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Pediatrics 1998;102:e51

DOI: 10.1542/peds.102.5.e51

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/102/5/e51>

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Randomized, Controlled Trial of Ibuprofen Syrup Administered During Febrile Illnesses to Prevent Febrile Seizure Recurrences

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ABSTRACT. *Objectives.* Febrile seizures recur frequently. Factors increasing the risk of febrile seizure recurrence include young age at onset, family history of febrile seizures, previous recurrent febrile seizures, time lapse since previous seizure <6 months, relative low temperature at the initial seizure, multiple type initial seizure, and frequent febrile illnesses. Prevention of seizure recurrences serves two useful purposes: meeting parental fear of recurrent febrile seizures in general and reducing the (small) risk of a long-lasting and eventually injurious recurrent seizure. In daily practice, children with febrile seizures often are treated with antipyretics during fever to prevent febrile seizure recurrences. Thus far, no randomized placebo-controlled trial has been performed to assess the efficacy of intermittent antipyretic treatment in the prevention of seizure recurrence.

Methods. We performed a randomized, double-blind, placebo-controlled trial. Children 1 to 4 years of age who had had at least one risk factor for febrile seizure recurrence were enrolled. They were randomly assigned to either ibuprofen syrup, 20 mg/mL, 0.25 mL (= 5 mg) per kilogram of body weight per dose, or matching placebo, to be administered every 6 hours during fever (temperature, $\geq 38.5^{\circ}\text{C}$). Parents were instructed to take the child's rectal temperature immediately when the child seemed ill or feverish and to promptly administer the study medication when the temperature was $\geq 38.5^{\circ}\text{C}$. Doses were to be administered every 6 hours until the child was afebrile for 24 hours. The parents were instructed not to administer any other antipyretic drug to the child. For measuring rectal temperature, a Philips HP5316 digital thermometer (Philips, Eindhoven, The Netherlands) was distributed. During subsequent treatment of the fever episode, parents had to call the investigator at least once each day to notify the investigator in case of febrile seizure recurrence. The investigator could be contacted by parents 24 hours per day.

The primary outcome was the first recurrence of a febrile seizure. Kaplan-Meier curves and Cox regression were used for the statistical analysis. The treatment effect on the course of the temperature was assessed using analysis of covariance, with temperature at fever onset as covariate. Two analyses were performed. In an intention-to-treat analysis, all first recur-

rences were considered regardless of study medication compliance. A per-protocol analysis was limited to those recurrences that occurred in the context of study medication compliance.

Results. Between October 1, 1994, and April 1, 1996, 230 children were randomly assigned to ibuprofen syrup (111 children) or placebo (119 children). Median follow-up time was 1.04 years (25th–75th percentiles; 0.7–1.8 years) in the ibuprofen group and 0.98 years (0.7–1.6 years) in the placebo group. Of all children, 67 had a first febrile seizure recurrence, with 31 in the ibuprofen group and 36 in the placebo group. The 2-year recurrence probabilities were 32% and 39%, respectively. The recurrence risk in the ibuprofen group was 0.9 (95% confidence interval: 0.6–1.5) times the recurrence risk in the placebo group (intention to treat). Adjustment for baseline characteristics did not affect the risk-reduction estimate. Of the 67 recurrences, 30 occurred in the context of study medication compliance (13 ibuprofen, 17 placebo). The per-protocol analysis, which was limited to these events, showed similar results.

A significant reduction in temperature (0.7°C) after fever onset in the ibuprofen group compared with the placebo group was demonstrated if all 555 fever episodes were considered. In the fever episodes with a seizure recurrence, a similar temperature increase was shown in both groups, with no significant difference between the intention-to-treat and the per-protocol analysis.

Discussion. The present study failed to demonstrate a preventive effect of intermittent antipyretic treatment during fever on the number of febrile seizure recurrences in children at increased risk. The possibility that antipyretics can reduce recurrence has been addressed before. None of these studies were placebo-controlled trials with a standardized antipyretic treatment schedule; hence, the results were inconclusive.

Although it had been described previously that ibuprofen reduces fever safely and adequately in children with febrile seizures, which is confirmed by the present study, we found that fever was not reduced in those fever episodes in which a recurrence occurred. Factors that may have influenced these results are discussed.

