Seizures that occur following traumatic brain injury have been classified into early posttraumatic seizures (occurring within 7 days postinjury) and late posttraumatic seizures (occurring more than 7 days postinjury). Anticonvulsant medications have been shown to reduce the incidence of early posttraumatic seizures after phenytoin administration was associated with a change in mortality rates in head-injured patients.

The rationale for the use of anticonvulsant medications for prevention of early posttraumatic seizure includes prevention (including secondary brain injury caused by seizures), maintenance of driving privileges, and the possibility of improved functional outcome after traumatic brain injury. In the acute period following head injury, seizures may precipitate adverse events in the injured brain due to elevations in intracranial pressure, blood pressure changes, changes in oxygen delivery, and also excess neurotransmitter release. The occurrence of seizures may also be associated with accidental injury, psychological effects, and loss of driving privileges. Disadvantages of posttraumatic seizure prophylaxis include cost and unwanted side effects of the medication.

We examined the data from our study of posttraumatic seizure prophylaxis in which phenytoin was used to determine whether early treatment with phenytoin for 1 to 2 weeks was associated with changes in mortality rates or adverse side effects.

Clinical Material and Methods

Patient Population

This study represents a secondary analysis of data previously collected as part of a large, placebo-controlled, clinical trial of the prophylactic use of phenytoin for preventing early and late posttraumatic seizures. The participants were 404 adults who were admitted to a Level I trauma center for evaluation and treatment of traumatic brain injury and who were randomly assigned to receive phenytoin or placebo under double-blind conditions. This study was conducted between November 1983 and December 1987; follow up was continued until December 1989. Eligibility criteria included the presence of at least one of the following: a depressed skull fracture; penetrat-
Early seizure prophylaxis

ing head wound; evidence on computerized tomography scans of a cortical contusion or acute intracranial hema-
oma (either intracerebral, subdural, or epidural); a Glasgow Coma Scale (GCS) score less than or equal to 10 on admission to the hospital; or immediate early seizures (that is, a seizure that occurred within 24 hours of the injury). Criteria for exclusion were age younger than 16 years, pregnancy or lactation, non-English speaker, a history of alcoholism, a previous brain injury or other neurological condition (including preinjury seizures), failure by hospital personnel to administer the initial loading dose of the study drug within 24 hours of injury, or the administration of an anticonvulsant medication before study-drug loading.

The initial loading dose of the study drug was adminis-
tered intravenously (20 mg/kg of body weight), and serum phenytoin levels were measured by an unblinded nurse who acted as the study monitor to make necessary dosing adjustments to keep phenytoin levels in the high therapeu-
tic range. Similar dosing adjustments were made in the placebo group to ensure that the double-blind condition would be maintained. In addition to being observed for seizure development, patients were also monitored by the study nurse for clinical signs of phenytoin toxicity (for example, nystagmus, ataxia, stupor) and for symptoms indic-
ing idiosyncratic phenytoin hypersensitivity reactions, including rash, fevers of unknown origin, and hepatic dys-
function. Furthermore, any abnormal clinical test findings suspected to be phenytoin related were documented in the study records, along with information about the attending physician’s decision to continue or discontinue the drug.

Medical staff who were not involved in the study, care-
givers, and the patients (when cognitively able) were also educated about the potential idiosyncratic and dose-de-
pendent side effects of phenytoin, and they were instruct-
ed to notify the study nurse if any characteristic symptoms developed that were suspected to be caused by the study drug. Patients continued to receive the assigned drug for 12 months unless serious adverse reactions occurred that were thought to be related to the study drug. Other reasons for stopping the assigned study drug were if the patient withdrew consent for treatment under the study on the recom-
mandation of their physician or for personal reasons. Phenytoin was administered in an unblinded fashion if seizures developed. Recurrent seizures were treated as clinically indicated.

