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A COMPARISON OF RECTAL DIAZEPAM GEL AND PLACEBO FOR ACUTE REPETITIVE SEIZURES

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ABSTRACT

Background Acute repetitive seizures are readily recognizable episodes involving increased seizure frequency. Urgent treatment is often required. Rectal diazepam gel is a promising therapy.

Methods We conducted a randomized, double-blind, parallel-group, placebo-controlled study of home-based treatment for acute repetitive seizures. Patients were randomly assigned to receive either rectal diazepam gel, at doses ranging from 0.2 to 0.5 mg per kilogram of body weight on the basis of age, or placebo. Children received one dose at the onset of acute repetitive seizures and a second dose four hours later. Adults received three doses — one dose at onset, and two more doses 4 and 12 hours after onset. Treatment was administered by a care giver, such as a parent, who had received special training. The number of seizures after the first dose was counted for 12 hours in children and for 24 hours in adults.

Results Of 125 study patients (64 assigned to diazepam and 61 to placebo) with a history of acute repetitive seizures, 91 (47 children and 44 adults) were treated for an exacerbation of seizures during the study period. Diazepam treatment was superior to placebo with regard to the outcome variables related to efficacy: reduced seizure frequency ($P<0.001$) and improved global assessment of treatment outcome by the care giver (frequency and severity of seizures and drug toxicity) ($P<0.001$). Post hoc analysis showed diazepam to be superior to placebo in reducing seizure frequency in both children ($P<0.001$) and adults ($P=0.02$), but only in children was it superior with regard to improvement in global outcome ($P<0.001$). The time to the first recurrence of seizures after initial treatment was longer for the patients receiving diazepam ($P<0.001$). Thirty-five patients reported at least one adverse effect of treatment; somnolence was the most frequent. Respiratory depression was not reported.

Conclusions Rectal diazepam gel, administered at home by trained care givers, is an effective and well-tolerated treatment for acute repetitive seizures. (N Engl J Med 1998;338:1869-75.)

EPILEPSY is among the most common neurologic disorders, affecting approximately two million people in the United States.[1] Epileptic-seizure recurrences sometimes follow a distinctive temporal pattern.[2,3] Some patients periodically have repetitive seizures, lasting minutes or hours, whose pattern is different from their usual seizure pattern. These exacerbations are termed serial, cluster, or acute repetitive seizures.[4,5]

Family members are often able to predict the onset of acute repetitive seizures according to the time of day when the seizures begin, the occurrence of a particular type of seizure, the severity of the seizure, and accompanying behavioral changes in the patient. If they are left untreated, acute repetitive seizures can evolve into more serious problems, including status epilepticus.[4-6]

Benzodiazepines are the treatment of choice for management of acute seizures.[4,7] They are active against many types of seizure, have a rapid onset of action, and are safe.[7] Oral diazepam and lorazepam, sublingual lorazepam, rectal solutions of lorazepam and diazepam, and diazepam suppositories have been used to treat acute repetitive seizures.[8-13] Oral or sublingual administration is frequently difficult and hazardous when the patient is actively convulsing, and absorption of diazepam and lorazepam tablets and rectal lorazepam solution is slower than that of rectal diazepam solutions.[8,14,15]

Rectal diazepam solutions have many characteristics sought in the ideal drug to treat acute repetitive seizures. Their high lipid solubility permits both prompt absorption and rapid penetration into the central nervous system.[16] Peak serum plasma concentrations are reached within 5 to 45 minutes, with

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bioavailability averaging between 80 and 100 percent.[8,9,13,16-20] In contrast, diazepam suppositories have slow, erratic absorption, which limits their use in the management of acute seizures.[13,17,19] Rectal diazepam solutions can be administered easily and safely by nonmedical personnel, irrespective of the patient's ability to cooperate.

Both European and North American clinicians have used rectal diazepam to treat acute repetitive, prolonged, and febrile seizures.[12,16,21,22] In the United States, rectal diazepam solutions have been prepared from commercial parenteral products.[8,23-25]

In 1988, Upsher–Smith Laboratories, in collaboration with the University of Minnesota, began developing a rectal diazepam delivery system to treat acute repetitive seizures. We conducted a clinical trial to assess the safety and efficacy of diazepam rectal gel for acute repetitive seizures.

