Acetaminophen and Febrile Seizure Recurrences During the Same Fever Episode

Shinya Murata, MD, PhD,[a] Keisuke Okasora, MD, PhD,[a] Takuya Tanabe, MD, PhD,[b] Motoko Ogino, MD,[a] Satoshi Yamazaki, MD,[a] Chizu Oba, MD,[a] Kohsuke Syabana, MD,[c] Shouhei Nomura, MD, PhD,[a] Akihiko Shirasu, MD, PhD,[a] Keisuke Inoue, MD, PhD,[a] Mitsuru Kashiwagi, MD, PhD,[a] Hiroshi Tamai, MD, PhD[c]

abstract

OBJECTIVES: To confirm the safety of using acetaminophen for febrile seizures (FSs) and to assess its efficacy in preventing FS recurrence during the same fever episode.

METHODS: In this single-center, prospective, open, randomized controlled study, we included children and infants (age range: 6–60 months) with FSs who visited our hospital between May 1, 2015, and April 30, 2017. The effectiveness of acetaminophen was examined by comparing the recurrence rates of patients in whom rectal acetaminophen (10 mg/kg) was administered every 6 hours until 24 hours after the first convulsion (if the fever remained >38.0°C) to the rates of patients in whom no antipyretics were administered. No placebo was administered to controls. The primary outcome measure was FS recurrence during the same fever episode.

RESULTS: We evaluated 423 patients; of these, 219 were in the rectal acetaminophen group, and 204 were in the no antipyretics group. In the univariate analysis, the FS recurrence rate was significantly lower in the rectal acetaminophen group (9.1%) than in the no antipyretics group (23.5%; $P < .001$). Among the variables in the final multiple logistic regression analysis, rectal acetaminophen use was the largest contributor to the prevention of FS recurrence during the same fever episode (odds ratio: 5.6; 95% confidence interval: 2.3–13.3).

CONCLUSIONS: Acetaminophen is a safe antipyretic against FSs and has the potential to prevent FS recurrence during the same fever episode.

[a]Department of Pediatrics, Hirakata City Hospital, Hirakata, Osaka, Japan; [b]Department of Child Neurology, Tanabe Children's Clinic, Hirakata, Osaka, Japan; and [c]Department of Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan

Drs Murata, Okasora, and Tanabe conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Ogino, Yamasaki, Oba, Syabana, Nomura, Shirasu, and Inoue created the sampling and analysis protocols, supervised the data collection, were involved in the data interpretation and discussion, and critically reviewed and edited the manuscript; Drs Kashiwagi and Tamai were involved in the study design and data acquisition and contributed to the writing of the manuscript; and all authors approved the manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered with the UMIN Clinical Trials Registry (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000032366) (identifier UMIN000028272).

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Address correspondence to Shinya Murata, MD, PhD, Department of Pediatrics, Hirakata City Hospital, 2-14-1 Kinya-honmachi, Hirakata, Osaka 573-1013, Japan. E-mail: wildwind1980@live.jp

WHAT'S KNOWN ON THIS SUBJECT: Acetaminophen has long been thought to be ineffective for preventing febrile seizure recurrence both in the same and another fever episode(s).

WHAT THIS STUDY ADDS: The current study is the first randomized controlled trial to assess the ability of acetaminophen to prevent febrile seizure recurrence during the same fever episode with bivariate and multiple logistic regression analyses.

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Febrile seizures (FSs) are the most common type of seizure in childhood, with a cumulative incidence of 2% to 5%.[1–3] In Japan, FSs occur in 7% to 11%[4] of children, and the risk of recurrence is ~15% during the same febrile illness.[5] However, clear evidence is lacking in many issues related to FS, and appropriate medical treatment has not yet been understood. The relationship between antipyretics and FSs is one such issue. Indeed, some pediatricians in Japan still counsel families of children with FS that antipyretics will increase the risk of FS recurrence.[6] On the other hand, the appropriate use of antipyretics is considered effective in alleviating discomfort in the patient. Although FSs are usually benign, they can be frightening for parents and caregivers. Therefore, understanding the relationship between antipyretics and FSs is critical for ensuring proper treatment.

