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A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus

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A COMPARISON OF FOUR TREATMENTS FOR GENERALIZED CONVULSIVE STATUS EPILEPTICUS

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ABSTRACT

Background and Methods Although generalized convulsive status epilepticus is a life-threatening emergency, the best initial drug treatment is uncertain. We conducted a five-year randomized, double-blind, multicenter trial of four intravenous regimens: diazepam (0.15 mg per kilogram of body weight) followed by phenytoin (18 mg per kilogram), lorazepam (0.1 mg per kilogram), phenobarbital (15 mg per kilogram), and phenytoin (18 mg per kilogram). Patients were classified as having either overt generalized status epilepticus (defined as easily visible generalized convulsions) or subtle status epilepticus (indicated by coma and ictal discharges on the electroencephalogram, with or without subtle convulsive movements such as rhythmic muscle twitches or tonic eye deviation). Treatment was considered successful when all motor and electroencephalographic seizure activity ceased within 20 minutes after the beginning of the drug infusion and there was no return of seizure activity during the next 40 minutes. Analyses were performed with data on only the 518 patients with verified generalized convulsive status epilepticus as well as with data on all 570 patients who were enrolled.

Results Three hundred eighty-four patients had a verified diagnosis of overt generalized convulsive status epilepticus. In this group, lorazepam was successful in 64.9 percent of those assigned to receive it, phenobarbital in 58.2 percent, diazepam and phenytoin in 55.8 percent, and phenobarbital in 58.2 percent, diazepam and phenytoin, it is easier to use. (N Engl J Med 1998;339:792-8.)

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S TATUS epilepticus is a life-threatening emergency that affects 65,0001 to 150,0002 people in the United States each year. Generalized convulsive status epilepticus is the most common and most dangerous type.

Phenobarbital,3-5 phenytoin,6-14 diazepam plus phenytoin,15-16 and lorazepam17-28 have been advocated for the initial treatment of generalized convulsive status epilepticus, and each is used by a substantial number of physicians.3 There are few data from controlled trials, however, to document the efficacy of these treatments, and they have not been directly compared. We therefore undertook this study to compare the efficacy of standard doses of these four drugs in the treatment of generalized convulsive status epilepticus.

METHODS

Study Design In a double-blind study conducted at 16 Veterans Affairs medical centers and 6 affiliated university hospitals between July 1, 1990, and June 30, 1995, patients with generalized convulsive status epilepticus were randomly assigned to receive intravenous

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*Other members of the study group are listed in the Appendix.
treatment with lorazepam, phenobarbital, phenytoin, or diazepam followed by phenytoin.

Overt generalized convulsive status epilepticus was defined as recurrent convulsions without complete recovery between seizures, and subtle generalized convulsive status epilepticus as the stage of generalized convulsive status when the patient is in continuous coma but only subtle motor convulsions are seen.29 Patients were classified as having one of these two types of status epilepticus according to the following operational definitions. Overt generalized convulsive status epilepticus was considered present when there were two or more generalized convulsions, without full recovery of consciousness between seizures, or continuous convulsive activity for more than 10 minutes (treatment after 10 minutes of continuous seizure activity was considered essential to protect against neuronal and systemic damage from ongoing seizure activity). Subtle generalized convulsive status epilepticus was considered present when the patient had coma and ictal discharges on the electroencephalogram,20 with or without subtle convulsive movements (rhythmic twitching of the arms, legs, trunk, or facial muscles; tonic eye deviation; or nystagmoid eye jerking). If the investigator required an electroencephalogram to diagnose generalized convulsive status epilepticus, the patient was considered to have subtle generalized convulsive status epilepticus.

The key criterion for study entry was evidence of overt or subtle generalized convulsive status epilepticus at the time of evaluation, regardless of prior drug treatment. Patients who had received treatment and whose seizures had stopped were not eligible for inclusion. Other exclusion criteria included status epilepticus of a type other than generalized convulsive, an age of less than 18 years, pregnancy, a neurologic emergency requiring immediate surgical intervention, and the presence of a specific contraindication to therapy with hydantoin, benzodiazepine, or barbiturate drugs. If patients with repeated episodes of generalized convulsive status epilepticus were inadvertently enrolled more than once, only the first episode was included in the analysis.