METHODS

Patients

The patients were boys and girls 2 to 14 years of age and adults, defined as 15 to 60 years of age, with a maximal weight of 100 kg, who had had at least four episodes of acute repetitive seizures during the preceding year and at least one in the preceding three months. We defined acute repetitive seizures as an episode of multiple complex partial or generalized (tonic, clonic, tonic–clonic, atypical absence, or myoclonic) seizures occurring within a 24-hour period in adults or a 12-hour period in children, with a pattern distinguishable from the patient's usual seizure pattern, and with onset readily recognizable by a care giver, such as a parent. All patients had been on a stable antiepileptic regimen for at least four weeks before enrollment. Brain computed tomography or magnetic resonance imaging and laboratory screening had shown no evidence of a treatable cause of the seizures. Women of childbearing potential were eligible if they used contraception and had a negative pregnancy test.

Patients were ineligible if they met any of the following criteria: plasma phenobarbital concentrations greater than 30 mg per liter (130 μmol per liter), current treatment with drugs other than anticonvulsants, long-term use of benzodiazepines, use of central nervous system depressants or drugs interacting with diazepam, more than one previous treatment with rectal diazepam, nonepileptic seizures within the preceding five years, habitual progression to status epilepticus, clinically significant psychiatric disorder, lack of a suitable care giver, or use of an investigational drug or device within the preceding five months. Each patient, parent, or legal guardian provided written informed consent, and children gave assent.

Study Design

The study was conducted between October 1991 and January 1995. We used a prospective, randomized, double-blind, placebo-controlled, parallel-group design. A sample size of 144 patients was planned on the basis of estimates of the sample size required for a two-sided test to detect a 50 percent reduction in seizure frequency with diazepam at a significance level of 0.05 and a power of 0.80.

Each center's institutional review board approved the protocol and consent procedures. Oversight included regular review by the National Institute of Neurological Disorders and Stroke Performance and Safety Monitoring Board. Because of the board's concern about the safety of the investigational formulation and the response of the acute repetitive seizures to treatment, it requested an unblinded interim analysis of efficacy and all safety data for the first 36 patients. The board did not disclose the results or change the study at the time of this analysis. Thereafter, the blinding was maintained until the trial had been completed and decisions about the inclusion of patients in the analyses had been made. Randomization was based on permuted blocks, with stratification according to center and age group.

Procedures

Using an instructional videotape, study nurses taught care givers how to identify episodes of acute repetitive seizures, give medication, and record respiration, skin color, seizures, adverse events, and global assessment of treatment outcome in a booklet. During episodes of acute repetitive seizures, study nurses maintained telephone contact with the care givers to review procedures, monitor patients, and intervene if patients needed additional treatment. The observation period began immediately after the first dose and continued for 12 hours in children and 24 hours in adults. The lengths of the observation periods were based on preliminary data showing that most episodes of acute repetitive seizures ended within these times. The care givers and patients returned to the clinic 72 hours after treatment to review the recorded data.

We removed patients from the study before treatment if they no longer met eligibility criteria or if they withdrew consent. All data were analyzed, including those on patients who did not complete the protocol.

Study Treatments

We employed an age-adjusted dosage regimen of diazepam rectal gel (Diastat, Athena Neurosciences, San Francisco), as follows: 0.5 mg per kilogram of body weight for children 2 to 5 years of age, 0.3 mg per kilogram for children 6 to 11 years of age, and 0.2 mg per kilogram for patients 12 or older. These schedules were based on the results of clinical trials showing that diazepam clearance in children declines until about the age of 12 years, when adult values are reached.[8,16,19,26] A second dose was given four hours after the first, and, for adults, a third dose was given eight hours after the second, since previous studies indicated that these schedules should maintain target plasma diazepam concentrations (150 to 300 ng per milliliter).[8,19,26] Diazepam rectal gel (5 mg per milliliter) and identical-looking placebo were supplied by the manufacturer in 2-ml syringes containing 0.5, 1.0, or 1.5 ml and 5-ml syringes containing 2.0, 2.5, 3.0, 3.5, or 4.0 ml. Diazepam doses ranged from 2.5 to 20 mg, in 2.5-mg increments. The doses were rounded up to the nearest 2.5 mg.

