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Valproate therapy for prevention of posttraumatic seizures: a randomized trial

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Object. Seizures frequently accompany moderate to severe traumatic brain injury. Phenytoin and carbamazepine are effective in preventing early, but not late, posttraumatic seizures. In this study the authors compare the safety and effectiveness of valproate with those of short-term phenytoin for prevention of seizures following traumatic brain injury.

Methods. The study was a randomized, double-blind, single-center, parallel-group clinical trial. Treatment began within 24 hours of injury. One hundred thirty-two patients at high risk for seizures were assigned to receive a 1-week course of phenytoin, 120 were assigned to receive a 1-month course of valproate, and 127 were assigned to receive a 6-month course of valproate. The cases were followed for up to 2 years.

The rates of early seizures were low and similar when using either valproate or phenytoin (1.5% in the phenytoin treatment group and 4.5% in the valproate arms of the study; $p = 0.14$, relative risk [RR] = 2.9, 95% confidence interval [CI] 0.7–13.3). The rates of late seizures did not differ among treatment groups (15% in patients receiving the 1-week course of phenytoin, 16% in patients receiving the 1-month course of valproate, and 24% in those receiving the 6-month course of valproate; $p = 0.19$, RR = 1.4, 95% CI 0.8–2.4). The rates of mortality were not significantly different between treatment groups, but there was a trend toward a higher mortality rate in patients treated with valproate (7.2% in patients receiving phenytoin and 13.4% in those receiving valproate; $p = 0.07$, RR = 2.0, 95% CI 0.9–4.1). The incidence of serious adverse events, including coagulation problems and liver abnormalities, was similar in phenytoin- and valproate-treated patients.

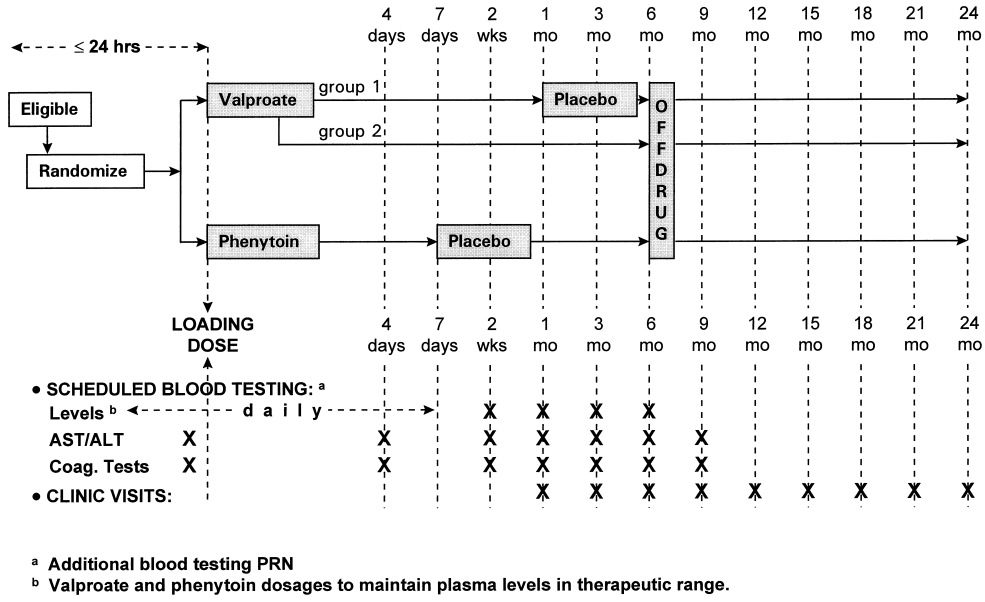
Conclusions. Valproate therapy shows no benefit over short-term phenytoin therapy for prevention of early seizures and neither treatment prevents late seizures. There was a trend toward a higher mortality rate among valproate-treated patients. The lack of additional benefit and the potentially higher mortality rate suggest that valproate should not be routinely used for the prevention of posttraumatic seizures.