Preventive treatment alternatives include primarily intermittent treatment with diazepam. Only children with a high recurrence risk may benefit from it. In a meta-analysis, its efficacy could not be demonstrated. The most important issue in treating children with febrile seizures is reducing parental anxiety by providing information about the excellent prognosis.

Conclusion. We found no evidence that ibuprofen administration during fever prevents febrile seizure recurrence. *Pediatrics* 1998;102(5). URL: <http://www.pediatrics.org/cgi/content/full/102/5/e51>; *child, febrile convulsions, recurrence, risk factors, ibuprofen, fever, comparative study, double blind method, survival analysis, proportional hazards model.*

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Received for publication Apr 8, 1998; accepted Jun 23, 1998.

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Febrile seizures are the most common type of seizures in childhood, with a cumulative incidence of 4%¹ and an average recurrence risk of 30% in 2 years. Factors increasing the risk of febrile seizure recurrences include young age at onset, family history of febrile seizures, previous recurrent febrile seizures, time lapse since previous seizure <6 months, temperature <40.0°C at initial febrile seizure, multiple type initial febrile seizure, and frequent febrile illnesses.²⁻⁸

In recent years, the prevention of recurrent febrile seizures has become a debatable issue; prevention may not be necessary because almost all febrile seizures are not injurious to the child.⁹⁻¹¹ However, prevention of seizure recurrences serves two useful purposes: meeting parental fear of recurrent febrile seizures in general^{12,13} and reducing the small risk of a long-lasting and eventually injurious recurrent seizure.⁹⁻¹¹

Intermittent treatment with diazepam during fever is associated with adverse effects and has not been proven efficacious to prevent febrile seizure recurrences.¹⁴ Intermittent treatment with antipyretic drugs is likely to be a rational alternative. Although children with febrile seizures often are treated with antipyretics in daily practice, until now, no proper evaluation of the efficacy of antipyretic treatment in comparison with placebo to prevent febrile seizure recurrences has been performed.¹⁵⁻¹⁷ The aim of this study is to assess the efficacy of ibuprofen to prevent febrile seizure recurrence in children at increased risk for recurrence.

PATIENTS AND METHODS

Patients

Children who were seen for febrile seizure at the Sophia Children's Hospital in Rotterdam and the Juliana Children's Hospital in The Hague, The Netherlands, between April 1, 1994, and April 1, 1996, were considered for inclusion in the study. These hospitals have pediatric emergency wards that are open 24 hours a day.

A febrile seizure was defined according to the National Institutes of Health consensus as "an event in infancy or childhood, associated with fever but without evidence of intracranial infection or defined cause."¹⁸ Criteria for inclusion were febrile seizure within the past 6 months, age between 1 and 4 years, and presence of one or more risk factors for febrile seizure recurrence. Risk factors were defined as a positive first-degree family history of febrile seizures; an initial febrile seizure of the multiple type; a temperature <40.0°C at the initial febrile seizure; and previous febrile seizure recurrence(s). All parents had to give written informed consent for their child's participation in the study. Criteria for exclusion were previous seizures without fever; known allergy for ibuprofen; current use of antiepileptic drugs; no telephone connection; non-Dutch- and non-English-speaking parents.

The study protocol was approved by the ethical review boards of both institutions.

Study Medication

Study medication consisted of either ibuprofen syrup, 20 mg/mL, 0.25 mL (= 5 mg) per kilogram of body weight per dose, or matching placebo, to be administered by the parents during fever. Parents were instructed to take the child's rectal temperature immediately when the child seemed ill or feverish and to administer study medication promptly when the temperature was $\geq 38.5^\circ\text{C}$. Each dose was to be administered every 6 hours until the child was afebrile for 24 hours. Parents were instructed not to administer any other antipyretic drug to their child.

According to a computer-generated randomization schedule, which was stratified by center, each child was assigned at study

entry to either the ibuprofen or the placebo arm of the study. Only the biostatistician and the hospital pharmacists knew the actual treatment allocation.

