Hosp Pharm 2013;48(9):757–761
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www.hospital-pharmacy.com
doi: 10.1310/hpj4809-757

Original Article

Retrospective Analysis of Levetiracetam Compared to Phenytoin for Seizure Prophylaxis in Adults with Traumatic Brain Injury

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Abstract

Background: Phenytoin is standard of care for seizure prophylaxis following traumatic brain injury (TBI). Levetiracetam, an alternative antiepileptic drug, is utilized for seizure prophylaxis despite limited data supporting its use.

Objective: Our primary outcome was post-TBI seizure activity measured by electroencephalogram (EEG) for levetiracetam versus phenytoin. Secondary outcomes were length of intensive care unit (ICU) stay, requirement for additional antiepileptic drugs (AED), and drug and monitoring costs.

Methods: A retrospective review was performed of patients admitted to neurosurgical or surgical trauma ICU. Adult patients with at least 1 day of EEG monitoring were included. Patients were excluded if they had history of epilepsy, prior TBI, less than 48 hours of AED therapy, or additional AED prior to EEG monitoring.

Results: A total 90 patients met inclusion criteria, with 18 receiving levetiracetam and 72 receiving phenytoin. Prevalence of EEG-confirmed seizure activity was similar between the levetiracetam and phenytoin groups (28% vs 29%; $P = .99$). ICU length of stay (13 vs 18 days; $P = .28$), time to EEG-confirmed seizure activity (4 vs 6 days; $P = .24$), and duration of seizure prophylaxis (9 vs 14 days; $P = .18$) were also similar. The median daily cost of levetiracetam therapy was $43 compared to $55 for phenytoin therapy and monitoring ($P = .08$). When all anticonvulsant therapy and monitoring were included, costs were lower for the levetiracetam group ($45 vs $83; $P = .02$).

Conclusion: Levetiracetam may provide an alternative treatment option for seizure prevention in TBI patients in the ICU. Total antiepileptic drug and monitoring costs were lower for levetiracetam patients.

Key Words—brain injuries, head injuries, intensive care units, levetiracetam, phenytoin, seizures

Hosp Pharm—*2013;48(9):757–761*

In the United States, approximately 1.4 million traumatic brain injuries (TBIs) occur each year.[1] Neurological damage after TBI is often related to secondary injuries, including posttraumatic seizures (PTS), which alter intracranial pressure, blood pressure, and oxygen delivery to cerebral tissue.[2] The incidence of PTS ranges from 2% to 30% for early PTS (≤7 days from injury) to 9% to 42% for late PTS (>7 days from injury).[2-4] Risk factors for early PTS include Glasgow Coma Score less than 8, depressed skull fracture, cerebral contusion, hematoma, penetrating head wounds, seizure within 24 hours of injury, and chronic alcoholism.[2-3,5]

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Guidelines from the Brain Trauma Foundation and American Association of Neurologic Surgeons recommend 7 days of phenytoin for early PTS prophylaxis.[2] Phenytoin prophylaxis decreased the incidence of early PTS from 14.2% to 3.6% when compared to placebo, but it has not shown benefit for late PTS.[6] Phenytoin has numerous side effects and drug interactions and exhibits complex nonlinear pharmacokinetics that necessitate therapeutic drug monitoring (TDM). Phenytoin steady state concentrations are often not achievable within the early PTS period of 7 days. However, the best trial data available utilized 3 times weekly monitoring, so many institutions consider TDM in the early PTS period standard of care.[6] Maintaining therapeutic phenytoin levels is challenging in a neurotrauma population, because levels are affected by decreased protein binding, variable gastrointestinal absorption, and increased drug clearance.[7-10]

Development of newer antiepileptic drugs (AEDs) has challenged phenytoin as the preferred first-line therapy. Levetiracetam is an AED with minimal side effects or drug interactions, excellent bioavailability, and no requirement for TDM.[11] Concerns with levetiracetam have been the limited data and higher drug cost. Studies comparing levetiracetam and phenytoin for PTS prophylaxis have yielded conflicting outcomes.[12,13]

The purpose of our study was to compare the prevalence of PTS with levetiracetam versus phenytoin in patients with TBI. The primary outcome was EEG-proven seizure activity.

