

Antipyretic Treatment in Young Children With Fever

Acetaminophen, Ibuprofen, or Both Alternating in a Randomized, Double-blind Study

E. Michael Sarrell, MD; Eliahu Wielunsky, MD; Herman Avner Cohen, MD

Objective: To compare the antipyretic benefit of acetaminophen or ibuprofen monotherapy with an alternating regimen of both drugs in young children aged 6 to 36 months.

Design: Randomized, double-blind, parallel-group trial.

Setting: Three primary pediatric community ambulatory centers in central Israel.

Participants: A total of 464 children aged 6 to 36 months with fever.

Intervention: Infants were assigned to receive either acetaminophen (12.5 mg/kg per dose every 6 hours) (n=154) or ibuprofen (5 mg/kg per dose every 8 hours) (n=155) or to receive alternating acetaminophen and ibuprofen (every 4 hours) (n=155) for 3 days after a loading dose.

Main Outcome Measures: Temperature, stress score, amount of antipyretic received, total days that the in-

fant or caregiver was absent from day care or work, respectively, at the 3-day time point, recurrence of fever, and number of emergency department visits.

Results: The group given the alternating regimen was characterized by a lower mean temperature, more rapid reduction of fever, receiving less antipyretic medication, less stress, and less absenteeism from day care as compared with the other groups; all of the differences were statistically significant ($P < .001$). None of the regimens were associated with a significantly higher number of emergency department visits ($P = .65$) or serious long-term complications ($P = .66$). The drug used for initial loading had no effect on outcome in any of the groups.

Conclusions: An alternating treatment regimen of acetaminophen (12.5 mg/kg per dose) and ibuprofen (5 mg/kg per dose) every 4 hours for 3 days, regardless of the initial loading medication, is more effective than monotherapy in lowering fever in infants and children.

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Author Affiliations: Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Drs Sarrell, Wielunsky, and Cohen); and Pediatric Ambulatory Center General Health Services (Drs Sarrell and Cohen) and Schneider Children's Medical Center of Israel (Dr Wielunsky), Petah Tiqva, Israel.

FEVER IS ONE OF THE MOST common presenting signs of illness in office-based primary care pediatric practice, accounting for 19% to 30% of visits.^{1,2} Infants and young children are particularly susceptible to fever because of their small body size, high ratio of body surface area to weight, and low amount of subcutaneous fat. Although most experts consider fever a beneficial physiologic response to the infectious process, it can lead to patient irritability and stress as well as high parental anxiety.³ Therefore, physicians usually prefer to prescribe antipyretic agents in addition to nonpharmacologic, physical fever-reducing modalities.⁴

Acetaminophen (paracetamol in Israel) is very widely used as an antipyretic owing to its high efficacy and good safety profile.⁵ Acetaminophen is a para-aminophenol derivative that inhibits cyclooxygenase, thereby inhibiting the formation and release of prostaglandins. It is absorbed in the gastrointestinal tract, reaching peak plasma

concentrations within 30 minutes. The time to maximal temperature reduction is approximately 2 hours.^{6,7} The recommended dose of acetaminophen is 12 to 15 mg/kg every 6 hours.

Ibuprofen is a propionic acid derivative that, like acetaminophen, inhibits the biosynthesis of prostaglandins. It, too, is absorbed in the gastrointestinal tract, reaching peak plasma concentrations in 1 hour; the maximal temperature reduction peaks within 3 hours. The recommended dose is 5 to 10 mg/kg every 8 hours.^{8,9}

Both antipyretics have been found to be equally safe in children. There are occasional descriptions of gastrointestinal bleeding or renal failure in adults using ibuprofen and of acetaminophen toxic effects in children and adults.¹⁰

Studies have reported that 50% or more of parents or caregivers give their children both antipyretics, but their method of alternation varies.¹¹ Furthermore, in about half of the cases, the dosage used is inaccurate.¹²

