A Review of Phenytoin Monotherapy in Adults With Nonrefractory Status Epilepticus

Journal of Pharmacy Technology
2015, Vol. 31(3) 99–103
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DOI: 10.1177/8755122514554457
pharmatech.sagepub.com

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Abstract

Objective: To review the literature evaluating the efficacy of phenytoin monotherapy in adults with nonrefractory status epilepticus. **Data Sources:** Articles were selected through a search of MEDLINE/PubMed (1966 to August 2014), using the terms phenytoin and status epilepticus. A further review of reference citations was performed to identify other relevant articles. **Study Selection and Data Extraction:** English-language case reports and clinical studies were reviewed. Publications evaluating the efficacy of phenytoin monotherapy primarily in adults with nonrefractory status epilepticus were included in the review. Two case studies and 5 clinical studies met the criteria. **Data Synthesis:** The ultimate goal for status epilepticus treatment is seizure cessation. Phenytoin, a venerable and oft-utilized antiepileptic, has been employed in first-line and second-line regimens for status epilepticus. Unfortunately, despite decades of use, data on the efficacy of phenytoin monotherapy in these nonrefractory cases have been limited. The available studies are quite heterogeneous in design, with variable underlying etiologies of status epilepticus, doses of study drugs, and comparators. Additionally, most are underpowered. When administered as second-line therapy, phenytoin monotherapy is comparable to valproic acid in abating status epilepticus. As first-line therapy, phenytoin monotherapy was inferior to lorazepam but not diazepam when used in combination with phenytoin or phenobarbital. Two other studies comparing phenytoin with valproic acid as first-line therapy had conflicting results. **Conclusions:** In adults with nonrefractory status epilepticus, phenytoin monotherapy is a viable option for second-line therapy. The data do not consistently support phenytoin monotherapy's use as first-line treatment. More robust and adequately powered clinical studies are needed to assess whether these results remain consistent and extend to more long-term efficacy measures, such as morbidity and mortality.

Keywords

epilepsy, anticonvulsants, neurology, critical care, clinical practice

Background

Status epilepticus is a life-threatening, medical emergency believed to affect up to 41 per 100 000 individuals (27 per 100 000 young adults and 86 per 100 000 elderly adults) annually in the United States.¹ It is characterized by continuous seizures for >5 minutes or ≥ 2 seizures without a return to consciousness in between.^{2–6} Its symptoms can include convulsions, altered mental status (including coma), personality changes, involuntary movements (ie, ocular, facial, and limb muscular twitching), and automatisms, which are sets of brief unconscious behaviors.⁷ The severity of these symptoms varies among individuals. Status epilepticus can also be associated with significant morbidity, including lasting neurologic deficits, and mortality. Mortality is heavily influenced by underlying seizure etiology and ranges from 14% in younger adults (16–59 years old) to 38% in the elderly, who more frequently have deadly etiologies.¹ The fact these high mortality rates persists despite several decades of modern pharmacologic treatment

may suggest that current treatment options are inadequate in a significant proportion of patients or are being employed suboptimally.²

A typical first-line regimen often consists of benzodiazepines, such as lorazepam or diazepam, either as monotherapy or in combination with phenytoin or valproic acid.⁸ Should initial therapy fail, treatment with a second-line regimen generally proceeds immediately following the conclusion of first-line therapy. Doing so minimizes treatment delays and capitalizes on potential synergies between the regimens. When at least 2 regimens have failed to abate status epilepticus, it is considered treatment-refractory.^{2,8}

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Through decades of use, phenytoin has emerged as one of the most popular and effective treatments for nonrefractory status epilepticus. Nonetheless, there is much ambiguity regarding its use as monotherapy in patients who are nonrefractory. Well-controlled, adequately powered studies comparing phenytoin monotherapy with other first-line and second-line regimens are lacking. Additionally, the published studies are considerably heterogenic. These differences include (a) the duration of epileptic activity used to diagnose status epilepticus, (b) the criteria used to assess treatment efficacy, (c) the length of time required before efficacy can reliably be assessed, (d) the impact that administering treatments in quick succession to one another has on assessing an individual treatment's contribution to efficacy, and (e) distinguishing between treatment effects and fundamental differences in underlying seizure etiologies. This review covers studies that investigated the effectiveness of phenytoin monotherapy in adults with nonrefractory status epilepticus.

