

The Safety of Acetaminophen and Ibuprofen Among Children Younger Than Two Years Old

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ABSTRACT. *Background.* Recently ibuprofen has been introduced as a nonprescription analgesic/antipyretic for use in children.

Objective. To compare the incidence of serious adverse clinical events among children <2 years old given ibuprofen and acetaminophen to control fever.

Study Design. A practitioner-based, randomized clinical trial. A total of 27 065 febrile children were randomized to receive acetaminophen (12 mg/kg), ibuprofen (5 mg/kg), or ibuprofen (10 mg/kg). Rates of hospitalization for acute gastrointestinal bleeding, acute renal failure, anaphylaxis, Reye's syndrome, asthma, bronchiolitis, and vomiting/gastritis were compared by randomization group.

Results. The risk of hospitalization with any diagnosis in the 4 weeks after enrollment was 1.4% (95% confidence interval, 1.3%–1.6%) and did not vary by antipyretic assignment. No children were hospitalized for acute renal failure, anaphylaxis, or Reye's syndrome. Three children were hospitalized with gastrointestinal bleeding; all 3 had been assigned to treatment with ibuprofen. The risk of hospitalization with gastrointestinal bleeding among children randomized to ibuprofen was 17 per 100 000 (95% confidence interval, 3.5–49 per 100 000) but was not significantly greater than the risk among children given acetaminophen. The risk of hospitalization with asthma, bronchiolitis, or vomiting/gastritis did not differ by antipyretic assignment.

Conclusions. The risk of serious adverse clinical events among children <2 years old receiving short-term treatment with either acetaminophen or ibuprofen suspension was small and did not vary by choice of medication. These data do not provide any information on the safety of these medications when used for prolonged periods or when used together, regardless of duration. *Pediatrics* 1999;104(4). URL: <http://www.pediatrics.org/cgi/content/full/104/4/e39>; randomized clinical trial, analgesics, antipyretics, risk of hospitalization, gastrointestinal bleeding, renal failure, anaphylaxis, asthma, gastritis.

ABBREVIATION. CI, 95% confidence interval.

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Presented in part to the US Food and Drug Administration's Nonprescription Drug Advisory Committee; September 18, 1997; Rockville, MD.

Received for publication Mar 1, 1999; accepted Apr 20, 1999.

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Recently ibuprofen has been introduced in nonprescription form for use as an analgesic/antipyretic in children. Serious adverse clinical events (eg, gastrointestinal bleeding, renal failure, and anaphylaxis) have been associated with use of ibuprofen and other nonsteroidal antiinflammatory drugs in adults. Such ibuprofen-associated events are rare in children <12 years old.^{1–3} However, there is little in the literature concerning the risks of serious events in children <2 years old, among whom there is concern that ibuprofen may be associated with unacceptable risks. We sought to expand our knowledge in this area by describing the risk of serious adverse clinical events after antipyretic use among children <2 years old using data collected as part of the Boston University Fever Study. This article expands on our previous reports by presenting age-specific information on the risks of serious adverse clinical events among children <24 months, including a substantial number of children <6 months.

METHODS

The study design and methods have been described^{1,4} and are only briefly summarized here. The study was a practitioner-based, double-blind, clinical trial designed to assess the safety of ibuprofen suspension when used to treat fever in children. Patients between 6 months and 12 years old with a febrile illness were randomly assigned to receive suspensions of either acetaminophen (12 mg/kg) or ibuprofen in 1 of 2 doses (5 or 10 mg/kg) and were followed for 4 weeks. Children were eligible if, in the opinion of the attending physician, their illness warranted treatment with an antipyretic; duration and height of fever were not criteria for participation. Written informed consent was obtained from each child's parent/guardian before randomization. Follow-up data, including information on hospital admissions, were collected by mailed questionnaire. Participants not returning the questionnaire were scheduled for a telephone interview; for families who could not be contacted by telephone vital status of the participant and hospitalization data were obtained from the enrolling physician-investigator.

