administration (i.e., > 150 mg PE/min) or overdose of fosphenytoin, and were likely due to the parent compound phenytoin, the cardiovascular concerns surrounding rapid administration of both products are relevant. As such, it is recommended that all patients receiving intravenous phenytoin or fosphenytoin be monitored by telemetry.

NEONATAL AND PEDIATRIC CONSIDERATIONS

Neonatal and pediatric patients are at high risk for phenytoin infusion-related adverse events and may benefit from fosphenytoin.[1,34] Specific risk factors for these adverse events include (1) the need for use of small veins (e.g., hand, wrist, foot, or scalp), (2) use of smaller gauge intravenous catheters, and (3) repeated use of a single vein.[34] Few investigations, however, have quantified the phenytoin-associated adverse event rate in neonatal and pediatric populations. One prospective, observational study of 22 patients ranging from 0.5 to 14.2 (median 5.2) years of age receiving 100 doses of intravenous phenytoin demonstrated that 6 (27%) patients experienced at least one infusion-related adverse event.[18] Three patients experienced extravasation and cutaneous infiltration, two patients had occluded peripheral lines, one patient had hypotension, and one patient had ECG changes (tachycardia). One patient experienced two adverse events (drug extravasation and venous occlusion); there were no cases of PGS. Infusion rates exceeded the maximum recommended rate in 7 of the 100 infusions, accounting for the three cardiovascular adverse events. Although the above study is small, the results suggest that phenytoin infusion-related adverse events are common in pediatric patients. As such, fosphenytoin administered either intravenously or intramuscularly may provide an opportunity to avoid specific phenytoin infusion-related adverse events in this population.

Few reports of fosphenytoin use in nonadult populations exist. The first included seven patients ranging 5 to 18 years of age with GCSE.[35] All patients received a single dose of fosphenytoin (10 to 20 mg/kg PE) administered at a range of 27 to 148.5 mg PE/min. Therapeutic unbound phenytoin plasma concentrations were attained within 15 minutes in all patients. Adverse events were similar to adult experiences. Vomiting was most common among the 5- to 11-year-olds compared to nystagmus in 12- to 18-year-old patients. Pruritus occurred in 2 (7.4%) of all patients. Injection site edema was noted in one patient on day 1 and progressed to peripheral edema on days 2 and 3. Additional data pooled from experience with fosphenytoin in 62 pediatric patients demonstrated similar time to phenytoin conversion as adults (mean 8.3, range 3–19 minutes) with no differences observed between patients aged less than 29 days to 17 years.[36] Therapeutic unbound phenytoin plasma concentrations were attained within 15 minutes in all patients. At lease one adverse event was reported in 49 (79%) patients. The most common adverse events were emesis (29%), nystagmus (13%), pruritus (11%), and fatigue (11%). Intravenous infusion rate or discontinuation of infusion was required in 5 (8%) patients. Bruising, tenderness, swelling, or erythema was seen at the infusion site in 3 (6%) of 52 evaluable patients.

One comparison trial of fosphenytoin with intravenous phenytoin in neonatal and pediatric patients has been published to date. The pharmacokinetics, efficacy, and cardiovascular effects of fosphenytoin and phenytoin were compared in 38 children ranging from 13 to 156 (median 29) months of age with malaria and GCSE.[37] Eleven patients received intravenous phenytoin, 16 received intravenous fosphenytoin, and 11 received intramuscular fosphenytoin. Equivalent doses of phenytoin were given as loading and maintenance doses. Phenytoin loading doses were infused intravenously over 20 minutes and maintenance doses were infused over 5 minutes. All intravenous fosphenytoin doses were infused at a rate of 50 mg PE/min. Intramuscular fosphenytoin was injected into the anterior aspect of the thigh. Overall, therapeutic unbound phenytoin plasma concentrations were achieved within 5 to 20 minutes for all patients; maximum plasma phenytoin concentrations were achieved most rapidly with intravenous fosphenytoin. Cerebrospinal fluid-to-plasma phenytoin concentration ratios ranged from 0.12 to 0.53 (median 0.28) for all patients. There were no differences in seizure control, neurologic sequelae, or death among patients. Adverse cardiovascular events (i.e., hypotension) were similar between agents and were most often attributed to seizures. Infusion-site and other infusion-related adverse events were not reported.

