A CONTROLLED TRIAL OF DIAZEPAM ADMINISTERED DURING FEBRILE ILLNESSES TO PREVENT RECURRENCE OF FEBRILE SEIZURES

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Abstract *Background.* Phenobarbital, once widely prescribed to prevent febrile seizures, is now in disfavor because of its side effects and lack of efficacy. Diazepam, administered only during episodes of fever, may be a safe, effective agent to prevent the recurrence of febrile seizures.

Methods. We conducted a randomized, double-blind, placebo-controlled trial among 406 children (mean age, 24 months) who had at least one febrile seizure. Diazepam (0.33 mg per kilogram of body weight) or placebo was administered orally every eight hours during all febrile illnesses.

Results. During a mean follow-up of 1.9 years (a period during which 90 percent of febrile seizures recur), our intention-to-treat analysis showed a reduction of 44 percent in the risk of febrile seizures per person-year with diazepam (relative risk = 0.56; 95 percent confidence interval, 0.38 to 0.81; P = 0.002). A survival analysis of the length of time to the first recurrent febrile seizure did not show a significant difference between the treatment groups (P = 0.064 by the log-rank test), but after adjustment for covariates, diazepam was found to have a benefit (P = 0.027 by Cox regression analysis). An analysis restricted to children who had seizures while actually receiving the study medication (7 in the diazepam group and 29 in the placebo group) showed an 82 percent reduction in the risk of febrile seizures with diazepam (relative risk = 0.18; 95 percent confidence interval, 0.09 to 0.37; P<0.001). Of the 153 children who took at least one dose of diazepam, 39 percent had ataxia, lethargy, or irritability or at least one other moderate side effect that was reversed after a reduction in the dose. There were no severe side effects.

Conclusions. Oral diazepam, given only when fever is present, is safe and reduces the risk of recurrent febrile seizures. (N Engl J Med 1993;329:79-84.)

CONVULSIONS triggered by fever (febrile seizures) are the most common type of seizure, with a prevalence of 3 to 4 percent.[1] Febrile seizures frequently recur, with a recurrence rate of 33 percent overall and 50 percent when the first febrile seizure occurs before one year of age.[1] The risk of recurrence increases when there is a family history of febrile seizures and, in some but not all studies, when there is a family history of afebrile seizures and when the child has a neurologic abnormality.[2,3] Half the recurrences occur within six months of the first febrile seizure, three quarters within a year, and 90 percent within two years.[4]

Prevention of febrile seizures is highly desirable, since seizures are upsetting to both parents and children,[5] and since the medical costs can be considerable. Any child with a convulsion is at risk for brain injury due to falls caused by seizures or due to hypoxia if there is accompanying respiratory compromise. Most studies,[2] though not all,[6] have found a relation between the number of febrile seizures, particularly those that are complex,[7] and the risk of later afebrile seizures.[2] Hence, prevention of febrile seizures might also lessen that risk.

For two decades, daily phenobarbital has been the drug of choice for the prevention of febrile seizures, and in most studies it has been effective.[2,8,9] More recently, however, its role in prophylaxis has been questioned.[10-12] Concern has centered on the frequency of behavioral side effects,[5,13] consistently poor compliance with the drug regimen,[9] and evidence of some accompanying decline in IQ.[12] Finally, assessments of the efficacy of daily phenobarbital, based on the intention to treat, have shown no advantage over placebo.[10,11] Studies have shown both daily primidone and daily valproate to be as effective as daily phenobarbital, but with limiting side effects.[2,14-16] With valproate, moreover, as with phenobarbital, analyses according to the intention to treat have not demonstrated efficacy.[10,11] Daily phenytoin and daily carbamazepine are ineffective as prophylaxis.[2]

There thus appears to be a need for a safe, effective medication, ideally one that does not require daily administration. The results of several uncontrolled studies indicate that diazepam, given either rectally or orally, may be effective in preventing recurrent febrile seizures.[17,18] We conducted a double-blind, randomized clinical trial of oral diazepam, taken only when fever was present, to prevent the recurrence of febrile seizures.