The medication kits contained two syringes for children and three syringes for adults, with one dose per syringe. A syringe with half the regular dose was available to be used if the regular dose was expelled within five minutes.

Outcome Variables Related to Efficacy

Seizure frequency and global assessment of treatment outcome by the care giver were the outcome variables related to efficacy. Seizure frequency was defined as the number of seizures per hour of observation. Global treatment outcome was a composite evaluation based on the care giver's assessment of the frequency and severity of seizures and drug toxicity. The global outcome was rated as better than, the same as, or worse than the outcome after previous episodes.

Two efficacy outcome variables were retrospectively defined: the time to the first recurrence of seizures after the initial treatment, and the number of patients remaining seizure-free during the first 12 hours after treatment.

Safety Variables

At the return visit, the notes in the care giver's booklet about respiratory rate, skin color, and adverse events were reviewed. All adverse events were categorized according to the preferred terms of the Food and Drug Administration's COSTART system.[27]

Statistical Analysis

All patients who received at least one dose of study medication were included in the analysis. For base-line comparisons between the treatment groups, we used Fisher's exact test for sex, numbers of adults and children, and race and analysis of variance for age and body weight. The seizure-frequency data failed to support the assumption of normality required for a t-test. Therefore, we used a stratified Wilcoxon rank-sum test[28] to analyze both continuous data (seizure frequency) and categorical data (global assessment of treatment outcome), incorporating "child" and "adult" as the stratifying variables. The latter statistical analyses (investigation of data for normality, t-test, and rank-based methods) were specified by the protocol before the study began.

A Spearman rank-correlation test[29] was used to determine the relation between seizure frequency and the global assessment of treatment outcome, and the Wilcoxon rank-sum test[30] was used for both primary efficacy variables for a post hoc analysis of treatment differences for children and for adults.

The statistical tests for the two primary efficacy variables were two-sided at the 0.025 level of significance, with a Bonferroni correction[31] for testing two outcomes. The significance level was 0.0246, with an adjustment by O'Brien–Fleming procedures[32] to incorporate a penalty for the interim analysis performed at the 0.001 level of significance. The time to a first seizure recurrence after initial treatment was displayed as Kaplan–Meier survival estimates.[33]

Fisher's exact test and the Wilcoxon rank-sum test[30] with exact P values were computed with StatXact software (version 3, Cytel Software, Cambridge, Mass.), and analyses of variance by JMP software (version 3.1, SAS Institute, Cary, N.C.).

RESULTS

Characteristics of the Patients

One hundred twenty-five patients (64 in the diazepam group and 61 in the placebo group) were enrolled and randomly assigned to treatment. This number was less than the 144 patients originally planned, since the eligibility criteria were very stringent and funding considerations limited the period of recruitment. Ninety-one of these patients were treated. The median times from randomization to treatment were 20 days for the diazepam group and 19 days for the placebo group (exact P=0.95 by the Wilcoxon rank-sum test). The diazepam and placebo groups did not differ significantly in sex, age, and weight (Table 1). Significantly more black patients were randomly assigned to receive diazepam than were assigned to receive placebo, and significantly more white patients were assigned to placebo than to diazepam (P=0.04 by Fisher's exact test). Data from all 91 treated patients were analyzed. A child in the placebo group who required medical intervention for seizures during treatment was assigned the most conservative scores (zero seizures, better global assessment).

At the end of the trial, 15 patients who had been randomly assigned to treatment had not yet had an episode of acute repetitive seizures: 8 in the diazepam group and 7 in the placebo group. Nineteen patients had been withdrawn before receiving treatment: 11 in the diazepam group and 8 in the placebo group. Of the 19, 12 became ineligible (6 because of withdrawn consent, 4 because of lack of a care giver, 1 because of an added investigational drug, and 1 because of possible drug allergy); 6 had no acute repetitive seizures within a year; and 1 was lost to follow-up. Thus, a total of 34 of the 125 patients received no treatment. Thirteen of the 91 patients who were treated had incomplete dosing (8 patients), incomplete observations (3 patients), or both (2 patients).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC	ALL RANDOMIZED PATIENTS (N=125)		TREATED PATIENTS (N=91)	
	DIAZEPAM (N=64)	PLACEBO (N=61)	DIAZEPAM (N=45)	PLACEBO (N=46)
Sex (no.)				
Male	38	32	29	22
Female	26	29	16	24
Race (no.)				
White	44	53	29	40
Black	14	7	12	5
Other	6	1	4	1
Age group (no.)				
Child	36	31	25	22
Adult	28	30	20	24
Median age (yr)				
Child	8.0	8.0	7.0	7.0
Adult	23.0	20.5	18.5	23.0
Median body weight (kg)				
Child	23.6	22.4	23.0	21.9
Adult	57.1	60.2	55.6	56.8