Medical records were reviewed for all hospitalizations that occurred during follow-up, and discharge diagnoses were recorded. When available, admission blood urea nitrogen and creatinine levels (or the first value of each reported within 24 hours of admission) were abstracted from the record blindly with respect to antipyretic assignment. **Note: None of the study participants were hospitalized with a diagnosis of acute renal failure.** Patients who did not have a creatinine level obtained within 24 hours of admission were excluded from the analysis of renal impairment.

We compared the proportion of children hospitalized for any reason and for specific diagnoses according to antipyretic assignment. The specific diagnoses considered in this report include acute gastrointestinal bleeding, acute renal failure, anaphylaxis, Reye's syndrome, asthma, bronchiolitis, and vomiting/gastritis. To assess the risk of renal impairment less severe than complete renal failure, we compared mean admission serum creatinine

levels by antipyretic assignment among children who were hospitalized. To assess potential drug-specific effects, we compared children randomized to acetaminophen with those randomized to ibuprofen. To simplify reporting and because there were no material differences according to dose, we have combined all participants randomized to ibuprofen into a single group, which is approximately twice as large as the acetaminophen group.

Differences in proportions were assessed using the χ^2 or Fisher's exact test, as appropriate. These analyses were conducted using *StatXact: Statistical Software for Exact Nonparametric Inference, Version 2* (Cytel, Cambridge, MA). Where the observed hospitalization rate was zero, we also calculated the upper bound of the 95% confidence interval [CI] for that rate.⁵ CIs for relative risk estimates were calculated using the Taylor Series variance approximation.⁶ Relative risks were not calculated when the number of subjects in any cell was <5. The difference in mean admission creatinine levels was assessed with the Student's *t* test and analysis of variance using the *Statistical Package for the Social Sciences (SPSS), Release 4* (SPSS, Chicago, IL).

RESULTS

From February 2, 1991 through June 12, 1993, 84 192 children <12 years old were enrolled in the study by 1735 primary care practitioners. Of these, follow-up data could not be obtained for 277 (0.3%), leaving a total of 83 915 children with analyzable data. The present report is limited to the 27 065 children <2 years old at the time of enrollment in the study.

Descriptive characteristics of these 27 065 children according to antipyretic assignment are shown in Table 1. The median age of participants was 13 months (range, 1–23 months), median weight was 10 kg, 54% were male, and the majority were white. Children in each of the 3 treatment groups were similar with respect to all these characteristics.

Despite the stated eligibility criteria, 463 children were reported to be <6 months of age when enrolled in the study. Although ineligible for the study according to the original protocol, this group is included in the present analysis to maximize identification of all potentially serious adverse clinical events. Because age was not routinely verified for all study participants, it may sometimes have been incorrectly recorded (eg, a 15-month-old reported as 3 months old). To reduce potential errors in interpre-

tation, we included as children <6 months of age only those whose reported weight was between the 5th and 95th sex-specific percentile for month of reported age.⁷ Among the 319 children meeting these criteria, 199 (62%), 76 (24%), 27 (8%), and 17 (5%) were 5, 4, 3, and <3 months of age, respectively. The median weight of these children was 7.3 kg, 54% were male, 74% white, 13% Hispanic, 7.9% black, and 112, 111, and 96 had been randomized to treatment with acetaminophen, ibuprofen 5 mg/kg, and ibuprofen 10 mg/kg, respectively. The demographic characteristics of these children did not differ by treatment group.

There were no apparent differences in cause of fever at the time of enrollment according to treatment groups (Table 1). Among children <6 months of age, the most commonly reported cause was otitis media (45%) followed by upper respiratory infection (40%), pharyngitis (15%), lower respiratory infection (7.4%), and gastrointestinal infection (2.2%); these distributions did not vary by treatment group.

Overall, 3.9% of participants did not receive any of the study medication. Among the 96% who did, a median of 6 to 10 doses were received over a median of 3 days. The proportion of children not receiving any of the assigned medication, and for those who did, the number of doses received and duration of treatment were similar in the 3 treatment groups. The median doses actually received among children randomized to acetaminophen 12 mg/kg, ibuprofen 5 mg/kg, and ibuprofen 10 mg/kg were 12, 4.8, and 9.6 mg/kg, respectively. Study medication use among children <6 months of age was similar to that observed in the study overall (eg, 4.5% did not receive any of the study medication) and did not vary by treatment assignment.