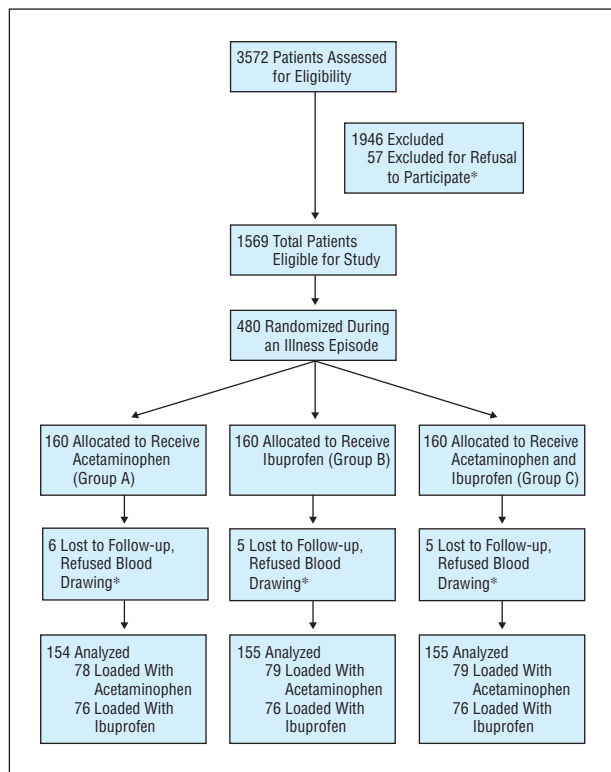


Figure. Flow of participants throughout the trial. Asterisk indicates that all of the children who were withdrawn from the study continued to attend the same practices.

The aim of the present study was to compare the clinical effectiveness of acetaminophen and ibuprofen alone with an alternating regimen in reducing fever and stress signs in infants and young children.

METHODS

SETTING

The study was approved by the local institutional human rights committee. It was conducted between September 15, 2003, and March 15, 2004, at 3 primary pediatric community centers, 2 urban and 1 rural, in central Israel.

PATIENTS

The sample included all consecutive children aged 6 to 36 months who had a rectal temperature of at least 38.4°C. Children who were not attending day care centers or had taken any temperature-altering drugs or antibiotics within 10 days before presentation were excluded, as were children with known abnormal liver or renal laboratory values, children with medical history of any of the following: renal or hepatic impairment, gastrointestinal bleeding, known allergy to any antipyretic, congenital or acquired immunodeficiency, Reye syndrome, asthma, bronchiolitis, or malignancy, and children whose caregivers were unable to apply the Noncommunicating Children's Pain Checklist (NCCPC) to measure stress.

DESIGN

Informed consent to participate in the study was obtained from a parent or guardian by the admitting physician (**Figure**). There-

after, the same physician recorded the patient's background data (demographics, medical history, previous diagnosis, use of other medications, and smoking in the home). Then, the admitting nurse used a computerized random-number generator to stratify according to the center in blocks of 60 numbers so that each block comprised 20 patients randomly assigned to each treatment group, with 10 patients assigned to each loading medication. The admitting nurse also weighed the patient and obtained the initial laboratory findings along with the child's temperature (admission fever) and level of distress according to the NCCPC stress test (admission NCCPC score). She then handed the parent or guardian a sealed opaque folder holding 3 sealed envelopes: 1 containing an advice sheet explaining the physiology of fever and its nonpharmacologic management; 1 containing the prescription for the loading medication (marked "initial medication"); and 1 containing the drug prescription (marked "home prescription"), according to the assigned group and subgroup as follows:

1. Group A received acetaminophen (12.5 mg/kg per dose every 6 hours; maximum, 50 mg/kg per day). One half of the group received initial loading with acetaminophen (25 mg/kg), and the other half received initial loading with ibuprofen (10 mg/kg).
2. Group B received ibuprofen (5 mg/kg per dose every 8 hours; maximum, 20 mg/kg per day). One half of the group received initial loading with acetaminophen (25 mg/kg), and the other half received initial loading with ibuprofen (10 mg/kg).
3. Group C received acetaminophen (12.5 mg/kg per dose; maximum, 50 mg/kg per day) alternating with ibuprofen (5 mg/kg per dose; maximum, 20 mg/kg per day) every 4 hours. One half of the group received initial loading with acetaminophen (25 mg/kg), and other half received initial loading with ibuprofen (10 mg/kg).