KEY WORDS • brain injury • traumatic epilepsy • valproate • phenytoin • primary prevention • clinical trial

TRAUMATIC brain injuries represent an important health problem. In the United States alone, more than 80,000 people are hospitalized each year with moderate or severe traumatic brain injuries.[13] The population affected is typically young, and these injuries are associated with substantial rates of morbidity and mortality.[4,5,16] Posttraumatic seizures are a recognized complication of brain injury and have been classified as early (occurring ≤ 7 days after injury) or late (occurring > 7 days following injury). Approximately 20% of survivors of a brain injury with a Glasgow Coma Scale[11] (GCS) score of 10 or lower experience early seizures and 32% experience at least one late seizure. Eleven well-controlled studies have previously been performed to evaluate whether administration of antiepileptic drugs can reduce the incidence of posttraumatic seizures. Investigators in these studies have evaluated phenytoin, carbamazepine, or phenobarbital alone or in combination.[3,9,10,19,20,27,28,30,31] Of the four studies in which findings on early seizures were reported separately, three (two in which phenytoin was used and one in which carbamazepine was used) found significantly fewer seizures with the active drug when compared with placebo. The results of a metaanalysis suggest that phenytoin produces a 67% reduction in early seizures (95% confidence interval [CI] 39–82% reduction).[28]

Studies on the ability of antiepileptic drugs to reduce the incidence of late seizures have been discouraging. Six studies specifically reported findings on late seizures, and in four of the six a higher seizure rate was actually observed in patients receiving the active drug. The one study that reported a significant reduction in the late seizure rate used alternate-day treatment assignment, was not blinded, and used no treatment for the control regimen.[19]

Several animal models have been used to evaluate the efficacy of anticonvulsant drugs in stopping the process of epileptogenesis. Investigators using these models have



[a] Additional blood testing PRN
[b] Valproate and phenytoin dosages to maintain plasma levels in therapeutic range.

FIG. 1. Study schema. AST = aspartate aminotransferase; coag. = coagulation; PRN = pro re nata (as needed).

found no antiepileptogenic effect for phenytoin or carbamazepine[14,21,24,29] but have found such an effect for valproate.[1,18,24,25] Consequently, we sought to determine the seizure-preventive effects of valproate in the clinical setting. Two durations of seizure prophylaxis with valproate were evaluated based on the recommendations of a National Institute of Neurological Disorders and Stroke–sponsored Workshop on the Prophylaxis of Post-Traumatic Epilepsy; the 1-week duration of treatment with phenytoin was based on findings of our previous trial.[27] In this report we compare the effect of valproate with that of short-term phenytoin on early and late seizures, incidence of mortality, and medical side effects. In this study we also evaluated groups at 1, 6, and 12 months after injury by using a comprehensive battery of neurobehavioral measures that are not reported in this paper.

Clinical Material and Methods

Study Design

The study had a randomized, double-blind, parallel-group design. Within 24 hours of injury, patients with a substantial risk of experiencing late posttraumatic seizures were randomized. One third of the patients were assigned to receive phenytoin for 1 week, one third would receive valproate for 1 month, and one third would receive valproate for 6 months. The patients' clinical courses were followed for 2 years. Figure 1 schematically represents the study design.

Drug Intervention

The intravenously administered loading dose of phenytoin was 20 mg/kg, with maintenance dosing beginning at 5 mg/kg/day in two divided doses. The intravenously administered loading dose of valproate was 20 mg/kg, with initial maintenance dosing of 15 mg/kg/day in four divided doses. Valproate and phenytoin plasma concentrations were analyzed frequently (Beckman Array 360; Beckman Instruments, Inc., Brea, CA), and doses of either drug or placebo were changed by the clinical pharmacist to maintain predosing levels in the range of 40 to 80 μmol/L (10–20 μg/ml) for phenytoin and 277 to 693 μmol/L (40–100 μg/ml) for valproate and for placebo to keep the study blinded. Medications were administered orally when patients were clinically able to receive them in that manner; however, an attempt was made to administer drug doses intravenously to all patients for at least 1 week.

Study Population

Patients admitted to Harborview Medical Center in Seattle, Washington, a Level I trauma center, between February 1991 and December 1995 were eligible for the study if they were at least 14 years of age (16 years of age at admission during the first 3 years of the study); had a qualifying traumatic injury; had no history of seizures, significant brain injury, or other neurological condition before sustaining the qualifying injury; received no antiseizure medications either before the injury or between the time of injury and study-drug loading; were not pregnant; and had adequate liver function, as indicated by a serum alanine aminotransferase (ALT) level below twice the upper limit of normal. A qualifying injury had at least one of the following characteristics: immediate posttraumatic seizures, depressed skull fracture, penetrating brain injury, or computerized tomography (CT) evidence of a cortical contusion or subdural, epidural, or intracerebral hematoma. The study required drug loading within 24 hours after injury.

