Antipyretic Agents for Preventing Recurrences of Febrile Seizures

Randomized Controlled Trial

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Objective: To evaluate the efficacy of different antipyretic agents and their highest recommended doses for preventing febrile seizures.

Design: Randomized, placebo-controlled, double-blind trial.

Setting: Five hospitals, each working as the only pediatric hospital in its region.

Participants: A total of 231 children who experienced their first febrile seizure between January 1, 1997, and December 31, 2003. The children were observed for 2 years.

Interventions: All febrile episodes during follow-up were treated first with either rectal diclofenac or placebo. After 8 hours, treatment was continued with oral ibuprofen, acetaminophen, or placebo.

Main Outcome Measure: Recurrence of febrile seizures.

Results: The children experienced 851 febrile episodes, and 89 of these included a febrile seizure. Febrile seizure recurrences occurred in 54 of the 231 children (23.4%). There were no significant differences between the groups in the main measure of effect, and the effect estimates were similar, as the rate was 23.4% (46 of 197) in those receiving antipyretic agents and 23.5% (8 of 34) in those receiving placebo (difference, 0.2; 95% confidence interval, −12.8 to 17.6; P= .99). Fever was significantly higher during the episodes with seizure than in those without seizure (39.7°C vs 38.9°C; difference, 0.7°C; 95% confidence interval, −0.9°C to −0.6°C; P< .001), and this phenomenon was independent of the medication given.

Conclusions: Antipyretic agents are ineffective for the prevention of recurrences of febrile seizures and for the lowering of body temperature in patients with a febrile episode that leads to a recurrent febrile seizure.

Trial Registration: clinicaltrials.gov Identifier: NCT00568217

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A FEbrILE SEIZURE IS A SEizure experienced in infancy or childhood that is associated with fever but with no evidence of intracranial infection, epilepsy, or any other defined cause for the seizure. It occurs in 3% to 5% of children aged 6 months to 6 years, and the recurrence rate is 20% to 30%. The most common cause of the fever is a viral infection. The number of febrile episodes, age, and family history of febrile seizures are significant risk factors for further occurrence of febrile seizures. Young age at the time of the first febrile seizure increases the risk of recurrence, but not after adjustment for the length of time at risk. Although frightening for the parents, febrile seizures in otherwise healthy children have no adverse long-term consequences.

The general assumption has been that fever is the key factor in the initiation of a febrile seizure, and it has, therefore, been supposed that the administration of antipyretic agents during febrile episodes will prevent seizures and their recurrences by the lowering of the fever. This has not proved to be the case in clinical trials, however. Antipyretic agents act mainly by the alteration of prostaglandin synthesis. It has been found in animal studies that some prostaglandins inhibit seizures (eg, prostaglandins D2, E1, and E2) and that some provoke seizures (eg, prostaglandin F2alpha). Elevated levels of prostaglandins E2 and F2alpha in the cerebrospinal fluid have been found to be associated with febrile seizures. Because antipyretic agents have different effects on prostaglandin synthesis, it may be that some would, in fact, provoke seizures.

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We wanted to compare certain antipyretic agents and their combinations to determine whether they could prevent recurrences of febrile seizures. Two prostaglandin inhibitors (diclofenac sodium and ibuprofen) were compared in view of their slightly different effects on prostaglandin synthesis, whereas acetaminophen was chosen because of its different mechanism compared with the prostaglandin inhibitors. In previous trials in which antipyretic agents had seemed to be ineffective, the doses of the drugs had been relatively low: ibuprofen, 5 mg/kg, was administered up to 4 times a day and acetaminophen, 10 mg/kg, up to 4 times a day. We chose maximal dosages for the present trial. To ensure rapid antipyresis, we decided to give the first drug, diclofenac, rectally.

**METHODS**

The effects of antipyretic agents for treating febrile seizures were evaluated in a placebo-controlled, double-blind, multicenter study. Patients who had experienced their first febrile seizure were recruited from 5 hospitals (Oulu, Satakunta, Central Finland, Päijät-Häme, and South-Carelian), each of which served in its area as the only pediatric hospital, between January 1, 1997, and December 31, 2003. The exclusion criteria were previous use of an anticonvulsant medication or a history of seizures of any type.

The main outcome was the recurrence of febrile seizures in the children allocated to the 3 oral treatment groups. Usually, 30.0% of children with febrile seizures will have a recurrence. We considered that a 20% absolute decrease in the rate of recurrent seizures would be clinically important, and we calculated that a total of 186 individuals (62 per group) would be required for a power of 80% and a type I error of 5%. The protocol was found to be ethically acceptable by the ethical committee of the University of Oulu Medical Faculty, and informed consent was obtained from the parents. To allow for the multiple comparison groups (placebo vs any of the antipyretic agents and placebo vs each of the antipyretic agents) and to obtain enough participants with febrile episodes (ie, at risk of recurring febrile seizures), we decided to accept up to 230 children into the trial.