The infant was then given the loading dose (from generic bottles marked "A" or "B") by a second nurse, who also instructed the parent or guardian in completion of a daily diary and stress questionnaire for follow-up.

The study medications were standard acetaminophen syrup (125 mg/5 mL; Acamoli; Teva Pharmaceutical Industries, Ltd, Netanya, Israel) and ibuprofen suspension (100 mg/5 mL; Nurofen Boots Healthcare International, Nottingham, England). All of the loading-dose medication bottles were outwardly identical. The medication bottles were clearly labeled by group and were distributed by the pharmacist. The doses were calculated by infant weight. The pharmacist also reinforced the physician's instructions to the parent or guardian regarding the amount and times of administration of the medication, emphasizing the importance of adhering to the prescription and not exceeding the maximal recommended daily dosage. The list of patients and medications was stored until the end of the study with the pharmacist in a sealed envelope to be opened in the event of an emergency. All of the children were evaluated and followed up by the same physician (E.M.S.), who was blinded to the group allocations (as were the parents or guardians).

FOLLOW-UP

For each child enrolled in the study, the physician prepared a computerized questionnaire on demographic data, height of fever, days of illness, physical signs, mode of therapy, pertinent laboratory findings, new onset of illness, and emergency department visits to be completed as the study progressed.

Follow-up was conducted by a daily diary record maintained by the parent or guardian, which was accompanied by a telephone interview at 24 hours (day 1) and 48 hours (day 2)

after enrollment. Parents were requested to measure the child's rectal temperature with a glass and mercury rectal thermometer at least 3 times daily during treatment, and then once daily for another 10 days. They also recorded the amount of antipyretic medication used and the number of missed work days because the child could not attend day care. In addition, they completed the NCCPC stress questionnaire.

The NCCPC stress test was designed for use in infants and young children who are unable to communicate verbally. It has been proven to be valid and reliable in the home setting.¹³ Studies show that caregiver reports based on the NCCPC can predict pain behavior¹⁴ and that caregiver pain estimates are closely related to children's self-reports.¹³

The caregiver was asked to rate how often each item in the scale occurred (not at all=0; occasionally=1; fairly often=2; and very often=3) during a 10-minute observation period in every 24-hour period in the morning before starting the day and twice more before lunch and dinner.

All of the patients were scheduled for an office visit on day 3 of the study, during which they were evaluated as they were on enrollment day, and the medication bottles were collected. Additional visits were conducted on days 5 and 10 after enrollment. Tests for renal and liver function and stool analysis for occult blood were repeated on the third and fifth days of follow-up and every 2 weeks thereafter for a total of 12 weeks. The diaries were collected on day 10 of the study.

OUTCOME MEASURES

We evaluated body temperature, stress score, amount of antipyretic used at the 3-day time point, total days that a primary caretaker had to stay home from work because the infant could not attend day care because of his illness, recurrence of fever within 5 and 10 days after initiation of treatment, number of emergency department visits within 10 days of enrollment, hepatic and renal function, appearance of gastrointestinal symptoms or bleeding, and the appearance of Reye syndrome. Fever was evaluated according to the maximal temperature registered on any day. Children with a temperature of less than 37.8°C were considered afebrile. A score of 4 or more on the NCCPC was considered abnormal. Therapy was considered successful if the mean temperature and mean NCCPC stress score were reduced.

Renal and hepatic function were followed up by clinical symptom and appropriate laboratory investigations. Abnormal laboratory findings were defined as follows: serum creatinine level, 0.9 mg/dL or higher ($\geq 68.6 \mu\text{mol/L}$); blood urea nitrogen level, 18 mg/dL or higher ($\geq 6.4 \text{ mmol/L}$); levels of liver enzymes serum glutamic oxaloacetic transaminase, serum glutamate pyruvate transaminase, and γ -glutamyltransferase, 20 U/L or higher; and total serum bilirubin level, 1 mg/dL or higher ($\geq 17 \mu\text{mol/L}$).

