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A COMPARISON OF LORAZEPAM, DIAZEPAM, AND PLACEBO FOR THE TREATMENT OF OUT-OF-HOSPITAL STATUS EPILEPTICUS

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ABSTRACT

Background It is uncertain whether the administration of benzodiazepines by paramedics is an effective and safe treatment for out-of-hospital status epilepticus.

Methods We conducted a randomized, double-blind trial to evaluate intravenous benzodiazepines administered by paramedics for the treatment of out-of-hospital status epilepticus. Adults with prolonged (lasting five minutes or more) or repetitive generalized convulsive seizures received intravenous diazepam (5 mg), lorazepam (2 mg), or placebo. An identical second injection was given if needed.

Results Of the 205 patients enrolled, 66 received lorazepam, 68 received diazepam, and 71 received placebo. Status epilepticus had been terminated on arrival at the emergency department in more patients treated with lorazepam (59.1 percent) or diazepam (42.6 percent) than patients given placebo (21.1 percent) ($P=0.001$). After adjustment for covariates, the odds ratio for termination of status epilepticus by the time of arrival in the lorazepam group as compared with the placebo group was 4.8 (95 percent confidence interval, 1.9 to 13.0). The odds ratio was 1.9 (95 percent confidence interval, 0.8 to 4.4) in the lorazepam group as compared with the diazepam group and 2.3 (95 percent confidence interval, 1.0 to 5.9) in the diazepam group as compared with the placebo group. The rates of respiratory or circulatory complications after the study treatment was administered were 10.6 percent for the lorazepam group, 10.3 percent for the diazepam group, and 22.5 percent for the placebo group ($P=0.08$).

Conclusions Benzodiazepines are safe and effective when administered by paramedics for out-of-hospital status epilepticus in adults. Lorazepam is likely to be a better therapy than diazepam. (N Engl J Med 2001; 345:631-7.)

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GENERALIZED convulsive status epilepticus is a condition of prolonged or repeated seizures requiring rapid treatment. Benzodiazepines are the drugs of choice for initial treatment because they are fast acting and effective.^{1,2} Several randomized trials of drug treatment for status epilepticus in hospitalized patients have been conducted.^{1,3,4} However, patients with seizures and status epilepticus are commonly encountered outside of the hospital by emergency-medical-services personnel. Traditionally, these patients have been transported quickly to emergency departments for treatment. In recent years, many emergency-medical-services systems have implemented protocols that allow the intravenous administration of benzodiazepines (principally diazepam) by paramedics. However, the risks and benefits of treatment with benzodiazepines outside of the hospital have not been studied. Potential benefits include the prevention of systemic and neurologic sequelae of prolonged convulsive seizures. Potential risks include respiratory depression and cardiovascular compromise associated with benzodiazepines and misdiagnosis leading to inappropriate treatment.² We conducted a randomized, double-blind, placebo-controlled trial to determine whether the administration of benzodiazepines by paramedics is an effective and safe out-of-hospital treatment for status epilepticus and to determine whether lorazepam is superior to diazepam.

METHODS

Enrollment

The study methods are described in detail elsewhere.⁵ Between January 4, 1994, and January 31, 1999, patients were enrolled and

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treated by paramedics of the San Francisco Department of Public Health. During this period, the emergency-medical-services system consisted of one physician-staffed base hospital and nine destination hospitals. Paramedics trained in the study protocol established radio contact with the base hospital and were authorized by a physician to enroll patients after review of inclusion and exclusion criteria.

Study Design

Adults (18 years of age or older) with an out-of-hospital diagnosis of status epilepticus were randomly assigned to receive 5 mg of diazepam, 2 mg of lorazepam, or placebo by intravenous injection (over a period of one to two minutes). Status epilepticus was defined as continuous or repeated seizure activity for more than five minutes without recovery of consciousness. The study drug was administered by paramedics only during generalized tonic-clonic seizure activity. If seizures recurred or continued four minutes or more after the first injection, then an identical second injection was administered. Thus, patients received a maximum of 10 mg of diazepam or 4 mg of lorazepam. Patients were excluded if they had a pulse of less than 60 beats per minute, a systolic blood pressure of less than 100 mm Hg, second- or third-degree atrioventricular block, sustained ventricular tachyarrhythmia, asthma or chronic obstructive pulmonary disease, a history of long-term use of benzodiazepines, or sensitivity to benzodiazepines. Patients were also excluded if they were pregnant, if intravenous access could not be established, or if they had been transported by a private ambulance company or were in police custody. Open-label diazepam was immediately available in the event of a difficult or unsafe extrication of a patient or if a patient was considered to be at high risk for a life-threatening complication.