Procedures

Baseline characteristics, including demographic characteristics, characteristics of the initial seizure, and previous seizure recurrences, were recorded at study entry. Parents were instructed to record the precise timing of study medication administration and the degree of the temperature on a standardized patient form. For measuring rectal temperature, a Philips HP5316 digital thermometer (Philips, Eindhoven, The Netherlands) was distributed. On the first day of fever onset, the child visited the outpatient clinic for assessment of the clinical condition, rectal temperature, compliance to the study protocol, and registration of concomitant therapy. No laboratory tests were performed unless indicated by the child's clinical condition. Antibiotic treatment was prescribed, if necessary. During subsequent treatment of the fever episode, parents had to call the investigator at least once each day to notify the investigator in case of febrile seizure recurrence. The investigator could be contacted by the parents 24 hours per day. If no fever had been reported after 3 months, the investigator contacted the parents to verify participation and to check the occurrence of fever or febrile seizure recurrence. Also, parents were instructed every 3 months about the dose of study medication to be used to account for body weight gain.

Statistical Analysis

The outcome was the first recurrent febrile seizure. Follow-up time at risk for this event was considered ended at the planned date of study termination (ie, October 1, 1996) or when any seizure (ie, febrile or nonfebrile) had occurred, the patient had left the outpatient clinic follow-up, additional participation was refused, or any medical condition occurred that precluded use of study medication to treat a fever episode. The cumulative probability over time at risk of a first febrile seizure recurrence was estimated using the Kaplan-Meier method.¹⁹ The two study medication groups were compared using Cox proportional hazards analysis,²⁰ with study medication allocation as the only covariate. Risk reduction by ibuprofen relative to placebo with its 95% confidence interval (CI) was estimated from the Cox model. Next, Cox proportional hazards modeling was used to assess whether correction for differences in baseline characteristics between the two study medication groups influenced the result.

Two analyses were performed. In an intention-to-treat analysis, all first recurrent febrile seizures over the follow-up time at risk defined earlier were considered, regardless of study medication compliance by the child's parents. A per-protocol analysis was limited to those febrile seizure recurrences that occurred in the context of study medication compliance, defined as administration of study medication during an episode of fever according to the protocol before any febrile seizure recurrence had occurred. The definition of follow-up time at risk was the same in both analyses.

The treatment effect on the temperature at 6 (± 2) hours from fever onset was assessed using analysis of covariance, with temperature at fever onset as covariate.²¹ Analysis of covariance also was used to assess the difference between temperature at seizure recurrence and temperature at fever onset and to assess the treatment effect on the temperature at seizure recurrence. Calculations were performed using SPSS for Windows, version 6.0.²²

Power Calculation

The 2-year probability of seizure recurrence was assumed to be 40% in the placebo group. This relatively high figure was assumed because of the inclusion criterion of having at least one risk factor for febrile seizure recurrence. The required power was set at 80% ($\beta = 0.20$) to detect a halving of the recurrence risk by ibuprofen (hazard ratio, 0.5) with a type I error (α) of 0.05. Using the Egret Size package, the required sample size was found to be 220 (110 in each study medication group).²³

RESULTS

Study Population and Protocol Compliance

In total, 478 children were considered for inclusion. Between October 1, 1994, and April 1, 1996, 230

of these were randomized (Fig 1), 111 to the ibuprofen group and 119 to the placebo group to treat any fever episode that might occur. Baseline characteristics are given in Table 1. The median follow-up time was 1.04 years (25th–75th percentiles; 0.7–1.8 years) for ibuprofen and 0.98 years (0.7–1.6 years) for placebo.

Reasons for termination of follow-up are shown in Fig 2; 67 children had a first febrile seizure recurrence.

During follow-up, 555 fever episodes were reported in 194 children distributed as follows in the treatment groups: 94 children allocated to ibuprofen (85% of 111) had a total of 271 fever episodes; 100 children allocated to placebo (84% of 119) had a total of 284 fever episodes. Table 2 shows that in 377 (68%) of all 555 fever episodes, study medication was administered according to the protocol. Also, the reported use of concomitant medication is given.

In 67 children (ibuprofen group, 31; placebo group, 36) (Fig 2), a first recurrent febrile seizure occurred during a fever episode. In the intention-to-treat analysis, these 67 children were considered as having reached the outcome studied. Of these, 30 first febrile seizure recurrences occurred in the context of study medication compliance (13 ibuprofen, 17 placebo). The per-protocol analysis was limited to these events.