A blood sample was obtained before treatment for hematologic and serum-chemistry tests and for screening for antiepileptic drug treatment. Intravenous access was established with normal saline. The order of the treatments was determined by random assignment. Separate randomization schemes were used at each site for each type of status epilepticus. Treatment kits were placed at three or four locations within each participating center, and for each patient the lowest-numbered kit at the location nearest to the patient was used. Electroencephalographic recording was started as soon as possible after the initiation of the protocol, but treatment was never delayed until the electroencephalogram could be obtained unless it was necessary to confirm the diagnosis. Blood pressure, heart rate, respiratory rate, level of consciousness, and seizure activity were recorded every 5 minutes for the first 20 minutes after the drug infusion began and then every 10 minutes for the next 40 minutes. Seizure activity and level of consciousness were recorded every hour thereafter until the completion of the 12-hour study period. Blood was obtained before the initial infusion, at the completion of the infusion, and 2 hours and 12 hours after the start of the infusion for the measurement of anti-convulsant-drug concentrations.

Treatment was considered successful if all clinical and electrical evidence of seizure activity stopped within 20 minutes after the start of the infusion and did not recur during the period from 20 to 60 minutes after the start of treatment. Electrical seizure activity included any of the five ictal patterns described previously.30

**Table 1.** Drug doses, rates of administration, and composition of drug-treatment kits.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>LORAZEPAM</th>
<th>PHENOバルBITRAL</th>
<th>DIAZEPAM AND PHENYTOIN</th>
<th>PHENYTOIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>0.1</td>
<td>15</td>
<td>0.15 and 18</td>
<td>18</td>
</tr>
<tr>
<td>Maximal rate of administration (mg/min)</td>
<td>2</td>
<td>100</td>
<td>5 and 50</td>
<td>50</td>
</tr>
<tr>
<td>Drug-solution concentration (mg/ml)*</td>
<td>4</td>
<td>100</td>
<td>5 and 50</td>
<td>50</td>
</tr>
<tr>
<td>Contents of first treatment box</td>
<td>Tubex</td>
<td>Lorazepam</td>
<td>Dummy</td>
<td>Dummy</td>
</tr>
<tr>
<td></td>
<td>Vial A</td>
<td>Dummy</td>
<td>Phenobarbital</td>
<td>Diazepam</td>
</tr>
<tr>
<td></td>
<td>Vial B</td>
<td>Dummy</td>
<td>Phenobarbital</td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Vial C</td>
<td>Dummy</td>
<td>Phenobarbital</td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Vial D</td>
<td>Dummy</td>
<td>Phenobarbital</td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Vial E</td>
<td>Dummy</td>
<td>Phenobarbital</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Active drug in second treatment box</td>
<td>Phenytoin</td>
<td>Phenytoin</td>
<td>Lorazepam</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Active drug in third treatment box</td>
<td>Phenobarbital</td>
<td>Lorazepam</td>
<td>Phenobarbital</td>
<td>Phenobarbital</td>
</tr>
</tbody>
</table>

*To convert drug concentration to millimoles per liter, multiply by the following: lorazepam, 3.11; phenobarbital, 4.31; diazepam, 2.51; and phenytoin, 3.96.
analyses.

794 were eligible but were not included because the
status epilepticus. Of the 1135 who were not enrolled,
tuberculous recordings obtained during the 12-hour
sive status epilepticus and the determination of treatment success.
A central procedure for review of electroencephalograms and data verification to ensure consistency among the
study was designed to analyze the patients with overt and
status before the current episode, whether or not
of seizures, cause of status epilepticus, functional
ined (data not shown), patients with overt and sub-
neurological cause (13), age of less
sence of generalized convulsive status epilepticus
cluded for one or more of the following reasons: ab-
study team was not called. The other 1022 were ex-
cluded at randomization. In addition, 18 patients classified
as having subtle status epilepticus at randomization
ne and from each vial to
produce the desired dose without compromising the blinded
ature of the study. The Tubex solution and the solution from vial
A were injected simultaneously. Tubexes and vials with active
drug contained propylene glycol, as did dummy Tubexes; dummy
vials contained normal saline. The second and third treatment
boxes were provided to allow subsequent treatment, if necessary,
without revealing the identity of the study drug. Active drugs in
the second and third boxes for each treatment regimen are listed
in Table 1.