Gastrointestinal irritability was diagnosed by the presence of abdominal pain associated with vomiting or diarrhea as reported by the parents or caregivers. Gastrointestinal bleeding was evaluated by the presence of occult blood in stool (Cenogenics Corp, Morganville, NJ).

SAMPLE SIZE CALCULATION

Our calculation of the minimum sample size formula for binomial proportion from an independent sample¹⁵ was based on a double-blind clinical trial of 2 study populations of febrile children assigned at random to receive treatment A (acetaminophen) or treatment B (ibuprofen).⁸ The groups were evaluated at 2 different dosages. Since the study found no significant difference between the groups in the decrease in fever, we used

the variations in irritability score for the sample size calculation. The protocol required that patients be withdrawn if continuing participation could at any time be considered detrimental to their well-being.

STATISTICAL ANALYSIS

Survey responses were analyzed using SPSS for Windows, version 12.01b (SPSS, Inc, Chicago, Ill). Between-group data were compared with a χ^2 analysis to test nominal or ordinal variables of the background data. Comparison of stress, fever, and dosage according to treatment in each time was assessed with analysis of variance. Paired *t* test was used to check the differences of pain and fever between times in each group. A 2-tailed *P* value of .05 was used to define statistical significance for differences between groups and to calculate confidence intervals around differences in sample means.

RESULTS

A total of 480 infants met the eligibility criteria, of whom 464 (96.7%) completed the study. Of the 16 infants (3.3%) who withdrew from the study, 7 (1.5%) failed to return for follow-up visits within the first 10 days, and 9 (1.9%) did not return for laboratory evaluation after symptoms were alleviated. There were no statistically significant differences ($P = .43$) between the study participants and those who dropped out in demographic data (age, sex, marital status of guardian, number of siblings in the household, neonatal or prenatal complications), diagnosis, amount of antipyretics used during the initial 3 days of treatment, other medications used, or primary outcome parameters. Although we have no long-term follow-up data for those who dropped out, all of the children in the study continued to attend the same practices, and none suffered any related illness or were lost during the study period (Figure).

Owing to the fact that the type of loading medication (acetaminophen or ibuprofen) had no statistical effect ($P = .52$), the patients were all grouped according to their maintenance medication. The groups were similar in sex, marital status of parents, number of siblings, smoking in the house, presence of prenatal or neonatal complications, and illness that caused the fever (**Table 1**).

There was no statistically significant difference among the groups in mean height of fever on the admission day ($P = .31$). Differences were significant on day 1 and continued on days 2 and 3 ($P < .001$) (**Table 2**). The mean fever of infants in group C (alternating ibuprofen and acetaminophen) was lower as the days progressed as compared with the others groups, with differences being statistically significant between groups C and A (acetaminophen) ($P < .001$) and groups C and B (ibuprofen) ($P < .001$) but not between groups A and B (Table 2).

A significant difference in the decline of stress levels (as measured with the NCCPC) was noted in all of the treatment groups ($P < .001$), but it was steeper in the infants in group C as compared with those in groups A and B. The difference was even more pronounced when we take into account that the children in group C began with a higher mean stress score ($P < .001$) (Table 2). When we