Most patients were too impaired neurologically to be able to provide informed consent before randomization. Usually, the legal next of kin or a family member provided this consent. In some cases no such person could be found in the allowed time, and if the patients were at least 18 years of age, they were entered into the study by using waived consent according to a protocol approved by the University of Washington institutional review board.

Assignment and Blinding

A computer-generated, blocked randomization list was generated by the statistician and was kept in a locked part of the pharmacy. The study nurse called the pharmacist to randomize a patient. Identical-appearing intravenous solutions and oral placebos, as well as placebo-dose changes and call backs to check placebo "drug levels" maintained the blind conditions.

Measures of Injury Severity, Outcome, and Side Effects

The severity of the brain injury was assessed using the GCS, the Traumatic Coma Data Bank CT classification,[17] and the occurrence of cortical contusion, intracranial hematoma, penetrating brain injury, depressed skull fracture, and acute posttraumatic seizures.

Occurrence of late seizures was the primary outcome; early seizures were a secondary outcome. Seizures were defined on the basis of clinical manifestations, especially involuntary movements; alterations in consciousness; or abnormal motor, sensory, or psychosensory phenomena. Electroencephalographic findings were sometimes used as adjunct criteria in making a diagnosis of seizures. Patients, families, and staff were instructed to call if any event occurred that might be a seizure. Most patients were in the hospital during the 1st week, so the majority of early seizures, occurring between study-drug loading and 7 days after injury, were witnessed by medical personnel. Because most patients were unconscious or had cognitive impairments during the first week, early seizures without a prominent motor component were likely to be overlooked. Late seizures, occurring more than 7 days after injury, were less frequently witnessed by medical personnel. Patients and caregivers were trained to recognize subtle manifestations of seizures and were carefully questioned by the study nurse at every contact. Information about any event suspected to be a seizure was reviewed by the blinded study neurologist (M.D.H. or A.J.W.) who made the final determination on seizure diagnosis for study purposes. If there was doubt, the event was not considered a seizure.

Liver function tests (ALT and aspartate aminotransferase) and blood coagulation tests (covering platelets, prothrombin time, partial thromboplastin time, fibrinogen, and thromboelastography) were routinely performed, as indicated in Fig. 1. Side effects were counted when they were observed by the study nurse, reported by patients or caregivers, or were recorded in the medical records. Specific questions about possible side effects were posed to the patient during at clinic visits.

Statistical Analysis

For analyses of early seizures and incidence of mortality, patients assigned to valproate treatment were considered to be one group regardless of the length of time they were to be treated. This was done because all early seizures and 88% of deaths occurred before 1 month, when both valproate groups received the same treatment. Additionally, this comparison was also reported for late seizures because we expected that the effect of valproate would be the same for the 1- and 6-month groups and, thus, the combined analysis was specified as the primary analysis in the protocol. Fisher's exact test was used to compare the groups with respect to the percentage of patients in specified categories. The Kruskal–Wallis test was used to compare patient ages and GCS scores. Kaplan–Meier curves with log-rank tests and Cox's proportional-hazard regression were used to compare groups with respect to times to death and early seizures. Because of the possibility of crossing hazard rates if valproate decreased seizures during administration, but did not prevent the process that causes the brain to generate seizures, the primary analysis for late seizures compared the difference of cumulative rates at 2 years with its standard error.

One interim analysis was planned, and its results indicated that the study should be continued. Planned subgroup analyses defined groups based on injury severity eligibility criteria. Secondary analyses adjusting for severity and demographics were also planned. All patients who had been observed for at least 8 days were included in the analysis of late seizures, regardless of whether they had experienced early seizures. Unless stated otherwise, all analyses included only eligible patients and are reported on an intent-to-treat basis. A two-sided significance level of 0.05 is used.

The sample size was planned to be approximately 385 to provide an 80% power to detect a halving of the late seizure rate (27% compared with 13.5%).

Results

Patient Population

Three hundred seventy-nine patients meeting all eligibility criteria were entered into the trial. The patient demographics and injury severity information are shown in Table 1. The treatment groups were well balanced with respect to these factors.