Study charts were reviewed, and all of the suspected side effects and idiosyncratic reactions viewed during the first 2 weeks of treatment were summarized for the patients who were assigned to phenytoin compared with placebo. Fisher’s exact test was used to compare the proportions of effects in each treatment group. Cox’s propor-
tional-hazards regression was used to compare mortality rates for patients who had early seizures with those of pa-
tients who were seizure free in the 1st week, after statisti-
cally controlling for the effects of the patients’ ages and the severity of their head injuries.4 The head injury sever-
ity variables were chosen by stepwise regression, from among the initial GCS scores on hospital admission, the presence of acute intracranial hematoma, cortical contu-

Clinical Efficacy of Phenytoin

The results concerning the effectiveness of prophylactic phenytoin in this cohort have already been reported.11 In brief, the findings revealed that prophylactic phenytoin was effective in preventing delayed early seizures (that is, seizures occurring after drug loading but within the first 7 days posttrauma) but not for preventing late seizures. The overall incidence of delayed early seizures was signifi-
cantly lower in the group randomized to phenytoin treat-
ment as compared with the group receiving the placebo (3.6 ± 1.3% by Day 7 in the phenytoin group compared with 14.2 ± 2.6% in the placebo group; p < 0.001). De-
spite maintenance of phenytoin levels in the high therapeu-
tic range for 1 year in the majority of patients, the inci-
dence of late seizures (that is, seizures occurring after Day 7) did not differ between patients who were assigned to phenytoin compared with placebo (27.5 ± 4% by 2 years compared with 21.1 ± 3.7%, respectively; p > 0.2).12

Side Effects of Phenytoin

Table 1 summarizes all instances of suspected adverse reactions to the medication that were documented in the 1st and 2nd weeks postinjury. A rash was the most fre-
quently suspected idiosyncratic reaction, with most occur-
cences in the 2nd week. The rash was maculopapular and consistent with a typical hypersensitivity reaction in one patient during the 1st week and in three patients during the 2nd week. These four patients were all receiving phenyt-
oin; the drug was promptly discontinued and all four re-
covered without experiencing any more serious cutaneous reactions or systemic hypersensitivity symptoms. The oth-
er rashes were not typical of hypersensitivity and cleared despite continuation of the study drug. One patient receiv-
ing phenytoin who developed leukocytosis had no clinical symptoms of hypersensitivity; the leukocytosis sponta-
neously resolved despite continuing treatment with phe-
ytoin. Three patients who were in the group receiving phenytoin developed unexplained fevers that resolved spontaneously despite continued treatment but had no oth-
er symptoms of hypersensitivity. Thus, it can be estimated that 0.6% (95% confidence interval [CI] 0.1–3.3%) of patients receiving phenytoin experience a hypersensitivity reaction if treated for the 1st week postinjury and a total of 2.5% of patients develop such reactions (95% CI 1–
with delayed early seizures. Thus, although phenytoin was
point estimate indicates a slightly reduced risk of death
0.3–1.4). In fact, after adjusting for injury severity, the
posttraumatic seizure (p = 0.3, relative risk 0.69, 95% CI
590
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Phenytoin is effective for preventing early seizures, but
it does not appear to be effective for preventing the onset
of late posttraumatic seizures.12,17 On the basis of these
findings, it has been suggested that a rational approach
to seizure prophylaxis with phenytoin would be to limit
treatment to the 1st week postinjury in patients at high risk
for developing seizures and to continue treatment beyond
the 1st week only if early seizures occur.1,13 However, the
decision to treat prophylactically with phenytoin even for
1 week still requires some consideration of the attendant
risk of adverse side effects of the medication. Our findings
indicate that the risk/benefit ratio associated with 1 week
of phenytoin treatment is likely to be rather favorable,
given the very low incidence of suspected idiosyncratic
reactions to the drug that were observed in the 1st week of
our study. Furthermore, because the patients we studied
received phenytoin for longer than 1 week, the incidence
of idiosyncratic reactions that we observed by the end of
the 2nd week may actually overestimate the number of ad-
verse reactions that would have occurred if phenytoin had
been discontinued after 7 days, the duration of treatment
that is now recommended given phenytoin’s lack of effec-
tiveness in preventing the onset of late seizures.1
Maculopapular rash was the symptom most frequently
suspected to be an idiosyncratic side effect of phenytoin
during the first 2 weeks of this study, with an incidence of
2.5% in patients treated for 2 weeks after head injury.
Other types of rashes were observed equally often in the
patients who received placebo or phenytoin. In our study,
diffuse maculopapular rash (the type that is highly indica-
tive of phenytoin hypersensitivity reaction) was only seen
in patients who had been treated with phenytoin. The inci-
dence of these characteristic hypersensitivity rashes by the
end of 1 week was 0.6%, and by the end of 2 weeks it was
2.5% of the head-injured patients treated with phenytoin.