Patients were randomly allocated first into 2 groups (rectal diclofenac vs placebo) and then into 3 groups (oral placebo vs acetaminophen vs ibuprofen) (Figure 1). The allocation sequence for rectal medications was generated by two of the authors (M.U. and H.R.) by the use of random-number tables. The allocation was performed as a block randomization with permuted blocks with a block size of 4. Rectal diclofenac was provided by Novartis Pharmaceuticals Corporation, Helsinki, Finland, and rectal placebo by the University Pharmacy, Helsinki, who labeled the drug containers in accordance with the random numbers. The allocation for oral mixtures of acetaminophen, ibuprofen, and placebo was performed in a similarly random fashion with a block size of 6 by Knoll Pharmaceuticals, Nottingham, England, who provided these drugs. Participants were observed for 2 years. Parents were instructed to measure the temperature of the child every time he or she had any signs of infection and to begin administration of the study medication immediately when the temperature was 38.0°C or higher.

Figure 1. Profile of the trial. Patients who dropped out of the follow-up were included in the analyses as long as information was available from them.
higher. Treatment was started with a placebo or diclofenac (1.5 mg/kg) suppository, and instructions were given for treatment to be continued after 8 hours with an oral mixture (placebo; acetaminophen, 15 mg/kg; or ibuprofen, 10 mg/kg, each in correspondence with 0.5 mL of liquid) up to 4 times a day for as long as the temperature remained greater than 38.0°C. The first antipyretic agent was given rectally to ensure rapid effect. If the temperature rose above 40.0°C, parents were allowed to give an extra dose of open-label acetaminophen. Parents were instructed not to use any external or other cooling measures. Febrile seizures were treated with diazepam rectoiles. All the episodes were recorded in detail by the parents by the use of a predesigned sheet that covered the symptoms experienced, the medications used, and the duration of the episode. Study nurses contacted the families by telephone at least once a month to ensure that we received information about every febrile event, to ascertain any medication given to the child, and to check the weight of the child. The dosage of the mixtures was increased after each kilogram of body weight gain. Parents were instructed to measure temperature at least twice a day (on awakening and at bedtime), during any episode of infection, and at the time of a seizure. Temperature measurements were not standardized and were performed either rectally or by the use of tympanic thermometry in accordance with the preference of each family. In a case of a nonfebrile seizure, the patient was excluded from any further follow-up. At the end of follow-up, an electroencephalogram and a neurological evaluation by a physician from the team were conducted, with the examining physician being unaware of the treatment given to the participants because all the follow-up visits were completed before the code was opened.

Differences between temperatures were compared by means of a 1-way analysis of variance and paired and unpaired t tests. Differences in the proportions of participants who experienced seizure recurrences between treatment groups were tested by the use of the standard normal deviate or binomial test.13 The effect of the type of the first febrile seizure on the number of recurrences was analyzed by the use of the χ² test. Time to the first recurrence in each treatment group was calculated, and the equality of the cumulative Kaplan-Meier survival functions across the groups was tested by the use of the log-rank test. The possible interaction between the first randomization and the oral treatment that followed was evaluated by analyzing the significance of the interaction term in the logistic regression analysis where recurrence was the end point. The data were analyzed by the use of a statistical software program (SPSS version 16.0.2; SPSS Inc, Chicago, Illinois). This study was approved by the ethics committee of the University of Oulu Medical Facility, Finland.

A total of 231 children, 95 girls and 136 boys aged 4 months to 4 years (mean, 1.7 years), were included in the trial; 63 children (27.3%) had experienced a complicated febrile seizure, and 27 of these had had more than 1 seizure episode during a 24-hour period when presenting with their index febrile seizure (Table). A further 31 of the 63 individuals had had a seizure lasting more than 15 minutes, and 15 children had had an asymmetrical seizure. Of the 231 participants, 181 completed the 2-year follow-up (Table and Figure 1). Those who dropped out of the follow-up prematurely were included in the analyses for as long as they participated in the trial because we used Kaplan-Meier analyses and, thus, we did not do any imputations for the dropouts (Table). Children who refused to participate and those who discontinued the study prematurely were not different from those who participated in the entire follow-up period. A total of 191 participants had 851 febrile episodes during follow-up, and there were 40 participants in whom no febrile episodes occurred. A total of 89 recurrent febrile seizures occurred in 54 of 231 participants (23.4%). One patient had as many as 7 recurrences. Febrile seizures recurred in 8 of 34 children (23.5%) who received placebo only and in 46 of 197 (23.4%) who received any of the antipyretic agents of the trial (difference, 0.2; 95% confidence interval [CI], −12.8 to 17.6; P = .99). For each febrile episode, recurrences of febrile seizures occurred in 7.4% of those in the placebo group and in 10.9% in the other groups. There were no significant differences between groups in the main measure of effect, and the effect estimates were similar. All the antipyretic agents were ineffective in the prevention of recurrences of febrile seizures (Figure 2 and Figure 3). The interaction term between the first randomization and the following oral treatment was not significant (P = .90).

