Research Article

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PREVENTION OF RECURRENT SEIZURES WITH LORAZEPAM

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Abstract

Background *and Methods Alcohol abuse is one of the most common causes of seizures in adults. In a randomized, double-blind study, we compared lorazepam with a placebo for the prevention of recurrent seizures related to alcohol. Over 21 months, we studied consecutive patients with chronic alcohol abuse who were at least 21 years of age and who presented to the emergency departments of two hospitals in Boston after a witnessed generalized seizure. The patients were randomly assigned to receive either 2 mg of lorazepam in 2 ml of normal saline or 4 ml of normal saline intravenously and then observed for six hours. The primary endpoint was the occurrence of a second seizure during the observation period.*

Results *of the 229 patients who were initially evaluated, 186 met the entry criteria. In the lorazepam group, 3 of 100 patients (3 percent) had a second seizure, as compared with 21 of 86 patients (24 percent) in the placebo group (odds ratio for seizure with the use of placebo, 10.4; 95 percent confidence interval, 3.6 to 30.2; P<0.001). Forty-two percent of the placebo group were admitted to the hospital, as compared with 29 percent of the lorazepam group (odds ratio for admission, 2.1; 95 percent confidence interval, 1.1 to 4.0; P=0.02). Seven patients in the placebo group and one in the lorazepam group were transported to an emergency department in Boston with a second seizure within 48 hours after hospital discharge.*

Conclusions

Treatment with intravenous lorazepam is associated with a significant reduction in the risk of recurrent seizures related to alcohol. Alcohol abuse may be accompanied by a variety of disorders of electrolyte and acid-base metabolism. The role of the kidney in the pathogenesis sis of these disturbances is obscure. We sought to evaluate the alcohol-induced abnormalities of renal function and improvement during abstinence and to assess the relation between renal dysfunction and electrolyte and acid-base disorders.

ALCOHOL abuse is one of the most common causes of adult-onset seizures.[1] Although primary prevention of seizures during alcohol withdrawal has been reported,[2-6] only a few studies have addressed the treatment and prevention of recurrent seizures related to alcohol in patients in the emergency department.[7-9] Multiple explanations have been postulated for the association between alcohol and seizure activity. The relation of seizures to withdrawal from alcohol was described by Huss in 1852.[10] Victor and Brausch[11] reported that seizures occurred in approximately 10 percent of adults during alcohol withdrawal. Generalized tonic-clonic seizures occurred in 95 percent of patients, with 60 percent of patients having multiple seizures. The interval from the first to the last seizure was 6 hours or less in 85 percent; and the first seizure occurred 7 to 48 hours after the last drink in 90 percent. Ninety percent of patients had normal electroencephalograms.

Other factors independent of abstinence may also increase the risk of seizures among patients who are dependent on alcohol. Alcohol itself may induce seizures[12] or exacerbate preexisting epilepsy.[13,14] In addition, people who chronically abuse alcohol have an increased frequency of structural abnormalities in the brain that may contribute to seizures, including cerebral vascular lesions and lesions due to head injury. [15-17] Prevention of recurrent seizures related to alcohol use is important, [18] and the ability of specific drugs to prevent seizures has been assessed. Phenytoin does not prevent recurrent alcohol-related seizures. [7-9] Benzodiazepines are effective in the management of acute alcohol syndrome, including the primary prevention of seizures in patients with alcohol dependence. [19-24] Because lorazepam is distributed in tissue less rapidly and less extensively than is diazepam, its ability to control seizures is prolonged. [25,26] Lorazepam has minimal depressant effects on respiration and circulation. [27-30] It uses the same γ-aminobutyric acid receptors in the brain as alcohol and has sedative and anxiolytic effects. [31] Lorazepam has a shorter half-life than diazepam and has no active metabolites. [32,33] Its half-life is not substantially prolonged in patients with liver or renal dysfunction, and parenteral administration is associated with a predictable pattern of absorption. [34-36] Therefore, we assessed the ability of lorazepam to prevent recurrent alcohol-related seizures in patients with alcohol abuse who presented with a seizure.