Additionally, 113 patients who were thought to be eligible at the time of randomization were found to be ineligible after randomization. This was typically due to some of the exclusion criteria not being known at the time of randomization (such as history of seizures or prior brain injury). The patients who were found to be ineligible after randomization were only observed for serious adverse experiences within 28 days of treatment and for incidence of mortality.

Participant Flow and Follow-Up Review

The duration of follow-up review and reasons why the patients were no longer observed are shown in Table 2. During the 1st month after injury, we primarily stopped observing patients because of death or our inability to obtain consent within 72 hours for patients entered under waived consent. This time limit was specified by the study's human subjects approval. Of the survivors for whom consent was obtained, 87% were followed throughout the full 2 years. Not all of these patients continued with their assigned treatment. The duration of treatment with blinded drug and the reasons for stopping treatment are shown in Table 3. Seventy-nine percent of patients in the 1-month valproate group, 83% of those in the 6-month valproate group, and 88% of those in the 1-week phenytoin group completed 1 week of treatment; 70%, 65%, and 71%, respectively, completed 1 month of treatment; and

TABLE 1
*Characteristics of 379 eligible patients**

Characteristic	Valproate 1 Mo	Valproate 6 Mos	Phenytoin 1 Wk	p Value
demographic				
no. of patients	120	127	132	
age (mean ± SD)	40 ± 19	36 ± 16	36 ± 16	0.26
gender (% male)	84	77	84	0.27
race (% Caucasian)	80	81	83	0.80
external cause of injury (%)				0.79
automobile	34	28	29	
motorcycle	4	7	7	
pedestrian or bicyclist	10	12	15	
fall	23	24	16	
struck, shot, or stabbed	24	24	28	
other	4	5	5	
injury severity				
GCS score (mean ± SD)	11.6 ± 3.6	11.1 ± 3.8	11.7 ± 3.8	0.25
inclusion criterion (%)				
contusion	77	80	70	0.23
subdural hematoma	47	43	40	0.57
epidural hematoma	18	26	23	0.27
intracerebral hematoma	8	12	8	0.39
depressed skull fracture	16	9	19	0.09
penetrating brain injury	7	4	7	0.56
immediate seizures	8	8	6	0.88
surgical procedure (%)				
evacuation of subdural hematoma	15	15	14	1.00
evacuation of epidural hematoma	9	14	7	0.14
evacuation of intracerebral hematoma	2	4	2	0.53
TCDB (%)				0.25
diffuse injury I (no visible pathology)	0	0	0	
diffuse injury II	62	57	60	
diffuse injury III (swelling)	14	17	21	
diffuse injury IV (shift)	9	7	11	
evacuated mass lesion	1	0	0	
nonevacuated mass lesion	14	18	8	

* SD = standard deviation; TCDB = Traumatic Coma Data Bank CT classification (1st scan).

TABLE 2
*Follow-up review of patients after randomization**

Factor	No. of Patients: Valproate 1 Mo	Valproate 6 Mos	Phenytoin 1 Wk
randomized	120	127	132
lost during Wk 1	14	12	9
waived consent expired	4	4	4
death	10	8	5
followed up through Wk 1	106	115	123
lost during Wks 2–4	7	11	6
death	4	7	2
lost/withdrawn	3	4	4
followed up through Wk 4	99	104	117
lost during Wks 5–26	5	4	3
death	0	1	0
lost/withdrawn	5	3	3
followed up through 6 mos	94	100	114
lost during Wks 27–52	2	7	4
death	1	1	0
lost/withdrawn	1	6	4
followed up through 1 yr	92	93	110
lost during Yr 2	2	4	6
death	0	0	2
lost/withdrawn	2	4	4
followed up through 2 yrs	90	89	104
% of randomized cases	75	70	79
% of consenting survivors	89	84	87

* The number of eligible cases followed to the different times is shown, as is the percentage of randomized cases and consenting survivors followed to the end of the study.

45%, 39%, and 45%, respectively, completed the 6 months of the study.

Drug Levels

As illustrated in Fig. 2, during the 1st week of treatment, mean valproate concentrations were at or above the target range (277–693 μmol/L or 40–100 μg/ml) for 97% of the patients in the two valproate treatment groups. During the remainder of the 1st month, 90% of patients and, during the subsequent 5 months, 85% of patients continuing on their active assigned treatment averaged at least the target range. Phenytoin plasma concentrations averaged at least the target range (40–80 μmol/L or 10–20 μg/ml) for 91% of the patients in that group during the week of treatment.