Paramedics documented seizure activity, respiratory status, cardiovascular function, and level of consciousness every five minutes. Standardized treatment for patients who remained in status epilepticus at the time of arrival at the hospital was not required. However, a suggested treatment protocol was given to study personnel and presented by paramedics in written form to physicians when the patient arrived at the emergency department.²

Oversight, Central Review, and Consent

The study was approved by the San Francisco Department of Public Health Emergency Medical Services Section, the California Emergency Medical Services Agency, and the institutional review boards of the University of California at San Francisco and at the participating destination hospitals. Oversight was provided by an external advisory committee, which was composed of four persons with expertise in epilepsy and emergency medicine who were not affiliated with the study. This group reviewed the study annually and was responsible for decisions regarding continuation or early termination of the study on the basis of interim safety analyses. Additional oversight was provided by a data safety and monitoring board of the National Institutes of Health, which independently carried out an annual review of the progress of the study and determined whether the study could continue on the basis of the interim safety analyses. All adverse events and deaths were reported promptly to the institutional review boards of the destination hospitals, the external advisory committee, and the data safety and monitoring board. Demographic data were ascertained from the patient's record; the ethnic or racial group was assigned by investigators.

Because of the emergency nature of status epilepticus and the unconscious state of the patient, enrollment took place under a waiver of informed consent pursuant to federal regulations. The rationale for the waiver was that diazepam, lorazepam, or no benzodiazepines were used by various emergency-medical-services systems for the management of status epilepticus at the time of the study and that insufficient data were available to determine the optimal out-of-hospital treatment for this condition.

Drug Treatment and Randomization

Coded study kits contained two 2.5-ml colored-glass syringes. The syringes in a single study kit had identical contents: a 1.0-ml solution of either 5 mg of diazepam (Schein, Florham Park, N.J.;

and Elkins-Sinn, Cherry Hill, N.J.) or 2 mg of lorazepam (Ativan, Wyeth-Ayerst, Philadelphia) or a placebo solution (20 percent propylene glycol [vol/vol] in 0.9 percent sodium chloride) formulated to mimic the viscosity of the active drugs. The number codes and syringe contents were determined with the use of a computer-generated sequence of random numbers. Kits were stored on ambulances in a light-proof, locked box without refrigeration and were restocked every 60 days.⁶

Outcomes and Measures

The primary outcome measure was termination of status epilepticus by the time of arrival at the emergency department. Status epilepticus was considered to end at the time convulsive seizures ceased if the patient subsequently regained consciousness. Status epilepticus was considered to be ongoing when seizures were clinically evident, when clinical seizures ended but the patient remained comatose and an electroencephalogram indicated ongoing electrical seizure activity, or when a patient remained unconscious and subsequently had a convulsive seizure requiring treatment with an antiseizure drug.

Five outcome measures were selected as secondary study end points: out-of-hospital complications, complications at transfer, the duration of status epilepticus before arrival at the hospital, the neurologic outcome at discharge, and the disposition of the patient from the emergency department. Out-of-hospital complications were defined by the occurrence of a respiratory or cardiovascular complication after the administration of the study drug. Standardized criteria for hypotension and cardiac dysrhythmias were applied.⁵ A respiratory complication was considered to be present if the patient received bag valve-mask ventilation or if intubation was attempted. Complications at transfer were defined by the presence of cardiorespiratory complications at the time the care of the patient was transferred from paramedics to emergency-department personnel.⁵ The duration of status epilepticus before arrival at the hospital was defined as the interval between administration of the study drug and the termination of status epilepticus. Times were censored on arrival at the emergency department (if seizures were ongoing) or when out-of-hospital open-label drug treatment was administered (as occurred with two patients in the placebo group and two patients in the diazepam group). The neurologic outcome at hospital discharge was evaluated relative to the base-line condition of the patient and categorized as an unchanged condition, a condition characterized by new neurologic deficits, or death. The location to which the patient was transferred from the emergency department or the discharge or death of the patient was also selected as a secondary end point. Since previous studies have shown that the cause of status epilepticus is an important determinant of outcome, we assigned patients into three prognostic groups (good, intermediate, and poor) according to the cause of status epilepticus.^{7,8}