METHODS

Study Design

We conducted a 21-month, prospective, randomized, double-blind trial in the emergency departments of Boston City Hospital and Carney Hospital, two teaching hospitals in Boston. Consecutive patients with chronic alcohol abuse who were at least 21 years of age, who presented after a witnessed generalized seizure, and who had had one or more drinks within the previous 72 hours were eligible for enrollment. A research nurse reviewed emergency department logs weekly to determine whether all eligible patients were enrolled. Patients were excluded from enrollment if there was another possible cause of the seizures given any of the following abnormal serum laboratory values: less than 60 mg of glucose per deciliter (3.3 mmol per liter), less than 120 mmol of sodium per liter or more than 160 mmol per liter, less than 6.0 mg of calcium per deciliter (1.5 mmol per liter), less than 1.0 mg of magnesium per deciliter (0.41 mmol per liter), more than 100 mg of urea nitrogen per deciliter (35.7 mmol per liter), or more than 10.0 mg of creatinine per deciliter (884 μmol per liter). Patients were also excluded from enrollment if they were taking drugs (as determined based on their history or the results of toxicologic screening) that cause or protect against recurrent seizures, including cocaine and phenobarbital, but not phenytoin; if they refused to provide consent; or if they had already been enrolled in the study. Patients were excluded after enrollment if they required treatment for symptoms of moderate-to-severe withdrawal other than seizures, according to the guidelines for the assessment of the severity of alcohol withdrawal symptoms used by both hospitals. These symptoms consisted of either changes in two of the following three vital signs: an increase in the pulse rate to more than 100 beats per minute, an increase in diastolic blood pressure to more than 100 mm Hg, and an increase in oral temperature to more than 37.7°C, or the presence of hallucinosis (auditory, visual, or tactile) or delirium (disorientation, abnormal sensorium, or agitation). These symptoms could appear in combination with any other, less severe symptoms of withdrawal, such as tremors, anxiety, hyperreflexia, nausea, vomiting, and diaphoresis.

Computed tomographic (CT) examinations of the head and electroencephalography were performed only when clinically indicated and were not a mandatory part of the protocol. An abnormal electroencephalogram was defined as one showing activity consistent with the presence of an epileptogenic focus. Abnormal CT results were those that showed any post-traumatic structural abnormalities, such as old contusions, skull fractures, evidence of craniotomy for blood evacuation, or mass lesions, that were potential seizure foci. For the study, CT findings of brain atrophy or small lacunar infarcts were not considered abnormal (positive).

An alcohol-related seizure was diagnosed based on the patient's history of alcohol use, the absence of recent trauma, and the medical record. Patients with new-onset seizures were admitted to the hospital and evaluated by the medical services, neurologic services, or both. All consultants were unaware of the patients' treatment assignments.

Blood was obtained in the emergency department for the measurement of serum sodium, potassium, chloride, carbon dioxide, urea nitrogen, creatinine, calcium, magnesium, glucose, and ethanol levels. If toxic effects were suggested based on the history or clinical signs, serum and urine were sent for toxicologic screening.

The study was approved by the institutional review boards of both hospitals, and patients provided written informed consent for participation. Consent was initially waived for any patients who were unable to give informed consent at presentation because of intoxication or postictal phenomena. Once treatment had been administered and the patient became alert, consent was required for the continued collection of data. The rationale for the waiver of consent was that lorazepam is an accepted treatment for seizures and that at the time, the standard treatment for recurrent seizures related to alcohol at both institutions was supportive care with referral to a detoxification unit.

Study Protocol

Patients were randomly assigned to receive 2 mg of lorazepam (Ativan, Wyeth–Ayerst, Philadelphia) or 2 ml of normal saline as a placebo according to a table of random numbers for each site. Before administration, 2 ml of normal saline was added to each sample to produce equal volumes and similar viscosity and to minimize irritation at the injection site. All patients underwent continuous electrocardiographic and oxygen-saturation monitoring, with blood measured every 15 minutes. The patients and all care providers were unaware of the treatment assignments.

All patients initially had their serum glucose levels measured in a sample obtained by a finger stick and received intravenous hydration with normal saline or 5 percent dextrose with normal saline, as well as 100 mg of thiamine intravenously, one ampule of multivitamins, and 2 g of magnesium in the first liter of intravenous fluid.

TABLE 1. REASONS FOR EXCLUSION FROM THE STUDY.

REASON FOR EXCLUSION	PLACEBO GROUP (N=16)	LORAZEPAM GROUP (N=27)	TOTAL (N=43)
Previously enrolled	14	21	35
Use of drugs that prevent or cause seizures			
Cocaine	1	2	3
Phenobarbital	0	2	2
Hypomagnesemia	0	1	1
Refusal to provide consent	1	0	1
Focal seizure	0	1	1

End Points

The observation period ended with the development of a second generalized seizure, witnessed by the emergency department physician or nurse, or six hours after the administration of lorazepam or placebo.

Follow-up

The Boston Emergency Medical Services database was used to determine whether the patients presented to any Boston hospital with a diagnosis of seizures within 48 hours after discharge.