In clinical practice, the majority of pediatricians consider that FS recurrence during the same fever episode will not be increased by using acetaminophen, the most common antipyretic administered to infants and children. However, to the best of our knowledge, no researchers have determined whether antipyretics, particularly acetaminophen, significantly increase the incidence and recurrence of FSs. As such, our aim in this study was to assess whether acetaminophen reduces the recurrence of FSs during the same fever episode and to confirm the safety of administering acetaminophen to children with FSs.

METHODS

Study Design and Patient Population

This study was approved by the ethics committee at Hirakata City Hospital. All parents provided written informed consent for their child to participate in this prospective, open, randomized controlled trial. We did not use a placebo in this study. Children with FSs who visited the emergency department at Hirakata City Hospital between May 1, 2015, and April 30, 2017, were considered for inclusion in this study. Our hospital has pediatric emergency wards that are open 24 hours every day and accept many emergency cases. FS was defined according to the criteria of the Japanese Society of Child Neurology[7] as "a seizure accompanied by fever (body temperature ≥38.0°C), without central nervous system infection, that occurs in infants and children 6 through 60 months of age."

Patients who had already experienced 2 or more FSs during the current fever episode were excluded from the study. Patients with seizures lasting >15 minutes were considered to have status epilepticus and were excluded from the study. Patients with epilepsy, chromosomal abnormalities, inborn errors of metabolism, brain tumor, intracranial hemorrhage, hydrocephalus, or a history of intracranial surgery were also excluded. Patients who had been administered diazepam suppository to prevent FSs and patients whose parents requested the use of diazepam suppository were excluded. Patients who had taken antihistamines were also excluded because antihistamines may increase seizure susceptibility in patients with FSs.[8–10]

Study Medication

Patients with FSs were randomly allocated to 2 groups, namely the rectal acetaminophen group and no antipyretics group. The allocation sequence was generated by 2 of the authors using random-number tables. The dose of rectal acetaminophen was set to be 10 mg/kg because most pediatricians in Japan prescribe acetaminophen at this dose. Patients in the rectal acetaminophen group were immediately administered an acetaminophen suppository (10 mg/kg) by a pediatrician within the emergency department. The parents were then instructed to administer an acetaminophen suppository (10 mg/kg) every 6 hours until 24 hours after the onset of the FS, if the fever remained >38.0°C. Parents in the no antipyretics group were instructed not to administer any antipyretics to their child for 24 hours after the FS. As mentioned earlier, no placebo was used.

Procedure

Baseline characteristics, including age, sex, past history of FSs, history of FSs in a first-degree relative, duration between onset of fever (>38.0°C) and initial FS, duration of seizure, body temperature on first arrival at our hospital, and laboratory data (white blood cell counts, hemoglobin, hematocrit, and platelet counts as well as the C-reactive protein, creatinine, albumin, sodium, potassium, chloride, and blood sugar levels) on first arrival at our hospital were recorded at study entry. Blood samples were collected from each patient before the administration of acetaminophen on arrival. Parents were instructed to bring the children back to our hospital immediately if the FSs recurred. Parents were also instructed to record the number of acetaminophen administrations and to send us this information on a postcard after the fever resolved. If we did not receive the postcard, an investigator contacted the parents to obtain the required information. We also checked adherence to the study protocol through the postcards and telephone interviews.

Patients With Diarrhea

Patients with diarrhea were excluded from random assignment because of difficulty in administering the suppositories. In addition, some of these patients were considered to be better categorized into other clinical entities such as convulsions with

mild gastroenteritis (CwG).[11] For patients with diarrhea, we checked the seizure recurrence rate during the same fever episode and compared it with the rate from patients without diarrhea who were included in our randomized trial.

Statistical Analysis

We used JMP version 13 software (SAS Institute, Inc, Cary, NC) for the statistical analyses. Statistical significance was set at $P < .05$. The primary outcome was seizure recurrence during the same fever episode. We estimated the sample size for the multiple logistic regression analysis using standard methods; at least 10 cases were presumed to be necessary for each independent variable. As the FS recurrence rate within the same fever episode was estimated to be 15%,[5] 400 children with FSs were required to perform a multiple logistic regression analysis with 5 independent variables.