Three hundred eighty-five participants were admitted to a hospital for any reason in the 4 weeks after enrollment in the study, for an absolute risk of hospitalization of 1.4% (95% CI, 1.3–1.6%). The distribution of children hospitalized according to antipyretic assignment (acetaminophen vs ibuprofen) is shown in Table 2. Compared with children who were randomized to acetaminophen, the relative risk of hospitalization among children who were randomized to ibuprofen was 1.1 (95% CI, 0.9–1.3).

Among the 319 children <6 months of age, 2 were hospitalized. One, randomized to ibuprofen 5 mg/kg, was hospitalized with a viral infection; the other,

TABLE 1. Demographic Characteristics of 27 065 Participants Less Than 2 Years Old According to Treatment Group

Characteristic	Treatment Group		
	Acetaminophen (12 mg/kg)	Ibuprofen (5 mg/kg)	Ibuprofen (10 mg/kg)
Total number	9127	9159	8779
Age in months, median	14	13	13
Weight (kg), median	10	10	10
Sex, % male	54	54	55
Race, % White	82	81	80
% Black	7	7	7
% Hispanic	7	7	8
Cause of fever			
% Upper respiratory infection	43	43	43
% Otitis media	48	48	48
% Pharyngitis	20	19	20
% Lower respiratory infection	7	6	6
% Gastrointestinal infection	3	3	3

TABLE 2. Risk of Hospitalization for Any Reason Among Children Less Than 2 Years Old According to Antipyretic Assignment

Antipyretic	Total No.	No. Hospitalized	Absolute Risk (95% CI)	Relative Risk* (95% CI)
Ibuprofen	17 938	261	1.5% (1.3–1.6%)	1.1 (0.9–1.3)
Acetaminophen	9127	124	1.4% (1.1–1.6%)	1.0† —

* Risk of hospitalization among children randomized to ibuprofen compared with the risk of hospitalization among children randomized to acetaminophen.

† Reference category.

randomized to ibuprofen 10 mg/kg, was hospitalized with pneumonia. The absolute risk of hospitalization in this age group, regardless of antipyretic assignment, was 0.63% (95% CI, 0.08–2.2%), which was not significantly different from the risk among children between 6 and 23 months of age ($P = .8$). Among children <6 months of age, risk of hospitalization did not vary significantly by antipyretic assignment ($P = .5$).

No children were hospitalized for acute renal failure, anaphylaxis, or Reye's syndrome. Three children were hospitalized with evidence of gastrointestinal bleeding; all 3 had been assigned to treatment with ibuprofen. The bleeds were not severe and resolved with conservative management; none required transfusion or surgery. Two of the 3 children had guaiac-positive coffee-ground emesis after a prolonged period of vomiting, and the remaining child had a blood-streaked stool. The risk of hospitalization with acute gastrointestinal bleeding among all children <2 years old, regardless of antipyretic assignment, was 11 per 100 000 (95% CI, 2.2–32 per 100 000). Among children randomized to ibuprofen, the risk was 17 per 100 000 (95% CI, 3.5–49 per 100 000). This risk did not vary significantly by ibuprofen dose, nor was it significantly greater than the corresponding risk among children randomized to receive acetaminophen (0 per 9127; 95% CI, 0–33 per 100 000; $P = .6$).

Among children who had been randomized to acetaminophen, the observed risks for hospitalization with acute renal failure, anaphylaxis, or Reye's syndrome were each 0 per 9127 (95% CI, 0–33 per 100 000). The corresponding risks among those randomized to treatment with ibuprofen were each 0 per 17 938 (95% CI, 0–17 per 100 000).