Literature Review

Literature evaluating phenytoin monotherapy in adults with nonrefractory status epilepticus was accessed through a search of MEDLINE/PubMed (1966 to August 2014). The search strategy used the terms "phenytoin" and "status epilepticus" and was limited to English-language articles. A further review of reference citations was conducted to identify other relevant articles. Publications evaluating the efficacy of phenytoin monotherapy primarily in adult patients with nonrefractory convulsive status epilepticus were included. Two case reports and 5 clinical studies met these criteria. Note that in one of these studies, prior treatment for the current status epilepticus event was noted in 49% of patients without specifying the number of prior treatments, thereby precluding assessment of treatment refractoriness in these subjects.⁹ Additionally, another study enrolled 38% pediatric or adolescent patients.¹⁰

One case study involving a 62-year-old male patient with hepatic encephalopathy complicated by status epilepticus explored phenytoin monotherapy as first-line treatment.¹¹ He had no history of brain injury or epilepsy. His status epilepticus was associated with loss of consciousness and generalized, tonic-clonic seizures that lasted several hours. Following phenytoin administration, the patient regained consciousness, and the status epilepticus resolved without recurrence. Neither the time elapsed between the phenytoin administration and the resolution of status epilepticus nor was the dosing regimen provided. A subsequent electroencephalogram (EEG), 33 days after admission, was normal. The dosing regimen, the specific criteria used to assess efficacy, and a comparison of a baseline EEG with an EEG immediately after infusion would be useful for evaluation. Additionally, the patient received continual treatment

with branched chain amino acids (BCAA) for hepatic encephalopathy. While the initial event of hepatic encephalopathy resolved, on follow-up evaluation, 7 months later, it was determined that the hepatic encephalopathy had recurred. No published data indicate that the administration of BCAA would directly influence the outcome of status epilepticus. However, the possibility that concomitant administration of phenytoin and BCAA confounded the efficacy assessment could not be excluded, particularly if the status epilepticus was precipitated or exacerbated by hepatic disease. No definitive inferences can be made from this case alone. Nonetheless, this report adds to the body of literature supporting phenytoin's effectiveness in this treatment setting.

A large double-blind, prospective study by Treiman and colleagues evaluated the efficacy of phenytoin monotherapy as the first-line treatment of overt status epilepticus in 384 adults (18 or older).⁹ Patients were randomized into 1 of 4 treatment groups: lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), diazepam and phenytoin (0.15 mg/kg and 18 mg/kg, respectively), or phenytoin (18 mg/kg). Phenytoin was administered at a maximum rate of 50 mg/min in both the diazepam and phenytoin and phenytoin monotherapy groups. Status epilepticus was considered abated if all of its clinical and electrographic symptoms stopped within 20 minutes from the start of the infusion and did not recur within 20 to 60 minutes after the start of treatment. The primary endpoint was cessation of motor and electrographic seizure activity. There was a significant overall difference between the treatment success rates: lorazepam was effective in 64.9%, phenobarbital in 58.2%, diazepam and phenytoin in 55.8%, and phenytoin in 43.6% ($P = .02$ for the overall comparison among all groups). Notably, lorazepam exhibited superior efficacy over phenytoin in a pairwise comparison ($P = .002$) but not the other regimens. The 4 treatment regimens were also separately evaluated in an additional cohort of patients with subtle status epilepticus ($N = 134$). These patients were comatose with ictal discharges on the electroencephalogram, regardless of whether the patient has subtle convulsive movements. There was no significant difference in treatments for subtle generalized convulsive status epilepticus. An important consideration when evaluating these data is that approximately 49% of patients received prior treatment for their current episodes, and their regimens were not published. Not only had these patients already received first-line regimens, but some of them could have been treatment refractory. The proportion of patients with prior treatment was evenly distributed between the 4 treatment groups.

Subsequent studies evaluating phenytoin in adults with convulsive status epilepticus as first-line treatment used valproic acid as a comparator. The first of these was a controlled, open-label, crossover, and prospective study, conducted by Misra and colleagues, in 68 patients.¹² No age

restrictions were specified; however, the majority of patients in both the valproic acid and phenytoin groups (77% and 88%, respectively) were adult (≥ 16 years). Patients were randomized to receive either valproic acid 30 mg/kg or phenytoin 18 mg/kg. Patients not controlled after infusion of randomized treatment would receive the other study drug. The primary endpoint was immediate clinical seizure cessation after infusion of randomized treatment. The secondary endpoint was seizure freedom at 24 hours posttreatment. Status epilepticus abated after phenytoin administration in 14 patients (42%) compared with 23 patients (66%) after valproic acid administration (one-sided $P = .046$). In patients initially randomized to phenytoin, valproic acid was effective in 79% of patients whereas phenytoin was effective in 25% of patients originally randomized to valproic acid ($P = .004$). There was no statistical difference in 24-hour seizure freedom between the treatment groups ($P = .32$). A limitation of this study is that it was somewhat underpowered (71% power) to detect a difference between the treatment groups, given phenytoin's reported effect size. Additionally, the secondary endpoint analysis in patients who failed randomized study drug is confounded by the fact that the responses could be due, at least partly, to residual activity of the former agent (ie, valproic acid could displace phenytoin from albumin thereby increasing the level of free phenytoin). Also, this study was open label, which might have introduced bias.