Patients' characteristics and laboratory data were compared between the rectal acetaminophen and no antipyretics groups. We stratified the patient characteristics and laboratory data by age (6–21 and 22–60 months). Continuous variables were compared by using Mann–Whitney *U* test. Binary variables were compared by using Pearson's χ^2 test.

We first conducted bivariate analyses and then used a multiple logistic regression analysis to identify the factors that contributed to the decrease in FS recurrence within the same fever episode. Bivariate analyses were performed by comparing the patient characteristics and laboratory data according to the presence or absence of FS recurrence during the same fever episode. Continuous variables were compared by using Mann–Whitney *U* test. Binary variables were compared by using Pearson's χ^2 test. Thereafter, in consideration of potential interactions, a multiple logistic regression analysis was performed with all variables showing $P < .05$ in the bivariate analysis. We determined the final multivariate logistic regression model by hierarchical background elimination. We also assessed the linearity of variables in the final multivariate logistic regression model to verify the validity of the model using the statistical software *R* (version 3.2.5).

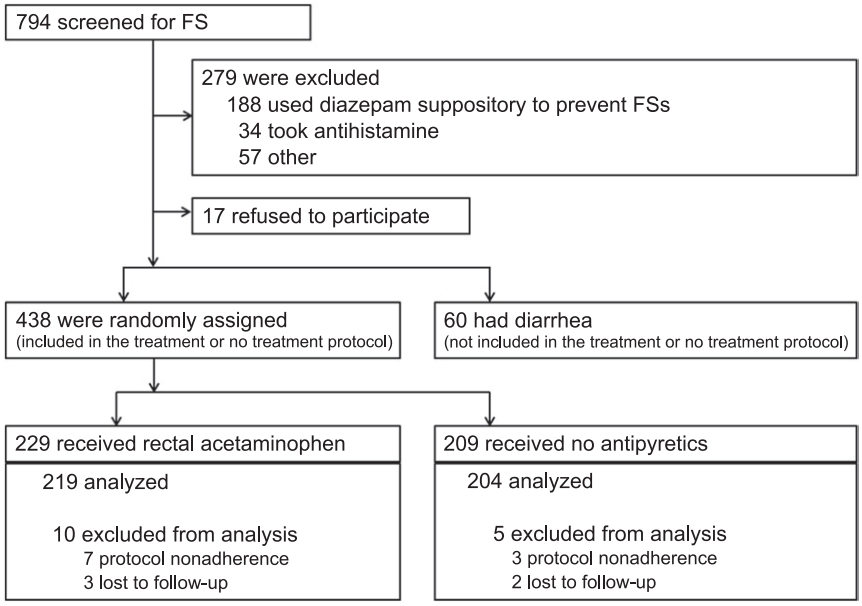

FIGURE 1
Study enrollment.

RESULTS

Patient Characteristics

During the study period, a total of 794 children visited our hospital for FSs. Of these, 279 children were excluded (188 who used diazepam suppository to prevent FSs, 34 who had taken antihistamines, and 57 others), and the parents of another 17 children declined to participate in this study. Sixty children with diarrhea were not included in the study protocol. Therefore, 438 patients were allocated to 1 of the following 2 groups: the rectal acetaminophen group (229 children) and the no antipyretics group (209 children). Ten patients in the rectal acetaminophen group and 5 patients in the no antipyretics group were excluded from the analysis because of nonadherence to the protocol or loss to follow-up. Finally, the data from 423 patients, 219 in the rectal acetaminophen group and 204 in the no antipyretics group, were analyzed (Fig 1). None of the patients used diazepam suppositories during the study period.

No significant differences in the patient characteristics or laboratory data were identified between the rectal acetaminophen and no antipyretics groups, regardless of stratification by age (6–21, 22–60 months, and all patients). The rate of FS recurrence during the same fever episode was 16.0% (68 out of 423 patients). All FS recurrences occurred within 24 hours after the initial FS. The rate of FS recurrence during the same fever episode was significantly lower in the rectal acetaminophen group than in the no antipyretics group for all age groups (Table 1). When including all patients regardless of age, the recurrence rate was 9.1% in the rectal acetaminophen group and 23.5% in the no antipyretics group ($P < .001$).