Statistical Analysis

The objective of the analysis was to compare the rates of recurrent seizures related to alcohol in patients who received lorazepam and patients who received placebo. Patients who were enrolled but who were later found to meet the initial exclusion criteria were not included in the analysis. If patients with repeated episodes of generalized seizures were inadvertently enrolled more than once, only the first episode was included. Patients who underwent randomization and who subsequently met exclusion criteria were included in an intention-to-treat analysis. Baseline characteristics were compared in the two groups with the use of the chi-square test or Fisher's exact test for categorical variables and the t-test for two independent samples for continuous variables. Unadjusted rates of recurrent seizures were compared with the use of the chi-square test. After adjustment for clinically important baseline characteristics, the rates of recurrent seizures were compared by multiple logistic regression analysis. All tests of significance were two-tailed. [37] A P value of 0.05 or less was considered to indicate statistical significance.

RESULTS

We enrolled all 229 eligible patients who presented at either institution between March 9, 1993, and December 15, 1994. Forty-three patients met the initial exclusion criteria, including one who refused to provide consent (Table 1). Thus, a total of 186 patients (152 from Boston City Hospital and 34 from Carney Hospital) met the criteria for study entry and were included in the intention-to-treat analysis. Sixteen patients met the exclusion criteria after enrollment but were included in the intention-to-treat analysis: 11 required benzodiazepine therapy, 3 had incomplete data, 1 received droperidol, and in 1 the cause of the seizure was unclear. Consent was obtained from 78 patients at study entry and from 108 patients before the completion of the study.

Base-Line Characteristics

Eighty-six patients (46 percent) were assigned to receive placebo, and 100 patients (54 percent) were assigned to receive lorazepam. The baseline characteristics of the two groups were similar (Table 2). Most of the patients were middle-aged men. Like the patients in an earlier study, [11] most of these patients had a long history of alcohol abuse and drank heavily. Eighty-five percent had consumed at least 1 pint (473 ml) of distilled alcohol per day for more than 10 years. Most patients had their first seizure 7 to 48 hours after their last drink. The time from the first seizure to the administration of lorazepam or placebo was also similar in both groups. Serum electrolyte, urea nitrogen, creatinine, glucose, magnesium, and calcium levels were similar in the two groups. The majority of the patients had an ethanol level of zero at entry; among those with detectable
ethanol levels, the levels were similar in the two groups. Among patients with detectable levels of phenytoin, the levels were similar in the two groups and were in the low therapeutic range.

Diagnostic Studies

A total of 109 patients had documented electroencephalograms, and 153 had CT examinations of the head (Table 2). The percentages of patients with abnormal electroencephalograms and CT examinations were similar in the two groups.

Recurrent Seizures

Twenty-four patients (13 percent) had a second seizure: 21 in the placebo group (24 percent) and 3 (3 percent) in the lorazepam group (odds ratio for seizure with the use of placebo, 10.4; 95 percent confidence interval, 3.6 to 30.2; P<0.001). The results were similar when the data for the 16 patients who met the exclusion criteria after enrollment were omitted from the analysis. Twenty-one of 77 patients
in the placebo group (27 percent) had a second seizure, as compared with 3 of 93 patients in the lorazepam group (3 percent; odds ratio for seizure, 11.25; 95 percent confidence interval, 3.9 to 32.5;
P<0.001). There were no complications related to the administration of lorazepam.

A review of the records of the three patients in the lorazepam group who had a second seizure did not identify any specific characteristics that were predictive of a second seizure. These patients were not taking antiepileptic drugs and had normal electroencephalograms.
One patient had findings on CT examination consistent with the presence of an old subdural hematoma. In another patient, delirium tremens developed within minutes after entry into the study; he was admitted to the intensive care unit, and the CT scan and electroencephalogram were normal. It is unclear whether this patient had a recurrent generalized tonic-clonic seizure or whether the initial "seizure activity" was early delirium tremens

TABLE 2. BASE-LINE CHARACTERISTICS OF THE STUDY GROUPS.*

CHARACTERISTIC	LORAZEPAM GROUP (N=100)	PLACEBO GROUP (N=86)
Male sex — no. (%)	97 (97)	81 (94)
Age — yr	45±10	44±9
Years of alcohol abuse — % of patients		
0–5 yr	6	6
6–10 yr	10	9
>10 yr	84	85
Daily consumption of distilled alcoholic beverages — % of patients		
<1 pint (473 ml)	21	25
1 pint–1 fifth (473–757 ml)	36	34
>1 fifth (757 ml)	43	41
Hours from last drink to first seizure — % of patients		
0–6 hr	16	17
7–24 hr	49	46
25–48 hr	24	33
>48 hr	11	4
Time from first seizure to administration of study drug — min	146±188	141±147
Serum levels†		
Ethanol — mg/dl‡	195±135	206±154
Phenytoin — μg/ml§	10±5	10±5
Sodium — mmol/liter	139±4	136±20
Carbon dioxide — mmol/liter	22±5	23±5
Urea nitrogen — mg/dl	11±5	11±4
Creatinine — mg/dl	1.0±0.4	0.9±0.3
Glucose — mg/dl	121±33	122±48
Calcium — mg/dl	9.2±0.58	9.3±0.56
Magnesium — mg/dl	1.8±0.45	1.8±0.39
Diagnostic studies — % positive (no. positive/total no. examined)		
Electroencephalography	11 (6/54)	7 (4/55)
Computed tomography	19 (15/80)	21 (15/73)

*Plus–minus values are means ±SD. There were no significant differences between the groups.