Central Review
We used a central procedure for review of electroencephalograms and data verification to ensure consistency among the
hospitals in the diagnosis and classification of generalized convulsive
status epilepticus and the determination of treatment success.
A committee consisting of the study chairman, project director, and an electrophysiology reviewer reviewed all clinical data and
electroencephalographic recordings obtained during the 12-hour
study period. Differences of opinion between the central com-
mitee and investigators at the study sites were resolved by discus-
sion. The review committee remained blinded to the identity
of the treatment drug in each case until the review of all cases was
completed.

Statistical Analysis
The study was designed to analyze the patients with overt and
subtle generalized convulsive status epilepticus separately, because we
anticipated a significant difference in outcome in the two
groups. Analyses were performed both on an intention-to-treat
basis, with all enrolled patients included, and with only patients
included who had a verified diagnosis of generalized convulsive
status epilepticus. The intention-to-treat analyses included pa-
tients who were mistakenly assigned to the wrong status group
(e.g., overt instead of subtle status epilepticus), had other types
of status epilepticus, or did not actually have status epilepticus. In
the intention-to-treat analysis, patients in the last group were clas-
sified as having been successfully treated. For the analyses restrict-
ed to patients with verified diagnoses, patients were assigned
to their correct status group (overt or subtle), as determined by the
central review. Patients who did not have a generalized convulsive
status epilepticus were excluded from the verified-diagnosis analy-
es. Chi-square techniques were used to analyze rates of treat-
ment success, recurrence, and adverse events. The alpha level was
set at 0.05 for analyses of all four treatments, and a two-tailed al-
pha level of 0.01 was used to determine the significance of differ-
ences between any two regimens. Statistical analyses were run
on the in-hospital treatment cases and on the 570 patients with
verified diagnosis of status epilepticus. No significant differences
among the four drug-treatment groups or in any of the characteristics
we examined (data not shown), patients with overt and sub-
tle status epilepticus differed significantly with respect to age, race, current use of anticonvulsants, history
of seizures, cause of status epilepticus, functional
status before the current episode, whether or not
they were veterans, the part of the hospital where
treatment took place (emergency room, ward, or in-

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>OVERT (N=384)</th>
<th>SUBTLE (N=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.6±15.6</td>
<td>62.0±15.1</td>
</tr>
<tr>
<td>Veteran (%)</td>
<td>70.1</td>
<td>80.6</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>82.3</td>
<td>85.1</td>
</tr>
<tr>
<td>Not previously treated for current episode (%)</td>
<td>51.3</td>
<td>51.5</td>
</tr>
<tr>
<td>History of acute seizures (%)</td>
<td>54.2</td>
<td>25.4</td>
</tr>
<tr>
<td>History of epilepsy (%)</td>
<td>42.4</td>
<td>12.7</td>
</tr>
<tr>
<td>History of status epilepticus (%)</td>
<td>12.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Median duration of status epilepticus at enrollment (hr)</td>
<td>2.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Causal factors (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote neurologic cause</td>
<td>69.5</td>
<td>34.3</td>
</tr>
<tr>
<td>Acute neurologic cause</td>
<td>27.3</td>
<td>37.3</td>
</tr>
<tr>
<td>Life-threatening medical condition</td>
<td>32.0</td>
<td>56.7</td>
</tr>
<tr>
<td>Cardiopulmonary arrest</td>
<td>6.3</td>
<td>38.1</td>
</tr>
<tr>
<td>Tonic effects of therapeutic or recreational drug</td>
<td>6.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Alcohol withdrawal</td>
<td>6.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

+Prior minus values are means ±SD.
†Some patients had more than one causal factor.

RESULTS
We attempted to enroll all eligible patients at each
participating hospital. We screened 1705 patients
during the study period; 570 were enrolled (395 with overt status epilepticus and 175 with subtle status
epilepticus). Of the 1135 who were not enrolled,
113 were eligible but were not included because the
tensive care unit), history of status epilepticus, history of excessive alcohol use, and duration of status epilepticus.

Table 3 gives the mean doses, serum concentrations after infusion, and length of time necessary to complete infusion for each of the four initial treatments. Lorazepam required the least time to infuse (P<0.001 in paired comparisons); the treatments that included phenytoin took the longest (P<0.001).

Figure 1 presents the results of the four treatment regimens with respect to efficacy. In the analysis of the 518 patients with verified diagnoses (Fig. 1A), the first treatment regimen was successful in 55.5 percent of patients with overt status epilepticus, but in only 14.9 percent of those with subtle status epilepticus. Among the patients with overt status epilepticus, chi-square analysis showed a significant difference overall (P=0.02) in the frequency of success among the four treatments, but no differences were detected in the group with subtle status epilepticus (P=0.18). Lorazepam was effective significantly more often than phenytoin (P=0.002) in patients with overt status epilepticus. Other pairwise comparisons did not show significant differences between individual treatments.