Effect of Ibuprofen on Febrile Seizure Recurrence

The cumulative probability over time of a first febrile seizure recurrence by treatment group as estimated by the Kaplan–Meier method based on intention-to-treat (ie, ibuprofen, 31 events; placebo, 36 events) is shown in Fig 3. The 2-year estimated re-

currence probability was 32% for ibuprofen and 39% for placebo ($P = .70$). The recurrence risk in the ibuprofen group was 0.9 times the recurrence risk in the placebo group (CI: 0.6–1.5). The risk reduction estimate was similar when the analysis was adjusted for baseline characteristics. A per-protocol analysis (ie, using the 13 events on ibuprofen and 17 on placebo for which study medication was used) showed similar results (risk reduction, 0.8; CI: 0.4–1.7).

Temperature

Table 3 shows that the median temperature at fever onset was similar in both treatment groups. A significant reduction of the temperature at 6 (± 2) hours after fever onset in the ibuprofen group compared with the placebo group was demonstrated, if all 555 fever episodes were considered (0.7°C , $P < .001$). In the fever episodes with a first febrile seizure recurrence, a temperature increase from fever onset until seizure recurrence was shown ($P < .001$); the increase was not significantly different in the ibuprofen group compared with the placebo group in neither the intention-to-treat analysis nor the per-protocol analysis (in both analyses, $P > .20$).

DISCUSSION

The present study failed to demonstrate a preventive effect of intermittent antipyretic treatment with ibuprofen during fever on the number of febrile seizure recurrences in children with an increased recurrence risk. The possibility of antipyretic treatment to reduce the risk of febrile seizure recurrence has been addressed before.^{15–17} Table 4 summarizes the characteristics of these studies. None were placebo-controlled trials with a standardized antipyretic treatment schedule; hence, it is difficult to draw conclusions from these studies with respect to the efficacy of antipyretic treatment to prevent febrile seizure recurrences. Because the present study is the first placebo-controlled trial of antipyretics to prevent febrile seizure recurrences, one cannot completely be convinced that ibuprofen does not make a difference. The results, however, indicate that it is unlikely that intermittent antipyretic treatment reduces the number of febrile seizure recurrences.

We considered ibuprofen to be a promising drug to reduce the risk of febrile seizure recurrence. Both ibuprofen and acetaminophen administered orally have shown to be safe and effective antipyretic drugs in children with fever.^{24–26} Because in these studies, children with febrile seizures were excluded, we assessed the antipyretic efficacy of ibuprofen syrup, 5 mg/kg per 6-hourly dose, versus acetaminophen syrup, 10 mg/kg per 6-hourly dose, during fever in children with febrile seizures in a previous study.²⁷ The results indicated that antipyretics administered orally reduce fever in children with febrile seizures safely. In the first hours after the initial dose, ibuprofen showed a stronger temperature-reducing effect compared with acetaminophen. We used a similar 6-hourly dose of ibuprofen of 5 mg/kg in the present study.

We confirmed the temperature-reducing effect of

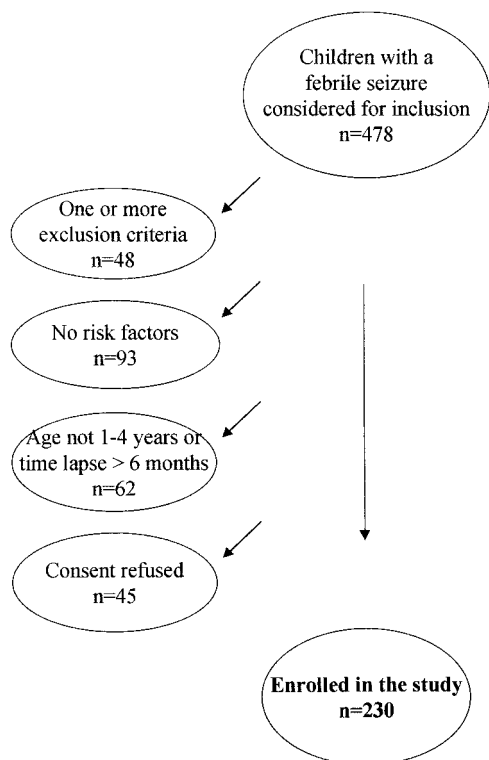


Fig 1. Recruitment of the study participants.

