REVIEW ARTICLE

Drug Safety 2000 Jun; 22 (6): 459-466
0114-5916/00/0006-0459/$20.00/0

Fosphenytoin and Phenytoin in Patients with Status Epilepticus

Improved Tolerability versus Increased Costs

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Contents

Abstract

Tonic-clonic status epilepticus (TCSE) is the most common neurological emergency and affects approximately 60 000 patients each year in the US. The risk of complications increases substantially as TCSE lasts longer than 60 minutes. Ideally, drugs used to treat this condition should be well tolerated when administered as rapid intravenous infusions and should not interfere with patients' state of consciousness or cardiovascular and respiratory functions. Because of its efficacy, absence of sedation or respiratory suppression, intravenous phenytoin has largely replaced phenobarbital (phenobarbitone) as the second agent of choice (following the administration of a benzodiazepine) in the treatment of TCSE. While the efficacy of phenytoin in the treatment of acute seizures and TCSE is well established, the parenteral formulation of phenytoin has several inherent shortcomings which compromise its tolerability and limit the rate of administration. Intravenous phenytoin has been associated with fatal haemodynamic complications and serious reactions at the injection site including skin necrosis and amputation of extremities.

Fosphenytoin, a phenytoin prodrug, has the same pharmacological properties as phenytoin but none of the injection site and cardiac rhythm complications of intravenous infusions of phenytoin. While fosphenytoin costs more than intravenous phenytoin, treating the acute and chronic complications of TCSE itself, and the complications of intravenous phenytoin can also be costly. All other factors being equal, there is no doubt that fosphenytoin is better tolerated and can be delivered faster than intravenous phenytoin; 2 measures that clearly improve outcome in patients with TCSE. The tolerability of intramuscular fosphenytoin also extends its use to clinical situations where prompt administration of a non-depressing anticonvulsant is indicated but secure intravenous access and cardiac monitoring are not available, such as treatment of seizures by rescue squads in

the field and serial seizures in the institutionalised, elderly and other patients with intractable epilepsy.

Seizures and epilepsy can have a devastating impact on the lives of affected individuals. These untoward medical and psychological effects, however, tend to be long term, usually taking years to develop. Convulsive status epilepticus, on the other hand, epitomises the dangers ascribed to chronic epilepsy as these complications can occur after a few hours of sustained seizures. Conversely, uneventful, optimal recovery is expected whenever immediate intervention is implemented in patients with tonic-clonic status epilepticus (TCSE). A number of pharmacoeconomic studies have attempted to assess the cost of treating the complications of prolonged TCSE [1,2] and managing adverse events related to the use of anticonvulsants in such cases [2-4]. There is a general agreement that treatment modalities that obviate the need for emergency department visits and the use of drugs that have less risk of adverse effects provide a substantial pharmacoeconomic benefit, despite the higher costs of some drugs. However, no study has been able to assign a dollar value to these benefits [3].

1. Treatment of Status Epilepticus

TCSE is the most common neurological emergency and affects approximately 60 000 patients each year in the US.[5,6] Approximately 1 in every 100 patients with epilepsy will have at least 1 episode of TCSE each year. Whereas TCSE can occur at any time, 20% of patients will have at least 1 episode of TCSE within the first 5 years after being diagnosed with epilepsy. It has been estimated that status epilepticus in general, accounts for about 3.5% of all admissions to neurological intensive care units[7] and 0.13% of all visits to a university emergency department.[8]

The options for the treatment of TCSE are limited and include the benzodiazepines (diazepam, lorazepam and midazolam), barbiturates [phenobarbital (phenobarbitone), pentobarbital (pentobarbitone), and thiopental sodium], and phenytoin.[9] The benzodiazepines are very effective but tolerance and loss of efficacy limit their usefulness in more chronic situations. Respiratory suppression and hypotension may complicate rapid intravenous infusions, particularly in children and patients previously given barbiturates. Phenobarbital was the primary agent used for the treatment of status epilepticus until the 1970s. Although very effective, loading doses of phenobarbital produce considerable sedation and may interfere with the neurological assessment of patients.[9] In addition, the vehicle of parenteral phenobarbital marketed in the US has been recently changed to propylene glycol. An increased risk of hypotension is expected whenever this new formulation is given as a bolus.