Perhaps the most sensitive issue surrounding the use of intravenous phenytoin in neonatal and pediatric patients is PGS.[24,25] PGS is a delayed soft tissue injury resulting from intravenous phenytoin administration, with or without extravasation. Three stages of PGS have been described based on time from phenytoin administration.[34,38] Stage 1 usually occurs between 2 and 12 hours post-phenytoin administration. This stage is character-

ized by local intravenous site pain, edema, and discoloration (blue-purple). Between 12 and 16 hours, stage II changes are evidenced by the presence of more generalized pain and edema, as well as migration of tissue discoloration to include more distal and proximal tissue. Severe cases may progress to tissue necrosis and compartment syndrome. Stage III is described as the resolution phase. This phase can last as long as 4 weeks, with pain usually representing the last sign or symptom to resolve. Management of PGS includes prompt recognition, cessation of intravenous infusion, elevation of extremity, local application of dry heat, and local compression. For more severe cases, aggressive wound care, preventative antibiotic therapy, surgical debridement, and, possibly, amputation may be required. Although rare in adults[21-23] the true incidence of PGS in nonadult populations is unknown. Inference from data indicating that the risk and sequelae from intravenous extravasation is higher in nonadult populations has led to the belief that the risk of PGS is greater in these patients. Also, the inability to avoid risk factors for phenytoin infusion-related adverse events is more likely due to anatomical differences between adult and nonadult populations. Regardless of the risk, the short- and long-term clinical and economic impact of this potentially severe phenytoin-specific complication to an individual can be staggering. As such, the potential for this adverse event alone may be the deciding factor between fosphenytoin and phenytoin for the individual clinician. Medicolegal ramifications for severe cases of PGS following phenytoin use are equally concerning, since reasonable consensus exists identifying specific high-risk populations for phenytoin adverse events. Prompted by the potential for improved safety with fosphenytoin, the FDA has listed fosphenytoin as an approved active moiety for which it issued a 1998 written request for pediatric studies under Section 505A of the Federal Food, Drug, and Cosmetic Act.[39] Although this is merely a suggestion from the FDA, it signifies the importance and need for studies evaluating the safety and efficacy of an alternative method for parenteral phenytoin delivery in the management of seizures in nonadult populations.

PHARMACOECONOMIC CONSIDERATIONS

Since efficacy is similar, differences in acquisition cost, administration route, infusion rate, and adverse events are central to pharmacoeconomic comparisons between phenytoin and fosphenytoin. The average wholesale price for fosphenytoin is 16 times that of parenteral phenytoin.[3] Locally, hospital pharmacy acquisition cost ratios for equivalent doses (fosphenytoin-to-phenytoin) range from 18.5 to 38.5. It has been suggested that the difference in acquisition cost is the lone obstacle hindering widespread use of fosphenytoin.[40-42] To date, there have been five pharmacoeconomic analyses evaluating fosphenytoin versus phenytoin.[43-47] All of these studies were conducted using information from adult populations; however, one analysis described how to perform a preliminary pharmacoeconomic analysis using published adverse event rates and data from chart review in emergency department patients,[47] and one developed a pharmacoeconomic model based on a survey of acute care hospital nurses.[43] Since these two analyses were not performed respective to the administration of fosphenytoin or phenytoin, they are only presented in summary in Table 1. The following discussion will focus on the three analyses that compared the cost-effectiveness of each agent following one-time administration of both drugs in the emergency department during a prospective clinical trial.[44-46] Although patient populations in which fosphenytoin is most often advocated over phenytoin (e.g., neonatal, pediatric, elderly, and GCSE patients) were excluded from all three of these comparisons, they represent the only published prospective, pharmacoeconomic comparisons to date. The design and results of all five pharmacoeconomic analyses are summarized in Table 1.