When the two groups were combined in a post hoc analysis, lorazepam was successful as the first treatment in 52.2 percent of the patients to whom it was administered, phenobarbital in 49.2 percent, diazepam followed by phenytoin in 43.1 percent, and phenytoin alone in 36.8 percent. Chi-square analysis revealed a significant difference (P=0.008) in the frequency of success among treatments. In paired comparisons, lorazepam was effective more often than phenytoin (P=0.001). The difference in efficacy between phenobarbital and phenytoin approached significance (P=0.02). The results of the intention-to-treat analysis (Fig. 1B) were similar, but...
TABLE 4. FREQUENCY OF COMMON DRUG-RELATED SIDE EFFECTS AMONG THE 518 PATIENTS WITH VERIFIED DIAGNOSES.

<table>
<thead>
<tr>
<th>TYPE OF GENERALIZED CONVULSIVE STATUS EPILEPTICUS AND SIDE EFFECT</th>
<th>LORAZEPAM</th>
<th>PHENOBARBITAL</th>
<th>DIAZEPAM AND PHENYTOIN</th>
<th>PHENYTOIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt</td>
<td>97</td>
<td>91</td>
<td>95</td>
<td>101</td>
</tr>
<tr>
<td>No. of patients</td>
<td>10.3</td>
<td>13.2</td>
<td>16.8</td>
<td>9.9</td>
</tr>
<tr>
<td>Hypotension (%)</td>
<td>25.8</td>
<td>34.1</td>
<td>31.6</td>
<td>27.0</td>
</tr>
<tr>
<td>Cardiac-rhythm disturbance (%)</td>
<td>7.2</td>
<td>3.3</td>
<td>2.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Subtle</td>
<td>39</td>
<td>33</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>No. of patients</td>
<td>12.8</td>
<td>15.2</td>
<td>2.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Hypotension (%)</td>
<td>59.0</td>
<td>48.5</td>
<td>58.3</td>
<td>57.7</td>
</tr>
<tr>
<td>Cardiac-rhythm disturbance (%)</td>
<td>7.7</td>
<td>9.1</td>
<td>5.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

differences between groups were not significant for either the patients with overt status epilepticus (P = 0.12) or those with subtle status epilepticus (P = 0.91). In the verified-diagnosis analysis, status epilepticus occurred during the 12-hour study period in 11 percent (24 of 213) of patients with successfully treated overt status epilepticus and 20 percent (4 of 20) of successfully treated patients with subtle cases. There were no significant differences in the rates of recurrence among the four treatments for either the patients with a verified diagnosis of overt generalized convulsive status epilepticus or those with verified subtle status epilepticus.

The commonly reported side effects of treatment are shown in Table 4. There were no significant differences among the four treatments in either group (those with overt or subtle generalized convulsive status epilepticus). However, hypotension requiring treatment occurred more often in the patients with subtle status epilepticus than those with overt status epilepticus (P < 0.001). Sixty-seven of the patients with overt status epilepticus (17 percent) regained full consciousness before the end of the 12-hour study period, with no significant differences among the four treatment groups (P = 0.59). None of the patients with subtle status epilepticus completely regained consciousness during the 12-hour study period.

Outcomes 30 days after treatment were significantly worse (P < 0.001) for patients with subtle status epilepticus. At 30 days, 50.1 percent of patients with overt status epilepticus had been discharged from the hospital, as compared with 8.8 percent of patients with subtle status epilepticus; 22.9 percent of those with overt status epilepticus were still in the hospital, as compared with 26.5 percent of those with subtle status epilepticus; mortality rates were 27.0 percent and 64.7 percent, respectively. There were no significant differences in outcome at 30 days among the four treatments for either the patients with overt status epilepticus or those with subtle status epilepticus. In both the overt and subtle status epilepticus groups, however, patients successfully treated with the first study drug had a better prognosis than did those in whom the first treatment was not successful (for patients with overt status epilepticus, P < 0.001; for those with subtle status epilepticus, P = 0.01). Among patients with overt and subtle status epilepticus, mortality was twice as high for patients whose status was not controlled with the first drug as for those in whom the first treatment was successful. No other follow-up data were collected.