Adverse Events

Serious adverse events, that is, events that resulted in prolonged hospitalization, were life-threatening, required treatment with prescription drugs, or could result in permanent disability are summarized in Table 4. There were two cases in which the event was probably related to treatment. A low neutrophil count was found in a 14-year-old girl in whom the results of blood chemistry analysis were normal at the start of valproate treatment. When the values were checked at 1 month, her neutrophil count was 850/ml. The neutrophil levels subsequently increased, but were still low 3 days later. Drug administration was stopped and the patient's levels were found to have returned to normal by the next test 2 months later. No other serious abnormalities were noted with respect to clinically obtained counts. In another case a rash, described as "bumpy, red from head to toe and very itchy," occurred in a 51-year-old woman 1 day after she completed her 7 days of phenytoin. The rash did not respond to 2 days of treatment with over-the-counter medication but responded within 24 hours to prednisone and hydroxyzine.

Because there have been reports of deaths of patients using valproate that were linked with bleeding and with liver failure, any event that involved either of these problems was considered "serious." Eleven bleeding episodes were diagnosed in the patients—five of whom were in the valproate 1-month arm, one of whom was in the valproate 6-month arm, and five of whom were in the phenytoin arm. Clinically, none of the bleeding episodes was thought to be related to treatment. In six of these cases, platelet counts were obtained within 24 hours of detection of bleeding; in one case the count was lower than normal range (63,000 platelets).

Laboratory Values

Tests of liver function and blood coagulation were per-

TABLE 3

Duration of treatment with blinded medication in 379 eligible patients

Factor	No. of Patients		
	Valproate		Phenytoin
	1 Mo	6 Mos	1 Wk
no. of randomized patients	120	127	132
drug stopped during Wk 1	25	21	16
waived consent expired	10	7	9
death/imminent death	9	9	4
side effects	4	3	3
seizures	2	1	0
other	0	1	0
medication used through Wk 1	95	106	116
drug stopped during Wks 2–4	11	23	22
death/imminent death	0	5	2
side effects	5	5	9
seizures	0	3	2
other	6	10	9
medication used through Wk 4	84	83	94
drug stopped during Wks 5–26	30	34	34
death/imminent death	0	1	0
side effects	10	6	8
seizures	3	4	2
other	17	23	24
medication used through Wk 26	54	49	60

formed five times during the 6 months of blinded treatment. Platelet counts were significantly lower in the active valproate arms of the study at each time (p = 0.0001–0.03), but levels were generally adequate and there was no

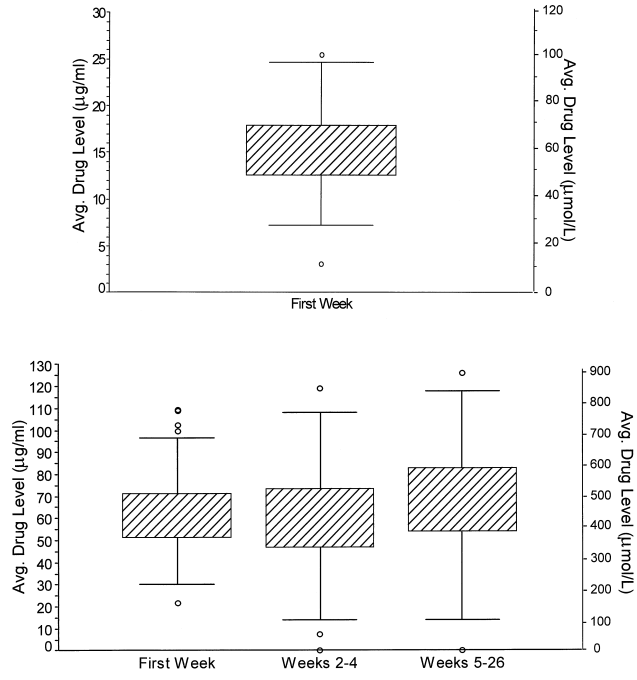


FIG. 2. Graphs displaying average (avg.) serum levels of drugs in patients continuing on their assigned treatment. The average value observed in an individual over the period indicated is summarized. The shaded boxes extend from the 25th to the 75th percentile. *Upper:* Graph depicting phenytoin levels. *Lower:* Graph depicting valproate levels. The two subgroups of patients receiving valproate therapy are combined.