MATERIALS AND METHODS

Study Design and Population

This is a retrospective review from University Hospital, a 600-bed, American College of Surgeons–verified Level I trauma center, which serves as the lead trauma center for 22 counties in South Central Texas. This study was approved by both the Institutional Review Board at the University of Texas Health Science Center at San Antonio and the University Hospital's research department.

We compared patients who received levetiracetam for PTS prophylaxis to patients who received phenytoin from January 2007 to July 2010. The primary outcome was EEG-proven seizure activity. Secondary outcomes included intensive care unit (ICU) length of stay, requirement for additional AEDs, and daily cost of therapy.

Patients were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes related to TBI, and they were included if they were 18 years of age or older, admitted to the ICU, had at least 1 day of EEG monitoring, and had more than 48 hours of either levetiracetam or phenytoin for PTS prophylaxis. Exclusion criteria included pregnancy, history of epilepsy, previous TBI, or hypersensitivity to study medication. Patients who received nonstudy AED prior to EEG monitoring were excluded.

Data points collected from electronic medical records included patient demographics; baseline laboratory values; cause and location of injury; neurological status on admission; seizure activity on EEG; dose, duration, and levels of study AEDs; additional AED therapy; and adverse reactions.

EEG examination occurred with suspicion of seizures in the presence of persistent coma, decreased mental status, or seizure activity. EEG monitoring conducted in the neurosurgical or surgical trauma ICU on at least 1 day for a minimum of 30 minutes was accepted for inclusion. Seizure activity was determined by EEG reports read by a faculty neurologist. Additional AED therapy was defined as any nonstudy AED with antiepileptic activity regardless of indication.

Total AED therapy and/or cost were defined as study AED plus all additional AED therapy and TDM. Phenytoin, valproic acid, and phenobarbital drug levels were included in the cost analysis. Phenytoin drug levels were corrected for hypoalbuminemia and renal dysfunction using the Winter-Tozer equation.[11,14] Time therapeutic was defined as the number of days a therapeutic phenytoin level (10-20 mg/L) was documented in the chart. Due to variability between levels and dose adjustments, days in which drug levels were not drawn were not included in time therapeutic even if prior and subsequent levels were therapeutic.

Statistical and Cost Analysis

Data were analyzed with *JMP* 8.0 (SAS Institute, Inc., Cary, NC). Descriptive statistics were used to summarize patient demographics and outcomes. Continuous data were analyzed using Wilcoxon rank sum test, and nominal data were analyzed using Fisher's exact test. An alpha level of $\leq .05$ was set to determine statistical significance for all comparisons. Drug costs for analyses were based on average wholesale price, whereas drug level costs were based on local hospital cost.

RESULTS

Study Population

A total of 402 adult patients with TBI were identified who received levetiracetam or phenytoin for

PTS, 125 had EEG monitoring, and 90 were included in the final analysis. Reasons for patient exclusion were more than 1 AED prior to EEG monitoring (n = 15), history of epilepsy (n = 13), less than 48 hours of therapy (n = 3), younger than 18 years of age (n = 2), and history of TBI (n = 1). One patient chart could not be accessed. Of the 90 patients in the final analysis, 18 received levetiracetam and 72 received phenytoin. The patient population was predominantly male (75.6%) and Caucasian (77.8%), with a median age of 50 (IQR, 33-65) years. Levetiracetam patients had a higher median age than phenytoin patients (57 vs 45 years; $P = .01$). The most common causes of injury were motor vehicle–related (41%) and falls (31%). Blunt head trauma (95.5%) was more common than penetrating head wounds (4.4%). Skull fracture was present in 12% of patients, loss of consciousness was documented in 54%, and seizure activity within 24 hours of injury was noted in 5.5% of patients. On admission, 63.3% of patients had severe brain injury with a median Glasgow Coma Score of 5 (IQR, 3-13). The most frequent location of injury was the frontal lobe (53.3%), and the most common type of injury was subdural hematoma (55.6%). The prevalence of temporal lobe injury was lower in the levetiracetam arm compared to the phenytoin arm (22.2% vs 61.1%; $P = .01$). All other baseline characteristics are summarized in **Table 1**.