As a consequence of its efficacy, absence of sedation or respiratory suppression, intravenous phenytoin has largely replaced phenobarbital as the second agent of choice (following the administration of a benzodiazepine) in the treatment of recurrent seizures and status epilepticus. Despite these advantages, the use of a rapid infusion of phenytoin is not without drawbacks. Although serious adverse effects of phenytoin were generally considered infrequent,[10-12] intravenous phenytoin has been associated with numerous cases of fatal haemodynamic complications and serious reactions at the injection site, including skin necrosis and amputation of extremities.

2. Experience with Phenytoin

The present formulation of parenteral phenytoin was developed by Murphy and Schwab.[13] Phenytoin is a weak organic acid (pKa = 8.2 to 8.3 at 20 to 25°C) with poor aqueous solubility. The solubility in aqueous solutions increases as the pH increases. The formulation of phenytoin that is stable enough for parenteral administration has a pH of 12 adjusted with sodium hydroxide, in a vehicle containing 40% propylene glycol and 10% alcohol. Phenytoin becomes increasingly more soluble in aqueous solutions as pH increases.

Whereas most poorly water soluble drugs can

be solubilised by water miscible co-solvents, such as propylene glycol/alcohol, the solubility of non-polar solutes such as phenytoin decreases exponentially as the propylene glycol/alcohol solvent is diluted with other intravenous solutions, and micro crystals may form.[14,15] Other factors, such as suspended matter present in the intravenous solution, may also affect the solubility of phenytoin.[14,15]

The high pH and the vehicle of parenteral phenytoin have been associated with several complications and, to some extent, limited its usefulness in acute situations. The 2 most serious adverse effects of intravenous phenytoin have been cardiovascular complications and problems at the injection site. Phenytoin has a negative inotropic action[16] and both phenytoin and propylene glycol can cause cardiac rhythm disturbances and hypotension.

Experimental evidence, now supported by recent intravenous fosphenytoin studies, suggests that propylene glycol played an important role in the cardiovascular complications of intravenous phenytoin.[17-19] Intravenous infusions of propylene glycol can cause convulsions, cardiac arrhythmias, haemolysis, hypotension and bradycardia.[20-26] Propylene glycol-induced hypotension and bradycardia occur within 3 to 5 seconds after intravenous administration, well before the compound reaches the CNS. Furthermore, efferent activity in sympathetic nerves is markedly decreased for 10 to 15 seconds, beginning within 3 to 5 seconds after administration of propylene glycol.

Administration of atropine prior to the injection abolishes the depression of heart rate and hypotension suggesting that both events are vagally mediated.[27] Fatal cardiac arrest reported with intravenous phenytoin usually results from a combination of hypotension and asystole.[28-34] Because of the cardiovascular complications of intravenous administration of phenytoin the manufacturer submitted a revision (with additional warnings and recommendations), for the package insert of parenteral phenytoin to the US Food and Drug Administration[35] recommending a maximum rate of infusion to 50 mg/min. Several other recommendations were made in order to improve the tolerability of parenteral phenytoin which included avoidance of small peripheral veins, the use of a large vein with good flow, piggybacking the infusion in saline, and ECG monitoring.[18,19] Nevertheless, at least 7 fatalities have been reported with infusion rates below the recommended 50 mg/min. Five of the 7 patients were above 60 years of age. Patients at risk of developing clinically significant hypotension include the elderly, and patients with either sepsis or underlying cardiovascular diseases.[12,28-33] As serious complications and fatalities were reported with the use of intravenous phenytoin despite adherence to the recommendations, several authors recommended that oral phenytoin should be used whenever possible.[36-39]

As opposed to the cardiovascular complications of parenteral phenytoin, complications occurring at the injection site with the intravenous formulation are probably related to the caustic pH of the solution. This type of complication has not been reported with propylene glycol by itself. A parenteral formulation of phenytoin dissolved in tetraglycerol,tris-buffer and water with a lower pH of approximately 10 is available in parts of Europe [40,41]. Reactions to local extravasation of intravenous phenytoin have ranged from skin discomfort and skin sloughing to limb amputation.[18,36-47] The pathology of an amputated necrotic hand secondary to extravasation of intravenous phenytoin showed thrombosed veins and venules with vascular fibrinoid necrosis and no involvement of arteries.[45]