Despite a 13-fold higher acquisition cost, Marchetti et al. found fosphenytoin to be more cost-effective than intravenous phenytoin.[44] This was primarily due to a lower incidence of adverse events. Specifically the two most costly adverse events to manage in this study were: (1) significant neurologic toxicity and (2) severe infusion site reactions requiring a change in administration site. A major limitation to this study is the use of an activity-based cost model. This model assumes that the total salary for a given unit of time for clinical personnel (e.g., nurse) is devoted entirely to the care of a single patient; however, it is more likely that the clinician is able to address the issues of more than one patient over a given period of time. Another limitation is the fosphenytoin adverse event rate may have been underestimated due to more conservative infu-

Table 1. Pharmacoeconomic studies comparing fosphenytoin and phenytoin

Ref	Clinical Data Source	Patients	Economic model (Costs)	AE	Results		Advantage
					AE	Cost	
47	Literature and chart review	39 ED pts receiving LD of IV PHT vs FOS clinical trial information	CE (Semifixed ED costs; AE costs estimated from chart review)	Retrospective, chart and literature review	67% PHT vs. 21% FOS	Per patient: PHT $222.60 vs FOS $152.30; $2,743 overall savings for FOS	FOS
43	Survey: ED and ICU nurses	Not applicable	CE (Marginal hospital costs; AE costs from survey)	AE rates and management obtained from survey	40-62% PHT 0.3% FOS	LD/pt: $57.59 PHT vs. $129.50 FOS MD/pt: $58.82 PHT vs $60.62 FOS	LD: PHT; MD: FOS
45	Prospective, open-label, observational trial and chart review	256 adults given IV PHT (20 mg/min) or FOS (100 mg PE/min) for non-emergent seizures	CM (Variable drug acquisition costs; AE costs and personnel time spent managing AEs from survey)	Prospective and retrospective; Tx via internal protocol	9.1% PHT vs 11.9% FOS	Per patient:$5.39 PHT vs. $110.14 FOS	PHT
46	Prospective, randomized, comparison of oral PHT, IV PHT, and IV FOS for PHT LD	52 adult on PHT who present to ED with subtherapeutic PHT level or seizures. PHT 50 mg/min,FOS 150 mg PE/min	CE (Variable drug acquisition costs, AE costs from personnel time managing AEs using time-and-motion studies, and time in ED	Prospective; Tx via internal protocol	AE ratios*: Oral PHT 1.06, IV PHT 1.93, IV FOS 2.13;	Per patient:Oral PHT $2.83 IV PHT $23.48 IV FOS $176.79	PHT

AE, adverse events; CE, cost-effectiveness; CM, cost miminization; ED, emergency department; FOS, fosphenytoin; ICU, intensive care unit; LD, loading dose; PE, phenytoin equivalent; PHT, phenytoin.

** = number of AEs/number of patients.*

sion rate of 100 mg PE/min.

In 2000, Touchette et al. performed a cost-minimization analysis from a hospital emergency department perspective using adverse event rates and associated estimated treatment costs from a previously conducted prospective, unblinded clinical trial.[7,45] The final cost-minimization model demonstrated the cost of phenytoin to be $5.39 per patient versus $110.14 per patient for fosphenytoin. The adverse event rate in the clinical trail was considerably lower than that reported in other investigations. Addressing this, the investigators performed several analyses using different adverse event rate scenarios with their own estimates for adverse event management costs. After increasing adverse event rates for both agents to levels consistent with other investigations, phenytoin remained the preferred agent with an estimated cost of $38.59 per patient versus $110.08 per patient for fosphenytoin. Phenytoin was the preferred agent even when maximum reported adverse event rates for both agents were used. Fosphenytoin was preferred only when the rate of PGS exceeded 1% or the cost of therapy for PGS exceeded $10,000 per episode. There are a number of limitations to this study. First, adverse event rates may have been underestimated compared to other centers and other patient populations receiving these agents. This is likely due to more conservative infusion rates, especially with the patients receiving phenytoin. In the clinical trial, phenytoin was infused at a rate of 20 mg/min and fosphenytoin at 100 mg PE/min. These infusion rates are 40% and 67% of the recommended maximum rates of 50 mg/min and 150 mg PE/min, respectively. The maximum infusion rates are more frequently used, especially in more emergent situations (e.g., GCSE). Second, the cost-minimization analysis was performed after a single dose of each agent. Adverse events for each agent could occur with any dose; therefore, extrapolation of these data beyond the emergency department should be done cautiously.