Antiepileptic Therapy

Antiepileptic dosing information is provided in **Table 2**. The median duration of treatment for levetiracetam versus phenytoin was 9 and 14 days, respectively ($P = .18$). A loading dose was given in 14/18 (77.8%) patients in the levetiracetam group and 66/72 (91.7%) patients in the phenytoin group ($P = .11$). TDM was not performed in any patients in the levetiracetam group, but was performed in 71/72 (98.8%) patients in the phenytoin group. Initial phenytoin levels were therapeutic (10-20 mg/L) in 52%

Table 1. Baseline characteristics of adult patients with traumatic brain injury

Characteristic	Overall (N = 90)	Levetiracetam (n = 18)	Phenytoin (n = 72)	*P* value
Median age, years (IQR)	50 (33-65)	57	45	.01
Male gender	68 (75.6)	14 (77.8)	54 (75)	.99
Race				
Caucasian	70 (77.8)	14 (77.8)	56 (77.8)	
Hispanic	7 (7.8)	2 (11.1)	5 (6.9)	
Black	2 (2.2)	0 (0)	2 (2.8)	
Asian	2 (2.2)	0 (0)	2 (2.8)	
Other	9 (10)	2 (11.1)	7 (9.7)	
Median GCS median (IQR)	5 (3-13)	6 (3-12)	5 (3-13)	.96
Mild (13-15)	26 (28.9)	5 (27.8)	21 (29.2)	.99
Moderate (9-12)	7 (7.8)	3 (16.7)	4 (5.6)	.14
Severe (3-8)	57 (63.3)	10 (55.6)	47 (65.3)	.59
Location of injury				
Frontal	48 (53.3)	4 (22.2)	44 (61.1)	.01
Temporal	39 (43.2)	7 (38.9)	32 (43)	.82
Parietal	35 (38.9)	6 (33.3)	29 (40.3)	.20
Occipital	10 (11.1)	0 (0)	10 (13.9)	.79
Type of bleed				
Subdural hematoma	50 (55.6)	13 (72.2)	37 (51.4)	.18
Subarachnoid hemorrhage	43 (47.8)	8 (44.4)	35 (48.6)	.80
Intraparenchymal hemorrhage	19 (21.1)	5 (27.8)	14 (19.4)	.52
Intraventricular hemorrhage	18 (20)	3 (16.7)	15 (20.8)	.99
Epidural hematoma	7 (7.8)	0 (0)	7 (9.7)	.34

Note: Values are reported as n (%), unless otherwise indicated. GCS = Glasgow Coma Scale; IQR = interquartile range.

Table 2. Study drug therapy

	Levetiracetam (n = 18)	Phenytoin (n = 72)
Duration of treatment, days†	9 (8-16)	14 (8-21)
Time to first dose, hours†	14 (7-24)	9.5 (4-24)
Dosing		
Loading dose, no. of patients (%)†	14 (77.8%)	66 (91.7%)
Loading dose	1,000 mg	13 (10-17) mg/kg
Maintenance dose	500 mg every 12 hours	4 (3-4.5) mg/kg/day

Note: All values are reported as median (IQR), unless otherwise indicated.
†Result was not statistically significant.

(37/71) of patients before and after correction for hypoalbuminemia and/or renal failure. Median initial phenytoin levels were 11.6 (IQR, 8.5-15) mg/L (actual) and 13.5 (IQR, 9-18) mg/L (corrected). Median number of phenytoin levels per patient was 5 (IQR, 3-10), time to a therapeutic level was 30 (IQR, 11-56) hours, and time therapeutic was 2 (IQR, 1-5) days.

Outcomes

The prevalence of EEG-proven seizure activity was similar for levetiracetam and phenytoin (28% vs 29%; $P = .99$). Furthermore, no statistical difference in the type of seizure activity was found between groups. EEG reports cited "seizure activity" without further classification in 12% (3/26) of patients. The median time to EEG-proven seizure activity was 5 days. Additional results related to seizure activity are listed in **Table 3**.

