Asthma Morbidity After the Short-Term Use of Ibuprofen in Children

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ABSTRACT. *Objective.* **To test the hypothesis that short-term use of ibuprofen increases asthma morbidity in children.**

Methods. **A randomized, double-blind, acetaminophen-controlled clinical trial was conducted. Children who had asthma and a febrile illness were randomly assigned to receive either acetaminophen suspension or ibuprofen suspension for fever control. Rates of hospitalization and outpatient visits for asthma during follow-up were compared by randomization group.**

Results. **A total of 1879 children receiving asthma medications were studied. Rates of hospitalization for asthma did not vary significantly by antipyretic assignment; compared with children who were randomized to acetaminophen, the relative risk for children who were assigned to ibuprofen was 0.63 (95% confidence interval: 0.25–1.6). However, the risk of an outpatient visit for asthma was significantly lower in the ibuprofen group; compared with children who were randomized to acetaminophen, the relative risk for children who were assigned to ibuprofen was 0.56 (95% confidence interval: 0.34–0.95).**

Conclusion. **Rather than supporting the hypothesis that ibuprofen increases asthma morbidity among children who are not known to be sensitive to aspirin or other nonsteroidal antiinflammatory drugs, these data suggest that compared with acetaminophen, ibuprofen may reduce such risks. Whether the observed difference in morbidity according to treatment group is attributable to increased risk after acetaminophen use or a decrease after ibuprofen cannot be determined. These data provide evidence of the relative safety of ibuprofen use in children with asthma.** *Pediatrics* **2002;109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e20;** ***ibuprofen, NSAIDs, acetaminophen, clinical trial, asthma, bronchospasm.***

ABBREVIATIONS. NSAIDs, nonsteroidal antiinflammatory drugs; CI, confidence interval.

Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) can trigger acute bronchospasm in sensitive adults and children,[1–3] and patients with the syndrome of nasal polyps, angioedema, and aspirin-induced bronchospasm are advised to avoid ibuprofen and other NSAIDs. Because of its known association with Reye syndrome, aspirin is only rarely given to children today. As a result, a sensitivity to aspirin or other NSAIDs may not be recognized in young children with asthma. We sought to test the hypothesis that among children without a history of aspirin sensitivity, the use of ibuprofen suspension for fever control increases the risk of acute bronchospasm and other morbidity from asthma.

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METHODS

The study design and methods of the Boston University Fever Study have been described[4,5] 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 who were between 6 months and 12 years of age and had a febrile illness were randomly assigned to receive suspensions of either acetaminophen (12 mg/kg) or ibuprofen in 1 of 2 dosages (5 or 10 mg/kg) and were followed for 4 weeks. Children were ineligible if they had a known sensitivity to acetaminophen, ibuprofen, aspirin, or any NSAID, as were children with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs.

At enrollment, parents were asked about medications taken by the child in the previous 24 hours. One month later, information documenting the number of doses of study medication given, the average volume of each dose (in contrast to the assigned dose), and the occurrence of outpatient medical visits and hospitalizations during the 4 weeks after enrollment was obtained from parents of all study children by mailed questionnaire or interview. Medical records were requested for all hospitalizations, and discharge diagnoses were recorded. Medical records were not reviewed to confirm the reason for outpatient visits.

For the current analysis, we restricted the data to include only children being treated for asthma, defined as those who had received a β-agonist, theophylline, or an inhaled steroid on the day before enrollment in the clinical trial. Morbidity from asthma was defined as a report of hospitalization or outpatient visit for asthma in the month after enrollment. We compared the proportion of children with such reports according to antipyretic assignment. Differences in proportions were assessed using the χ^2 or Fisher exact test, as appropriate. The Mantel-Haenszel procedure was used to control for confounding in stratified data. Relative risk estimates were not computed for any comparison that involved a cell with 5 or fewer children.