TABLE 1 Patient Characteristics, Recurrence of FSs, and Laboratory Data

	All Patients		Age 6–21 mo		Age 22–60 mo	
	Rectal Acetaminophen, *n* = 219	No Antipyretics, *n* = 204	Rectal Acetaminophen, *n* = 121	No Antipyretics, *n* = 111	Rectal Acetaminophen, *n* = 98	No Antipyretics, *n* = 93
Age in mo, median (IQR)	20 (16–31)	21 (16–30)	17 (13–19)	16 (13–19)	33 (26–44)	31 (25–42.5)
Sex, *n*						
Male	118	111	55	56	63	55
Female	101	93	66	55	35	38
Past history of FS, *n*						
Yes	57	55	27	14	30	41
No	162	149	94	97	68	52
Familial history of FS, *n*						
Yes	54	43	31	20	23	23
No	165	161	90	91	75	70
Interval between fever and FS in h, median (IQR)	9 (3.5–17.3)	7.5 (2.5–17.4)	11 (4–24)	9 (2.5–19)	7 (3–13)	6 (2.8–13)
Duration of seizure in min, median (IQR)	3 (1–4)	3 (1–5)	3 (2–5)	3 (1–5)	2 (1–4)	2 (1–5)
BT on arrival in °C, median (IQR)	39.7 (39.1–40.1)	39.5 (39.1–39.9)	39.7 (39.3–40.2)	39.4 (38.8–40.0)	39.5 (38.7–40.0)	39.4 (38.9–39.9)
Recurrence of FS, *n* (%)	20 yes, 199 no (9.1)	48 yes, 156 no (23.5)	16 yes, 105 no (13.2)	27 yes, 84 no (24.3)	4 yes, 94 no (4.1)	21 yes, 72 no (22.6)
Laboratory data						
WBC count per μL, median (IQR)	10 990 (8400–14 930)	11 390 (8460–16 370)	10 440 (7750–13 680)	11 330 (8450–17 500)	11 910 (8730–15 960)	11 560 (8310–15 330)
Hemoglobin, g/dL, median (IQR)	12.1 (11.5–12.5)	12.0 (11.4–12.5)	11.9 (11.3–12.4)	11.7 (11.2–12.4)	12.3 (11.8–12.7)	12.3 (11.7–12.7)
Hematocrit, %, median (IQR)	35.2 (33.9–36.5)	35.1 (33.7–36.6)	34.9 (33.9–36.4)	34.5 (33.1–35.9)	35.6 (34.4–36.8)	35.9 (34.4–37.4)
PLT, $\times 10^4/\mu L$, median (IQR)	27.7 (23.0–35.7)	29.5 (23.5–34.5)	29.2 (22.7–36.8)	29.7 (23.6–35.4)	27.2 (23.6–32.3)	27.8 (23.1–32.8)
C-reactive protein, mg/dL, median (IQR)	0.5 (0.2–1.2)	0.5 (0.2–1.1)	0.4 (0.2–1.2)	0.5 (0.2–1.1)	0.6 (0.3–1.2)	0.5 (0.1–1.4)
Creatinine, mg/dL, median (IQR)	0.27 (0.24–0.30)	0.27 (0.24–0.30)	0.26 (0.23–0.29)	0.26 (0.23–0.28)	0.29 (0.25–0.34)	0.29 (0.26–0.33)
Albumin, g/dL, median (IQR)	4.4 (4.2–4.6)	4.4 (4.2–4.6)	4.3 (4.1–4.5)	4.4 (4.1–4.5)	4.5 (4.3–4.6)	4.4 (4.2–4.6)
Sodium, mEq/L, median (IQR)	136 (134–137)	136 (134–137)	136 (134–137)	136 (134–137)	136 (135–138)	136 (135–137)
Potassium, mEq/L, median (IQR)	4.1 (3.9–4.4)	4.1 (3.9–4.4)	4.2 (4.0–4.4)	4.3 (4.0–4.4)	4.0 (3.7–4.29)	4 (3.8–4.2)
Chloride, mEq/L, median (IQR)	101 (100–102)	101 (99–103)	101 (100–103)	101 (100–103)	101 (99–102)	101 (99–102)
Blood sugar, mg/dL, median (IQR)	120 (107–135)	116 (107–130)	118 (106–136)	117 (108–132)	121 (109–134)	115 (106–129)

BT, body temperature; IQR, interquartile range; PLT, platelet count; WBC, white blood cell.