ICU and hospital length of stay was similar for levetiracetam and phenytoin (13 vs 18 days; $P = .28$) and (13 vs 20 days; $P = .11$). No difference was demonstrated between levetiracetam and phenytoin in additional AED administration (22% vs 49%; $P = .062$). Phenytoin was used in 4/4 (100%) patients in the levetiracetam group as the most common adjunctive AED, and levetiracetam was used in 33/35 (94.3%) phenytoin patients. Study AED and monitoring costs were similar for levetiracetam and phenytoin patients ($43/day vs $55/day; $P = .08$); however, total AED costs were significantly less in the levetiracetam group compared to the phenytoin group ($45/day vs $83/day; $P = .019$). Wholesale cost for levetiracetam ranged from $3 to $22 per dose depending on dosage form and from $1 to $11.50 per dose for phenytoin. Total phenytoin level cost was $141 per level. Phenytoin TDM was frequent at this institution so therapy costs will be different depending on local practices.

DISCUSSION

Phenytoin has been shown to decrease the incidence of early PTS and is guideline-recommended therapy for early PTS prophylaxis. However, phenytoin has numerous drug interactions and challenging pharmacokinetics; coupled with the availability of newer AEDs, this has led to questioning of its place as

Table 3. Character of EEG-documented seizure activity

	Overall (N = 90)	Levetiracetam (n = 18)	Phenytoin (n = 72)	*P* value
EEG findings	26 (29)	5 (28)	21 (29)	.99
Generalized convulsive status epilepticus	2 (8)	0 (0)	2 (10)	.99
Nonconvulsive status epilepticus	13 (50)	2 (40)	11 (52)	.99
Periodic epileptiform discharges	17 (65)	2 (40)	15 (71)	.30
Seizure not otherwise specified	3 (12)	2 (40)	1 (5)	.08
Clinical seizure activity	13 (14.4)	2 (11)	11 (15.3)	.79
Time to seizure activity, days (IQR)	5 (4-10)	4 (3-11)	6 (4-19)	.24
Continuous EEG monitoring	48 (53.3)	8 (44.4)	40 (55.6)	.40

Note: Values are given as n (%), unless otherwise indicated.

first-line therapy.[7-10] Our results demonstrate that incidence of PTS was not significantly different between therapies, although phenytoin-treated patients had higher associated total AED and monitoring costs.

Our study utilized EEG monitoring to evaluate seizure activity. Nonconvulsive seizure activity is common in ICU settings, and multiple factors including continuous mechanical ventilation, sedation, and paralysis can mask physical signs of seizure. Our results validate previous findings that seizure activity and tendency are more commonly recognized with the use of intermittent EEG.[12] Intermittent EEG identified more than double the rate of seizure activity and tendency than clinical findings alone; of patients who had seizure activity on EEG, only 30.8% had clinical signs of seizure activity. Therefore, EEG monitoring is essential to accurately detect seizure activity in this patient population. Our findings also validate previous work that shows levetiracetam and phenytoin have similar efficacy for prevention of PTS.

Limitations

The retrospective design resulted in differences in sample size, baseline age, and TBI location between groups, which may have led to differences in clinical outcome. In addition, the nonrandomized design allows for confounding variables and prescribing bias in selecting initial and additional AEDs and therapy duration. Patients were identified using ICD-9 codes related to TBI, but some patients may have been missed if they did not have the appropriate code. Phenytoin levels were drawn at physician discretion and therefore were inconsistent and difficult to interpret.

This was a single-center analysis with inadequate power to detect a difference in the primary outcome, which may have led to Type II error; however, given the small difference in seizure activity between groups (1%), an adequately powered study would be difficult to conduct. Despite these limitations, this is the first economic comparison of clinical outcomes of levetiracetam and phenytoin for PTS prophylaxis.

Conclusions

Levetiracetam treatment resulted in a similar incidence of EEG-proven PTS when compared to phenytoin with similar ICU, hospital, and study drug cost. Phenytoin prophylaxis was associated with a higher total AED cost than levetiracetam. Prospective, randomized trials are needed to validate levetiracetam's efficacy compared to phenytoin for PTS prevention in TBI patients and should include pharmacoeconomic analysis of total AED therapy.

ACKNOWLEDGMENTS

No financial support was provided for this study, and the authors have no conflicts of interest to report. The authors are affiliated with University Health System and the University of Texas Health and Sciences Center in San Antonio, Texas.

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