TABLE 1. Baseline Characteristics by Treatment Group

| | Ibuprofen <i>n</i> = 111 (100%) | Placebo <i>n</i> = 119 (100%) |
|--|------------------------------------|----------------------------------|
| Demographic characteristics | | |
| Female gender | 41 (37%) | 49 (41%) |
| Age at study entry ^a | 1.9 (1.4–2.4) | 1.9 (1.4–2.7) |
| First-degree family history of febrile seizures* | 27 (24%) | 32 (27%) |
| Family history of any seizures | 44 (40%) | 49 (41%) |
| Day-care attendance | 39 (35%) | 49 (41%) |
| First born | 70 (63%) | 59 (50%) |
| Caucasian origin | 67 (60%) | 78 (66%) |
| Immunization completed ^b | 85 (77%) | 88 (74%) |
| Initial seizure characteristics | | |
| Age at onset ^a | 1.4 (1.1–1.9) | 1.5 (1.0–2.1) |
| FSE ^c | 8 (7%) | 12 (10%) |
| Focal type ^d | 16 (14%) | 10 (8%) |
| Multiple type ^{e*} | 47 (42%) | 40 (34%) |
| Rectal temperature below 40.0°C* | 55 (50%) | 66 (56%) |
| Previous recurrent febrile seizures | | |
| Previous recurrent febrile seizures* | 39 (35%) | 45 (38%) |
| Time lapse between last seizure and study entry ^a | 0.10 (0.05–0.21) | 0.07 (0.04–0.18) |
| Number of risk factors | | |
| 1 | 66 (60%) | 66 (56%) |
| 2 | 33 (30%) | 44 (37%) |
| ≥3 | 12 (11%) | 9 (8%) |

^a In years, median (25th–75th percentiles).

^b According to the national guidelines for immunization in the Netherlands.

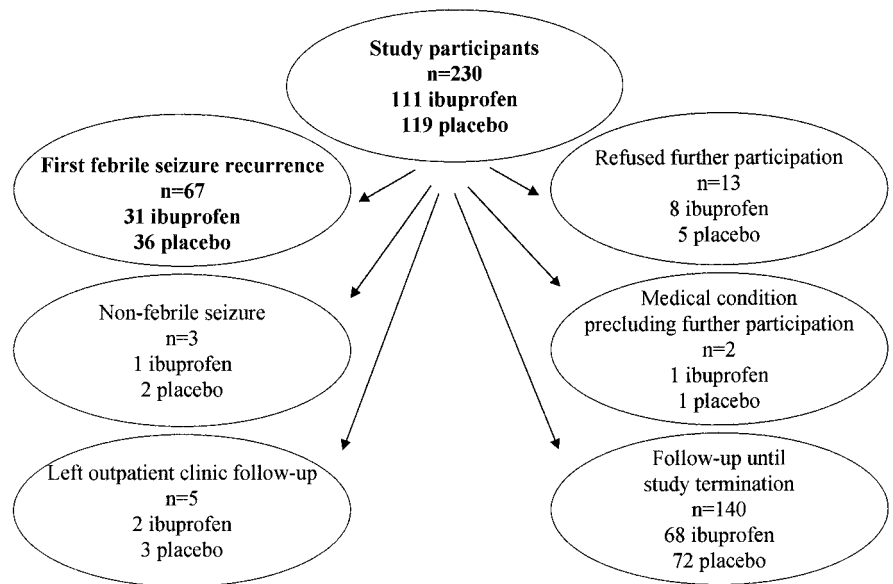
^c Febrile status epilepticus, seizure duration ≥30 min.

^d Focal onset of the seizure or postictal Todd's paresis.

^e Seizure recurrence within 24 hours.

* Risk factor for febrile seizure recurrence discussed in "Patients".

Fig 2. Events terminating follow-up time at risk (see "Methods," Statistical Analysis).



ibuprofen at 6 hours after administration of the first dose, when the second dose was to be administered. The temperature-lowering effect of ibuprofen could not be demonstrated in those fever episodes in which a recurrent febrile seizure occurred, in neither the intention-to-treat analysis nor the per-protocol analysis (Table 3). Some factors might have played a role in the reported inability of ibuprofen to reduce fever in those fever episodes.

The timing of temperature measurement was unfavorable to demonstrate the maximum antipyretic efficacy of ibuprofen; if the temperature had been measured earlier, we might have found a stronger antipyretic effect.²⁷ However, for the convenience of

the study participants and their parents, the temperature measurements were not taken more frequently than every 6 hours when the next dose of the study medication was administered. In addition, the parents may have taken the temperature under some stress because of their fear of a recurrent seizure, resulting in a less than optimal reliability of the measurements. Because this has probably occurred equally in the ibuprofen and the placebo groups, it is unlikely that the reported inability of ibuprofen to reduce fever in those fever episodes with a recurrence is attributable to unreliable measurements.