TABLE 4

*Serious adverse events by assigned treatment and time interval**

Event	No. of Patients								
	Valproate—1 Mo			Valproate—6 Mos			Phenytoin—1 Wk		
	Wk 1	Wks 2–4	Wks 5–26†	Wk 1	Wks 2–4	Wks 5–26	Wk 1	Wks 2–4†	Wks 5–26†
recurrent subdural bleeding	0	0	0	0	0	0	0	2	0
chronic subdural bleeding	0	0	1	0	0	0	0	0	1
intracerebral rebleeding	0	0	0	1	0	0	0	0	0
aneurysm rupture	0	0	0	0	0	0	0	1	0
pseudoaneurysm bleeding	0	1‡	0	0	0	0	0	0	0
hemopneumothorax	1‡	0	0	0	0	0	0	0	0
GI bleeding	0	1	1	0	0	0	0	0	0
maxillary artery hemorrhage	0	0	0	0	0	0	0	1	0
cerebral reinfarction	0	0	0	0	0	0	0	1	0
DVT	1	0	0	0	1	0	0	1	1
pulmonary embolism	0	1	0	0	0	0	0	0	0
pancreatitis	0	0	0	0	1	1§	1	1	0
sepsis	1	1	0	0	0	0	0	3	0
psychiatric hospitalization	0	0	0	0	0	0	0	1	1
low neutrophil count	0	0	0	0	1‖	0	0	0	0
multiple organ failure	0	1	0	0	0	0	0	0	0
anemia	0	0	0	1	0	0	0	0	0
rash requiring prescription medication	0	0	0	0	0	0	1‖	0	0
SIADH	0	0	0	0	0	0	1	0	0

* All randomized patients are included, regardless of eligibility. Abbreviations: DVT = deep vein thrombosis; GI = gastrointestinal; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

† Time period during which patients received placebo.

‡ Patient died. Note that the patient who had pseudoaneurysm bleeding had stopped taking valproate and had switched to phenytoin on Day 6 because of an elevated ALT; the fatal event occurred on Day 20.

§ The event occurred at 7 months; however, the patient was receiving a course of unblinded valproate because of seizures.

‖ Event was probably drug related.

TABLE 5

*Side effects experienced by at least 10 people or those with significant differences among treatments**

Event	No. of Patients								
	Valproate—1 Mo			Valproate—6 Mos			Phenytoin—1 Wk		
	Wk 1	Wks 2–4	Wks 5–26†	Wk 1	Wks 2–4	Wks 5–26	Wk 1	Wks 2–4†	Wks 5–26†
fatigue/lethargy‡	5	10	11	3	7	12	2	4	6
dizziness/lightheadedness	1	4	2	2	2	3	3	2	3
cognitive problems	2	4	3	1	2	5	0	2	2
cerebellar signs	0	2	1	2	3	3	2	1	2
GI problems	2	0	2	2	1	1	1	1	3
headache	1	3	1	1	0	4	2	1	0
sleep disturbance	0	2	1	2	1	1	1	0	4
rash‡	3	2	0	0	0	0	1	3	2
IV site problems‡	1	0	0	0	0	0	6	0	0

* Each side effect is counted during the first time period in which it was reported. Abbreviation: IV = intravenous.
† Time period during which patients received placebo.
‡ $p < 0.05$.

significant difference in the fraction with counts below 100,000. No other traditional coagulation parameters differed. Levels of ALT were significantly higher in the phenytoin treatment group than in either of the valproate treatment groups when measured on Days 4 and 14 and at 1 month (p = 0.0001–0.02). Also, significantly more patients assigned to the phenytoin treatment group had ALT levels that were greater than three times the upper limit of normal (p = 0.002).

Side Effects

Side effects that were reported by at least 10 people or those that occurred significantly more frequently with one treatment group are shown in Table 5. Many "side effects" were reported by patients who were taking placebo, indicating that the blinding had been effective. The low rate of side effects (other than lethargy or fatigue) in patients undergoing valproate therapy is especially remarkable because valproate was given for 1 or 6 months, whereas phenytoin was given for only 1 week.