Extravasation of intravenous infusions can cause serious complications.[18,39,42] It has been recommended that before administering intravenous medications, the nurse should instruct the patient to immediately report any unusual sensation such as pain, burning or tightness at the injection site, and in the area of infusion.[48] In our experience, this recommendation has been of limited value with parenteral administration of phenytoin because otherwise uncomplicated injections are accompanied by a burning sensation that propagates proximally along the vessel and is probably secondary irritation of the vessel wall by phenytoin that mimics the signs of more serious, complicated

extravasations. These reactions are more common with infusions in smaller veins and correlate with the rate of infusion and the concentration of phenytoin solution. In cases of phenytoin extravasation, a delayed skin reaction is not uncommon and presents as a bluish discolouration of the tissue surrounding the intravenous site. This type of reaction usually stabilises, in which case it is of no major consequence. In cases in which it progresses, 4 to 6 hours after the initial reaction there is erythema and oedema that tends to spread circumferentially from the site of injection. 10 to 12 hours after the onset of symptoms, vesicles and bullae also develop and may ultimately progress to skin necrosis.

Intramuscular administration of phenytoin is associated with considerable local pain and discomfort, and the absorption of the drug is erratic and significantly delayed.[49] Extensive microscopic crystallisation and sterile abscesses can occur at the injection site and may be associated with muscle necrosis. Crystallisation can also occur in normal muscular tissue in the absence of necrosis. Phenytoin is not suitable for intramuscular injections.

3. Experience with Fosphenytoin

Fosphenytoin is a water soluble disodium phosphate ester of phenytoin that can be given parenterally without the need for the propylene glycol vehicle.[50] The water solubility of fosphenytoin makes it compatible with common intravenous solutions. It is a better tolerated compound to administer intravenously than phenytoin since propylene glycol itself was probably the cause of bradycardia and many of the cardiac arrhythmias reported with the use of intravenous phenytoin.[17,18] With the addition of the phosphate moiety to the phenytoin molecule, fosphenytoin weighs more than phenytoin; 150mg of fosphenytoin is equivalent to 100mg of phenytoin.

Dose administration can be reported actual weight of fosphenytoin or as the phenytoin equivalence (PE). The PE refers, on a one to one basis, to a dose of phenytoin. Upon entry into the vascular compartment, the phosphate molecule is removed by phosphatases converting fosphenytoin into active phenytoin. The conversion of fosphenytoin after intravenous administration averages 8.4 minutes,[51] and the time to reach maximum concentration (t_{max}) of fosphenytoin averages 5.7 minutes. Because of the time required for dephosphorylation to produce phenytoin, fosphenytoin must be given at a dosage of 225mg fosphenytoin/min (150mg PE/min) to produce free phenytoin concentrations bioequilavent to that produced by 50 mg/min of phenytoin. The pharmacokinetics, tolerability and tolerance of intravenous fosphenytoin have been investigated in 17 clinical studies which enrolled 925 study participants. Nine clinical trials involving 136 healthy participants were completed using doses of 100 to 1200mg and infusion rates of 3.3 to 150 mg/min.

Fosphenytoin, total phenytoin, and free phenytoin concentrations and pharmacokinetic parameters were similar in patients compared with healthy participants. Plasma fosphenytoin concentrations increase with increasing dose and infusion rate, peak at the end of infusion, and then decline with a half-life of approximately 0.25 hours. The half-life is independent of dose and infusion rate.[52]