A second study, by Gilad and colleagues, evaluating phenytoin and valproic acid monotherapy as first-line treatment was conducted in 74 adults (≥ 18 years) with status epilepticus ($N = 27$) or acute repetitive seizures ($N = 47$) and open-label, crossover, and prospective.¹³ Patients were randomized to receive either valproic acid 30 mg/kg or phenytoin 18 mg/kg. Patients not controlled after infusion of randomized treatment would receive the other study drug. The endpoints were clinical seizure cessation (primary) and evaluation of drug tolerability (secondary). Study drugs were considered effective if clinical seizures ceased within 20 minutes of infusion without any rescue medication. Overall, seizures discontinued in 43 patients (87.8%) on valproic acid compared with 22 patients (88%) on phenytoin. In the status epilepticus cohort, 5 patients (27.2%) on valproic acid and 2 patients (22.2%) on phenytoin required rescue medication. The tolerability data were inconclusive. Importantly, this study might have been underpowered, considering the small number of patients with status epilepticus. Additionally, the seizure duration for diagnosis of status epilepticus was 3 times longer than in the Treiman and Misra studies (30 minutes as opposed to 10 minutes), suggesting that patients in this study could have sustained more neuronal injury since treatment was administered only after diagnosis.^{3,9,12} Also, the efficacy rate of phenytoin was notably higher in this study compared with the Treiman and Misra studies.^{9,12} This may be due to this study's disproportionately high incidence

(62%) of treatment-responsive status epilepticus etiologies, such as subtherapeutic levels or noncompliance of antiepileptic treatment. Moreover, there was a mixture of generalized convulsive and complex partial status epilepticus diagnoses, each of which carries a distinct prognosis. Additional bias might have been introduced because the study was open label. Also, the authors did not specify whether the 20-minute interval for the assessment of seizure cessation begun at the beginning or conclusion study drug administration.

Phenytoin has also been investigated as second-line monotherapy for status epilepticus, as in the case of a 22-year-old female patient.¹⁴ Her past medical history was significant for epilepsy. On admission, she had clinical and electrographic evidence of status epilepticus and received intravenous lorazepam 4 mg twice over two 15-minute intervals with no symptomatic relief. She subsequently received intravenous phenytoin 1000 mg over 20 minutes followed by an infusion of phenytoin 750 mg over 24 hours. Both clinical and electrographic abnormalities rapidly improved on phenytoin administration, completely resolved after 40 minutes from the start of the infusion, and did not recur. The patient developed severe hypoglycemia (blood glucose < 20 mg/dL) assessed as related to phenytoin administration. The phenytoin infusion was withdrawn; oxcarbazepine and an intravenous 50% glucose were administered; and the patient consequently recovered without recurrence of hypoglycemia. No definitive conclusions can be made from a single case. For comparison to other studies, it would be helpful to know the weight-adjusted phenytoin dose and the specific criteria used to assess efficacy. Since 40 minutes passed before the status epilepticus was completely resolved, patients with similar clinical courses could be considered to have failed treatment in the other studies evaluated. Nonetheless, this report adds to the body of literature supporting phenytoin's efficacy as second-line monotherapy.

Agarwal and colleagues evaluated phenytoin monotherapy as second-line treatment for status epilepticus in a controlled, open-label, prospective study.¹⁰ Eligible patients ($N = 100$) had failed treatment with benzodiazepines (specific benzodiazepines and the number of previous doses were not specified) and were at least 2 years old. Patients were randomized to receive either valproic acid 20 mg/kg (loading dose) or phenytoin 20 mg/kg. If status epilepticus was non-responsive after infusion of study drug, therapy was changed per the treatment center's standard protocols. The primary endpoint was cessation of clinical and electrographic status epilepticus within 20 minutes of administration of study drug without symptomatic recurrence for the following 12 hours. The secondary endpoints were adverse events to treatment, in hospital complications, and neurological outcomes at discharge. Status epilepticus was considered abated when convulsive seizures ceased and the patient regained

consciousness. Valproic acid and phenytoin were statistically comparable and highly effective (successful in 88% and 84%, respectively, $P > .05$). Shorter duration of status epilepticus (less than 2 hours) was associated with higher efficacy ($P < .05$). There were no differences in the secondary endpoints. One limitation to extrapolating these data to adults with nonrefractory status epilepticus is that this study enrolled a high number of pediatric subjects (22/50 patients on valproic acid [mean age 27.4 ± 16.8 years] and 16/50 patients on phenytoin [mean age 27 ± 15.1 years] were under 18 years old). Also, given the small sample size, it is possible that this study was underpowered to detect a difference between treatment groups. The lower dose of valproic acid (20 mg/kg) used in this study compared with the Misra and Gilad studies (valproic acid 30 mg/kg) could have contributed to the observed lack of treatment difference.