Methods

Subjects

Beginning on September 15, 1986, we recruited subjects from New England and elsewhere in the United States. The criteria for eligibility were a history of at least one febrile seizure of any type; no history of afebrile seizures; age from six months to five years; no anticonvulsant medication or a willingness on the part of the physician and parents to discontinue such medication; and an absence of liver disease.

Procedures

At the Floating Hospital in Boston, a nurse practitioner evaluated each potentially eligible child, confirmed his or her eligibility, reviewed a questionnaire on the child's history previously completed by a parent, and obtained the parent's consent. Both the nurse and, subsequently, a staff pediatric neurologist conducted base-line physical, developmental, and neurologic assessments.

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Discussion with the family emphasized the following steps to be taken by the parents and other care givers: taking the temperature promptly whenever the child seemed ill; giving study medication as soon as the child became febrile (rectal temperature >38.1°C) and continuing the medication until the child had been afebrile for 24 hours; following instructions from the child's pediatrician, including those on the use of other medications; and keeping the study medication available at all times. Parents were provided with information booklets and charts on which to record details of all febrile illnesses (including temperatures and medications given), recurrences of febrile seizures (the principal end point of the trial), and the occurrence of any afebrile seizures. The family also received vials for the daily collection of urine samples during all episodes of fever and addressed, stamped mailers for the return of the completed charts and the urine specimens. The parents were asked to telephone the study staff at the onset of every febrile illness and immediately whenever a febrile or afebrile seizure occurred.

Each child was then randomly assigned to a treatment group, and the family was provided with the study medication. The subjects were stratified according to age (<12 months vs. ≥12 months) and randomly assigned by blocks of four within each stratum. Only the pharmacist and the biostatisticians knew the details of the randomization schedule.

Medications

In a pilot study of children hospitalized for febrile seizures, we determined that a dose of 0.33 mg of diazepam per kilogram of body weight, given every eight hours, could produce blood levels of 150 to 300 ng per milliliter within an hour. Such levels have been found to prevent seizures in children, both clinically[19,20] and according to electroencephalographic data.[21] We therefore used a dose of 0.33 mg per kilogram every eight hours in the trial.

The pharmacy provided individual doses of medication in sealed foil packages containing either a white 2-mg tablet of diazepam or an identical-appearing placebo (kindly supplied by Zenith Laboratories, Northvale, N.J.) packaged with a yellow 6-mg tablet of riboflavin. Riboflavin, which is excreted in the urine, causes it to fluoresce under ultraviolet light and thus serves as an indicator of compliance with the drug regimen.

The parents were given written instructions explaining the number of packets of medications to give (based on the child's body weight) every 8 hours during each episode of fever, continuing until the child had been afebrile for 24 hours. We sent the families new supplies of medication as needed, with adjustments in the dosage according to changes in the child's body weight.

Follow-up

We telephoned families daily throughout all febrile illnesses to provide support, assess compliance with medication, confirm and bring up to date information on the child's fever and seizure charts, and assess the child's clinical progress, including possible side effects of medication. Side effects were classified as either mild or moderate (none were severe). If they were mild, we reassured family members and instructed them to call back promptly if the symptoms worsened. If they were moderate, we sometimes instructed them to reduce the drug dose by one third. If the symptoms did not improve within a day or two, a further reduction to one half the original dose was suggested. We also attempted to telephone each family every 8 to 12 weeks to reinforce the study procedures, inquire about any unreported fevers or seizures, and confirm medication use. We also sent written reminders at least yearly to all families.

Withdrawals from the Study

There were three specified reasons for breaking the randomization code, thereby terminating the child's participation in the study: frequently recurrent simple febrile seizures (three by one year of age, four by two years of age, or five, regardless of age); recurrent complex febrile seizures (two, regardless of age); or the development of possible side effects of medication that caused concern (such as a rash) or that persisted even after reductions in the dose (such as lethargy). Children were also withdrawn from the study for other reasons. Some left the study because afebrile seizures developed or because of their parents' preference, or were lost to follow-up. We accrued person-time and outcome events up to the time when each such child left the study.