Early Seizures

Early seizures were rare in patients receiving either medication, and the rates were not significantly different from each other. Between drug loading and Day 7, among the phenytoin-treated group two patients (1.5%) had at least one seizure; and among the groups assigned 1 or 6 months of valproate therapy 11 patients (4.5%) had a seizure (p = 0.14; RR 2.9 for early seizure with valproate compared with phenytoin; 95% CI 0.7–13.3).

Late Seizures

Kaplan–Meier curves showing no significant difference in the percentage of patients developing late seizures over time are shown in Fig. 3 (p = 0.19). When the two valproate subgroups are considered together, there is also no significant difference (p = 0.27; RR 1.4 for late seizures with valproate compared with phenytoin; 95% CI 0.8–2.4).

A supplementary efficacy analysis censoring observations at the time that patients prematurely stopped drug therapy also showed no significant difference between treatments (p = 0.7; RR 1.2; 95% CI 0.6–2.4).

Exploratory analyses were performed to determine whether the late seizure rates in patients on drug therapy differ according to subgroups based on injury severity inclusion criteria, time until treatment was initiated (< 12 hours compared with 12–24 hours), and patient gender, age (< 40 compared with ≥ 40 years), or race (Caucasian compared with non-Caucasian). The only nominally significant treatment effect was found among patients with cortical contusion: more patients in the valproate groups than in the phenytoin group developed late seizures (p = 0.03 without correction for multiple tests).

Of those patients who developed late seizures while under observation for the study, 11 (73%) of those assigned to valproate therapy for 1 month, 17 (71%) of those assigned to valproate therapy for 6 months, and 15 (88%) of those assigned to phenytoin therapy had at least two late seizures and, thus, met the criteria for a diagnosis of posttraumatic epilepsy. The median numbers of late seizures among patients who had at least one was 4, 2.5, and 4 in the three groups respectively, which was not significantly different (p = 0.11).

Incidence of Mortality

The estimated death rate by 2 years was 13.4% (32 cases) for "eligible" patients assigned to either of the valproate arms and 7.2% (nine cases) for those assigned to the phenytoin arm of the study (Fig. 4; p = 0.07; RR 2.0; 95% CI 0.9–4.1). When all randomized patients, including those who were "ineligible," were considered, the death rates became 15.6% and 10.4%, respectively (p = 0.13; RR 1.6; 95% CI 0.9–2.8). Whereas this analysis shows a trend toward higher mortality rates, earlier safety analyses showed the difference as being significant, and the study was stopped by its Data and Safety Monitoring Board. This occurred after the planned sample size had been attained. Five patients still in the 1st month after injury (when most deaths occur) received placebo without breaking the blind. Twenty patients further along in the study were informed of the difference in mortality rates and

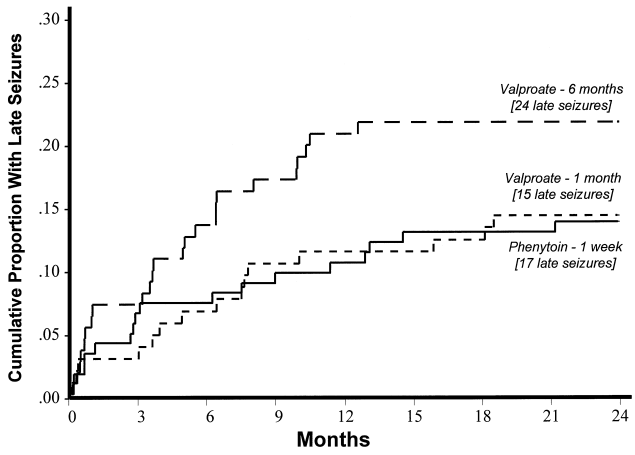


FIG. 3. Graph showing the Kaplan–Meier estimate of cumulative late seizure rates in patients assigned to the three treatment arms of the study. The differences are not significant ($p = 0.19$).