While discussing factors influencing both the inability of the present study to show fever reduction

TABLE 2. Compliance and Concomitant Medication Per Fever Episode by Treatment Group

| | Ibuprofen <i>n</i> = 271 (100%) | Placebo <i>n</i> = 284 (100%) |
|---|------------------------------------|----------------------------------|
| Fever episodes without febrile seizure recurrence | | |
| Fully compliant | 164 (61%) | 183 (64%) |
| Not fully compliant | | |
| Parents did not give the study medication and did not report fever promptly | 17 (6%) | 6 (2%) |
| Parents deviated from the prescribed dose: and gave additional acetaminophen and gave diazepam rectal solution ^a | 54 (20%) 4 (1%) 1 (<1%) | 56 (20%) 3 (1%) – |
| Fever episodes with febrile seizure recurrence | | |
| Fully compliant | 13 (5%) | 17 (6%) |
| Not fully compliant | | |
| Parents did not give the study medication, because fever was not recognized before the seizure occurred | 11 (4%) | 11 (4%) |
| Parents did not give the study medication for other reasons | 7 (3%) | 8 (3%) |

* Administered of the parents' own accord to prevent febrile seizure recurrence.

Note: Antibiotic treatment for suspected bacterial infection of the respiratory tract was prescribed for 8 children (1 in the ibuprofen group and 7 in the placebo group). Two children received continuous antibiotic prophylaxis because of preexisting vesicoureteral reflux (1 in the ibuprofen group vs 1 in the placebo group).

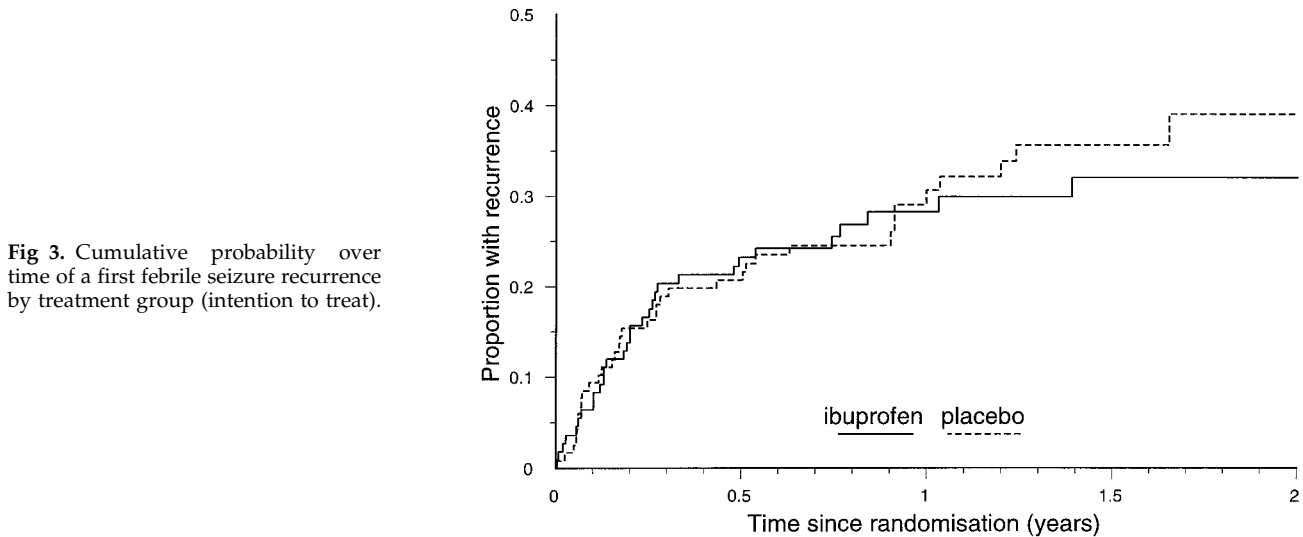


Fig 3. Cumulative probability over time of a first febrile seizure recurrence by treatment group (intention to treat).