Among children <6 months of age, none was hospitalized for any of the primary study outcomes; irrespective of antipyretic assignment, the observed risk was 0 per 319 for each outcome (95% CI, 0%–0.94%). Among children randomized to acetaminophen, the risk was 0 per 112 (95% CI, 0%–2.7%) for each outcome; the corresponding risks among children randomized to ibuprofen were 0 per 207 (95% CI, 0%–1.5%). In this and the previous two comparisons, the difference in the upper bound of the 95% CIs is solely attributable to the difference in the size of the study group.

We also examined the risk of hospitalization for other conditions that might represent a particular risk to young children treated with antipyretics. For reasons of statistical stability, we considered only those that occurred among at least 5 children. Hospitalizations for asthma and vomiting/gastritis are of particular interest, the latter because it may represent the mild end of the spectrum of illness that includes acute upper gastrointestinal bleeding. The distribution of children hospitalized with these diagnoses according to antipyretic assignment is shown in Table 3.

Because there may be diagnostic misclassification between asthma and bronchiolitis among young children, we combined both diagnoses in this analysis. Sixty-five children were hospitalized with asthma/

TABLE 3. Risk of Hospitalization With Selected Secondary Diagnoses Among Participants Less Than 2 Years Old According to Antipyretic Assignment

Diagnosis	Antipyretic Assignment	
	Acetaminophen (<i>n</i> = 9127)	Ibuprofen (<i>n</i> = 17 938)
Asthma/bronchiolitis		
No. hospitalized	24	41
Absolute risk/100 000 (95% CI)	260 (170–390)	230 (160–310)
Relative risk* (95% CI)	1.0†	0.9 (0.5–1.4)
Vomiting/gastritis		
No. hospitalized	2	7
Absolute risk/100 000 (95% CI)	22 (2.6–79)	39 (16–80)

* Risk of hospitalization among children randomized to ibuprofen relative to children randomized to acetaminophen.

† Reference category.

bronchiolitis, for a hospitalization rate of 240 per 100 000. Antipyretic assignment was not associated with risk of hospitalization for asthma/bronchiolitis; the relative risk for ibuprofen (compared with acetaminophen) was 0.9 (95% CI, 0.5–1.4). There was no association between antipyretic assignment when either diagnosis was analyzed separately (data not shown).

Nine children were hospitalized with vomiting or gastritis, for a rate of 33 per 100 000. This risk did not vary significantly by antipyretic assignment ($P = .7$). Among children <6 months of age, none was hospitalized with asthma, bronchiolitis, or vomiting/gastritis. The upper bound of the 95% CI for the absolute risk of hospitalization for each of these conditions is 2.7% among these younger children who were randomized to acetaminophen and 1.5% among those randomized to ibuprofen.

Of the 385 children who were hospitalized, admission creatinine levels were available for 112 (29%). Among the 29 children randomized to acetaminophen, the mean creatinine level was 30 $\mu\text{mol/L}$ (0.34 mg/dL) (standard error of the mean, 2.2 $\mu\text{mol/L}$ [0.025 mg/dL]), and none had a level greater than 62 $\mu\text{mol/L}$ (0.7 mg/dL); among the 83 children randomized to ibuprofen, the mean was 37 $\mu\text{mol/L}$ (0.42 mg/dL) (standard error of the mean, 2.0 $\mu\text{mol/L}$ [0.023 mg/dL]), and 5 (6%) had levels >62 $\mu\text{mol/L}$ (0.7 mg/dL). The difference in mean creatinine levels (7 $\mu\text{mol/L}$ [0.08 mg/dL]) was of borderline statistical significance; the P value by the unpaired Student's t test was .03, while by analysis of covariance taking into account, age (in months), weight, sex, and an admission diagnosis of dehydration, the P value was .08. The creatinine level did not increase with increasing ibuprofen dose. Among the 46 children randomized to the 5 mg/kg dose of ibuprofen, the mean creatinine was 38 $\mu\text{mol/L}$ (0.43 mg/dL); the corresponding figure among the 37 randomized to the 10 mg/kg dose was 35 $\mu\text{mol/L}$ (0.40 mg/dL). Compared with children randomized to acetaminophen, the prevalence of creatinine levels above 62 $\mu\text{mol/L}$ (0.7 mg/dL) was not significantly greater among all children randomized to ibuprofen ($P = .32$). When alternate cut points were used to

define an elevated creatinine level (ie, 53 $\mu\text{mol/L}$ [0.6 mg/dL], 44 $\mu\text{mol/L}$ [0.5 mg/dL]), the proportions of children with elevated levels increased accordingly in both antipyretic groups, but there were no statistically significant differences between groups.