Study Medication

Forty-one of the 45 treated patients assigned to diazepam and 40 of the 46 treated patients assigned to placebo received all their scheduled doses. One of the 20 adults given diazepam received two doses instead of three, and 3 of the 25 children given diazepam received one dose instead of two. The reasons included reluctance to give additional doses to a lethargic patient (one patient), rash (one patient), and the care giver's noncompliance with the protocol (two patients). Four of the 24 adults and 2 of the 22 children in the placebo group received fewer doses than planned. In five instances, medical intervention was required for seizures; one care giver misunderstood the treatment directions. Seven patients (three in the diazepam group and four in the placebo group) received the replacement dose.

The median total dose of diazepam was 20 mg (range, 7.5 to 25) for the 25 children and 37.5 mg (range, 15 to 60) for the 20 adults. Most patients received a slightly higher dose than the targeted dose because of rounding. The median increase over the target dose was 13.6 percent (range, 4.3 percent decrease to 51.5 percent increase) for the diazepam group. Six patients, all children, received doses at least 25 percent greater than the target dose, with one adverse reaction (moderate somnolence).

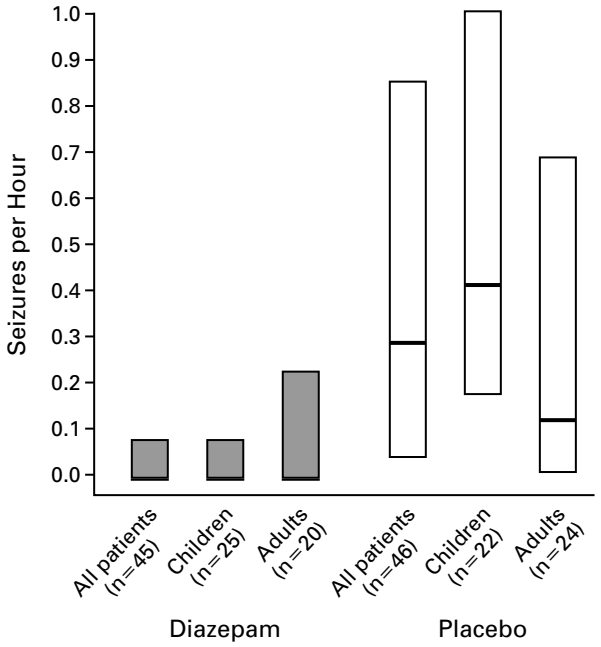


Figure 1. Frequency of Seizures in the Study Groups.

The lower and upper limits of the boxes represent the interquartile range (25th and 75th percentiles, respectively); the heavy bars represent the median values (for each diazepam group, the median was zero). The frequency of seizures with diazepam was significantly lower than that with placebo for all patients ($P<0.001$ by stratified Wilcoxon rank-sum test) and, by post hoc analysis, for children and adults analyzed separately ($P<0.001$ and $P=0.02$, respectively, by the Wilcoxon rank-sum test).