†To convert the values for ethanol to millimoles per liter, multiply by 0.2171; to convert the values for phenytoin to micromoles per liter, multiply by 3.96; to convert the values for urea nitrogen to millimoles per liter, multiply by 0.357; to convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for glucose to millimoles per liter, multiply by 0.0556; to convert the values for calcium to millimoles per liter, multiply by 0.250; and to convert the values for magnesium to millimoles per liter, multiply by 0.41.

‡Ethanol levels are given for the 24 patients in the lorazepam group and the 27 patients in the placebo group who had levels of more than 0.

§Phenytoin levels are given for the 15 patients in the lorazepam group and the 17 patients in the placebo group who had levels of more than 0.

Three additional patients who remained in the emergency department for other reasons had a second seizure after the end of the six-hour study period All three of these patients were in the placebo group and were subsequently hospitalized.

Predictors of Recurrent Seizures

We used logistic regression analysis to determine whether any of the following characteristics were independent predictors of recurrent seizures: age, sex, treatment group, hospital, serum ethanol level, the number of years of alcohol use, and the time since the last drink. Variables for electroencephalographic and CT results were not included because of the large number of patients (77 in the case of electroencephalography and 33 in the case of CT scanning) who did not undergo these examinations. Age (P=0.10), sex (P=0.49), hospital (P=0.15), the number of years of alcohol use (P=0.24), the time since the last drink (P=0.75), and ethanol level (P=0.09) were not significantly associated with the likelihood of recurrent seizures. The only statistically significant independent predictor was the treatment group (P<0.001).

Disposition of Patients

Thirty-six patients in the placebo group (42 percent) were admitted to the hospital, as compared with 29 patients (29 percent) in the lorazepam group (odds ratio for admission, 2.1; 95 percent confidence interval, 1.1 to 4.0; P=0.02). Of the patients who were discharged directly from the emergency department, 14 patients in the placebo group (28 percent) nd 9 patients in the lorazepam group (13 percent) agreed to be referred to a detoxification unit directly from the emergency department.

Follow-up

Eighty-five percent of the enrolled patients had been transported to the emergency departments by ambulances owned by Boston Emergency Medical Services. Therefore, we used that data base to determine which study patients were transported to emergency departments in Boston within 48 hours after discharge from the study hospitals' emergency departments. Of the 50 patients in the placebo group who were discharged from the emergency department after the study, 7 (14 percent) were transported to an emergency department in Boston within 48 hours with a second seizure. The respective number in the lorazepam group was 1; this patient was readmitted for a second seizure 2.5 hours after discharge.

DISCUSSION

We found that intravenous lorazepam significantly reduced the risk of recurrent seizures related to alcohol. We attempted to enroll patients soon after they arrived at the emergency department to avoid the occurrence of a second seizure before enrollment. One strength of this study is that we included all patients with alcohol-related seizures. Persons with alcohol dependence and seizures may have various underlying structural causes of seizures in addition to alcohol withdrawal. Some may benefit from long-term therapy with anticonvulsant medications, such as phenytoin, and should be encouraged to take their medication. [38,39] Noncompliant patients may be at risk for seizures.[40] When an alcohol-dependent patient with documented poor compliance with medication makes repeated visits to the emergency department, the primary physician and neurologist should be consulted about improving compliance.

Our findings suggest that all patients with acute and chronic alcohol abuse who present with seizures may benefit from the use of lorazepam. For patients who do not require admission to the hospital, treatment in a detoxification unit may be beneficial. It is likely, however, that many such patients will be sent home or to shelters, where their use of alcohol may resume. Our findings suggest that lorazepam is safe and effective for such patients

One limitation of our study is that the observation period lasted only six hours. In a study by Victor and Brausch,[11] in 15 percent of patients who had recurrent alcohol-related seizures, the last seizure occurred more than six hours after the first. It is possible that the administration of lorazepam simply delayed the occurrence of additional seizures. However, our follow-up data from the Boston Emergency Medical Services database suggest that this explanation is unlikely. It is important to note that there may have been patients who had recurrent seizures who were not transported to the emergency department by the emergency medical services and therefore were not included in the database.

In this as well as a previous study,[9] we found that the rate of recurrent seizures was 24 percent in the placebo group. In institutions in which

hospital admission is required after a second observed seizure related to alcohol, treatment with lorazepam may avert many such hospitalizations. In our study, the rate of hospital admission was lower in the lorazepam group than in the placebo group.

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