Interim Safety Analyses

Interim safety analyses were performed after the enrollment of 25, 50, 100, and 150 patients. The O'Brien-Fleming procedure was applied to each of the comparisons of active treatments and placebo with the use of a two-tailed alpha level of 0.025.⁹ Secondary analyses were performed with adjustment for covariates. The interim analyses conducted when 150 subjects had been enrolled yielded one significantly different pairwise comparison for the rate of termination of status epilepticus on arrival at the emergency department. However, the data safety and monitoring board and external advisory committee both concluded that the data as a whole did not support early termination.

Statistical Analysis

The target sample size of 210 patients was based on estimated response rates (for the primary outcome) of 75 percent for lorazepam, 50 percent for diazepam, and 25 percent for placebo, with 80 percent power and a two-sided significance level of 5 percent. Some patients were enrolled more than once. Patients who received the study drug were included in all analyses of the primary and secondary outcomes.

Logistic-regression analysis was used to estimate the effects of treatment on the primary outcome and to adjust for the potential confounding effects of covariates (the intervals from the onset of status epilepticus to treatment and from treatment to arrival at the emergency department and the cause of status epilepticus).¹⁰ We compared the treatment groups with regard to the covariates using analysis of variance for continuous covariates and chi-square tests for categorical covariates. The logistic models included potentially confounding covariates as well as those with significantly different distributions among the study groups. The fit of the logistic model was assessed with use of Hosmer–Lemeshow tests, and there was no evidence of lack of fit. We calculated simultaneous 95 percent confidence intervals using the Bonferroni method¹¹ for the comparisons of lorazepam with the other study treatments; that is, we

calculated 97.5 percent confidence intervals. We also calculated 97.5 percent confidence intervals for the comparisons of diazepam with placebo. Differences in the duration of status epilepticus before arrival at the hospital among the treatment groups were examined with the use of proportional-hazards models.¹² Initially, the distributions of durations were compared with the use of Kaplan–Meier curves and a log-rank test. Adjustments for potential confounders were made with the use of proportional-hazards models and covariates.

RESULTS

A total of 567 events met the study definition of status epilepticus. After exclusions (Fig. 1), the study population consisted of 258 enrollments, representing