In children 6 to 21 months of age, the recurrence rate was 13.2% in the rectal acetaminophen group and 24.3% in the no antipyretics group ($P = .0297$). In children 22 to 60 months of age, the recurrence rate was 4.1% in the rectal acetaminophen group and 22.6% in the no antipyretics group ($P < .001$).

No serious complications related to acetaminophen, such as hypotension, hypothermia, or anaphylaxis, were observed. None of the patients who experienced FS recurrence showed neurologic sequelae.

Bivariate Analyses

In the bivariate analyses, we identified significant relationships between FS seizure recurrence and rectal acetaminophen use, age, and duration of seizure (Supplemental Table 3). Age was significantly lower and the duration of seizure was significantly shorter in children with versus without FS recurrence ($P < .05$ for both). We found that 29% and 56% of patients with and without FS recurrence, respectively, used rectal acetaminophen ($P < .001$).

Multiple Logistic Regression Analysis

A multiple logistic regression analysis was performed with the following 3 variables, which showed significant differences in the bivariate analyses, with consideration of interactions: rectal acetaminophen use, age, and duration of seizure. We selected the variables for the final multivariate logistic

regression model using hierarchical background elimination starting from the following 6 variables: rectal acetaminophen use, age, duration of seizure, rectal acetaminophen use and age, rectal acetaminophen use and duration of seizure, and age and duration of seizure. As a result of this selection, the 4 variables of rectal acetaminophen use, age, duration of seizure, and rectal acetaminophen use and age were retained. The continuous variables, namely duration of convulsion as well as age, satisfied the criteria for linearity. We reanalyzed the final model with the 4 variables of rectal acetaminophen use, age, duration of seizure, and rectal acetaminophen use and age using a multivariate logistic regression test (Table 2). All 4 variables were independently and significantly associated with FS recurrence. Among these variables, rectal acetaminophen use had the highest odds ratio of 5.6 (95% confidence interval: 2.3–13.3).

TABLE 2 Multiple Logistic Regression Analysis

	Odds Ratio (95% Confidence Interval)	*P*
Rectal acetaminophen		
Yes	Reference	<.001
No	5.6 (2.3–13.3)	—
Age, mo		
1 mo decrement	1.08 (1.03–1.11)	<.001
Duration of seizure, min		
1 min decrement	1.15 (0.99–1.32)	.0481
Rectal acetaminophen and age	—	.0026

—, not applicable.

Patients With Diarrhea

The FS recurrence rate during the same fever episode was 35% in the 60 children with diarrhea, which was significantly higher than the rates in the rectal acetaminophen group and no antipyretics group (Supplemental Fig 2).

DISCUSSION

This is the first randomized controlled trial to indicate that acetaminophen could prevent the recurrence of FSs during the same fever episode. In this study, the FS recurrence rate was significantly lower in the rectal acetaminophen group than in the no antipyretics group. In our multiple logistic regression analysis it was suggested that, among the variables in the final model, rectal acetaminophen was the largest contributor to the prevention of FS recurrence during the same fever episode. The multiple logistic regression analysis also revealed that a younger age and shorter duration of seizure were associated with higher FS recurrence rates during the same fever episode.

In our comparison of the recurrence rates between the rectal acetaminophen and no antipyretics groups, it was demonstrated that acetaminophen has the potential to prevent FS recurrence during the same fever episode. This is in contrast to the findings of Schnaiderman et al[12] who examined the effectiveness of acetaminophen during the same febrile illness by comparing the FS recurrence rates between a regular usage group (4-hour intervals; $n = 53$) and a sporadic usage group ($n = 51$; sporadic use contingent on a body temperature >37.9°C) in 104 children presenting with simple FS. In that study, 4 children in the regular usage group (7.5%) and 4 children in the sporadic usage group (7.8%) experienced a second FS. The authors concluded that the prophylactic administration of acetaminophen in children with FS was ineffective for preventing FS recurrence given the lack of a significant difference in the FS recurrence rate between the 2 groups, although a larger amount of acetaminophen was administered to the regular usage group. The different findings between our study and the study by Schnaiderman et al[12] can be explained by the inclusion of different control groups; whereas no antipyretics were used in our study, the study by Schnaiderman et al[12] permitted the sporadic use of antipyretics. Therefore, the effectiveness of acetaminophen was likely underestimated in the previous study.