RESULTS

From February 2, 1991, through June 12, 1993, 84 192 children were enrolled in the study. Follow-up data could not be obtained for 277 (0.3%), leaving a total of 83 915 children with analyzable data, 95% of whom received at least 1 dose of the assigned study medication. Of these, 1879 met our definition of treated asthma; among these, 632, 636, and 611 had been randomized to receive acetaminophen, ibuprofen 5 mg/kg, and ibuprofen 10 mg/kg, respectively. Descriptive characteristics and cause of fever for these children according to randomization group are shown in Table 1. Except for ibuprofen 10

TABLE 1. Demographic Characteristics of 1879 Children With Asthma According to Antipyretic Assignment

Characteristic	Antipyretic		
	Acetaminophen	Ibuprofen (5 mg/kg)	Ibuprofen (10 mg/kg)
Total number	632	636	611
Age (mo; median)	46	44	49
Weight (kg; median)	17	16	17
Gender (% male)	62	62	62
Race			
White (%)	77	77	77
Black (%)	8.4	9.8	14
Hispanic (%)	8.0	8.6	4.8
Cause of fever			
Upper respiratory infection (%)	46	46	42
Otitis media (%)	29	33	30
Pharyngitis (%)	23	24	21
Lower respiratory infection* (%)	23	23	25
Gastrointestinal infection (%)	1.8	3.8	2.2

* Includes patients with bronchitis and pneumonia.

mg/kg, which had a slightly higher proportion of black and a lower proportion of Hispanic children, the 3 groups were comparable.

A total of 18 children were hospitalized with complications of asthma during the 4-week follow-up period: 8, 4, and 6 in the acetaminophen, ibuprofen 5 mg/kg, and ibuprofen 10 mg/kg courses of therapy, respectively. The rate of hospitalization with asthma overall was 96 per 10 000. Compared with children who were randomized to receive acetaminophen, the relative risk estimate for those who were randomized to ibuprofen was 0.63 (95% confidence interval [CI]: 0.25–1.6). There were too few hospitalizations to permit computation of stable dose-specific risk estimates.

During follow-up, 69 children had an outpatient visit for asthma. The rate of outpatient visits for asthma was 335 per 10 000 courses of therapy (3.4%). The risk of an outpatient visit for asthma according to antipyretic assignment is shown in Table 2. Compared with children who were assigned to receive acetaminophen, the relative risk estimate for those assigned ibuprofen was 0.56 (95% CI: 0.34–0.95) after adjusting for age, gender, and race. This estimate did not vary materially when the data were stratified according to the number of asthma medications used before antipyretic assignment (1, 2+), the use of cromolyn sodium (no, yes), the duration of treatment with the assigned antipyretic (1–3, 4+ days), or the number of doses of the study antipyretic actually received (1–5, 6+). After excluding children who had been taking any antiinflammatory medication (steroids, NSAIDs, or cromolyn sodium) before antipyretic assignment (138 randomized to acetaminophen and 249 to ibuprofen), the relative risk estimate was 0.54 (95% CI: 0.30–0.99). The risk of an outpatient visit for asthma did not vary by assigned ibuprofen dose (ie, 5 mg/kg, 10 mg/kg).

The data stratified according to the cause of fever at the time of enrollment are shown in Table 3. Among children with fever attributable to a respiratory illness, the relative risk was 0.43 (95% CI: 0.24–0.79); for those with fever from other causes, the relative risk was 0.93 (95% CI: 0.44–2.0). The cumulative incidence (ie, absolute risk) according to dose of antipyretic actually received per kilogram of body weight is shown in Table 4. Cumulative incidence was greatest among those who received doses of acetaminophen averaging 11 mg/kg or more (6.3%) and was significantly greater than that observed among children who received either dose of ibuprofen ($\chi^2 = 4.7$, $P = .03$ for each comparison). Incidence among children who had received <11 mg/kg acetaminophen (4.4%) was not significantly different from that observed among children who had received higher doses of acetaminophen ($\chi^2 = 0.9$, $P = .34$) or either dose of ibuprofen ($P > .05$ for each).