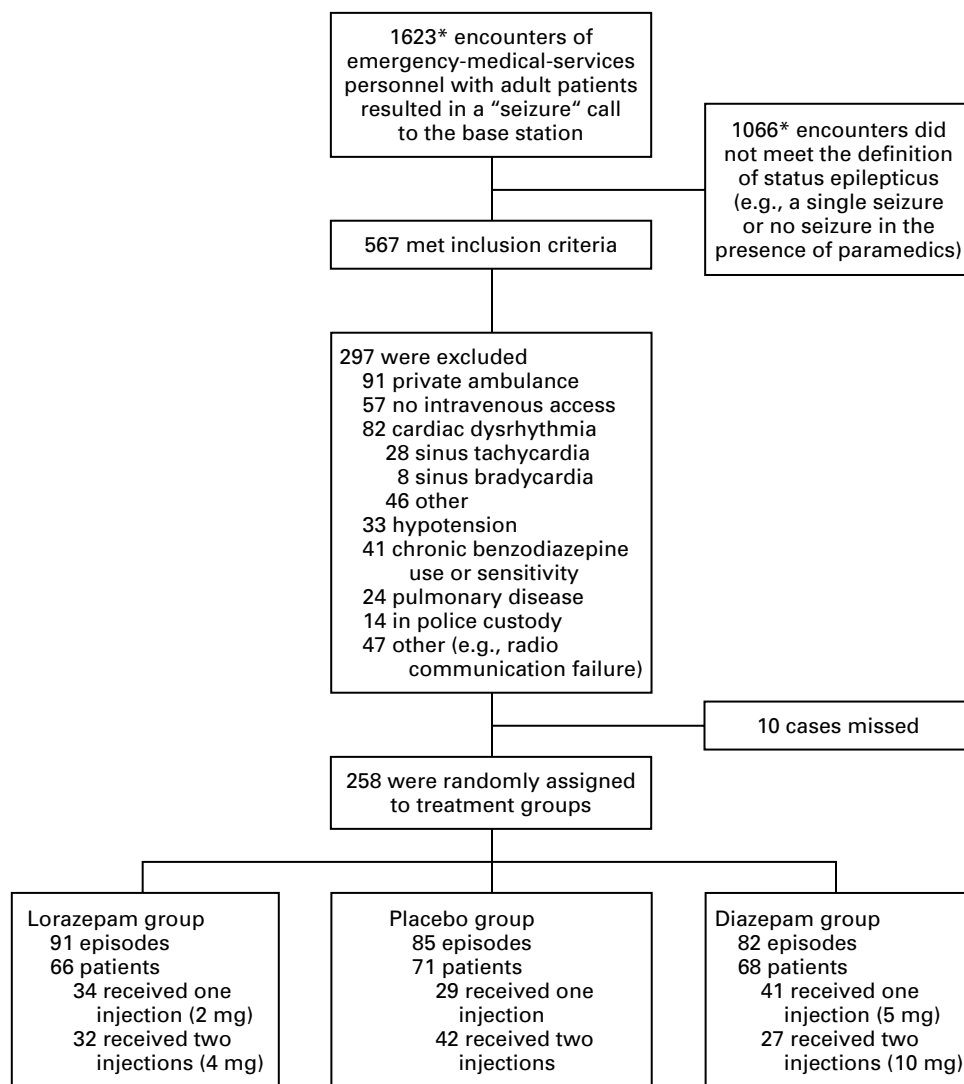


Figure 1. Study Population.

Values marked with an asterisk are for the first 55 months of the study; for the final 5 months, emergency-medical-services procedures were changed and paramedics were not required to call the base hospital for all seizures. All other values are for the entire 61-month study period. The cases that were missed involved qualified patients, identified during retrospective review of the ambulance logs, who had not been enrolled. For excluded patients, more than one criterion may apply. In one patient who received diazepam as the study treatment, the injection infiltrated the surrounding tissue.

205 patients. We report only data from the first enrollment of each patient.

Patients in the three treatment groups did not differ significantly with regard to age, sex, history of seizures, cause of status epilepticus, or interval from treatment to arrival at the emergency department; however, the racial and ethnic groups of study patients were unevenly distributed (Table 1). Race or ethnic group was added to subsequent regression analyses, but the effect was minimal. The interval from the onset of status epilepticus to administration of the study treatment was significantly longer in the placebo group than in the active-treatment groups ($P=0.001$) but was not significantly associated with outcome. This variable was added to subsequent regression analyses.

TABLE 1. CHARACTERISTICS OF THE 205 PATIENTS ENROLLED IN THE STUDY.*

CHARACTERISTIC	LORAZEPAM GROUP (N=66)	DIAZEPAM GROUP (N=68)	PLACEBO GROUP (N=71)
Age (yr)	49.9±20.1	50.4±19.1	52.0±18.2
Male sex (%)	69.7	60.3	59.1
Race or ethnic group (%)†			
American Indian or Alaskan	1.5	1.5	4.2
Asian or Pacific Islander	21.2	7.4	9.9
Black	18.2	16.2	29.6
Hispanic	9.1	20.6	8.5
White	48.5	54.4	46.5
Other	1.5	0	0
Unknown	0	0	1.4
History of seizures (%)	54.6	69.1	66.2
Cause of status epilepticus (%)			
Low blood levels of antiepileptic drugs‡	16.7	25.0	23.9
Refractory epilepsy	13.6	13.2	8.5
Alcohol abuse	9.1	11.8	9.9
Metabolic derangement	3.0	2.9	7.0
Toxic effects of drugs (recreational or prescribed)	10.6	7.4	7.0
Anoxia or cardiopulmonary arrest	1.5	0	0
Infection in the central nervous system	7.6	7.4	5.6
Trauma	6.1	8.8	4.2
Tumor in the central nervous system	6.1	4.4	9.9
Stroke	16.7	13.2	9.9
Nonepileptic seizures	3.0	4.4	7.0
Other	0	0	1.4
Unknown	6.1	1.5	5.6
Duration of status epilepticus before study treatment (min)§	34.0±17.8	31.3±14.5	46.7±38.8
Interval from study treatment to arrival at emergency department (min)	16.2±9.3	15.9±9.3	16.5±8.2

*Plus-minus values are means ±SD. Except as noted, differences among the groups were not significant ($P>0.05$). Because of rounding, not all percentages total 100.

