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The use of Levetiracetam and Phenytoin for Seizure Prophylaxis in the Setting of Severe Traumatic Brain Injury

Gregg V. Kosloff

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The use of Levetiracetam and Phenytoin for Seizure Prophylaxis in the Setting of Severe Traumatic Brain Injury

Abstract

Background: Each year in the United States an estimated 1.7 million people suffer a traumatic brain injury (TBI). Current standard of care for these patients is seven days of phenytoin (PHT) for seizure prophylaxis. Given the known side effect profile and drug interactions associated with the use of PHT, levetiracetam (LEV) has been proposed as an alternative for seizure prophylaxis. This systematic review examined available literature to determine whether or not there is sufficient evidence to recommend the use of LEV in lieu of PHT.

Method: A highly sensitive search of Medline, CINAHL, and EBMRMultifile was conducted looking for studies comparing the efficacy of phenytoin vs. levetiracetam in the setting of severe TBI (sTBI) using the terms phenytoin and either levetiracetam or piracetam. In an effort to ensure that no articles that met inclusion criteria were missed, additional searches were conducted using Google Scholar and Web of Science. A manual search of the bibliographies of the articles to be reviewed as well as the bibliographies of background articles was conducted.

Results: Two articles comparing LEV and PHT in the setting of sTBI were found. Neither article was able to show a difference in the rate of seizure between patients treated with PHT and LEV. An increase in seizure tendency on EEG for patients taking PHT was reported, as was an increase in gastrointestinal upset and worsening of neurologic status. A modest improvement in some long term outcome measures was reported in patients treated with LEV. Both of the studies that were found were hampered by a small n (52 and 73), which was further limited by the studies’ methodology.

Conclusion: There is insufficient evidence to recommend the use of LEV instead of PHT for seizure prophylaxis in the setting of sTBI. Further studies, with larger patient populations and more sound methodology, are needed to continue to examine this issue.

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Keywords
seizure, phenytoin, levetiracetam, dilantin, traumatic brain injury

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The use of Levetiracetam and Phenytoin for Seizure Prophylaxis in the Setting of Severe Traumatic Brain Injury

Gregg V. Kosloff

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Dr. Mark Pedemonte, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Gregg Kosloff was born in New York and began working as an EMT before moving to Oregon for college. While working towards a B.S. in psychology at Pacific University he met his wife, Trisha. They returned to New York where he worked as an EMT and then as a paramedic. Gregg and Trisha hope to settle in Oregon after graduation.
Abstract

**Background:** Each year in the United States an estimated 1.7 million people suffer a traumatic brain injury (TBI). Current standard of care for these patients is seven days of phenytoin (PHT) for seizure prophylaxis. Given the known side effect profile and drug interactions associated with the use of PHT, levetiracetam (LEV) has been proposed as an alternative for seizure prophylaxis. This systematic review examined available literature to determine whether or not there is sufficient evidence to recommend the use of LEV in lieu of PHT.

**Method:** A highly sensitive search of Medline, CINAHL, and EBMRMultifile was conducted looking for studies comparing the efficacy of phenytoin vs. levetiracetam in the setting of severe TBI (sTBI) using the terms *phenytoin* and either *levetiracetam* or *piracetam*. In an effort to ensure that no articles that met inclusion criteria were missed, additional searches were conducted using Google Scholar and Web of Science. A manual search of the bibliographies of the articles to be reviewed as well as the bibliographies of background articles was conducted.

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hampered by a small $n$ (52 and 73), which was further limited by the studies’ methodology.

**Conclusion:** There is insufficient evidence to recommend the use of LEV instead of PHT for seizure prophylaxis in the setting of sTBI. Further studies, with larger patient populations and more sound methodology, are needed to continue to examine this issue.

**Keywords:** phenytoin, levetiracetam, seizure prevention, traumatic brain injury, severe traumatic brain injury.
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To Trisha Kosloff. Your support and understanding over the past 27 months has been phenomenal. I could not have made it through this program without you. Thank you.

To my parents: Thank you for always pushing me to expect the best from myself. Your time and dedication to my education were essential to my success.