All other children continued in the study and continued to receive the originally assigned medication. Since few febrile seizures occur after five years of age, that age was chosen as the study's termination point. Thus, unless previously withdrawn, all children continued in the study until they reached five years of age or until the study ended on April 30, 1992.

Statistical Analysis

The chief outcome events for analysis were febrile seizures reported by the parents. We conducted two analyses. In one, we counted each seizure that occurred during a fever separately, as long as it occurred more than one hour after the previous seizure; in the other, we counted only one seizure per episode of fever, regardless of how many occurred. Both analyses yielded similar results, with the former showing a somewhat stronger treatment effect. We decided to take the more conservative approach and counted only one seizure per episode of fever. Throughout this paper, therefore, the calculations of the recurrence of febrile seizures refer to episodes of fever in which one or more seizures occurred.

For base-line comparisons of groups and for univariate analyses of factors related to the recurrence of febrile seizures, we used independent-sample t-tests for quantitative variables and chi-square tests for categorical variables. Our calculation of 95 percent confidence intervals for relative risks was based on Poisson models for incidence-density data.[22] For the analysis of the time to the first recurrence of a febrile seizure, we used the Kaplan–Meier method to plot the cumulative incidence curves and the log-rank test to compare groups.[23] We used the Cox proportional-hazards regression model[23] to adjust survival analyses for the following covariates: age, number of febrile seizures before study entry, interval between the last febrile seizure and study entry, perinatal history, neurologic history, and results of the developmental assessment.

Results

We screened 960 children, of whom 406 were randomly assigned to treatment. Of the remaining 554, 30 did not meet the eligibility criteria, the parents of 402 were unable or unwilling to participate, the parents of 56 could not be contacted, and 66 were not enrolled for a variety of other reasons. The study groups were comparable at base line in terms of pertinent demographic and clinical characteristics (Table 1).

Compliance and Withdrawal from the Study

We received more than 2200 urine samples obtained from study subjects during episodes of fever. Of the 1257 and 982 samples from diazepam and placebo groups, respectively (representing 66 percent and 69 percent of the total days of fever reported), 96 percent and 95 percent tested positive for riboflavin.

The protocol called for the subjects to continue to receive their assigned medications until their fifth birthdays or until the end of the study. For each study group, Table 2 shows the numbers of subjects for whom these goals were not achieved and the reasons why. The distributions of the reasons for withdrawal in the two study groups were similar. Twelve subjects in the diazepam group and 17 in the placebo group were withdrawn because of afebrile seizures, side effects of medication, frequent simple febrile seizures, or recurrent complex febrile seizures. Most withdrawals

Table 1. Base-Line Characteristics of the Treatment Groups.*

Characteristic	Diazepam (N = 202)	Placebo (N = 204)
Age (mo)	23.0±10.0	24.3±10.1
Male (%)	55.5	63.2
White (%)	87.6	87.3
Normal history (%)		
Perinatal	44.8	42.2
Pediatric	58.7	58.8
Developmental	74.3	77.5
Neurologic	89.6	94.6
Family	76.4	72.6
Normal base-line examination (%)		
Physical	93.1	90.1
Developmental	75.7	67.7
Neurologic	74.3	73.0
No family history of seizures (%)		
Febrile	71.3	72.1
Afebrile	95.1	94.1
Age at first febrile seizure (mo)	16.3±7.4	16.6±7.2
Percentile for head circumference†	61.8±25.2	61.1±28.9
No. of febrile seizures before entry (%)		
1	45.5	42.7
2	29.2	30.4
≥3	25.3	26.9
Type of febrile seizure before entry (%)		
Simple only	60.4	58.8
Complex only	14.4	17.7
Both	25.3	23.5
Time from first febrile seizure to entry (mo)	6.8±7.8	7.7±8.8
Time from most recent febrile seizure to entry (mo)	2.3±2.8	2.8±3.9
Anticonvulsant therapy (no. of children)	44	44

*Plus–minus values are means ±SD.
†Adjusted for age.

occurred at the parents' request (usually because the child had been free of seizures for many months) or through loss to follow-up. Table 2 shows the length of follow-up to the time of withdrawal. Among the withdrawals, more than half occurred after at least one year of follow-up.

