Antiseizure Prophylaxis for Penetrating Brain Injury


I. RECOMMENDATIONS

A. Standards
The available data are not sufficient to support a practice Standard for the role of antiseizure prophylaxis after penetrating brain injury (PBI).

B. Guidelines
The available data are not sufficient to support a practice Guideline for this topic.

C. Options
Antiseizure medications in the first week after PBI are recommended to prevent early posttraumatic seizures in patients with PBI (e.g., with phenytoin, carbamazepine, valproate, or phenobarbital). Prophylactic treatment with anticonvulsants beyond the first week after PBI has not been shown to prevent the development of new seizures, and is not recommended.

II. OVERVIEW
The use of anticonvulsants in survivors of severe traumatic brain injury (TBI) must balance the potential benefit of these drugs against their demonstrated toxicity and side effects. Two separate aspects should be distinguished regarding the use of anticonvulsants for posttraumatic seizures (PTS). The first relates to the therapeutic use of anticonvulsants to prevent further seizures in patients who have already developed posttraumatic epilepsy (PTE). Because most patients with PTS after the first postinjury week will have recurrent seizures for some time, use of anticonvulsant therapy is indicated in documented cases. The second and more controversial aspect is the practice of administering prophylactic anticonvulsants to patients after PBI in order to prevent the development of PTE.

III. PROCESS (METHODOLOGY)
A MEDLINE search from January 1966 to January 2000 using the search terms wounds, gunshot, and brain injuries or head injuries, when limited to human subjects, identified 382 articles. Eighty-eight articles were rejected on the basis of clearly irrelevant titles. An additional 33 articles were then pulled from the bibliographies of reviewed articles. The primary selection process, therefore, identified 327 articles for further review. Two independent reviewers read the abstracts of all 327 and selected 65 for further inclusion. Articles were rejected on the basis of relevance to the topic (e.g., pediatric population, non-English language, case reports, irrelevance to project, atypical mechanisms of injury, and series of less than 10 subjects with no other unique reasons for inclusion). Further articles were brought up for consideration from the bibliographies of the 65 originally selected articles and rejected or added to the active list using the above algorithm. Of these 65 articles, 9 provided evidence that was relevant to prophylaxis of posttraumatic epilepsy after PBI. Four of these are Class I studies that included a relatively small number of PBI patients with a larger number of patients with nonpenetrating TBI. PBI patients were not analyzed separately in those therapeutic trials. The other articles are Class III reports of military PBI that include anticonvulsant treatment data. Three of these articles are derived from various cohorts from the Vietnam military series.

IV. SCIENTIFIC FOUNDATION

Incidence
Selected long-term follow-up studies of 20th century military casualties who had penetrating craniocerebral missile wounds indicate that, despite impressive advances in evacuation and early surgical management, the incidence of early and late posttraumatic seizures has stayed relatively constant. Between 30% and 50% of patients with PBI develop seizures; 4% to 10% of those have their first seizure within the first week after injury and 80% during the first 2 years, but about 18% may not have their first seizure until 5 or more years after injury. This contrasts with a somewhat lower risk of PTE after nonpenetrating TBI of 4% to 42%. When followed for 15 years after a PBI, nearly 50% of patients with epilepsy eventually stop having seizures. Thus, the risk decreases markedly with time. Although the relative risk of developing epilepsy 10 to 15 years after injury is still 25 times higher than in the normal age-matched population, 95% of patients with PBI remain seizure-free if they have no seizures during the first 3 years after injury.

Early Posttraumatic Seizures
Posttraumatic epilepsy can be classified as early or late. Although the term early epilepsy is arbitrarily applied to seizures occurring within the first 7 days after the PBI, this notion is not uniformly accepted in the literature. Of the 50 patients reported by Whitty, 37 had their first seizure in the first week and 13 in the second week. Adeloye and Odeku reported 35 casualties with seizures after PBI, of which 9 had seizure onset during the first week and one in the second week. Among Vietnam War veterans with PTE after PBI, 10% had their seizure onset in the first week. Whitty also noted an increased incidence of late epilepsy in his series of patients with early seizures. In a Class III study, Rish and Caveness could not ascertain the effectiveness of phenytoin with or without phenobarbital in preventing early seizures. The patient’s wound, clinical, radiologic, and surgical...
characteristics do not identify major risk factors for the genesis of early seizures.

**Late Posttraumatic Seizures**

Several Class III studies have defined major variables influential in the development of late seizures. These include penetration near the parietal vertex, extent of injury, coma score, and focal neurologic deficit. Other factors include wound track hematomas, retained metal fragments, and total brain volume loss on computed tomographic scan. In a retrospective study of 157 (32%) of 489 patients from the Iran-Iraq War, Arabi et al. examined the above factors plus the Glasgow Outcome Scale score, infection of the central nervous system, and focal motor neurologic deficit as prognostic factors for PTE. By univariate analysis, the factors that did not have a statistically significant influence on PTE were the type of projectile, the cranial site of injury, age, number of affected lobes, related hemorrhagic complications, and retained metallic or bone fragments. Using multivariate analysis, only the Glasgow Outcome Scale score and focal motor neurologic deficit were significant predictors of PTE after PBI.