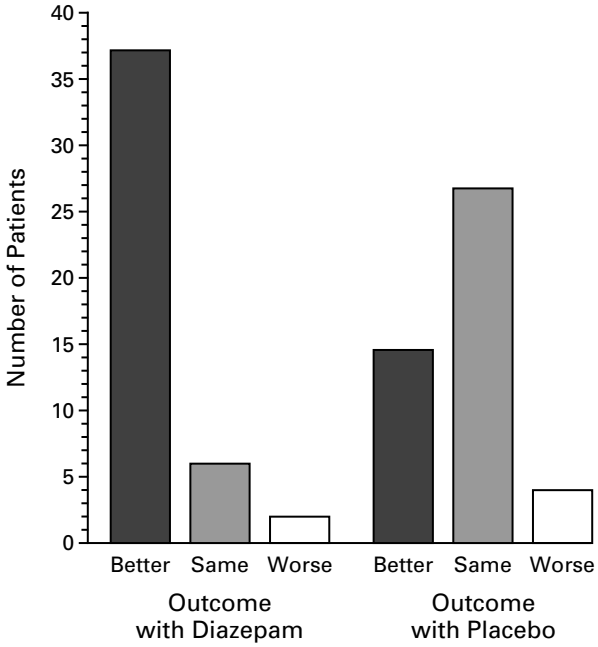


Figure 2. Care Giver's Global Assessment of Treatment Outcome.

The ratings for global assessment of treatment outcome were significantly higher for the diazepam group ($P<0.001$ by the stratified Wilcoxon rank-sum test for ordinal data).

Efficacy

Diazepam was significantly more effective than placebo both for reducing seizure frequency and for improving the care giver's global assessment of the treatment outcome ($P<0.001$) (Fig. 1 and 2). Seizure frequency and global assessment of treatment outcome were strongly correlated (Spearman $r=0.62$, $P<0.001$).

For each variable, we compared the treatment responses in children and adults separately. In both subgroups, the frequency of seizures was significantly lower in the patients receiving diazepam than in those receiving placebo ($P<0.001$ for children and $P=0.02$ for adults by the Wilcoxon rank-sum test). The care giver's global assessment of treatment outcome was significantly higher for children receiving diazepam than for children receiving placebo ($P<0.001$ by the Wilcoxon rank-sum test), but there was no significant difference in this outcome variable between the diazepam and placebo groups among adults ($P=0.09$).

Patients in the diazepam group had greater protection from seizure recurrence throughout the observation period than those in the placebo group. Differences between the groups were apparent as early as 30 minutes after initial treatment and continued throughout the 12-hour observation period (Fig. 3). The time to the first seizure recurrence was significantly longer in the diazepam group than in the placebo group (chi-square=13.75 with 1 df, $P<0.001$ by the modified Wilcoxon test).

Safety

Fifty-six patients reported no adverse effects of treatment. There were no reports of respiratory difficulty in patients receiving diazepam. One patient in the placebo group reported cyanosis. Thirty-five patients reported at least one adverse effect, but the difference between the diazepam and placebo groups was not significant: 46.7 percent of the diazepam group and 30.4 percent of the placebo group ($P=0.13$ by Fisher's exact test). Table 2 lists the adverse effects reported by more than one patient.

The most frequent adverse effects involved the nervous system, with at least one such adverse effect in 40 percent of the diazepam group and 22 percent of the placebo group. Somnolence, seen in 33 percent of the diazepam group and 11 percent of the placebo group, was the most frequent. Six patients receiving placebo required anticonvulsant treatment at a medical facility for continuing seizures.

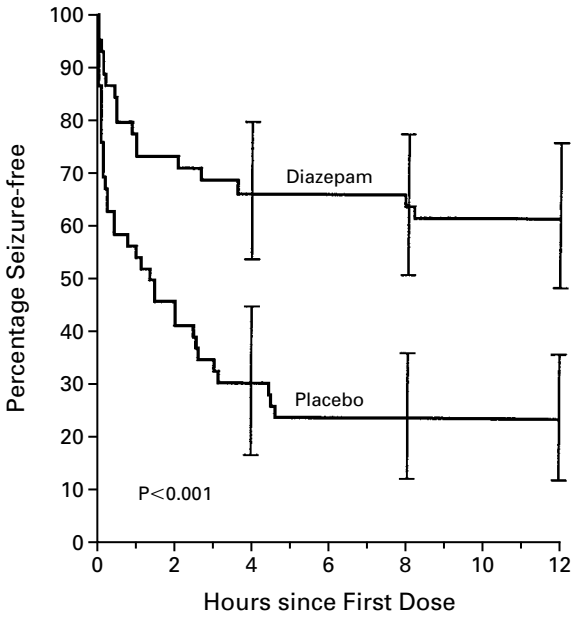
Two patients receiving diazepam and two receiving placebo did not complete treatment because of adverse effects. The third dose was withheld because

of marked lethargy in an adult given diazepam, and the second dose was withheld because of rash in a child given diazepam. The second and third doses were withheld because of sedation in an adult given placebo. The second dose was withheld because of seizures requiring intravenous diazepam in a child given placebo.