**Discussion**

Phenytoin is effective for preventing early seizures, but
6.4%) if treated for 2 weeks (p = 0.12 by Fisher’s exact
test, placebo compared with phenytoin for 2 weeks).

**Mortality Rates**

Figure 1 shows the Kaplan–Meier estimate of survival
for the head-injured patients as a function of the study
drug they were assigned to take. As can be seen in this fig-
ure, there was a fairly high mortality rate during the first
few weeks, which is expected given the severity of the
brain injuries and concomitant injuries to other systems
seen in this cohort. There was no significant difference in
mortality between the patients who were assigned to re-
ceive phenytoin compared with the placebo group (p = 0.67,
relative risk 1.1, 95% CI 0.7–1.7). However, there were
significantly more deaths (p = 0.03, relative risk 2,
95% CI 1.1–3.7) among the patients who developed early
seizures compared with those who remained seizure free
(Fig. 2). This effect was entirely explained by the more se-
vere initial injuries in the participants who developed ear-
y seizures. The severity variables selected to predict best
the mortality rates were number of nonreactive pupils; AIS
head score; subdural hematoma; and intracerebral he-
matoma. When the effects of age and head-injury severity
were controlled for by using Cox’s proportional-hazards
regression (Fig. 3), there was no significant difference in
the survival rate between patients with and without early
posttraumatic seizure (p = 0.3, relative risk 0.69, 95% CI
0.3–1.4). In fact, after adjusting for injury severity, the
point estimate indicates a slightly reduced risk of death
with delayed early seizures. Thus, although phenytoin was

**Table 1**

<table>
<thead>
<tr>
<th>Time Posttrauma &amp; Symptom</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Days 1–7</td>
<td></td>
</tr>
<tr>
<td>no. of patients*</td>
<td>169</td>
</tr>
<tr>
<td>rash</td>
<td></td>
</tr>
<tr>
<td>maculopapular</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>other</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>nystagmus</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>leukocytosis</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>phlebitis</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>headache</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>total side effects</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>hypersensitivity reaction</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Days 8–14</td>
<td></td>
</tr>
<tr>
<td>no. of patients*</td>
<td>157</td>
</tr>
<tr>
<td>rash</td>
<td></td>
</tr>
<tr>
<td>maculopapular</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>other</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>fever</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>nystagmus</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>nausea &amp; dizziness</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>leukopenia</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>leukocytosis</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>lethargy</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>total side effects, Days 1–14</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>hypersensitivity reaction</td>
<td>4 (2.5%)</td>
</tr>
</tbody>
</table>

* The number of patients indicates those who were followed and who survived to the end of the interval specified.