Table 1. Background Variables of Study Sample by Group

Variable	Acetaminophen (Group A) (n = 154)	Ibuprofen (Group B) (n = 155)	Acetaminophen and Ibuprofen (Group C) (n = 155)	P Value
Age, mo (SD)	18.6 (8.72)	19.5 (9.09)	19.3 (9.29)	.64
Sex, No. (%)				
Male	71 (46)	73 (40)	62 (38)	.40
Female	83 (54)	82 (60)	93 (62)	
Parental status, No. (%)				
2 Parents	128 (83)	131 (85)	133 (86)	.81
1 Parent	26 (17)	24 (15)	22 (14)	
Other siblings, No. (%)	117 (76)	113 (73)	114 (74)	.81
Prenatal or neonatal complications, No. (%)	22 (14)	13 (8)	17 (11)	.26
Smoking at home, No. (%)				
None	135 (88)	140 (90)	127 (82)	.09
Occasional	19 (12)	15 (10)	28 (18)	
Initial medical illness associated with fever, No. (%)				
URI	66 (43)	81 (52)	80 (51)	.70
AOM	16 (10)	13 (8)	17 (11)	
Pharyngitis	10 (7)	7 (5)	3 (2)	
Bronchiolitis	8 (5)	7 (5)	9 (6)	
Gastroenteritis	7 (5)	7 (5)	6 (4)	
Viral illness	47 (30)	40 (25)	40 (26)	

Abbreviations: AOM, acute otitis media; URI, upper respiratory tract infection.

Table 2. Primary Outcome Measures of Treatment by Group

Outcome	Acetaminophen (Group A), % ± SD (95% CI) (n = 154)	Ibuprofen (Group B), % ± SD (95% CI) (n = 155)	Acetaminophen and Ibuprofen (Group C), % ± SD (95% CI) (n = 155)	P Value
Fever				
Admission	40.74 ± 1.01 (40.58-40.90)	40.58 ± 1.02 (40.42-40.74)	40.71 ± 0.93 (40.56-40.86)	.31
Day 1	40.55 ± 1.31 (40.34-40.76)	40.6 ± 1.46 (40.37-40.83)	39.64 ± 1.17 (39.45-39.82)	<.001
Day 2	39.74 ± 1.37 (39.51-39.95)	39.66 ± 1.48 (39.42-39.89)	38.78 ± 0.87 (38.64-38.92)	<.001
Day 3	39.34 ± 1.19 (39.15-39.53)	39.64 ± 1.46 (39.41-39.87)	38.54 ± 0.74 (38.42-38.66)	<.001
NCCPC				
Admission	18.30 ± 1.67 (18.03-18.56)	19.00 ± 1.27 (18.80-19.20)	19.46 ± 2.40 (19.08-19.84)	<.001
NCCPC day 1	11.77 ± 2.64 (11.35-12.19)	11.48 ± 2.58 (11.07-11.89)	9.26 ± 2.49 (8.86-9.65)	<.001
NCCPC day 2	8.87 ± 2.54 (8.47-9.27)	8.83 ± 2.67 (8.40-9.25)	5.09 ± 2.78 (4.65-5.53)	<.001
NCCPC day 3	7.66 ± 2.96 (7.19-8.13)	7.96 ± 2.71 (7.53-8.39)	4.18 ± 2.74 (3.75-4.62)	<.001
Medication				
Day 1	4.33 ± 0.85 (4.20-4.47)	2.99 ± 0.11 (2.97-3.01)	2.57 ± 0.88 (2.43-2.71)	<.001
Day 2	3.84 ± 0.73 (3.73-3.96)	2.92 ± 0.27 (2.88-2.96)	1.99 ± 0.58 (1.89-2.08)	<.001
Day 3	2.90 ± 0.73 (2.79-3.02)	2.84 ± 0.46 (2.77-2.92)	1.48 ± 0.71 (1.37-1.59)	<.001

Abbreviations: CI, confidence interval; NCCPC, Noncommunicating Children's Pain Checklist.

calculated the percentage change through each of the days, group C showed a stress level reduction of 52.4%, 45.0%, and 17.7% from admission to day 1, from day 1 to day 2, and from day 2 to day 3, respectively, as compared with only 39.6%, 23.2%, and 9.8%, respectively, in group B and 35.7%, 24.6%, and 13.7%, respectively, in group A. Group C required significantly fewer doses of antipyretic medication per infant as compared with the other groups ($P < .001$) (Table 2). Analysis of the change in the mean rate of intake of medication by time showed that group C received a lower mean number of doses of medication per child in days 1, 2, and 3 than groups A and B; these differences were statistically significant among all of the groups on days 1 and 2, but on day 3, the differ-

ence was statistically significant only between group C and the other groups ($P < .001$) (Table 2).