Frequency of Fevers and Recurrent Febrile Seizures

Table 3 shows person-years of follow-up (mean, 1.9 years in each study group), the frequency of the outcome events, and the frequency of fever and of febrile seizures.

The differences between the diazepam and placebo groups in the number of febrile seizures (41 vs. 72) and the number of febrile seizures while receiving the study medication (7 vs. 38) are striking. There were 34 febrile seizures in children in the diazepam group while they were not receiving medication (41 − 7) and 34 in the placebo group (72 − 38). Parents were asked why the medication had not been given. The main reasons were that the parents did not take the child's temperature, that the seizure was the first sign of illness, and that the last recorded temperature had been normal. On other occasions the medication was not with the parent, the parents misunderstood the instructions, the child spat up the medicine, or the parents were worried about the side effects.

As Table 3 shows, the two groups differed significantly in the rate of fever ($P<0.001$), with fevers occurring 26 percent more often in the diazepam group than in the placebo group. An intention-to-treat analysis of the number of recurrent febrile seizures per person-year of follow-up indicates a significant treatment effect ($P = 0.002$), with a relative risk of 0.56 (95 percent confidence interval, 0.38 to 0.81) for the children in the diazepam group as compared with those in the placebo group. Thus, with the use of diazepam, we found a 44 percent reduction in the frequency of recurrent febrile seizures. An analysis of the occurrence of febrile seizures while the study medication was actually being taken (45 seizures in 36 children) indicates a striking and significant effect of diazepam ($P<0.001$), with a relative risk of 0.18 (95 percent confidence interval, 0.09 to 0.37) and an 82 percent reduction in the rate of recurrent febrile seizures with diazepam.

Time to the First Recurrent Febrile Seizure

The results of more conservative analyses, based on survival methods, in which the end point was the length of time to the first recurrent febrile seizure are shown in Figure 1, along with the cumulative incidence of first recurrent febrile seizures. The difference between the two curves, in the intention-to-treat analysis, was not statistically significant ($P = 0.064$ by the log-rank test). Nonetheless, two years after randomization, the cumulative incidence of first recurrences of febrile seizures was 21.2 percent in the diazepam group and 31.1 percent in the placebo group — a 32 percent reduction with diazepam.

We also conducted Cox regression analyses to account for the effects of covariates. Characteristics that in univariate analyses showed some association with the first recurrence of febrile seizures after study entry included the child's age, the number of febrile seizures

Table 2. Subjects Withdrawn from the Study, According to Treatment Group.

Variable	Diazepam (N = 202)	Placebo (N = 204)
Reason		
Afebrile seizures	11	10
Side effects (code broken)	1	2
Frequent simple or recurrent complex febrile seizures (code broken)	0	5
Parental preference	23	25
Loss to follow-up	15	13
Total	50	55
Duration of follow-up at withdrawal (mo)		
<6	15	15
6–11	9	7
12–23	15	19
≥24	11	14
Total	50	55

before study entry, the interval between the last febrile seizure and study entry, the perinatal history, the neurologic history, and the results of the developmental assessment. After adjustment by Cox regression, the effect of diazepam, as compared with placebo, was significant (P = 0.027), with an estimated relative risk of 0.61 (95 percent confidence interval, 0.39 to 0.94).

Side Effects of Medication

Only three children had side effects that were sufficiently worrisome for us to break the randomization code and withdraw them from the study (Table 2). All the other side effects were either moderate (and lessened by a reduction in drug dosage) or, more often, mild.