DISCUSSION

We conducted a rigorous, placebo-controlled trial evaluating the use of diazepam rectal gel in patients with exacerbations of epileptic seizures. Clinical observations of patients during hospitalization and at home have suggested that rectal diazepam shortens the duration of seizures, prevents recurrence, or both.[6,8,16,20-25,34-41] The importance of these studies is difficult to gauge, however. They were retrospective, unblinded, or nonrandomized, and they did not use placebo controls or rigorously define treatment end points.[42] A study similar to ours was conducted by Milligan et al.,[12] who gave 20-mg diazepam suppositories to adults with seizure clusters in a residential epilepsy center. The investigators used a double-blind, placebo-controlled design, with each subject as his or her own control. The nursing staff administered the medications and observed the patients for 24 hours. Seventy-eight percent of the patients given diazepam remained seizure-free, as compared with 19 percent of the patients given placebo. The analysis was not conducted on intention-to-treat principles, however, since it excluded data from patients from whom blood specimens were not obtained. Also, results from institutionalized adults treated by nurses are difficult to extrapolate to patients treated at home, many of whom are children.

We found that diazepam rectal gel was effective and safe when given outside the hospital for the treatment of acute repetitive seizures. The superiority of diazepam over placebo was found for both measures of efficacy: reduction in seizure frequency and the care giver's global assessment of treatment outcome (combining seizure frequency, seizure severity, and drug toxicity). Also, the time to a recurrence of seizures after the initial treatment and the proportion of patients remaining seizure-free during the observation period were greater in the diazepam group. When the efficacy variables were analyzed separately for children and adults, the reduction in seizure frequency was significantly greater with diazepam in both age groups, but the care giver's global assessment of treatment outcome was significantly better with diazepam only among children. The difference in outcome between children and adults may be related to the study design. Three doses were given to adults but only two to children, regardless of treatment response, and the extra dose of diazepam may have made the adults more sedated. Also, the care givers may have watched the children more



No. of Patients							
Diazepam	45	33	30	30	29	28	28
Placebo	46	19	14	11	11	11	11

Figure 3. Kaplan–Meier Estimate of the Time to a First Recurrence of Seizures.

Data from all patients were censored at 12 hours, the observation period for children. Only two patients, both in the placebo group, had their first seizure recurrence between 12 and 24 hours after the initial treatment. The vertical bars show 95 percent confidence intervals.

Table 2. Adverse Effects Reported by More Than One Patient.

Adverse Effect*	Diazepam Group	Placebo Group
	no. of patients	
General		
Fever	2	2
Headache	1	2
Cardiovascular system		
Vasodilatation	2	0
Digestive system		
Anorexia	1	2
Vomiting	1	2
Nervous system		
Abnormal coordination	3	0
Dizziness	2	1
Euphoria	3	0
Nervousness	1	2
Somnolence	15	5
Respiratory system		
Rhinitis	0	2
Skin		
Pruritus	2	0

*The adverse-effect descriptors are from COSTART.[27]

closely, resulting in better recognition of differences in global outcome.

The majority of patients had no adverse effects. The patients given diazepam had more adverse effects involving the nervous system but fewer digestive and systemic adverse effects than the patients given placebo. There were no respiratory difficulties.

The benefits of a safe and effective treatment for acute repetitive seizures were highlighted by Alldredge et al.,[43] who reviewed 45 episodes of convulsive status epilepticus in 38 children given prehospital treatment with rectal or intravenous diazepam. Treatment shortened the duration of status epilepticus by one half and reduced the likelihood that seizures would recur in the emergency department by one third. In our study, no patients given diazepam and 13 percent of the patients in the placebo group required emergency medical care. Kriel et al.[23] computed the cost savings associated with in-home rectal diazepam treatment of cluster and prolonged seizures. They found a 67 percent decrease in emergency room visits and a cost savings of $1,000 per family in the year after the families begin using rectal diazepam, with reduced family disruption and improved quality of life.