We also examined admission creatinine levels according to treatment group and age (<12 months vs 12–23 months). Among children 12 to 23 months of age, mean creatinine levels were 33 $\mu\text{mol/L}$ (0.37 mg/dL), 39 $\mu\text{mol/L}$ (0.44 mg/dL), and 38 $\mu\text{mol/L}$ (0.43 mg/dL) for children randomized to acetaminophen, ibuprofen 5 mg/kg, and ibuprofen 10 mg/kg, respectively. Among children <12 months of age, the corresponding mean creatinine levels were 28 $\mu\text{mol/L}$ (0.32 mg/dL), 38 $\mu\text{mol/L}$ (0.43 mg/dL), and 32 $\mu\text{mol/L}$ (0.36 mg/dL). The number of children <6 months of age who were hospitalized was too small to permit analysis of renal function in this age group.

DISCUSSION

In this study, the risk of serious adverse clinical events among children <2 years treated for a median of 3 days with either acetaminophen or ibuprofen was quite low. Overall, the risk of hospitalization for any reason during the 4-week follow-up period was 1.4%, and the risk of hospitalization with acute gastrointestinal bleeding was 11 per 100 000. There were no hospitalizations for acute renal failure, anaphylaxis, or Reye's syndrome, and among children <6 months of age, none was hospitalized with acute gastrointestinal bleeding. When antipyretic assignment was considered, neither the risk of hospitalization for any reason nor hospitalization with gastrointestinal bleeding differed significantly by treatment. Likewise, the risk of hospitalization for secondary study outcomes such as asthma/bronchiolitis and vomiting/gastritis did not differ significantly by antipyretic assignment. Among children <6 months, the observed rate for each of the primary study outcomes, overall, (0 per 319) is one measure of safety of antipyretic use in this age group. However, because of the limited sample size, the 95% CIs for these rates are compatible with risks as high as 0.9 per 100 treated children.

Hospitalization rates for asthma are increasing and have been documented to be highest among children under 4 years old.^{8,9} Among aspirin-sensitive children and adults, ibuprofen and other nonsteroidal antiinflammatory drugs have been reported to precipitate acute bronchospasm and exacerbate asthma.^{10,11} Bronchiolitis is a condition of infancy, and this diagnosis is often given to any respiratory illness accompanied by wheezing in this age group. Our observations suggest that among children <2 years old with no known sensitivity to aspirin or other nonsteroidal antiinflammatory drugs, the risk of hospitalization with acute bronchospasm is small and not significantly increased by the use of ibuprofen.

That the mean admission creatinine level among hospitalized children <2 years old who were randomized to receive ibuprofen was slightly greater than the corresponding level among children randomized to acetaminophen must be interpreted with caution. From a clinical perspective, the difference

was small (0.08 mg/dL) and likely to be transient. Further, the association was of borderline statistical significance, and because this posthoc analysis was conducted in the setting of multiple comparisons, the calculated *P* values likely underestimate the true probability that chance could account for the observed difference. Other considerations raise questions about biologic plausibility. First, there was no evidence of a dose-response effect for ibuprofen; compared with children randomized to the 5 mg/kg dose, creatinine levels were not higher among children randomized to the 10 mg/kg dose. Second, there was no evidence of a consistent relationship with age. In our previous report that included all study participants with analyzable creatinine data, regardless of age, there was no overall difference in creatinine levels according to antipyretic assignment.³ In contrast, in this analysis of children <2 years old, creatinine levels among children treated with ibuprofen were slightly higher than those treated with acetaminophen. If ibuprofen had an effect on renal function that was inversely related to age (ie, greatest effect among the youngest children), we would expect to see the highest creatinine levels in children <1 year of age. However, such an effect was not observed.