Rudis et al. compared the cost-effectiveness of phenytoin loading between oral phenytoin, intravenous phenytoin, and intravenous fosphenytoin.[46] Patients were monitored for adverse events during the 24 hours after medication administration. Adverse events were treated according to a standard internal protocol. The adverse events included in the final model included ataxia, disorientation, dizziness/headache, hypotension, pruritus, nausea/vomiting, nystagmus, phlebitis, and tachycardia. Pain during infusion was not included. Adverse event ratios (total number of adverse events/total number of patients) were 1.06 for patients receiving oral phenytoin, 1.93 for patients receiving intravenous phenytoin, and

2.13 for patients receiving intravenous fosphenytoin. Mean times to safe emergency department discharge were 6.4, 1.7, and 1.3 hours, respectively. The results of the primary analysis demonstrated administration of oral phenytoin to cost $2.83 per patient versus $23.48 per patient for intravenous phenytoin and $176.79 for intravenous fosphenytoin. Overall, oral phenytoin was most cost-effective because of a lower adverse event rate and lower cost. When time to safe emergency department discharge was used as the primary outcome, intravenous phenytoin was more cost-effective than both oral phenytoin and fosphenytoin. Fosphenytoin was not found to be most cost-effective in the scenarios evaluated. The major limitation of this study is that the antiseizure efficacy of each regimen was not included in the model. In contrast to patients receiving intravenous phenytoin and fosphenytoin, oral phenytoin patients required 4–5 additional hours to be safely discharged from the emergency department. These times allow for absorption and ideally attainment of therapeutic phenytoin plasma concentrations. Although the authors reported no seizure activity in any patient during time in the emergency department, due to the small number of patients a type II statistical error may have occurred. This is important since the cost of treating an active seizure because of a delay in attaining therapeutic phenytoin plasma concentrations could have a dramatic impact on the cost estimates of this study.

Future Considerations

It is only a matter of time until the patent for the branded formulation of fosphenytoin expires. This will assuredly change the pharmacoeconomic climate surrounding the therapeutic decision to use phenytoin or fosphenytoin. It is conceivable that if the acquisition prices for equivalent doses of both agents were equal, fosphenytoin would become the mainstay for intravenous phenytoin delivery. Although this situation is unlikely to occur in the short-term, once off patent, fosphenytoin will likely undergo more competitive pricing, lending to decreased formulary pressures and a greater opportunity for a broader range of clinical disciplines to become familiar with fosphenytoin. This increased familiarity may be most evident in pediatric practices and institutions.

CONCLUSION

The decision to use fosphenytoin over phenytoin is multifactorial. Both agents result in similar times to therapeutic total phenytoin concentrations, and both possess similar concentration-dependent (e.g., nystagmus, dizziness, ataxia, somnolence) and cardiovascular adverse events. Benefits to fosphenytoin use are more rapid attainment of therapeutic unbound phenytoin plasma concentrations and less infusion-related pain, venous irritation, phlebitis, and, possibly, decreased risk for PGS. The only adverse events more common with fosphenytoin are infusion-related, non-allergic, transient paresthesias and pruritus. Intramuscular administration of fosphenytoin also allows greater flexibility for parenteral phenytoin delivery, particularly in patients with limited intravenous access.

The potential clinical benefits of fosphenytoin are countered, however, by its increased acquisition cost. If the acquisition costs for fosphenytoin and phenytoin were equal, fosphenytoin would arguably replace phenytoin universally. Because their costs are significantly different, however, institution-specific cost analyses should be done to assure that the most appropriate agent is being used, while being sensitive to the potential disparate risk profiles between patient populations. It should also be realized that the institutional burden of a single case of phenytoin-related PGS, especially in a pediatric or neonatal patient, could be immense relative to the increased acquisition cost associated with fosphenytoin. Until the issues of safety and cost are objectively ameliorated, individual clinicians will likely use their own experience to dictate the place of fosphenytoin in their respective practices. Each patient should be evaluated individually to identify those who will benefit most from fosphenytoin.

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