**Prophylactic Anticonvulsants**

The evidence regarding the use of prophylactic anticonvulsants for the prevention of PTE is limited to three Class I studies and five Class III studies. The Class I randomized controlled trials included a relatively small number of PBI patients. These studies showed that the prophylactic use of phenytoin, phenobarbital, carbamazepine, or valproate does not prevent the development of late posttraumatic epilepsy in patients with nonpenetrating TBI. These and other similar Class I studies in nonpenetrating TBI patients are the basis for the recommendation in the Guidelines for the Management of Severe Head Injury that these anticonvulsants not be used for preventing late posttraumatic seizures. The small number of PBI patients included in these studies do not permit extrapolation of this recommendation to the PBI population at the level of a standard. Although nonpenetrating and penetrating brain injuries share the same biologic substrate and similar causes, they also have important differences, one of which is the higher incidence of PTE after PBI. Whether this difference in incidence reflects a qualitative or quantitative difference in disease is unknown. The five Class III descriptive studies in military patients also confirm the lack of a prophylactic effect of phenytoin or phenobarbital on late posttraumatic seizures.

**V. SUMMARY**

At present, there is only limited Class I and some Class III evidence regarding prophylactic use of anticonvulsants in survivors of PBI. Nevertheless, these data uniformly appear to suggest a lack of efficacy of anticonvulsants in the prophylaxis of late posttraumatic epilepsy in this population.

**VI. KEY ISSUES FOR FUTURE INVESTIGATION**

Class I studies of prophylaxis of posttraumatic seizures with newer anticonvulsants are needed in PBI patients. A promising approach might also use neuroprotectant strategies to prevent the chronic evolution of pathologic changes contributing to PTS after PBI.

### VII. Evidentiary Table: Anti-Seizure Prophylaxis

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Description of Data</th>
<th>Study Class</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al., 1983</td>
<td>Civilian nonpenetrating TBI and PBI (n = 179, 156 nonpenetrating TBI and 23 PBI). 18-mo follow-up.</td>
<td>I</td>
<td>No difference in late seizures between phenytoin and placebo (p = 0.75).</td>
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<tr>
<td>Glotzner et al., 1983</td>
<td>Civilian nonpenetrating TBI and PBI (n = 139, 105 nonpenetrating TBI and 34 PBI).</td>
<td>I</td>
<td>No difference in late seizures between carbamazepine and placebo. Fewer early seizures in carbamazepine group (p = 0.05).</td>
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<tr>
<td>Temkin et al., 1990</td>
<td>Civilian nonpenetrating TBI and PBI (n = 404, 389 nonpenetrating TBI and 15 PBI).</td>
<td>I</td>
<td>No difference in late seizures between phenytoin and placebo (p &gt; 0.2).</td>
</tr>
<tr>
<td>Temkin et al., 1999</td>
<td>Civilian nonpenetrating TBI and PBI (n = 379, 361 nonpenetrating TBI [Haynes, 1945] and 18 PBI).</td>
<td>I</td>
<td>No difference in late seizures between 1 or 6 mo of valproate vs. phenytoin.</td>
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<tr>
<td>Adeloye and Odeku, 1971</td>
<td>Combat PBI case control study (n = 237, Nigeria).</td>
<td>III</td>
<td>33% PTE at 5 y. No prophylactic effect of phenytoin/phenobarbitone.</td>
</tr>
<tr>
<td>Caveness et al., 1979</td>
<td>Combat PBI prospective cohort (n = 1,031, Vietnam).</td>
<td>III</td>
<td>84% on phenytoin for ≥1 y, yet PTE incidence same as in prior wars and as in patients on interrupted phenytoin regimen.</td>
</tr>
<tr>
<td>Meirowsky, 1982</td>
<td>Combat PBI prospective cohort. Case control study (n = 378).</td>
<td>III</td>
<td>Prophylactic phenytoin did not prevent late PTE after PBI.</td>
</tr>
<tr>
<td>Rish and Caveness, 1973</td>
<td>Combat PBI prospective cohort, (n = 1,614, Vietnam).</td>
<td>III</td>
<td>1.6% of treated and 3.7% of untreated had early seizures after PBI (p = 0.01).</td>
</tr>
<tr>
<td>Salazar et al., 1985</td>
<td>Combat PBI prospective cohort (n = 421, Vietnam).</td>
<td>III</td>
<td>85% received phenytoin for ≥ 1 y, yet incidence of PTE was same as prior wars.</td>
</tr>
</tbody>
</table>
REFERENCES