There are several limitations to these data. The study was designed to assess the risk of serious adverse events (ie, requiring hospitalization) and does not provide data on minor clinical events (eg, abdominal pain or nausea not requiring hospitalization). The duration of antipyretic treatment in this study was short (median, 3 days), and the study provides no information on the safety of these drugs when used for longer periods or on a chronic basis. Likewise, these children were randomly assigned to treatment with either acetaminophen or ibuprofen but not both; these data provide no information on the safety or effectiveness of alternating doses of acetaminophen and ibuprofen or any other pattern of combined use. Neither do these results apply to children ineligible for the study (eg, children with a known sensitivity to aspirin or other nonsteroidal antiinflammatory drugs, any form of chronic renal disease, blood coagulation defect, anemia secondary to blood loss, or hepatic, metabolic, endocrine, neoplastic, or peptic ulcer disease). Although these data represent the largest controlled study of antipyretic use among children <6 months of age and are generally reassuring, our power to detect serious adverse events in this group is limited. Because little information was collected regarding patient selection and socioeconomic status, it is difficult to fully assess the representativeness of this sample. However, the available clinical and demographic information suggests that study participants reflect the wide spectrum of febrile illness among nonhospitalized children. Physician-investigators could have chosen not to enroll their sickest patients, but because study participants were seen by a physician, they were likely to be more seriously ill than most children who receive over-the-counter antipyretics. If severity of illness is associated with the risk of adverse clinical events, then the risks to the general population of

febrile children treated with acetaminophen and ibuprofen are likely to be less than those observed here. Finally, laboratory data were not available for all participants, and changes in creatinine level could not be systematically evaluated. However, creatinine data were available for the sickest children (ie, those hospitalized during follow-up) who were likely to be at the greatest risk for renal impairment.

These limitations notwithstanding, this study represents the largest randomized controlled clinical trial ever conducted to assess the safety of antipyretic use in children <2 years old. These data indicate that incidence rates for serious adverse clinical events requiring hospitalization among febrile children treated with acetaminophen or ibuprofen are low and do not vary significantly with choice of antipyretic.

ACKNOWLEDGMENTS

This work was supported by McNeil Consumer Products Company, Fort Washington, Pennsylvania. The authors are currently conducting a study of serious group A streptococcal infections in relation to the use of nonsteroidal antiinflammatory drugs in children, in collaboration with investigators from the Centers for Disease Control and Prevention, which is being supported by McNeil Consumer Products Company and Whitehall-Robins Healthcare (Madison, NJ). The Slone Epidemiology Unit has received or is currently receiving research support from the US Food and Drug Administration, the National Institutes of Health, and a number of pharmaceutical companies.

We thank the study Advisory Committee for their valuable advice and guidance throughout the study: Ralph E. Kauffman, MD (Chair), Director of Medical Research, Children's Mercy Hospital, Kansas City, MO; Michael E. Bailie, MD, PhD, University of Illinois College of Medicine at Peoria; William Gerson, MD, private practice, Burlington, VT; Alan M. Leichtner, MD, Division of Gastroenterology and Nutrition, Children's Hospital, Boston; Alan Leviton, MD, Neuroepidemiology Unit, Children's Hospital, Boston; and Frederick H. Lovejoy, Jr, MD, Children's Hospital, Boston. Liaison to the Advisory Committee: Sumner J. Yaffe, MD, Center for Research for Mothers and Children, National Institute

of Child Health and Human Development, Bethesda, MD; Anthony R. Temple, MD, Medical Affairs, and Barbara H. Korberly, PharmD, Medical New Product Development, McNeil Consumer Products Company, Fort Washington, PA.

We also wish to thank Richard Vezina, MPH, who coordinated data collection and supervised our field staff; Mary Joan Denisco, PharmD, (McNeil Consumer Products Company) for technical support; David P. Harrington, PhD, for statistical advice; and Samuel Shapiro, MB, FRCP(E), for his guidance and review of the manuscript. We are especially grateful to the more than 1700 physician-investigators without whose participation the study would not have been possible.

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DOI: 10.1542/peds.104.4.e39

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