To David and Deena Biglen. Thank you for taking me in. Having a comfortable place to call home for my first year (and uncounted nights since) allowed me to focus on my schooling in a way that would not have otherwise been possible.
# Table of Contents

Biography .................................................................................................................. 2  
Abstract ...................................................................................................................... 3  
Acknowledgements .................................................................................................... 5  
Table of Contents ..................................................................................................... 6  
List of Tables ............................................................................................................ 7  
List of Abbreviations ................................................................................................ 7  
Background ............................................................................................................. 8  
Method ..................................................................................................................... 9  
Results ..................................................................................................................... 10  
Discussion ............................................................................................................... 13  
Conclusion ............................................................................................................. 16  
References ............................................................................................................. 17  
Tables ..................................................................................................................... 18
List of Tables

Table I: Characteristics of Reviewed Studies
Table II: Summary of Findings

List of Abbreviations

DRS.................................................................Disability Rating Scale
EEG...............................................................Electroencephalography
GI.................................................................Gastrointestinal
GOSE..........................................................Glasgow Outcome Scale-Extended
GCS..............................................................Glasgow Coma Scale
LEV...............................................................Levetiracetam (Keppra)
PHT....................................................................Phenytoin (Dilantin)
SAH.................................................................Subarachnoid Hemorrhage
sTBI..............................................................Severe Traumatic Brain Injury
TBI.................................................................Traumatic Brain Injury
The use of Levetiracetam and Phenytoin for Seizure Prophylaxis in the Setting of Severe Traumatic Brain Injury

BACKGROUND

Each year in the United States an estimated 1.7 million people suffer a traumatic brain injury (TBI). Of those, 1.64 million are seen in the ED, 275 000 will be admitted to the hospital, and 52 000 patients will die. Patients who suffer severe traumatic brain injury (sTBI) are at an increased risk of developing post-traumatic seizure (PTS), so in 2003 the American Academy of Neurology issued a practice parameter regarding the use of seizure prophylaxis in the setting of sTBI. The practice parameter recommends the use of phenytoin (PHT) for the prevention of early PTS, which they define as seizures occurring within seven days of injury. The use of seizure prophylaxis beyond seven days was not recommended. The practice parameter did not include a definition of “severe,” and research has shown that clinicians use a wide variety of criteria when deciding whether or not to use seizure prophylaxis in the setting of TBI.

Seizures, including those following sTBI, are associated with an increase in hypoxic events, acute and sustained rises in intracranial pressure, acute blood pressure changes, aneurysm rupture, physical injury, and death. There is wide agreement that the use of seizure prophylaxis for the first week after sTBI is beneficial, the question now is whether PHT is still the most appropriate medication for the prevention of PTS. There is concern over the risk of medication interactions, as well as cutaneous hypersensitivity reactions associated with the use of PHT. PHT also requires monitoring of serum levels and frequent dosage adjustments in order to maintain a narrow therapeutic window, which can increase cost as well as complexity of management.
Levetiracetam (LEV) (Keppra) is a non-enzyme inducing anti-epileptic drug that is a possible alternative to PHT for the prevention of PTS. In addition to a small side effect profile, LEV does not require serum level monitoring and, because it does not interact with CYP 450, there are far fewer drug interactions associated with its use. Importantly, LEV was approved for intravenous administration in 2006, which is critical for patients with sTBI who are often unable to take oral medication immediately following their injury.

Given the known issues with the use of PHT, the search for a safe, effective alternative for use in prevention of PTS is certainly worthwhile. The purpose of this systematic review is to evaluate the existing evidence to determine whether or not LEV is an appropriate alternative to PHT for seizure prophylaxis in adults with sTBI.

METHODS

A highly sensitive search of Medline, CINAHL, and EBMRMultifile was conducted looking for studies comparing the efficacy of phenytoin vs. levetiracetam in the setting of TBI. The databases were searched using the terms phenytoin and either levetiracetam or piracetam. In an effort to ensure that no articles that met inclusion criteria were missed, additional searches were conducted using Google Scholar and Web of Science. A manual search of the bibliographies of the articles to be reviewed as well as the bibliographies of background articles was conducted. Articles meeting inclusion criteria were assessed for quality using the GRADE system.
RESULTS

A total of two articles were found that met inclusion criteria for the review. One study was a mixed prospective/retrospective cohort design (Jones et al)\(^5\), the other was a prospective randomized controlled trial (Szaflarski et al).\(^4\) Neither article reported a significant decrease in the number of seizures in patients treated with levetiracetam (LEV) when compared to phenytoin (PHT). See Table I for characteristics of reviewed studies and Table II for a summary of findings.