The results of the current study support that acetaminophen can effectively prevent FS recurrence within the same fever episode, despite the fact that acetaminophen has long been considered ineffective for preventing FS recurrence both in the same and different fever episode(s). Indeed, in the randomized controlled trials performed by Uhari et al[13] and Strengell et al[14] to evaluate the effectiveness of acetaminophen during separate fever episodes, no significant differences in the FS recurrence rates were observed between the acetaminophen and placebo groups in either trial. In addition, Rosenbloom et al[15] concluded that acetaminophen was ineffective for preventing FS recurrence in a meta-analysis of these randomized controlled trials.[13,14] As such, our data should be interpreted with caution, particularly because the included patients were children who visited our hospital after FS had already occurred. Therefore, in the current study, we could not determine the preventive effects of acetaminophen in children who had not yet had a FS during a fever episode.

There may be several explanations of the mechanisms by which acetaminophen reduces the recurrence of FS. First, acetaminophen may reduce FS

recurrence by lowering body temperature. However, in the current study, no significant difference in body temperature was observed 2 hours after the first acetaminophen administration between children with and without FS recurrence. That said, the monitoring of body temperature was insufficient in our study; thus, the difference in body temperature during the study period was unclear. Additional studies in which researchers use close or continuous monitoring of body temperature are necessary to elucidate the relationship between FS recurrence and the antipyretic effects of acetaminophen. Second, acetaminophen may reduce FS recurrence through effects other than antipyretic effects, although these effects currently remain unknown. An extensive exploration of biomarkers such as metabolites and humoral factors may be useful in solving this problem. Comparisons between acetaminophen and other antipyretics such as ibuprofen may also help to clarify the association between FS recurrence and the nonantipyretic effects of acetaminophen.

In our study, patients with diarrhea were excluded from the randomized controlled trial because we considered that such patients were not suitable for direct comparison with children with FSs without diarrhea. First, suppositories may be difficult to use in children with diarrhea because they stimulate defecation. Second, some of these patients met the criteria for CwG,[11,16,17] which is characterized by frequent seizure clusters. CwG was first described in Japan in 1982[16] and is now recognized worldwide as a distinct clinical entity. CwG is characterized by the following features: (1) clustered seizures occurring within 24 to 48 hours as the most distinctive clinical feature, (2) occurrence in previously healthy 6-month- to 3-year-old infants and children, (3) at least 1 convulsive episode occurring at 38°C or less, (4) association with mild gastroenteritis, and (5) good prognosis.[18–24] The rate of seizure recurrence was significantly higher in children with diarrhea than in those without diarrhea. Therefore, seizures with pyrexia associated with diarrhea are presumed to have strong susceptibility to seizure recurrence. Exclusion of children with diarrhea from randomized trial may have resulted in reduction of FS recurrence in our study. This may be related to the difference in the efficacy of acetaminophen from that in previous studies. Further investigation of FS in children with diarrhea is necessary.

Our study has some limitations. First, as mentioned above, the information on body temperature was insufficient because close monitoring of body temperature was not performed in our study; thus, evaluating the exact antipyretic effects of acetaminophen was difficult. Second, patients who used diazepam suppositories were excluded from the study. In clinical settings, clinicians occasionally use both diazepam and antipyretics. Therefore, the combined effects of diazepam and acetaminophen should be assessed in future studies. Finally, the causative pathogens and origins of fever were not considered in our study. Because it is possible that the rate of FS recurrence is influenced by these factors, future researchers investigating the effects of acetaminophen should consider the causative pathogens and origins of fever.

CONCLUSIONS

In our study, it was shown that acetaminophen may reduce the recurrence of FSs during the same fever episode and thus can be considered safe for use in children with FSs. Nevertheless, the constant use of acetaminophen in children with FSs is not recommended because the outcome of FS is usually favorable. The most important aspect of clinical practice against FS is providing appropriate explanations to parents to relieve anxiety and to ensure appropriate use of acetaminophen on the basis of the individual conditions.

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ABBREVIATIONS

CwG: convulsions with mild gastroenteritis
FS: febrile seizure

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