**Fig. 1.** Graph showing cumulative mortality as a function of assigned treatment. Forty-two deaths occurred in the placebo group and 50 in the phenytoin group (p = 0.67). The Kaplan–Meier estimates are shown through 3 months because more than 90% of the deaths had occurred by that time.
This is roughly comparable with the 4% incidence of morbilliform rash observed in the first 15 days in a previous clinical trial of phenytoin for posttraumatic seizure prophylaxis.10 Because these mild cutaneous hypersensitivity reactions to phenytoin have occasionally been observed to be the forerunners of more serious dermatological reactions such as toxic epidermal necrolysis or Stevens–Johnson syndrome, it has been recommended that phenytoin be discontinued promptly if a characteristic hypersensitivity rash develops.7 In our patients who developed maculopapular rash, the study drug was promptly discontinued, and all affected patients recovered from the rash without experiencing more serious cutaneous reactions. Furthermore, none of the patients who developed a rash experienced other concurrent symptoms of a more severe systemic hypersensitivity syndrome.

Because of the number of patients enrolled, the results of this study may underestimate the potential for phenytoin to cause severe hypersensitivity syndromes such as Stevens–Johnson or the more severe toxic epidermal necrolysis syndromes, which are life threatening.8 The possibility remains that even 1 week of treatment could lead to serious toxicity on rare occasions. The occurrence of these syndromes is usually associated with treatment with the offending medication for weeks to months.8 The incidence of Stevens–Johnson syndrome with phenytoin therapy has been reported to be 1.5 cases per million users per week, usually occurring within the first 2 months of treatment.11 Concerns were raised about isolated fever in a few cases, and although these patients were in fact treated with phenytoin, these fevers were not confirmed to be drug related. Indeed, in each of these cases, the fever resolved despite continued treatment with the study medication, which strongly indicates that they were not symptomatic of phenytoin hypersensitivity.

Reduction in posttraumatic seizures by administration of phenytoin was not associated with a significant reduction in mortality rates in this group of patients. Although the mortality rate was higher in patients who experienced seizures, when adjustments were made based on head injury severity and the patient’s age, mortality rates were not significantly different in those patients with and without early posttraumatic seizures. These data indicate that the reduction of posttraumatic seizures produced by phenytoin did not improve survival. Although these data do not indicate an effect of early posttraumatic seizure reduction on mortality rates, the CI is rather wide, so a small effect could have been missed. It is possible that in a larger number of patients a certain number of fatal posttraumatic seizures may be prevented.

This study was not designed to address the effects of reduction of early posttraumatic seizures on other outcome measures such as impaired neurobehavioral functioning. Theoretically, prevention of seizures during the acute period following traumatic brain injury could prevent secondary brain insults at a time when the brain is vulnerable to secondary injury. Patients in this study were maintained on phenytoin or placebo for 1 year postinjury. To evaluate the effects of reduction of early posttraumatic seizures by using short-term administration of anticonvulsant agents to improve neurobehavioral outcome, an additional study is needed. One benefit of early posttraumatic seizure reduction that is likely to be realized is maintenance of the patient’s driving privileges.

Because we did not formally assess cognitive functioning in the first few weeks postinjury, we are not able to determine if phenytoin treatment in this short period of time has any impact on neuropsychological functioning or recovery. Long-term prophylactic treatment with phenytoin was associated with cognitive impairment in severely head injured patients tested at 1 month during this study; however, this effect was no longer observable at 1 year.6 We know of no studies in which the neurobehavioral effects of phenytoin during the 1st week postinjury or the later effects of short-term phenytoin use have been examined.

**Conclusions**

The primary focus of early treatment for severely head injured patients is to stabilize their medical condition to
minimize the risk of death and to prevent secondary brain injury that might otherwise be the cause of a worse neurological or neurobehavioral outcome. Use of phenytoin prophylactically can reduce the incidence of early seizures and their potential adverse sequelae with little attendant risk of causing serious medical side effects. Considering the available data, it is reasonable to administer phenytoin routinely as prophylaxis for 1 week in head-injured patients whose risk of developing posttraumatic seizures is high or for whom the repercussions of having an early seizure may be great.

Disclosure

None of the authors has any financial interest in the product described in this report.

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