The recurrence rate of febrile seizures did not differ between children whose initial febrile seizure was simple vs complex (P = .38). During the 2-year follow-up period, there were 23 complicated recurrences in 17 individuals, with the highest number in a single patient being 3. The recurrent seizures took place predominantly during the first 2 days of the febrile episode, and the mean duration of the seizures was 5.7 minutes. Seven partici-

| Table. Demographic Data of the 231 Children Allocated to Initially Receive Diclofenac or Placebo Suppositories and to Continue Treatment With Acetaminophen, Ibuprofen, or Placebo Oral Mixture |
|---|---|---|---|---|
| | Suppositories | Oral Mixture | |
| | Diclofenac (n=117) | Placebo (n=114) | Acetaminophen (n=77) | Ibuprofen (n=76) | Placebo (n=78) |
| Female sex, No. (%) | 51 (43.6) | 44 (38.6) | 26 (33.8) | 33 (43.4) | 36 (46.2) |
| Age, mean (range), y | 1.7 (0.4-3.9) | 1.6 (0.4-4.0) | 1.6 (0.4-3.0) | 1.8 (0.7-4.0) | 1.6 (0.6-3.8) |
| Type of first febrile seizure, No. | | | | | |
| Simple | 87 | 81 | 56 | 54 | 58 |
| Complex | 30 | 33 | 21 | 22 | 20 |
| Family history of febrile seizures, No. | 36 | 29 | 19 | 26 | 20 |
| Family history of epilepsy, No. | 4 | 5 | 5 | 2 | 2 |
| Highest temperature during the first seizure, mean (SD), °C | 39.8 (0.8) | 39.7 (0.7) | 39.7 (0.8) | 39.7 (0.7) | 39.8 (0.7) |
pants (5 in the diclofenac group and 2 in the placebo group) experienced their seizures during the 8 hours after receiving the rectal medication but before administration of the oral medication. Forty-seven of the 54 children (87.0%) with seizures had received their oral medication before the seizure. A total of 142 participants received extra antipyretic agents from their parents during febrile episodes because of a persistent high temperature despite use of the trial medication. The distribution of children who received extra antipyretic agents did not differ between study groups (54%-71%; \( P = .32 \)), but children with recurrences more often received extra antipyretic agents (51 of 54 [94.4%]) during their febrile episodes than those without recurrences (91 of 134 [67.9%]) (difference, 28; 95% CI, 16 to 37; \( P < .001 \)).

Two individuals were excluded from the trial because of an afebrile seizure and 1 because of the initiation of antiepileptic medication by her physician owing to epileptiform discharges in her electroencephalogram during follow-up. All of them had had a complicated first seizure.

The maximum temperature measured during a febrile episode was higher in those that led to a febrile seizure (39.7°C) than in those that did not (38.9°C; difference, 0.7°C; 95% CI, −0.9°C to −0.6°C; \( P < .001 \)) (Figure 4). All the antipyretic drugs were ineffective in the lowering of the temperature during an episode that led to a febrile seizure, and there were no significant differences between the treatment groups (Figure 4). On the other hand, all the antipyretic agents were effective in the lowering of the fever in episodes that did not lead to a febrile seizure (Figure 4).

The seizures started slightly earlier in the group whose medication was initiated with a suppository that contained diclofenac than in the placebo group (5 children in the diclofenac group and 2 in the placebo group experienced the seizure during the 8 hours after receiving the rectal medication but before administration of the oral medication), and the children in the diclofenac group had a slightly higher fever during the first day of the febrile episode that led to a febrile seizure (38.6°C for the placebo group and 39.0°C for the diclofenac group; difference, −0.4°C; 95% CI, −0.7°C to −0.1°C; \( P = .01 \)), but there were no differences between the oral medication groups. There were no differences between any of the groups in the maximum temperature during the whole febrile episode that led to a seizure or in the temperature measured at the time of the seizure (Figure 4). All the neurologic and electroencephalographic findings after follow-up were normal, and no adverse effects were reported.