Among the 135 children who took at least one dose of placebo, only 1 child had a possible moderate side effect (a maculopapular rash). Among the 153 children who took at least one dose of diazepam, 59 (39 percent) reported at least one moderate side effect. As Table 4 shows, the side effects most frequently seen were ataxia, lethargy, and irritability (reported in approximately one quarter to one third of the children given diazepam). A much smaller proportion of children receiving diazepam (roughly 1 in 20) had moderate side effects involving speech, activity level, or sleep. The frequency of mild side effects in children receiving diazepam (data not shown) paralleled that of side effects of moderate severity.

Discussion

The management of febrile convulsions continues to be controversial.[24,25] With the use of daily medication falling into disfavor, investigators have sought drugs that can effectively and safely prevent febrile seizures but that can be given only when fever is present. The most extensive experience has been with diazepam, a medication that has a wide margin of safety.[5,26] Studies of the use of rectal diazepam (in the form of suppositories or solution) report rates of recurrence of febrile seizures of 10 to 36 percent. Only a few investigators have studied the use of oral diazepam; they report recurrence rates of 0 to 16 percent.[17,18] In the one double-blind study with a placebo control, compliance was extremely poor.[27] Thus, the results so far have been inconclusive.

Table 3. Person-Years of Follow-up and Outcome Events, According to Treatment Group.

Variable	Diazepam	Placebo	RR (95% CI)*	P Value
Person-years			—	—
Total	392.3	384.2		
Mean	1.9	1.9		
Subjects			—	—
Total no.	202	204		
No. with fevers	155	142		
No. who took medication at least once	153	135		
No. with febrile seizures†	37	53		
No. with febrile seizures while receiving medication†	7	29		
No. of fevers	675	526	—	—
No. of febrile seizures			—	—
Total	41	72		
While receiving medication	7	38		
Frequency per person-year				
Fever	1.72	1.37	1.26 (1.12–1.41)	<0.001
Febrile seizure				
Total	0.10	0.19	0.56 (0.38–0.81)	0.002
While receiving medication	0.02	0.10	0.18 (0.09–0.37)	<0.001

*RR denotes relative risk, and CI confidence interval.

†Some children in the placebo group had more than one febrile seizure.

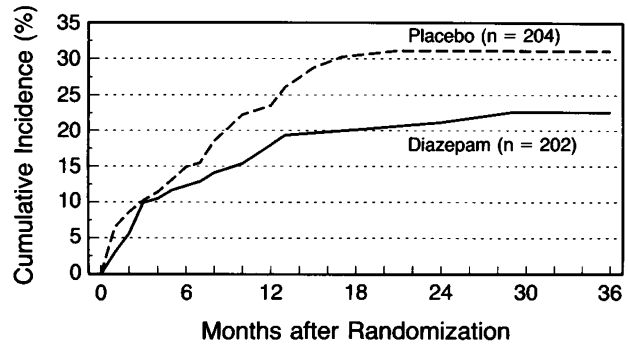

Figure 1. Cumulative Incidence of Recurrent Febrile Seizures, According to Treatment Group.

The difference between the curves, calculated according to intention to treat, was not significant (P = 0.064 by the log-rank test).

We chose to study oral diazepam because of its ease and convenience of administration, because diazepam suppositories are commercially unavailable, and because diazepam solution for rectal administration is not approved in the United States. Furthermore, with oral diazepam, peak serum levels occur more quickly in children than in adults,[26] with absorption rates that are as rapid as those with the rectal solution[28] and more rapid than with rectal suppositories.[29] In our pilot study, we found that a daily dose of 1 mg of diazepam per kilogram per day, administered orally in three equal doses given every eight hours, was well tolerated and produced a therapeutic blood level within an hour or less.

In the intention-to-treat analysis, our results show a distinct benefit of diazepam, which reduced the risk of recurrence of febrile seizures by nearly half. In estimating the true efficacy of diazepam in preventing febrile seizures, there are three factors to consider: the dilution effect (because of imperfect compliance) inherent in the intention-to-treat analysis; possible differences in the reporting of end points in the two study groups; and the possible lack of statistical independence of repeated events in the same subjects.