Analysis over time showed that group C required 22.6% fewer doses from day 1 to day 2 and 25.7% fewer from day 2 to day 3 whereas group A required 11.2% and 24.4% fewer doses, respectively, and group B required 2.2% and 2.7% fewer doses, respectively. These changes were statistically significant ($P < .001$) (Table 2).

Recurrence of fever was evaluated 2 days after therapy ended (day 5 of the study) and 1 week after therapy (day 10 of the study). We found that alternating acetaminophen and ibuprofen maintenance therapy (group C), regardless of the type of initial loading medication, was associated with fewer fever recurrences on days 5 and 10

Table 3. Secondary Outcome Measures and Follow-up by Group

Outcome	Acetaminophen (Group A) (n = 154)	Ibuprofen (Group B) (n = 155)	Acetaminophen and Ibuprofen (Group C) (n = 155)	P Value
Fever recurrence, No. (%)				
At 5 d	33 (21)	27 (17)	15 (10)	.02
At 10 d	18 (12)	19 (12)	14 (9)	.62
Absent from day care, d, No. ± SD (95% CI)	2.64 ± 0.58 (2.55-2.74)	2.58 ± 0.61 (2.48-2.68)	1.76 ± 0.69 (1.66-1.87)	<.001
Patients visiting emergency department, No. (%)	21 (14)	20 (13)	16 (10)	.65
Patients with abnormal renal laboratory values, No. (%)*				
Acute stage	5 (3.3)	4 (3.8)	5 (3.2)	.93
Follow-up	0	0	0	NA
Patients with abnormal liver laboratory values, No. (%)†				
Acute stage	4 (2.6)	2 (1.3)	2 (1.3)	.60
Follow-up	0	0	0	NA

Abbreviations: CI, confidence interval; NA, not applicable.

*Blood urea nitrogen level of 18 mg/dL or higher (≥ 6.4 mmol/L), or serum creatinine level of 0.9 mg/dL or higher (≥ 68.6 μ mol/L).

† γ -Glutamyltransferase, serum glutamic oxaloacetic transaminase, or serum glutamate pyruvate transaminase level of 20 U/L or higher, or total serum bilirubin level of 1 mg/dL or higher (≥ 17 μ mol/L).

as compared with acetaminophen or ibuprofen monotherapy (groups A and B, respectively). On day 5, there was a statistically significant difference among the groups ($P = .02$), but not on day 10 ($P = .62$) (Table 3).

The alternating group (group C) also had statistically significantly fewer day care absentees, thus requiring less work absenteeism from the parents, than the other groups (groups A and B) ($P < .001$) (Table 3).

In all of the groups, there were some cases of emergency department self-referral by the parents, but the differences were not significant by group ($P = .65$) (Table 3).

A multivariate stepwise linear regression analysis showed that the mode of therapy alone was the only significant factor influencing the result ($P = .047$).

None of the patients in any of the groups had a drug-related adverse event or serious illness. Mild elevation in levels of liver enzymes and renal findings were observed in 8 children (1.7%) and 14 children (3.0%), respectively, but none of the acute-stage laboratory abnormalities persisted to the 14-day follow-up evaluation, and there were no statistically significant differences among the groups ($P = .60$ for abnormal liver function and $P = .93$ for abnormal renal function) (Table 3).

COMMENT

Reduction of fever in children and the maintenance of a comfortable state are important to caretakers and primary physicians. Antipyretic use therefore plays a major role in daily pediatric practice, and it must be both effective and safe.