**COMMENT**

We found that all the antipyretic agents tested were ineffective in the prevention of recurrent febrile seizures and in the lowering of the raised temperature during a febrile episode that led to a recurrent febrile seizure. The fever was significantly higher during episodes that led to a seizure regardless of the patient or the medication. Thus, we found no evidence that antipyretic agents could significantly reduce the risk of seizure recurrence, a finding that is in accordance with those of previous randomized trials.9,10 Also, antipyretic instruction, which includes the use of antipyretic agents (either aspirin or acetaminophen), and the sponge bathing of the child have been ineffective in the prevention of the recurrence of febrile seizures.16 Consequently, indications for the use of antipyretic agents should be the same for children with or without previous febrile seizures.

The 3 antipyretic agents used in this trial have different effects on prostaglandin synthesis. Ibuprofen is a more potent inhibitor of cyclooxygenase-1 than of cyclooxygenase-2, whereas diclofenac inhibits both enzymes.17 The exact mechanism of acetaminophen is not known, but it seems to act preferentially in the central nervous system, lowering prostaglandin \( E_2 \) levels during fever.18 Theoretically, the inhibition of different prostaglandins may have opposite effects on seizure recurrence, which may produce some dilutional bias in these results.

The sample size calculation was based on a consideration that a 20% absolute decrease in the rate of recurrent
seizures would be clinically important. These results do not exclude the possibility of a lesser effect that could be detected with a greater sample size. Participation in this study was relatively good, and the dropout rate was acceptable and similar in each treatment group (Figure 1). Parents were allowed to give their child an extra dose of open-label acetaminophen if his or her temperature rose above 40.0°C. This might cause some dilutional bias but, because the distribution of extra acetaminophen was comparable in each treatment group, we assert that this kind of bias does not materially affect the results.

It has been often stated that the fever in children prone to febrile seizures should be treated very early to prevent the seizures, although there is no evidence that a rapid rise in temperature provokes seizures.18 The present study indicates that early aggressive use of antipyretic agents does not prevent seizures because most of the children (87.0%) who had a recurrence had received their oral medication and all had received their rectal medication before the recurrent seizure. On the other hand, children with recurrences in the present study had received extra antipyretic agents more often than those without recurrences, which further indicates the ineffectiveness of antipyretic agents in the prevention of febrile seizures.

Previous studies have been criticized because of the relatively low doses of antipyretic agents used and the possibly slow onset of the effect of the drug because of oral administration.9,10 In addition, only one antipyretic drug was compared with the placebo in each trial. Herein, we used the highest recommended doses, administration was started rectally to ensure a rapid effect, and antipyretic agents with different mechanisms of action were used. Despite this, all the antipyretic agents were inefficient in the lowering of the fever in episodes that led to a seizure and in the prevention of the recurrence of febrile seizures. Rectal administration of the antipyretic agent did not improve efficacy because the temperatures of children during the first day of a febrile episode that led to a febrile seizure were, in fact, slightly higher in the group that received rectal diclofenac. Diclofenac suppositories were chosen for the initiation of therapy because they have been shown to produce a rapid and strong decrease of fever in children.19,20

All the antipyretic agents were, nevertheless, efficient in lowering the temperature during a febrile episode without a seizure (Figure 4). This, again, supports previous findings, as ibuprofen and acetaminophen have been found to be effective in lowering the temperature of patients with a history of febrile seizures when administered during febrile episodes without seizures.21 This allows us to speculate that the mechanism of fever is different in febrile episodes with vs without a seizure.

In conclusion, we found that antipyretic agents were ineffective in the prevention of the recurrence of febrile seizures and in the lowering of the fever during an episode that leads to a recurrent seizure. Because antipyretic agents are effective during a febrile episode that does not lead to a seizure, their use should not differ between patients with and without previous febrile seizures. Parents should be informed about the inefficacy of antipyretic agents during a febrile episode that leads to a febrile seizure and about the benign nature of febrile seizures themselves.

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Author Contributions: Dr Rantala had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Figure 4. Maximum fever measured during a febrile episode leading to a seizure in children with recurrences (A), during an episode that does not lead to a seizure in those with recurrences (B), and during an episode in those without seizure recurrences (C), in the oral antipyretic drug treatment groups. The horizontal bars denote means.
Study concept and design: Strengell, Uhari, Tarkka, Alen, and Rantala. Acquisition of data: Uhari, Tarkka, Uusimaa, Alen, Lautala, and Rantala. Analysis and interpretation of data: Strengell, Uhari, and Rantala. Drafting of the manuscript: Strengell, Uhari, Tarkka, Uusimaa, and Rantala. Critical revision of the manuscript for important intellectual content: Uhari, Alen, Lautala, and Rantala. Statistical analysis: Uhari and Rantala. Obtained funding: Uhari, Tarkka, Alen, and Rantala. Administrative, technical, or material support: Strengell, Uhari, Uusimaa, Alen, and Rantala. Study supervision: Uhari and Rantala.

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REFERENCES


Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Pediatrics and Adolescent Medicine will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2003. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archpediatrics.com.