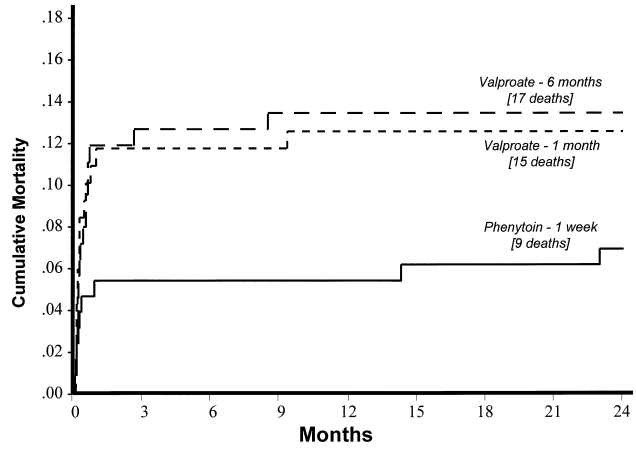


FIG. 4. Graph showing the Kaplan–Meier estimate of cumulative mortality rates in patients assigned to the three treatment arms of the study. The difference between the phenytoin group and the combined valproate groups is not significant ($p = 0.07$).

given the option to discontinue medication early, but all continued therapy.

Two adjustments for injury severity, one stratifying according to patient age (< 40 compared with ≥ 40 years) and GCS score (3–5, 6–8, 9–12, and 13–15) and the other covarying the value of the equation predictive of mortality rate[12] caused very little difference in the comparison of mortality rates between treatments.

Discussion

Early Seizures

In this double-blind randomized trial, early seizure rates were low in patients receiving either drug. Phenytoin previously was shown to reduce early posttraumatic seizures in several trials.[28] In the present study, early seizure rates of 4.5% with valproate and 1.5% with phenytoin administration are similar to the 3.6% seen with phenytoin administration in our earlier study and are substantially lower than the 14.2% rate when administering placebo.[27] Although the two studies were similar in their stated entrance requirements, improved CT technology might have detected smaller abnormalities during the current study and, hence, possibly included less severely injured patients. This raises a cautionary note on drawing conclusions from comparisons between current valproate results and those from the placebo group in the earlier phenytoin study. The combination of these factors (no significant difference from a proven treatment, low seizure rates and correspondingly wide confidence intervals on relative risk, and the potential severity difference from the earlier study) leads us to draw no conclusion about whether valproate is effective in preventing early seizures.

Late Seizures

Valproate showed no indication of a preventive or suppressive effect on late seizures. The late seizure rate for patients in each valproate group was at least as high as for patients in the group assigned to receive 1 week of phenytoin. Although laboratory studies have found that valproate prevents epileptogenesis in the kindling model and in other models,[1,18,24,25] no beneficial effect was seen in this study.

Compliance is always a concern in long-term outpatient studies such as this. Despite vigorous efforts to encourage patients to continue their study medication, 16% of consenting survivors stopped taking the blinded medication before 1 month because of patient preference or mostly minor side effects; 21% stopped before 6 months. Of those continuing to take medication, 85 to 90% had drug levels in the target range when they came for their follow-up visits. No unannounced blood tests to assess compliance were attempted. Although noncompliance was considerable, we believe that it did not cause a negative effect because of the lack of a positive trend overall, the lack of a trend even when patients were excluded on stopping their blinded medication, and the relatively high serum levels of drug among those continuing on their blinded treatment.

Incidence of Mortality

There was a trend toward a higher mortality rate in the groups receiving valproate. Injury severity was comparable among the groups and a risk adjustment did not diminish the difference between treatments.

Potential mechanisms that might suggest that the difference was something other than a chance finding have been examined. Fatal liver function problems and coagulopathy have been reported with use of valproate.[2,6–8,15,22,23,26] None of the deaths in this study was attributed to either of these problems; the serious adverse events (Table 4) suggest no excess of either type of nonfatal difficulty in the valproate groups; no differences were seen in coagulopathy (for example, platelets $> 100{,}000$), although platelet counts were lower in patients receiving valproate; and elevated liver enzymes were significantly more common in the phenytoin treatment group. Examination of intracranial pressure also showed no significant differences among the groups.

The mortality rates for both treatments in the current study (7.2% with phenytoin and 13.4% with valproate) are lower than the 22% mortality rate observed in our earlier study.[27] When all these factors are taken together, it is un-

clear if there is any clinical importance to the trend observed.

Conclusions

Valproate therapy shows no benefit over 1 week of treatment with phenytoin with respect to prevention of early seizures. Valproate fails to prevent late posttraumatic seizures, as is the case for phenytoin and carbamazepine. The mortality rates of the treatment groups are not significantly different, but there is a trend toward a higher mortality rate in the valproate treatment groups. No cause for such a difference could be determined. The lack of additional benefit and the potentially higher mortality rate suggest that valproate should not be routinely used for the prevention of early or late posttraumatic seizures.

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