TABLE 3. Temperature by Treatment Group

| | Ibuprofen Group | Placebo Group |
|-----------------------------------|------------------|------------------|
| All fever episodes | 271 | 284 |
| At fever onset | 39.1 (38.7–39.4) | 39.0 (38.7–39.3) |
| At 6 (±2) hours after fever onset | 38.2 (37.3–39.0) | 38.9 (38.2–39.3) |
| Fever episodes with recurrence | | |
| Intention-to-treat analysis | 31 | 36 |
| At fever onset | 39.0 (38.7–39.7) | 39.4 (38.8–39.7) |
| At febrile seizure recurrence | 39.9 (39.0–40.3) | 39.6 (39.1–40.0) |
| Per-protocol analysis | 13 | 17 |
| At fever onset | 39.0 (38.6–39.1) | 39.5 (38.7–39.8) |
| At febrile seizure recurrence | 40.1 (39.9–40.4) | 40.0 (39.4–40.3) |

Note: Median temperatures, Celsius (25th–75th percentiles).

and prevention of seizure recurrences by ibuprofen, parents' noncompliance to the study protocol and unreported additional use of antipyretics also should be addressed. Compliance was ensured by using a standardized patient form on which administration of the study medication had to be written down by the parents. We used no marker of medication nor performed measurement of ibuprofen and acetaminophen blood levels to assess the compliance. The analysis of the temperature measurements in the total study group showed a clinically relevant and

statistically significant temperature reduction in the ibuprofen group. Therefore, substantial compliance failures and unreported use of antipyretics are rather unlikely the cause of the inability of our study to show temperature reduction in those fever episodes in which a recurrence occurred and also are unlikely the cause of the inability of the study to show preventive efficacy on seizure recurrences.

If adequate reduction of fever prevents seizure recurrences, prevention may be possible only with the use of a much stronger temperature-reducing

TABLE 4. Previous Randomized Controlled Studies of Prevention of Febrile Seizure Recurrences, Including Antipyretic Treatment

| | Camfield, 1980 | Schnaiderman, 1993 | Uhari, 1995 |
|---|---|---|--|
| Treatment groups (number of children) | Single daily dose of phenobarbital per os 5 mg/kg plus antipyretic instruction of the parents ($n = 39$) versus antipyretic instruction including oral antipyretics only ($n = 40$) | Prophylaxis of acetaminophen orally 15–20 mg/kg per 4-hourly dose ($n = 53$) versus sporadic usage of acetaminophen of a similar oral dose contingent at fever $>37.9^{\circ}\text{C}$ ($n = 51$) | Diazepam 0.2 mg/kg 8-hourly during fever $>38.5^{\circ}\text{C}$ ($n = 81$), of which the first dose to be given rectally and additional doses per os, versus placebo ($n = 80$); additional: cross-over per fever episode with acetaminophen 10 mg/kg 6-hourly during fever $>40.0^{\circ}\text{C}$ (route of administration not reported) versus placebo |
| Temperature measurements | Oral and rectal measurements by the parents at home | Rectal measurements by nurses or parents during hospitalization | Measurements by the parents at home (oral or rectal) |
| Outcome measure | First febrile seizure recurrence in the same or following fever episodes | First febrile seizure recurrence in the same fever episode (multiple type) | Number of febrile seizure recurrences in any of the following fever episodes |
| Maximum study duration | 12 mo | Body temperature | Body temperature |
| Patient inclusion | Simple initial febrile seizure | One fever episode | 2 y |
| Major difficulties in the evaluation of the results | No standardization of the antipyretic treatment ^a No placebo control group of antipyretic treatment | No placebo control group of antipyretic treatment Noncomparable outcome measure | No standardization of the antipyretic treatment ^b |
| Results | 2 of the 39 patients using phenobarbital plus antipyretic instruction and 10 of the 40 patients with only instruction had a recurrent febrile seizure ^c | 4 of the 53 children using ongoing prophylaxis vs 5 of the 51 children in the sporadic-use group had a recurrent seizure in the same fever episode | 9 of the 173 fever episodes were associated with a recurrence in the acetaminophen group vs 14 of the 170 fever episodes in the placebo group ^d |
| Efficacy of antipyretic preventive treatment as concluded | Not effective | Not effective | Not effective |

^a All parents received instructions about fever control; no standardized dose per kilogram of bodyweight was administered.