A single dose, double-blind study compared the tolerability of intravenous fosphenytoin in patients requiring a loading dose of phenytoin. A total of 52 patients were randomised to receive either intravenous fosphenytoin (n = 39) or intravenous phenytoin (n = 13). Patients in the treatment group received similar doses of study drug (899mg PE; 12.7 mg/kg) or phenytoin (879mg; 11.3 mg/kg). However, fosphenytoin was infused at nearly twice the rate of administration (82mg PE/min; range 40 to 103mg PE/min) compared with patients in the phenytoin group (42.4 mg/min). Despite the faster rate of infusion, fosphenytoin produced no significant cardiac arrhythmias or changes in heart rate, respiration, or diastolic blood pressure. A drop in systolic blood pressure occurred and was reported to be statistically but not clinically significant. A similar study was subsequently conducted but patients were given maintenance doses of intravenous fosphenytoin or intravenous phenytoin for 3 to 14 days after receiving a loading dose. Patients

were randomised to receive intravenous fosphenytoin (n = 88, mean dose = 1088mg PE or 15.3mg PE/kg) or intravenous phenytoin (n = 28, mean dose = 1082mg or 15.0 mg/kg). Maintenance therapy was given for more than 4 days (fosphenytoin = 4.3 days, phenytoin = 4.7 days). Similar infusion rates were used (fosphenytoin 37mg PE/min, phenytoin 33 mg/min).

A significantly greater number of patients reported pain in the infusion site with phenytoin (17%) compared with fosphenytoin (2%). A subset of 10 patients had serial-timed total and free plasma fosphenytoin and phenytoin concentrations measured after the loading dose. At the first sample drawn at 1h postinfusion, all patients had total phenytoin concentrations above 10 μg/ml and the mean concentrations were essentially the same for the 2 groups.

A double-blind parallel tolerability study was conducted comparing intravenous fosphenytoin given at 225 mg/min (150mg PE/min) vs phenytoin at 50 mg/min[53]. Patients were randomised on a 4 : 1 basis to receive intravenous fosphenytoin (n = 90) or phenytoin (n = 22). The loading dose was either 20 mg/kg (patients with no detectable phenytoin in the plasma) or 15 mg/kg if the plasma phenytoin concentration was 7 μg/ml or less. Infusions had to be slowed or discontinued significantly more often with intravenous phenytoin than with fosphenytoin. Adverse events with the 2 drugs were different. Pruritus, at times very uncomfortable, was more common with fosphenytoin (48.6%), and pain at the site of infusion was more frequently reported with phenytoin (63.6%). The incidence of dizziness, somnolence and ataxia, typical of phenytoin, was the same for both drugs. The pruritus with fosphenytoin typically affects the trunk, especially in the groin region, or the back of the head. Pruritus, when reported, presented soon after initiation of the infusion and abated rapidly when the infusion was discontinued. The occurrence and severity of the pruritus was a rate-dependent phenomenon as lowering the rate reduced or abolished the symptom. Changes in blood pressure were noted in both groups, with a mean decline in systolic blood pressure of 13.7mm Hg with fosphenytoin and 5.9mm Hg with phenytoin. Pruritus has not been reported after the intramuscular administration of fosphenytoin.[54,55]

We recently completed an open label study of the pharmacokinetics and tolerability of intramuscular fosphenytoin compared with a 2ml saline placebo injection (unpublished data). Patients received either a 10 mg/kg dose of fosphenytoin intramuscularly or a saline injection. Typically, this full loading dose is divided into 2 injections of 10 mg/kg each. However, since study participants would be receiving saline injections on the opposite side for tolerability comparisons, we used a loading dose of 10 mg/kg to abide by standard clinical practice and avoid multiple injections of fosphenytoin. The primary intent of the study was to establish how quickly effective serum concentrations were achieved following intramuscular administration of fosphenytoin. Intramuscular injections were administered into each gluteal muscle using a 22 gauge needle. Time between injections ranged from 2 to 4 minutes. Each injection was administered by applying gentle pressure to the syringe plunger. A total of 24 patients were given intramuscular doses of fosphenytoin ranging from 491 to 973mg PE which corresponded to injection volumes ranging from 9.8 to 19.5ml. Blood sampling, starting at 10 minutes after intramuscular administration of fosphenytoin in the first 8 patients yielded very high concentrations. The remaining 16 patients had their initial sample taken at 5 minutes, and 4 of them achieved serum concentrations greater than 10 μg/ml.

