Status Epilepticus: The Slow and Agonizing Death of Phenytoin

Elizabeth A. Hall, PharmD; James W. Wheless, BScPharm, MD; and Stephanie J. Phelps, BScPharm, PharmD

Since its introduction in 1950, phenytoin (PHT) has been the premier parenteral anticonvulsant used in the management of generalized convulsive status epileptics (GCSE) that is refractory to benzodiazepines. Without question, its arrival was vital to the care of patients with acute seizures and was a welcomed alternative to paraldehyde and phenobarbital. However, after more than half a century of use, there continues to be insufficient evidence-based data to support its efficacy over other anticonvulsants as a first-line agent in pediatric or adult patients with GCSE. This coupled with its narrow mechanism of action, complex pharmacokinetics and pharmacogenomics, drug-drug interactions, unique adverse effects, and formulation issues that make administration difficult mandates that PHT be replaced by safer and superiorly effective anticonvulsants for the treatment of GCSE when benzodiazepines are ineffective. We believe that levetiracetam should become the preferred agent for seizures unresponsive to or recurring after treatment with a benzodiazepine as it is at least equally effective to PHT and has several important advantages. PHT has overstayed its welcome and it is simply time for it to exit the realm of acute seizure management as a first-line agent for benzodiazepine-refractory GCSE.

ABBREVIATIONS AED, antiepileptic drug; ECG, electrocardiogram; GCSE, generalized convulsive status epilepticus; ICER, incremental cost-effectiveness ratio; IV, intravenous; PHT, phenytoin; SS, seizure stopped

KEYWORDS epilepsy; fosphenytoin; guidelines; levetiracetam; phenytoin; status epilepticus

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Phenytoin (PHT) has long been a mainstay of therapy for the management of acute and chronic seizures. It was synthesized in 1908, and oral and parenteral formulations were introduced in 1938 and 1950, respectively.^{1,2} Despite the arrival of countless new antiepileptic drugs (AEDs), PHT continues to be used as a first-line agent in the management of generalized convulsive status epileptics (GCSE) when benzodiazepines have proven ineffective.

The 2016 American Epilepsy Society Guidelines for treatment of GCSE in children and adults³ recommends PHT and/or fosphenytoin as 1 of 3 options for the treatment of seizures unresponsive to or recurring after treatment with a benzodiazepine. However, the guidelines note that there is little evidence-based data supporting this practice, and a separate meta-analysis⁴ concluded that evidence does not support the use of PHT as a first- or second-line agent.³

When used alone, PHT is inferior to lorazepam, phenobarbital, or diazepam plus PHT at stopping GCSE within 20 minutes of infusion. Shaner et al⁵ prospectively compared phenobarbital to diazepam plus PHT and found that phenobarbital was as effective and comparable in safety to diazepam plus PHT. Although it is impossible to determine if diazepam was responsible for efficacy in the diazepam plus PHT group, a randomized controlled trial suggests that might be the case. In this study,⁶ lorazepam successfully stopped seizures

in 64.9% of patients as compared with 58.2%, 55.8%, and 43.6% of those given phenobarbital, diazepam plus PHT, or PHT alone, respectively.

PHT has also been compared with levetiracetam and valproate as first-line agents for GCSE. A randomized study found that levetiracetam was equally effective at terminating seizures and preventing recurrence at 24 hours when compared with PHT.⁷ Another study in patients with benzodiazepine-refractory GCSE showed no differences in efficacy with IV PHT (88%) and IV valproate (84%).⁸ A subgroup analysis of pediatric patients found that seizures stopped in 91% and 75% of those given valproate and PHT, respectively.⁸

Two independently conducted randomized controlled trials investigated whether levetiracetam was superior to PHT in the treatment of benzodiazepine-refractory GCSE in pediatric patients. In the Convulsive Status Epilepticus Paediatric Trial (ConSEPT), seizure cessation occurred in 60% of those receiving PHT and 50% of those receiving levetiracetam (risk difference −9.2%, 95% CI: −21.9 to 3.5; $p = 0.16$).⁹ In the Emergency Status Epilepticus in children (ECLIPSE) trial, seizures were terminated in 70% and 64% of those given levetiracetam or PHT, respectively. Patients achieved seizure cessation in 35 minutes versus 45 minutes in the levetiracetam and PHT groups, respectively (hazard ratio 1.20, 95% CI: 0.91–1.60; $p = 0.20$). Although

levetiracetam was not statistically superior to PHT, the authors concluded that it is a reasonable alternative to PHT for benzodiazepine-refractory GCSE given these results along with its safety profile and ease of use.¹⁰ It remains to be determined if PHT should be administered in larger doses, or at all when seizures fail to respond or recur following administration of first- or second-line therapies.