We also showed that informed and educated care givers can identify the onset of acute repetitive seizures, safely and successfully administer diazepam rectally, and assess the patient's response. The number of doses was fixed to standardize conditions for this trial. Administration of the second dose in children and adults and of the third dose in adults was not based on response. In practice, the number and timing of doses might better be based on the individual patient's seizure profile and initial response to treatment.

We did not assess rectal diazepam gel in patients with acute repetitive seizures who typically progress to status epilepticus; such patients were ineligible. Although one patient in the placebo group was apparently in status epilepticus when given the first dose, no patient in either study group had status epilepticus after treatment was begun.

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REFERENCES

1. Hauser WA, Annegers JF, Kurland LT. The prevalence of epilepsy in Rochester, Minnesota: 1940-1980. Epilepsia 1991;32:429-45.
2. Smolensky MH, Reinberg A. Medical chronobiology with special reference to temporal patterns in epileptic seizures. In: Dreifuss FE, Meinardi H, Stefan H, eds. Chronopharmacology in therapy of the epilepsies. New York: Raven Press, 1990:71-87.
3. Newmark ME, Dubinsky A. The significance of seizure clustering: a review of 343 outpatients in an epilepsy clinic. In: Dreifuss FE, Meinardi H, Stefan H, eds. Chronopharmacology in therapy of the epilepsies. New York: Raven Press, 1990:89-103.
4. Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment. Epilepsia 1996;37:Suppl 1:S74-S80.
5. Status epilepticus. In: Aicardi J. Epilepsy in children. 2nd ed. New York: Raven Press, 1994:284-309.
6. Remy C, Jourdil N, Villemain D, Favel P, Genton P. Intrarectal diazepam in epileptic adults. Epilepsia 1992;33:353-8.
7. Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993;270:854-9.
8. Lombroso CT. Intermittent home treatment of status and clusters of seizures. Epilepsia 1989;30:Suppl 2:S11-S14.
9. Schroeder MC, Wolff DL, Maister BH, Norstrom S, Leppik IE, Graves NM. Lorazepam Intensol for the management of hospitalized pediatric patients with epilepsy. Epilepsia 1996;37:Suppl 5:S154. abstract.
10. Yager JY, Seshia SS. Sublingual lorazepam in childhood serial seizures. Am J Dis Child 1988;142:931-2.
11. Garofalo EA, Hirschorn KA, Komarynski MA. Improved control of seizure clusters with rectal diazepam and lorazepam. Cleve Clin J Med 1989;56:Suppl:S-277. abstract.
12. Milligan NM, Dhillon S, Griffiths A, Oxley J, Richens A. A clinical trial of single dose rectal and oral administration of diazepam for the prevention of serial seizures in adult epileptic patients. J Neurol Neurosurg Psychiatry 1984;47:235-40.
13. Dhillon S, Oxley J, Richens A. Bioavailability of diazepam after intravenous, oral and rectal administration in adult epileptic patients. Br J Clin Pharmacol 1982;13:427-32.
14. Graves NM, Kriel RL, Jones-Saete C. Bioavailability of rectally administered lorazepam. Clin Neuropharmacol 1987;10:555-9.
15. Greenblatt DJ, Divoll M, Harmatz JS, Shader RJ. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci 1982;71:248-52.
16. Schmidt D. Benzodiazepines: diazepam. In: Levy RH, Mattson RH, Meldrum BS, eds. Antiepileptic drugs. 4th ed. New York: Raven Press, 1995:705-24.
17. Moolenaar F, Bakker S, Visser J, Huizinga T. Biopharmaceutics of rectal administration of drugs in man. IX. Comparative biopharmaceutics of diazepam after single rectal, oral, intramuscular and intravenous administration in man. Int J Pharm 1980;5:127-37.
18. Browne TR. The pharmacokinetics of agents used to treat status epilepticus. Neurology 1990;40:Suppl 2:28-32.
19. Milligan N, Dhillon S, Oxley J, Richens A. Absorption of diazepam from the rectum and its effect on interictal spikes in the EEG. Epilepsia 1982;23:323-31.
20. Agurell S, Berlin A, Ferngren H, Hellstrom B. Plasma levels of diazepam after parenteral and rectal administration in children. Epilepsia 1975; 16:277-83.
21. Hoppu K, Santavuori P. Diazepam rectal solution for home treatment of acute seizures in children. Acta Paediatr Scand 1981;70:369-72.
22. Knudsen FU. Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. Arch Dis Child 1979;54:855-7.
23. Kriel RL, Cloyd JC, Hadsall RS, Carlson AM, Floren KL, Jones-Saete CM. Home use of rectal diazepam for cluster and prolonged seizures: efficacy, adverse reactions, quality of life, and cost analysis. Pediatr Neurol 1991;7:13-7.
24. Camfield CS, Camfield PR, Smith E, Dooley JM. Home use of rectal