Previous studies have described a lack of consistency among physicians, nurses, and parents with regard to the appropriate management of a febrile child.¹⁶ The most commonly prescribed pharmacologic regimen consists of acetaminophen every 6 hours or ibuprofen every 8 hours according to the manufacturer's instructions. However, inappropriate dosing or overdosing is not uncommon. There are very few reported data on the use of an alternating regimen of acetaminophen and ibuprofen.^{11,12}

In the present study, we compared the effectiveness of acetaminophen and ibuprofen alone with alternating acetaminophen and ibuprofen in reducing fever in young children. Initial loading doses of 25 mg/kg for acetaminophen or 10 mg/kg for ibuprofen were used to decrease the time to reach effective drug serum concentrations and to improve the rate of temperature decrease. Treluyer et al¹⁷ found that without a loading dose, the time from administration of the first maintenance dose of acetaminophen to a steady-state plasma concentration is 10 to 50 hours in a febrile infant. The maintenance dose of ibuprofen (5 mg/kg per dose) was chosen on the basis of the study by Lesko and Mitchell,¹⁰ who failed to detect a dose-response effect in children with this dose as compared with a dose of 10 mg/kg. Furthermore, doubling the maintenance dose from 5 mg/kg to 10 mg/kg increased the area under the receiver operating curve by only 1.5-fold without significant pharmacokinetic-pharmacodynamic benefit.⁶ The maintenance dose of acetaminophen (12 mg/kg) was based on previous studies^{4-6,12} showing that this dose is the most appropriate for fever reduction.

In a study of 27 065 children younger than 2 years, Lesko and Mitchell¹⁰ noted that the risk of hospitalization for gastrointestinal bleeding among those receiving ibuprofen was no greater than in those receiving acetaminophen. Adverse effects of acetaminophen were mostly due to allergic reactions or inappropriate dosing because of parental failure to read or understand the label instructions, their use of an incorrect measuring device, or their use of an adult rather than pediatric preparation.^{18,19} Adverse renal effects from ibuprofen have been described in adults. However, in children, the renal impairment is not significant because they use ibuprofen for only a short time.⁷ In our study, none of the patients in any of the groups had serious adverse effects of the medication. The ibuprofen group had significantly more gastrointestinal irritability than the acetaminophen group because of the inflammatory action of the drug on the intestinal lining.⁷ No such difference was noted in the

alternating regimen group, perhaps because those patients required a lower overall dose of ibuprofen.

This study provides information only on the short-term (3-day) safety and efficacy of these drugs. We did not evaluate the repeated-dose pharmacokinetics, the biological safety, or the effect of prolonged dehydration on the likelihood of renal complications in the alternating regimen group. Acetaminophen is metabolized by the liver, but it is excreted in urine.²⁰ Therefore, it is important that physicians be aware that in an alternating regimen, acetaminophen may accumulate in the renal medulla—causing tubular necrosis and renal toxicity—because ibuprofen blocks the production of renal prostaglandin and inhibits the production of glutathione, which detoxifies the toxic metabolite of acetaminophen.²¹

These results cannot be extrapolated to children younger than 6 months, children with malnutrition, renal or hepatic abnormalities, metabolic, endocrine, or neoplastic disease, or peptic ulceration, or children with known adverse reactions to anti-inflammatory or antipyretic drugs. Furthermore, the small number of infants and the short time of therapy (3 days) in our sample reduces the statistical power to detect serious adverse events. It should also be noted that all of the study participants visited the physicians for treatment, so they may have been more seriously ill than most of the children who receive over-the-counter antipyretics.

These limitations notwithstanding, this study is the first randomized, double-blind, controlled clinical trial to our knowledge to assess the safety and effectiveness of an alternating regimen of acetaminophen and ibuprofen against each agent alone in children aged 6 to 36 months.

CONCLUSIONS

Our study suggests that the alternating use of acetaminophen (12.5 mg/kg per dose) and ibuprofen (5 mg/kg per dose) every 4 hours, together with double-dose loading, reduces fever faster and for a longer duration than either agent alone with no increase in adverse events. Both dosages are easy to measure, lessening parental confusion.

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Correspondence: E. Michael Sarrell, MD, 7 Hairis St, Moshav Gan-Haim, 44910, Israel (sarrell@netvision.net.il or michaelasar@clalit.org.il).

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My mother loved children—she would have given anything if I had been one.
—Groucho Marx