In this sample population, total serum phenytoin concentrations ranged from <0.5 μg/ml (undetectable) at 5 minutes postinjection to 46.72 μg/ml at 20 minutes. Mean phenytoin concentrations and standard deviations were determined at each time interval. The standard deviation declined steadily after 10 minutes. By 30 minutes, more than half of the participants achieved effective phenytoin concentrations. Additionally, free phenytoin concentrations were analysed and remained relatively stable for each patient. The average total serum phenytoin

concentration (C_{max}) was 19.28 μg/ml with an average t_{max} of 113.04 minutes. Fosphenytoin was considerably better tolerated than saline; 13 patients (54.2%) reported no pain on the fosphenytoin side immediately postinjection compared with 21 patients (87.5%) on the saline side. Of the 45.8% reporting discomfort immediately postinjection on the fosphenytoin side, 6 reported mild, 4 reported moderate, and only 1 patient reported severe discomfort. The difference in total pain scores between fosphenytoin and saline steadily decreased at 30 and 60 minutes, and no difference between the groups was detected at 120 minutes postinjection.

4. Discussion

The most important factors determining outcome in patients with TCSE are the aetiology and the time elapsed from the onset of seizures until treatment is initiated. In addition, the combination of a prolonged convulsion and the sequential administration of a benzodiazepine, phenytoin and phenobarbital almost invariably results in stupor, hyperthermia, and aspiration. In the Veterans Affair Status Epilepticus Cooperative Study, respiratory suppression requiring intubation and assisted ventilation occurred in 18.9 %, and hypotension severe enough to require the use of pressor agents occurred in 32.6% of all cases.[56] In the absence of a previous history or a family member to provide information, the persisting depression of consciousness, elevated body temperature and elevated white blood cell count in the peripheral blood should raise the question of CNS infection in such patients. At our institution, 92% of these cases receive a computed tomography scan of the head, and 63% of these cases receive a lumbar puncture. Prolonged seizures are often associated with CSF pleocytosis[56-58] which also requires further medical observation. Many of these patients end up being treated with systemic antibiotics for presumed CNS infection. Increased secretion, decreased airways protection and intubation are commonly associated with aspiration pneumonia. It is clear that anything less than immediate intervention will not prevent hospital admission and the costly investigations associated with patients with TCSE. Ideally, the drugs used to treat patients with status epilepticus should be well tolerated when administered as rapid intravenous infusions and should not interfere with the patient's state of consciousness or cardiovascular and respiratory functions.

While the efficacy of phenytoin in the treatment of acute seizures and status epilepticus is well established, the parenteral formulation of this drug has several inherent shortcomings which compromise its tolerability and rate of administration. With the development of fosphenytoin, these concerns regarding complications with the intravenous infusion of phenytoin are addressed. Fosphenytoin, however, costs more than intravenous phenytoin. Being a prodrug of phenytoin, cost conscious decision-makers have occasionally argued that there is no justification for choosing fosphenytoin over intravenous phenytoin. Some institutions in the US have attempted to reserve fosphenytoin for cases of status epilepticus, whereas nonemergency situations were treated with intravenous phenytoin. This approach however, has not worked well. As a consequence of the different rates of infusion of the 2 drugs, we have seen serious cardiocirculatory complications after phenytoin being mistaken for fosphenytoin administration, and given at infusion rates of 150 mg/min or faster. For this reason, the pharmacy at our institution no longer carries intravenous phenytoin.

5. Conclusion

All other factors being equal, there is no doubt that fosphenytoin is better tolerated and can be delivered faster than intravenous phenytoin; 2 factors that clearly improve outcome in patients with TCSE. The tolerability of intramuscular fosphenytoin extends its use to other clinical situations where prompt administration of a nondepressing anticonvulsant is indicated but secure intravenous access and cardiac monitoring are not available, such as treatment of tonic-clonic status epilepticus by the rescue squad team in the field and serial seizures in patients with intractable epilepsy. The

cost difference between fosphenytoin and intravenous phenytoin is clearly less than the medical costs to treat any of the complications of prolonged TCSE or the potential malpractice costs due to complications resulting from the use of intravenous phenytoin in the US.

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