In our trial, the parents had the primary responsibility for the administration of medication. Despite our intensive educational efforts, regular contact with all enrolled families, and frequent reminders about the importance of strict compliance with the study protocol, there were times when parents did not give the

Table 4. Moderate Side Effects of Medication among the Children Who Received at Least One Dose of Diazepam.*

SIDE EFFECT	PERCENT
Ataxia	30.0
Lethargy	28.8
Irritability	24.2
Unclear speech	5.9
Hyperactivity	5.9
Insomnia	5.2
Hallucinations	0.7
Other	1.3
Any moderate side effect	38.6

*A total of 153 children received at least one dose of diazepam; 59 of them had at least one side effect. Some children reported more than one moderate side effect.

study medications despite the presence of fever. In only a quarter of these cases, however, was the failure to give study medication unavoidable (as in cases in which the febrile seizure was the first sign of illness). In all the other instances, greater vigilance on the part of the child's care giver would have resulted in the child's receiving the medication. Some children never received medication because they had no fevers after study entry. In an intention-to-treat analysis, children to whom medication was not administered during fever and those who had no indications for the use of medication (i.e., no fevers) are combined in the denominators and dilute the true effect of treatment. Thus, our intention-to-treat analyses may have resulted in a substantial underestimation of the true efficacy of diazepam.

Although study personnel and parents remained blinded to the children's group assignment throughout the study, more fevers were reported in the diazepam group than in the placebo group, perhaps because some parents suspected, correctly, that their children had been randomly assigned to placebo (because of an absence of side effects) and thus were less vigilant about reporting subsequent fevers. It is most unlikely, however, that there was differential reporting of febrile seizures.

Our analysis of the frequency of recurrent seizures was based on the assumption that in a given subject, each repeated febrile illness, the use of study medication, and the recurrence of febrile seizures were statistically independent of previous events. One might argue against this statistical assumption if the occurrence of a febrile seizure (or its absence) when the study medication was given influenced parents' compliance with the medication regimen during the next episode of fever. The more conservative survival analysis, in which only the data on the length of time to the first recurrence of a febrile seizure were used, reduced the statistical power of the analysis considerably. Nonetheless, the intention-to-treat survival analysis still showed a reduction of one third in the two-year cumulative incidence of first recurrences of febrile seizures in the children given diazepam. The unadjusted comparison of the length of time to the first recurrent seizure in the two groups was not statistically significant ($P = 0.064$ by the log-rank test). After adjustment for covariates by Cox regression analysis, however, the intention-to-treat survival analysis showed a significant effect of diazepam ($P = 0.027$), with a 39 percent reduction in risk.

Oral diazepam, given only when fever is present, is an effective means of reducing the risk of recurrences of febrile seizures. Though side effects of diazepam were not infrequent, in no instance were they severe. Most moderate side effects (usually ataxia, lethargy, or irritability) were well tolerated, since most children needed to take the medicine for only two to three days. When the drug was taken longer (because of persistent fever), the adverse effects always lessened after the dose of the drug was reduced. Although we found no indication of adverse effects of long-term, intermittent use of diazepam, it will be important to be watchful for them in future longitudinal studies.

Do febrile seizures need to be prevented? We believe they do, because they are frightening events, because they result in substantial costs, and because any seizure — if generalized and severe — is potentially injurious to the brain. No therapy is perfect, but we believe that oral diazepam, taken only during episodes of fever, is now the optimal prophylactic medication. Diazepam is rapidly absorbed by mouth, has no serious side effects, and is effective in preventing recurrences of febrile seizures. The key to success is the prompt administration of diazepam as soon as the child becomes febrile. In the few children in whom a seizure is the first manifestation of fever, we recommend starting oral diazepam at the first sign of illness. Treatment with diazepam should continue if the child becomes febrile, and should stop after a day or two if no fever develops.

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