^b All parents were allowed to administer extra antipyretics whenever they believed they should.

^c Survival analysis was performed to compare seizure recurrence in the phenobarbital-plus-instruction group and the instruction-only group ($P < .02$, log-rank).

^d Survival analysis was performed to compare seizure recurrence in the diazepam group and the placebo group ($P = .41$, log-rank).

agent, such as a higher dose of ibuprofen, or other temperature-reducing methods. For example, a dose of 10 mg of ibuprofen per kilogram might be administered, which is twice the dose we have used, and which has been recommended in children with high fever. It is unknown, however, whether stronger fever-reducing methods are able to lower the temperature in children with febrile seizures sufficiently to prevent febrile seizure recurrences.

In addition, specific conditions may affect the child's susceptibility to febrile seizure recurrence, such as conditions determined by the underlying cause of the feverish illness. The underlying cause of the fever either may be responsible for antipyretic treatment to fail in lowering the body temperature and therefore being ineffective to prevent seizure recurrences or may provoke a febrile seizure, regardless of resistance to any fever-reducing treatment.

In the present study, the per-protocol and the intention-to-treat analyses showed similar results. Thus, a strong preventive efficacy of ibuprofen is unlikely, even when it has been administered in compliance with the study protocol. Nevertheless, it should be made clear that even if ibuprofen had been effective, then recurrences would occur frequently before an upcoming feverish illness is recognized.

This is a problem inherent to any intermittent preventive treatment of febrile seizure recurrences, because it reduces the preventive efficacy. We found a recurrent febrile seizure the presenting sign of fever in 22 (33%) of all 67 recurrences (Table 2). Likewise, in a study comparing intermittent diazepam administered rectally during fever and no preventive treatment, the fever was not recognized previously in 7 (33%) of the 21 recurrences in the intermittent diazepam group.²⁸ In another study of oral intermittent diazepam versus placebo, the seizure was the first manifestation of fever in 42% (14/33) of all seizure recurrences.²⁹ In a study comparing diazepam with valproic acid, both administered rectally during fever only, there were no signals of an upcoming feverish illness in 31% (11/36) of all seizure recurrences.³⁰ In a study comparing oral diazepam with placebo during fever, 60% (68/113) of febrile seizure recurrences occurred without the child receiving the study medication, in part because the seizure was the first sign of illness.³¹

Until recently, children with recurrent febrile seizures were treated with continuous antiepileptic drugs to prevent further recurrences. Because of the severe negative side effects and the debatable efficacy, continuous antiepileptic treatment of children

with febrile seizures nowadays is considered obsolete in general, unless there are strong indications for its use.¹⁴ Accordingly, intermittent preventive treatment with diazepam during fever is associated with adverse effects and has not been proven effective in a meta-analysis¹⁴; only children with a high risk of febrile seizure recurrence may benefit from intermittent diazepam in an oral dose of 0.33 mg/kg administered every 8 hours during fever.³¹ The decision to prescribe it should be made in consultation with the parents because of its negative side effects, the necessity of regular medical check ups, and the difficulty of early recognition of a feverish illness. Negative consequences of focusing on prevention of seizure recurrence may entail an iatrogenous fear of the parents unwittingly encouraged by the pediatrician.³² Probably the most important issue in treating children with febrile seizures is to make efforts to reduce parental anxiety by providing information about the excellent prognosis for children with febrile seizures.^{9–11,33}

We conclude that there is no evidence supporting intermittent antipyretic treatment to prevent febrile seizure recurrences. Antipyretics may be given during a febrile illness, with the aim to make the child feel more comfortable. Consultation with the parents should emphasize the generally benign character of febrile seizures.

ACKNOWLEDGMENTS

This study was supported by a grant from the Sophia Foundation for Medical Research; a grant and supply of the study medication from Boots Pharmaceuticals, Hilversum, The Netherlands; and Philips HP5316 digital thermometers from Philips, Eindhoven, The Netherlands.

We thank the Emergency and Outpatient Clinic Department employees and the house staff of the pediatrics departments of Sophia Children's Hospital and Juliana Children's Hospital for their assistance with patient evaluation. We also thank M. Oftringa, MD, PhD, and A. van Esch, MD, PhD, for their contribution to the design of the study.

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Pediatrics 1998;102:e51

DOI: 10.1542/peds.102.5.e51

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