† $P=0.03$ for the comparison among groups.

‡Values are for patients with a history of epilepsy for whom antiepileptic drugs were prescribed.

§ $P=0.001$ for the comparison among groups by analysis of variance.

Out-of-Hospital Treatment and Response

Status epilepticus was terminated by the time of arrival at the emergency department in 59.1 percent of patients given lorazepam, 42.6 percent of patients given diazepam, and 21.1 percent of patients given placebo ($P=0.001$) (Table 2). The odds ratios indicated that termination of status epilepticus was more likely with lorazepam than placebo (odds ratio, 5.4; 95 percent confidence interval, 2.3 to 13.2) and with diazepam than placebo (odds ratio, 2.8; 95 percent confidence interval, 1.2 to 6.7). The odds ratio favored lorazepam over diazepam, but the difference was not significant (odds ratio, 1.9; 95 percent confidence interval, 0.9 to 4.3). We obtained similar results using a logistic-regression model for the binary variable of the presence or absence of status epilepticus on arrival at the emergency department and adjusting for covariates. The odds of termination of status epilepticus on arrival at the emergency department were 4.8 times as high for the lorazepam group as for the placebo group (95 percent confidence interval, 1.9 to 13.0), 1.9 times as high for the lorazepam group as for the diazepam group (95 percent confidence interval, 0.8 to 4.4), and 2.3 times as high for the diazepam group as for the placebo group (95 percent confidence interval, 1.0 to 5.9).

Figure 2 presents Kaplan–Meier curves for the distribution of duration of status epilepticus before arrival at the hospital in the three groups. These curves were significantly different by the log-rank test ($P<0.001$). When we used a proportional-hazards model and adjusted for covariates, the times were significantly shorter in the lorazepam group than in the placebo group (relative hazard of ongoing status epilepticus, 0.34; 95 percent confidence interval, 0.17 to 0.71). Times were shorter for patients in the lorazepam group than for those in the diazepam group (adjusted relative hazard, 0.65; 95 percent confidence interval, 0.36 to 1.17), but the difference was not significant.

Out-of-Hospital and Transfer Complications

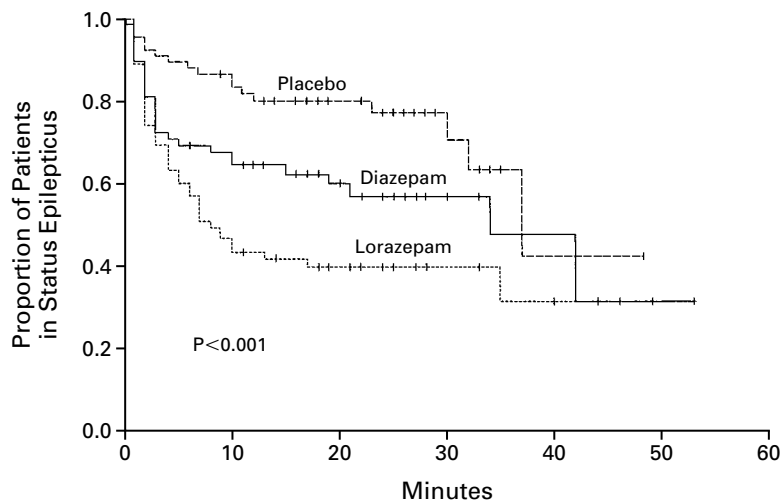
An out-of-hospital complication (hypotension, cardiac dysrhythmia, or respiratory intervention) occurred in 7 (10.6 percent) of the patients treated with lorazepam, 7 (10.3 percent) of the patients treated with diazepam, and 16 (22.5 percent) of the patients given placebo ($P=0.08$). The most common complication was a change in respiratory status requiring ventilation assistance by bag valve-mask or an attempt at intubation (7 patients given lorazepam, 6 given diazepam, and 11 given placebo). Cardiorespiratory complications that persisted to the time when patients were transferred to emergency-department personnel (complications at transfer) occurred in 13 patients (7.0 percent), with no significant differences between groups ($P=0.39$).