**Jones et al**

In a mixed prospective/retrospective design, Jones et al\(^5\) enrolled 32 consecutive patients with severe traumatic brain injury (sTBI). Severe traumatic brain injury was defined as a post-resuscitation GCS of 3-8. Patients prospectively enrolled were treated with seven days of LEV. This cohort was compared to an historical cohort of 41 patients who had been treated with seven days of PHT. Patients who exhibited clinical signs of seizure, decrease in level of consciousness, or persistent comatose state had an electroencephalogram examination (EEG) to look for evidence of subclinical seizure. EEG results were read as either normal or abnormal, with abnormal results further classified as status epilepticus, seizure activity, or seizure tendency. Only patients who warranted and received an EEG were included in the analysis.\(^5\)

A total of fifteen patients in the LEV cohort (47%) and twelve patients in the PHT group (29%) were included in the statistical analysis. One patient in the LEV group had seizure activity recorded (6.667%), no seizure activity was recorded in the PHT group. This difference was not statistically significant (\(P = 0.556\)). There was an increase in
seizure tendency on EEG in the LEV group (46.667%) compared to none in the PHT group (P = 0.007). Adverse drug reactions were not reported. Szaflarski et al

Szaflarski et al4 conducted a prospective, randomized trial with the goal of comparing the safety and efficacy of PHT and LEV for seizure prophylaxis. The study included 52 patients with either sTBI or subarachnoid hemorrhage (SAH), with 89% having sTBI. This was a change from the original intent, which was to have 52 patients in each group. Patients were considered to have sTBI if their GCS score was 3-8, or if the GCS motor score was five or less and the head CT scan showed intracranial pathology. Patients were analyzed together, and data was unavailable for either the sTBI or SAH group independently. Patients were randomized to receive either LEV (n = 34) or PHT (n = 18) for seven days. All patients were placed on continuous EEG monitoring for 72 hours or until they were able to follow commands, whichever came first. Szaflarski et al4 cite research indicating that 93% of seizures in this setting occur within two days of admission to the ICU as the reason for ceasing EEG monitoring at 72 hours.4

The study pharmacist made dosage adjustments in both groups. Patients receiving PHT had their dose adjusted to maintain serum levels of 10-20 mcg/dl. Patients in both groups could also have their dose increased to the maximum recommended dose if seizure occurred. The study methodology provided for the addition of LEV to patients in the PHT group, and PHT to patients in the LEV group, as well as the addition of other anti-epileptic drugs if seizures were not suppressed at maximum dose of monotherapy, but there is no indication of whether or not this was necessary.4
Four out of 18 (22.2%) of patients in the PHT and 14 out of 34 (41.1%) of patients in the LEV group expired within six months of injury ($P = 0.227$). Cause of death was evaluated for each patient and classified as either being due to the injury itself, withdrawal of care within thirty days of injury, or withdrawal of care beyond thirty days. There was no significant difference between the LEV and PHT groups for each classification of death.$^4$

No significant difference was found in the rate of seizure between the PHT group (3/18, 11%) and the LEV group (5/34, 15%). All seizures that were recorded were noted to be non-convulsive in nature. The number of seizures that were subclinical versus those that were clinically evident was not reported. The incidence of gastrointestinal problems was higher in the PHT group than in the LEV group (22.2% vs. 2.9%, $P = 0.043$), though the type, severity, and duration were not reported. The incidence of worsening neurological status was also higher in the PHT group than the LEV group (50% vs. 17.6%, $P = 0.024$). The definition of worsening neurological status was not reported.$^4$

Patients who survived at least six months who had been treated with LEV were reported to have better long term outcomes than those treated with PHT. Surviving patients treated with LEV had higher Glasgow Outcome Scale-Extended (GOSE) scores at six months ($P = 0.016$), but not at discharge or three months. After adjusting for initial GCS, GOSE was not significantly different at discharge or three months, but at six months patients in the LEV group were 1.5 points higher (95%CI 0.1-3.9, $P = 0.039$) than those in the PHT group. Disability Rating Scale (DRS) was lower at three and six months ($P = 0.006$ and $P = 0.037$, respectively), but not at discharge. After adjusting for
initial GCS, patients treated with LEV scored 5.2 points lower (95%CI 0.2-10.3, $P = 0.042$) on the DRS than those patients treated with PHT at three months, but not at discharge or six months. All other outcomes showed no statistical difference.\textsuperscript{4}