PHT is associated with many disadvantages that are clinically relevant. It has a narrow “therapeutic” index. It is highly bound to albumin and has saturable and disease-influenced protein binding, which requires therapeutic drug monitoring of both total and free serum PHT concentrations. The non-linear, partially saturated elimination (i.e., Michaelis-Menten pharmacokinetics) causes the relationship between the PHT dose and serum concentration to be extremely unpredictable. All of the above may contribute to severe and potentially fatal complications. PHT is a strong inducer of CYP3A4 and CYP2C19; hence, it is subject to a multitude of drug-drug interactions that can limit its usefulness. Patients with a CYP2C19 polymorphism may also experience significant increases in PHT serum concentrations.

There are also concerns regarding the administration of the parenteral PHT formulation. This product has an alkaline pH, which may cause pain and burning during infusion or phlebitis with chronic administration. Vaso-spasm near the infusion site can cause infiltration and/or extravasation with subsequent tissue necrosis. The PHT product also contains propylene glycol, a pharmaceutical solvent, that restricts the solubility of PHT in other parenteral solutions and limits the rate at which a loading dose may be given. Large doses of propylene glycol have been associated with lactic acidosis, acute kidney failure, and multiorgan failure. Intramuscular use is not recommended due to delayed and erratic absorption, and PHT can crystallize in tissue. Although using a PHT prodrug (i.e., fosphenytoin) resolves these administration issues, the same pharmacokinetic and pharmacogenomic disadvantages are observed with fosphenytoin.

A final disadvantage of PHT is its comparatively higher cost. In a systematic review, meta-analysis, and cost-effectiveness study of IV formulations of PHT (PHT and fosphenytoin), phenobarbital, valproic acid, levetiracetam, and lacosamide, levetiracetam was the most cost-effective (incremental cost-effectiveness ratio [ICER]: \$18.55/seizure stopped [SS]). Comparatively, fosphenytoin (ICER: -\$96.56/SS), PHT (ICER: -\$72.22/SS), and lacosamide (ICER: -\$221.07/SS) were not cost-effective.¹¹

There are now many alternative AEDs that boast more attractive features than PHT. We believe that levetiracetam should become the preferred first-line agent for benzodiazepine-refractory GCSE as it is at least as effective as PHT and has several important advantages.

It does not contain propylene glycol; hence, it has no infusion rate-related side effects and does not require simultaneous ECG monitoring during the infusion. Unlike PHT, levetiracetam has linear pharmacokinetics and is not highly protein bound. Likewise, there are no pharmacogenomic considerations for levetiracetam. Importantly, it is associated with significantly fewer drug-drug interactions because it is not highly protein bound and its metabolism is not dependent on nor does it affect hepatic isoenzymes. Finally, it has few severe adverse effects.

When the lack of evidence-based data to support the continued use of PHT is accompanied by its significant disadvantages, it escapes all reason that PHT continues to be used as a first-line AED for benzodiazepine-refractory GCSE. There is little question that it should be replaced by other safer and more effective, or equally effective, parenteral AEDs such as levetiracetam. The slow and agonizing death of PHT is torturous for all practitioners, and its use is unnecessary in the care of today's patient. Although PHT has played a critical role in acute seizure management, it should now be relegated to an important place in history.

ARTICLE INFORMATION

Affiliations Department of Clinical Pharmacy and Translational Science (EAH, SJP), Pediatrics (JWW, SJP), and Pediatrics, Division of Pediatric Neurology (JWW), The University of Tennessee Health Science Center, Memphis, TN

Correspondence Elizabeth A. Hall, PharmD; ealford2@uthsc.edu

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