diazepam to prevent status epilepticus in children with convulsive disorders. J Child Neurol 1989;4:125-6.
25. Woody RC, Golladay ES, Fiedorek SC. Rectal anticonvulsants in seizure patients undergoing gastrointestinal surgery. J Pediatr Surg 1989;24: 474-7.
26. Cloyd J, Arbit H, Beniak T, Freeman R, Jones-Saete C, Lalonde R. Rectal diazepam: absolute bioavailability and cognitive effects in healthy volunteers. Epilepsia 1993;34:Suppl 2:123. abstract.
27. 'COSTART': coding symbols for thesaurus of adverse reaction terms. 3rd ed. Rockville, Md.: Center for Drug Evaluation and Research, 1989.
28. Lehmann EL, D'Abrera HJM. Nonparametrics: statistical methods based on ranks. San Francisco: Holden-Day, 1975:5-13, 132-8.
29. Fisher LD, van Belle G. Biostatistics: a methodology for the health sciences. New York: John Wiley, 1993:385-6.
30. Moses LE, Emerson JD, Hosseini H. Analyzing data from ordered categories. In: Bailar JC III, Mosteller F, eds. Medical uses of statistics. 2nd ed. Boston: NEJM Books, 1992:259-79.
31. Fisher LD, van Belle G. Biostatistics: a methodology for the health sciences. New York: John Wiley, 1993:611-3.
32. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
33. Marubini E, Valsecchi MG. Analysing survival data from clinical trials and observational studies. Chichester, England: John Wiley, 1994:42-8.
34. Langslet A, Meberg A, Bredesen JE, Lunde PKM. Plasma concentrations of diazepam and N-desmethyldiazepam in newborn infants after intravenous, intramuscular, rectal and oral administration. Acta Paediatr Scand 1978;67:699-704.
35. Knudsen FU. Plasma-diazepam in infants after rectal administration in solution and by suppository. Acta Paediatr Scand 1977;66:563-7.
36. Meberg A, Langslet A, Bredesen JE, Lunde PKM. Plasma concentration of diazepam and N-desmethyldiazepam in children after a single rectal or intramuscular dose of diazepam. Eur J Clin Pharmacol 1978;14:273-6.
37. Milligan N, Dhillon S, Richens A, Oxley J. Rectal diazepam in the treatment of absence status: a pharmacodynamic study. J Neurol Neurosurg Psychiatry 1981;44:914-7.
38. Sykes RM, Okonofua JA. Rectal diazepam solution in the treatment of convulsions in the children's emergency room. Ann Trop Paediatr 1988; 8:259-61.
39. De Negri M, Gaggero R, Veneselli E, Pessagno A, Baglietto MG, Pallecchi A. Rapid diazepam introduction (venous or rectal) in childhood epilepsy: taxonomic and therapeutic considerations. Brain Dev 1991;13:21-6.
40. Albano A, Reisdorff EJ, Wiegenstein JG. Rectal diazepam in pediatric status epilepticus. Am J Emerg Med 1989;70:168-72.
41. Franzoni E, Carboni C, Lambertini A. Rectal diazepam: a clinical and EEG study after a single dose in children. Epilepsia 1983;24:35-41.
42. Kramer LD, Pledger GW, Kamin M. Prototype antiepileptic drug clinical development plan. Epilepsia 1993;34:1075-84.
43. Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol 1995;12: 213-6.