**DISCUSSION**

An exhaustive literature search found only two articles that compare levetiracetam (LEV) and phenytoin (PHT) for seizure prophylaxis in the setting of severe traumatic brain injury (sTBI), and neither was able to demonstrate a reduction in seizure frequency when using LEV. Jones et al\textsuperscript{5} reported an increase frequency of abnormal and seizure tendency EEG with LEV when compared to PHT, but they did not see a difference in actual seizure activity. They did not address whether or not seizure tendency on EEG, without actual seizure activity, leads to harm.

Szaflarski et al\textsuperscript{4} reported an increase in gastrointestinal side effects and increased frequency of worsening neurologic status with the use of PHT compared to LEV, but critical information is missing. In particular, the magnitude and duration of the gastrointestinal side effects was not reported. Clinically, there is a big difference between mild GI upset and bowel obstruction or pancreatitis, and side effects that would make a drug contraindicated if they are persistent might be tolerable if they resolve within minutes or hours. The same information is missing for the worsening of neurologic status. While a decrease in neurologic status is certainly concerning, it may be tolerable if it is brief and transient.

Szaflarski et al\textsuperscript{4} report an improvement in long term outcome with the use of LEV, though the data to support this are tenuous. While surviving patients treated with LEV have an improvement in their Glasgow Outcome Score-Extended (GOSE) at six
months, and Disability Rating Score (DRS) at three and six months, the results are much less dramatic after controlling for initial Glasgow Coma Scale (GCS). Controlling for GCS at admission does show an increase in GOSE at 6 months only, and a decrease in DRS at six months only, for patients treated with LEV compared to PHT, but the 95% confidence intervals (0.1 - 3.0 and 0.2 - 10.3, respectively) suggest that the magnitude of effect may be very modest. These results only apply to surviving patients in each group, ignoring death, which is clearly a negative long term outcome. Death is specifically measured by the GOSE, and excluding part of the scale calls into question the validity of the reported results.

Both Jones et al\textsuperscript{5} and Szaflarski et al\textsuperscript{4} used GCS as the determinant of whether or not a traumatic brain injury (TBI) qualified as severe. While a GCS score of less than or equal to eight is commonly accepted as severe, this has not been widely applied to seizure research. In developing their practice parameter recommending the use of PHT for seizure prophylaxis in the setting of sTBI, the American Academy of Neurology did not attempt to define “severe,” relying instead on the definitions used in the individual articles that they reviewed. GCS was not listed as a criterion used by any of the contributing articles, with the authors instead using presence of intracranial hematomas, loss of consciousness or amnesia for more than 12 or 24 hours, depressed skull fracture, and/or presence of brain contusion.\textsuperscript{2} This lack of a validated, agreed upon definition for severe led Debenham et al\textsuperscript{3} to retrospectively examine what led physicians at their institution to prescribe seizure prophylaxis, and they found that the only two factors that significantly correlated with the use of prophylaxis were Marshall CT grade of four or more, and the presence of any positive findings on head CT. This lack of a universal
definition of “severe,” and the reliance on GCS alone by Jones et al\textsuperscript{5} and Szaflarski et al\textsuperscript{4}, may limit the applicability of their findings to centers that use other criteria in defining which patients qualify as “severe.”

The power of both the Jones et al and Szaflarski et al studies\textsuperscript{4,5} were limited by a small sample size. The small initial $n$, 73 for the Jones et al\textsuperscript{5} study and 52 for the Szaflarski et al\textsuperscript{4} study, were further reduced by restricting the groups that were analyzed. Jones limited analysis to patients who warranted EEG, which reduced the $n$ to 27. While it was necessary for Szaflarski et al\textsuperscript{4} to limit long term analysis to surviving patients, this reduced the $n$ to 34. This lack of power makes it difficult to apply the already modest results to a larger population. Debenham et al\textsuperscript{3} in their retrospective analysis found 653 patients who were prescribed seizure prophylaxis after sTBI over a two year period at their institution alone. This suggests that, at some centers at least, there is a sufficient pool of patients to allow for more powerful research.