A subsequent retrospective analysis by Alvarez and colleagues investigated phenytoin, valproic acid, and levetiracetam monotherapy as second-line treatments of 167 adults (16 years or older) with status epilepticus.¹⁵ The primary endpoint was failure of the second-line treatment (need to introduce another agent to control status epilepticus). Other endpoints were morbidity, new handicap, and cessation of electrographic seizures. Efficacy was considered when no change in antiepileptic medication was needed for at least 48 hours after clinical and electrographic resolution. Each compound was used as second-line treatment in about one third of the status epilepticus episodes at the following doses: phenytoin 20 mg/kg, valproic acid 20 mg/kg, and levetiracetam 20 mg/kg. The failure rate of phenytoin was not significantly different than valproic acid (odds ratio = 1.88, $P = .119$). Levetiracetam failed significantly more than valproic acid (odds ratio = 2.69, $P = .017$). There was no significant difference in the secondary endpoints. Limitations to this analysis include the fact that patients were not confirmed to be refractory to benzodiazepines prior to initiation of second-line therapy, as patients were administered study drug between 1 and 30 minutes following benzodiazepine therapy. Therefore, an undisclosed number of patients were treated with a combination of benzodiazepine and study drug to prevent seizure recurrence rather than second-line therapy due to treatment failure. Additionally, more patients in the phenytoin and levetiracetam cohorts had acute deadly etiologies ($P < .001$ and $P = .035$, respectively). The phenytoin cohort likewise had a significantly higher incidence (58.6%; $P = .002$) of patients with concurrent convulsive and nonconvulsive status epilepticus diagnoses compared with the valproic acid (37.3%) and levetiracetam (29.3%) cohorts. Nonconvulsive status epilepticus is frequently associated with more pathological etiologies.^{16,17} Together, these confounders suggest a possible underestimation of phenytoin and levetiracetam's effects. Also, the relatively small cohort sizes (58-70 patients) could suggest that the study was underpowered.

Other considerations include that this study employed a significantly more stringent criterion for efficacy (no recurrence within 48 hours) than used in other studies and that the lower dose of valproic acid used in this study (20 mg/kg) could contribute to the reported lack of treatment difference.

Discussion

Despite extensive experience with phenytoin, clarity on its role in the treatment of nonrefractory status epilepticus is relatively recent. In the literature reviewed in this article, phenytoin yielded comparable efficacy to valproic acid and levetiracetam when used as second-line treatment.^{10,14,15} As first-line therapy, phenytoin was significantly less effective than lorazepam and possibly valproic acid.^{9,12}

The studies reviewed were particularly heterogeneous. While they all enrolled patients with convulsive status epilepticus, one included patients with concurrent convulsive and nonconvulsive status epilepticus.¹⁵ The etiologies of status epilepticus were also inconsistent and in some cases clearly skewed data, as sicker patients were more likely to receive one particular study drug over another.¹⁵ Additionally, different criteria for defining status epilepticus and treatment efficacy were used. Therefore, patients who met the enrollment or efficacy criteria for one study would not necessarily have met the criteria in other studies. Although the majority of patients were adults in all studies, 2 studies enrolled a subset of pediatric patients, in whom status epilepticus is typically more treatment responsive.¹⁰ Nonetheless, despite a high proportion of pediatric and adolescent patients (38%) in the Agarwal and colleagues study, the overall status epilepticus cessation rates for both treatment cohorts were comparable to that seen in Gilad and colleagues, which did not enroll minors.^{10,13} The Agarwal et al study did not include subgroup analyses comparing the status epilepticus cessation rates of pediatric and adolescent patients with adult patients. However, whatever impact enrolling pediatric and adolescent patients might have had on efficacy comparisons between treatment cohorts was presumably mitigated by the cohorts being age-matched.¹⁰ Additionally, the mean (or median) ages of patients was not provided in the study conducted by Misra and colleagues.¹² The rates of administration and weight-adjusted doses of phenytoin and comparator agents were inconsistent between studies and unspecified in one case study. The identities of previous treatments for current status epilepticus episodes were not always disclosed, and the temporal relationship between previous treatments and study drug was inconsistent. Thus, distinguishing between residual activity from the previously prescribed agents, synergistic activity, and the treatment effects of study drugs is challenging. Nearly all of these studies were small and underpowered or neglected to address power.

Summary

In adults with nonrefractory status epilepticus, phenytoin monotherapy is a viable option for second-line therapy. It resulted in comparable efficacy to second-line treatments valproic acid and levetiracetam. Phenytoin also has a well-established safety profile. The data do not consistently support phenytoin monotherapy's use as first-line treatment of status epilepticus. More robust and adequately powered clinical studies are needed to assess whether these results remain consistent and extend to more long-term efficacy measures, such as morbidity and mortality.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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