DISCUSSION

Our results show that lorazepam is more likely than phenytoin to be successful when used as the initial intravenous treatment for overt generalized convulsive status epilepticus. Although this study was sponsored by the Department of Veterans Affairs, 30 percent of the patients with overt status epilepticus were not veterans, and 18 percent were female, suggesting that our results are widely applicable to the treatment of generalized convulsive status epilepticus in adults.

The lower overall efficacy rates reported here, as compared with data from earlier studies,10-14,16-26 probably result from our including only patients with generalized convulsive status epilepticus and our use of a stringent definition of treatment success: cessation of all clinical and electrical evidence of seizure activity within 20 minutes, with no recurrence during the next 40 minutes. The use of a period longer than 20 minutes in the definition of treatment success was discussed during the development of this protocol, but it was rejected as exposing patients to unnecessary risk. It is desirable that medications for this condition be given in a short intravenous infusion and enter the brain rapidly during infusion. Lorazepam, the most effective drug in the paired comparisons, required the least time to administer. It could be argued that the 20-minute time limit constituted an advantage for phenytoin, because of its mandatory slow infusion rate. On the other hand, phenobarbital, which enters the brain slowly,33 was not significantly less effective than lorazepam in patients with overt generalized convulsive status epilepticus. Thus, it appears that the 20-minute criterion for success does not in itself explain the differences we found.

We found no differences among the treatments in the frequency of recurrence of overt or subtle status epilepticus during the 12-hour study period, suggesting that any of the four treatments, if successful, can protect equally well against recurrence. We also found no differences among the treatments in the
incidence of hypotension requiring treatment, respiratory depression, or cardiac-rhythm disturbances in patients with either overt or subtle generalized convulsive status epilepticus. Thus, the risk of these adverse events appears similar with any of the four regimens if the drugs are administered at a safe rate to patients who have been appropriately screened for contraindications. Hypotension requiring treatment occurred more often in the patients with subtle generalized convulsive status epilepticus; this difference probably reflects the fact that patients with subtle status epilepticus were sicker than those with overt status epilepticus. Life-threatening medical conditions and cardiopulmonary arrest associated with generalized convulsive status epilepticus were more common among the patients with subtle status epilepticus (Table 2). The longer duration of status epilepticus in the patients with subtle cases (Table 2) may also have contributed to their greater susceptibility to drug-induced hypotension. Even patients with overt status epilepticus had a long delay between onset and treatment. Many of these episodes occurred at night, and paramedics were not called until after several seizures had occurred. For such patients, we considered status epilepticus to have begun at the time of the first seizure.

The rapidity of recovery of consciousness after treatment of status epilepticus is another clinically important factor when choosing a treatment regimen. The small number of patients who recovered fully within 12 hours suggests, however, that rapid, complete recovery may not be a realistic goal when treating generalized convulsive status epilepticus. The condition causing the episode and the effects of drug-induced impairment of consciousness also contribute to the impairment of consciousness. Identifying significant differences in the rates at which patients recover from drug-induced impairment of consciousness is difficult, because such a comparison would have to be made in a group of patients in whom the causative factors and duration and intensity of seizures before treatment were identical.

Overall, the patients with subtle generalized convulsive status epilepticus did much worse than those with overt generalized convulsive status epilepticus. The first drug treatment was successful in less than 15 percent of the patients with subtle status epilepticus, and their outcome was poor. Sixty-five percent of the patients with overt status epilepticus died within 30 days after the episode, as compared with 27 percent of the patients with overt status epilepticus. Death in a patient with generalized convulsive status epilepticus is probably attributable largely to the underlying cause and duration of the episode. Nonetheless, successful treatment was significantly associated with improved outcomes in both patients with overt episodes and those with subtle episodes, although it is not clear whether the success of treatment was the cause or the effect of the better prognosis, or a combination of both.

Because even the best treatments were successful in only about two thirds of the patients with overt status epilepticus and one fourth of the patients with subtle status epilepticus, our study underscores the need for better methods of treating generalized convulsive status epilepticus and its underlying causes. Until new therapies become available, however, we recommend lorazepam for the initial intravenous treatment of generalized convulsive status epilepticus. Although lorazepam was no more efficacious than phenobarbital or than diazepam and phenytoin, it is easier to use.

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APPENDIX


REFERENCES