Given the lack of power, and modest differences between the LEV and PHT groups, the cost of using either medication becomes an important consideration. Cotton et al\textsuperscript{6} performed a cost analysis of PHT vs. LEV, and found that a seven day course of PHT, including the associated laboratory costs, was $37.50. This is far less than the $480 cost of seven days of LEV.

The flaws in the methodology of both the Jones et al and Szaflarski et al studies,\textsuperscript{4,5} in particular the small sample size, dramatically decreased the confidence in the results of the studies. This increases the possibility of bias being introduced. The risk of bias was further exacerbated by the selective way in which the results of the Szaflarski et al\textsuperscript{4} study were reported, in particular ignoring death as a measurable outcome on the GOSE and
reporting results after controlling for initial GCS for only some outcomes. Finally, the Szaflarski et al study was funded by the company which manufactures LEV, which also increases the risk of bias.

CONCLUSION

The use of phenytoin (PHT) for seizure prophylaxis for seven days in the setting of severe traumatic brain injury (sTBI) is the current standard of care. This systematic review examined the available literature to determine if there is sufficient evidence to recommend the use of levetiracetam (LEV) in lieu of PHT for seizure prophylaxis, given the known side effect profile and drug interactions associated with PHT. This review has found that there is a paucity of evidence comparing LEV and PHT in the setting of sTBI. The evidence that is available does not show a difference in the rate of seizure, or a substantial difference in the rate of side effects or long term outcomes when comparing LEV and PHT. Ultimately, there is insufficient evidence to recommend a change in standard practice, and at this time patients with sTBI should continue to receive PHT as seizure prophylaxis for the first seven days post injury.

There are legitimate concerns regarding the side effects and drug interactions associated with the use of PHT. There is evidence that a sufficient patient population exists to conduct a randomized controlled trial comparing PHT and LEV in the setting of sTBI in a fashion that will allow the results to have sufficient power to allow broad applicability. Further high quality research is needed to focus on the efficacy of these two medications in preventing seizures, differences in long term outcomes, and the frequency and severity of side effects and drug interactions.
References


Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Quality Assessment</th>
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</thead>
<tbody>
<tr>
<td>Design</td>
</tr>
<tr>
<td>Mixed retrospective/prospective</td>
</tr>
<tr>
<td>Jones et al²</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Szaflarski et al³</td>
</tr>
</tbody>
</table>

* Small sample size
⊗ Only patients who experienced seizure were included in analysis
✓ Few studies available for comparison
⊕ Use of additional AEDs allowed including LEV + PHT, not reported if this occurred
+ Primary outcomes poorly defined
Table II. Summary of Findings

<table>
<thead>
<tr>
<th>Jones et al⁵</th>
<th>Levetiracetam n (%)</th>
<th>Phenytoin n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included in analysis</td>
<td>15/32 (49.6)</td>
<td>12/41 (29.3)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Any abnormal EEG</td>
<td>8/15 (53.3)</td>
<td>0/12</td>
<td>0.003</td>
</tr>
<tr>
<td>Seizure tendency EEG</td>
<td>7/15 (46.66)</td>
<td>0/12</td>
<td>0.007</td>
</tr>
<tr>
<td>Seizure activity EEG</td>
<td>1/15 (6.67)</td>
<td>0/12</td>
<td>0.556</td>
</tr>
<tr>
<td>Suspicion of clinical seizure activity</td>
<td>2/15 (13.3)</td>
<td>3/12 (25)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

| Szaflarski et al⁴ | |
|-------------------|-----------------------|------------------|
| Early Seizure    | 5/34 (14.7)           | 3/18 (16.6)      | 1     |
| Seizure at 6 months | 1/20 (0.05) | 0/14 | 1     |
| Mortality        | 14/34 (41.2)          | 4/18 (22.2)      | 0.227 |
| Gastrointestinal (all pts) | 1/34 (2.9) | 4/18 (22.2) | 0.043 |
| Gastrointestinal (surviving pts) | 1/20 (5) | 3/14 (21.4) | 0.283 |
| Worsening neuro status (all pts) | 6/34 (17.6) | 9/18 (50.0) | 0.024 |
| Worsening neuro status (surviving pts) | 4/20 (20.0) | 6/14 (42.9) | 0.012 |