TABLE 2. STATUS EPILEPTICUS AT THE TIME OF ARRIVAL AT THE EMERGENCY DEPARTMENT.*

VARIABLE	LORAZEPAM GROUP (N=66)	DIAZEPAM GROUP (N=68)	PLACEBO GROUP (N=71)
	no. of patients (%)		
Status epilepticus terminated	39 (59.1)	29 (42.6)	15 (21.1)
Ongoing status epilepticus	27 (40.9)	39 (57.4)	56 (78.9)
	LORAZEPAM VS. PLACEBO	LORAZEPAM VS. DIAZEPAM	DIAZEPAM VS. PLACEBO
Odds ratio (simultaneous 95 percent CI) for termination of status epilepticus			
Unadjusted	5.4 (2.3–13.2)	1.9 (0.9–4.3)	2.8 (1.2–6.7)
Adjusted†	4.8 (1.9–13.0)	1.9 (0.8–4.4)	2.3 (1.0–5.9)

*CI denotes confidence interval.

†Each odds ratio was adjusted for race or ethnic group, the intervals from the onset of status epilepticus to study treatment and from study treatment to arrival at the emergency department, and cause of status epilepticus within each prognostic group.



No. AT RISK	0	10	20	30	40	50	60
Diazepam	68	41	21	8	2	1	
Lorazepam	65	29	15	6	2	0	
Placebo	67	53	26	10	1	0	

Figure 2. Kaplan–Meier Curves Comparing the Durations of Out-of-Hospital Status Epilepticus after Treatment with Lorazepam, Diazepam, or Placebo.

Tick marks indicate censoring of data. The curves were significantly different from one another by the log-rank test (P<0.001).

Hospital Care and Outcome

After arrival at an emergency department, active (open-label) antiseizure-drug treatment was used at the discretion of the treating physician for each patient. For patients still in status epilepticus, the interval from arrival at the emergency department to the termination of status epilepticus did not differ signif-

icantly among the three treatment groups. There were no significant differences among the groups in the rate of occurrence of new cardiorespiratory complications in the emergency department.

The transfer location, discharge, or death of patients after treatment in the emergency department and the neurologic outcome of patients at hospital discharge

did not differ significantly among the treatment groups (Table 3). Regardless of treatment, patients in status epilepticus on arrival at the emergency department were more likely to require admission to the intensive care unit than those whose seizures were terminated before arrival at the hospital (73 percent vs. 32 percent, likelihood-ratio chi-square <0.001). When these two groups of patients were compared according to the cause of the episode (prognosis group), no significant differences were found. Thus, it is likely that the higher rate of admission to the intensive care unit among patients remaining in status epilepticus on arrival at the emergency department was related to ongoing seizures rather than to the severity of underlying neurologic or medical disease.

At hospital discharge, 150 patients (74.3 percent) had returned to their base-line neurologic condition and 33 patients (16.3 percent) had new neurologic deficits. Nineteen patients (9.4 percent) died between enrollment and discharge from the hospital. No patients died before reaching the hospital. Calculated with the use of contingency-table analysis, the differences in death rates among the treatment groups were not significant ($P=0.08$ by Fisher's exact test). The small numbers of deaths precluded adjustment for potentially confounding covariates. Severe underlying illnesses were the probable causes of death in most patients.

DISCUSSION

We found clear evidence that intravenous benzodiazepines are safe and effective when administered by paramedics for the treatment of out-of-hospital status epilepticus in adults. At the doses we used, lorazepam and diazepam were more effective than placebo, and

there was a trend favoring lorazepam over diazepam. The rates of response (59 percent for 2 to 4 mg of lorazepam and 43 percent for 5 to 10 mg of diazepam) are slightly lower than those reported in in-hospital studies of status epilepticus.^{3,13} However, unlike in-hospital studies that assess response at a defined time after treatment, we assessed the rate of termination of status epilepticus at the time of arrival at the emergency department. The interval between the study treatment and the assessment of response varied among patients. This factor may partially explain the differences in response rates between our study and previous reports.

Cardiorespiratory complications before arrival at the hospital and at the time of transfer were important secondary outcomes that relate to the safety of out-of-hospital therapy with intravenous benzodiazepines. Despite concern regarding the adverse effects of these agents, we found a trend toward lower rates of out-of-hospital complications (primarily respiratory compromise) in the active-treatment groups than in the placebo group. This suggests that respiratory complications associated with prolonged seizures may be more pronounced than those caused by intravenous lorazepam and diazepam given at relatively low doses. The lower rate of complications at transfer than of out-of-hospital complications among patients in all groups suggests that the paramedics effectively managed the care of these patients. Although San Francisco paramedics received training on the clinical recognition of status epilepticus, in addition to study procedures, the education was relatively basic. Thus, we believe that our results are likely to be applicable to other emergency-medical-services systems that employ paramedics.

We used multiple levels of regulatory review and interim safety analyses to ensure that the study was appropriate in design and was not continued unnecessarily. Given the potential cardiorespiratory complications of intravenous benzodiazepines, and the difficulty of monitoring for these complications during transport in an ambulance, we believed that the placebo comparison was justified. Although the use of intravenous diazepam before arrival at the hospital has been reported in children,¹⁴ it has also been discouraged because of an unacceptable rate of respiratory depression and intubation-related aspiration and trauma.¹⁵ Also, paramedics receive limited training in the recognition of status epilepticus, and their ability to identify this condition accurately is unknown. Misdiagnosis may expose patients to unnecessary risks associated with treatment. Furthermore, the interval from the time the paramedics reach the patient to the time of arrival at an emergency department (where additional diagnostic and support measures are available) is short in our emergency-medical-services system (approximately 15 minutes). Finally, relatively few out-of-hospital interventions have been evaluated in randomized controlled trials,¹⁶ and when they have been

TABLE 3. OUTCOME OF PATIENTS AFTER LEAVING THE EMERGENCY DEPARTMENT AND NEUROLOGIC OUTCOME AT HOSPITAL DISCHARGE.

VARIABLE	LORAZEPAM GROUP (N=66)	DIAZEPAM GROUP (N=68)	PLACEBO GROUP (N=71)	P VALUE
	no. of patients (%)			
Reason for leaving emergency department*				0.26
Moved to intensive care unit	37 (56.9)	32 (47.8)	45 (63.4)	
Moved to hospital ward	19 (29.2)	18 (26.9)	17 (23.9)	
Sent home	9 (13.8)	17 (25.4)	8 (11.3)	
Died	0	0	1 (1.4)	
Neurologic outcome at hospital discharge†				0.25
Unchanged	49 (75.4)	52 (77.6)	49 (70.0)	
Neurologic deficit	11 (16.9)	12 (17.9)	10 (14.3)	
Death	5 (7.7)	3 (4.5)	11 (15.7)	

*Data were unavailable for two patients.

†Data were unavailable for three patients.

evaluated carefully, therapies with intuitive appeal have often been found either to lack benefit or to cause harm to patients.¹⁷⁻²⁰

On the basis of these results, and given the preference for lorazepam as in-hospital therapy,² we recommend lorazepam as out-of-hospital therapy for adults in status epilepticus. One practical concern is that refrigerated storage is recommended for lorazepam but not for diazepam. In a previous study, we found that lorazepam retained 90 percent of its original concentration for five months while stored in ambulances without refrigeration. However, lorazepam was less stable at 37°C and during the warmer months in San Francisco.⁶ We recommend that ambulances carrying lorazepam be restocked every 60 days when ambient temperatures are 30°C or more. In warmer climates, more frequent restocking or refrigerated storage is necessary.

Despite the beneficial outcomes associated with intravenous lorazepam and diazepam, 41 to 57 percent of patients who received active treatment were still in status epilepticus at the time of arrival at the emergency department. These patients were more than twice as likely to require intensive medical care as those whose seizures ended outside the hospital. Differences in the causes of the episodes of status epilepticus are unlikely to account for this difference. These observations, coupled with the favorable risk-benefit profile associated with lorazepam and diazepam in this trial, suggest that higher doses should be studied to define the optimal therapy for patients with out-of-hospital status epilepticus.

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CORRECTION

**A Comparison of Lorazepam, Diazepam, and Placebo
for the Treatment of Out-of-Hospital Status
Epilepticus**

A Comparison of Lorazepam, Diazepam, and Placebo for the Treatment of Out-of-Hospital Status Epilepticus. On page 637, the sentence that begins on line 14 of the left-hand column should have read, "We recommend that ambulances carrying lorazepam be restocked every 60 days when ambient temperatures are 30°C or *less*," not "30°C or *more*," as printed.