DISCUSSION

The hypothesis that ibuprofen is more likely than acetaminophen to increase the risk of acute bronchospasm in children with asthma and no history of aspirin sensitivity is not supported by these data. Although the analysis was restricted to a group of children who were judged to be likely to be at highest risk for such an occurrence, ie, children taking

TABLE 2. Distribution of Outpatient Visits for Asthma During Follow-up According to Antipyretic Assignment Among Children With Asthma

Antipyretic	Number of Visits	Total Number	Unadjusted Relative Risk Estimate (95% CI)	Adjusted Relative Risk Estimate* (95% CI)
Acetaminophen	32	632	1.0† (—)	1.0† (—)
Ibuprofen	37	1247	0.59 (0.37–0.93)	0.56 (0.34–0.95)

* Calculated using the Mantel-Haenszel procedure adjusting for age, gender, and race.
† Reference category.

TABLE 3. Distribution of Outpatient Visits for Asthma During Follow-up According to Antipyretic Assignment and Cause of Fever

Cause of Fever	Antipyretic	Number of Visits	Total Number	Relative Risk Estimate	95% CI
Respiratory infection*	Acetaminophen	22	374	1.0†	(—)
	Ibuprofen	19	749	0.43	(0.24–0.79)
Other	Acetaminophen	10	258	1.0†	(—)
	Ibuprofen	18	498	0.93	(0.44–2.0)

* Includes patients with either upper or lower respiratory tract infections.
† Reference category.

TABLE 4. Distribution of Outpatient Visits for Asthma During Follow-up According to Antipyretic Dose* Among Children With Asthma

Antipyretic	Dose (mg/kg)	Number of Visits	Total Number	Cumulative Incidence (%)	95% CI
Acetaminophen	<11	10	226	4.4	1.7–7.1
	≥11	19	300	6.3	3.6–9.1
Ibuprofen	<7.5	20	617	3.2	1.8–4.6
	≥7.5	13	433	3.0	1.4–4.6

* Patients were excluded if administered antipyretic dose/kg of ibuprofen ($n = 197$) or acetaminophen ($n = 106$) was unknown.

asthma medications, we found no evidence that ibuprofen precipitates asthma attacks more often than acetaminophen among these children. On the contrary, we found that children who took ibuprofen had lower rates of both hospitalization and outpatient visits for asthma relative to those who took acetaminophen, although the former was not statistically significant. Because the study did not include a placebo control, it is not possible to determine whether acetaminophen increased or ibuprofen decreased short-term asthma morbidity in these children.

The observed difference could be attributable to a decreased risk among ibuprofen users. Airway inflammation is a dominant feature of asthma, and it is plausible that an antiinflammatory agent such as ibuprofen could offer some protection in the presence of an acute febrile illness. Ibuprofen has been shown to preserve pulmonary function better than placebo in children with cystic fibrosis and mild lung disease,[6] and there have been anecdotal reports of improvements in forced expiratory volume in 1 second in individuals who have asthma and are challenged with aspirin or other NSAIDs.[7,8] Furthermore, it was suggested recently that in young children, antiinflammatory medications might modulate the immune response to allergens.[9] Viral infections during childhood initially promote a TH1-type, or nonallergic, lymphocyte response, but during the resolution of the illness, a localized TH2, or allergic, lymphocyte response may predominate, and simultaneous allergen exposure could enhance the development of TH2 memory lymphocytes. Aspirin and possibly other NSAIDs tend to block the TH2 response. This mechanism has been hypothesized to explain the increase in allergic illness in children, including asthma, which has been observed subsequent to the discontinuation of aspirin use in pediatrics.[10] Our observation that the protective effect of ibuprofen was greatest among children who were treated for respiratory infections but not other infections is compatible with this hypothesis. However, if these results were attributable simply to an antiinflammatory effect of ibuprofen, then one might expect to find a dose-response relationship, which was not observed. In addition, the apparent reduction in risk followed a relatively short treatment period.

An alternative possibility is that these results could actually reflect an increased risk among children who are treated with acetaminophen. Acetaminophen has been reported to cause bronchospasm, particularly in aspirin-sensitive patients, although these reactions are not as common or as intense as those after aspirin use and seem to be dose related.[2,11–13] Also in a case-control study, Shaheen et al[14] reported a positive association between acetaminophen use and asthma in adults, and in an international correlational study, Newson et al[15] observed a positive relationship between acetaminophen sales and asthma symptoms among adolescents. Depletion of glutathione in the respiratory tract by acetaminophen and the resulting loss of antioxidant protection in the lung have been suggested as the possible mechanisms for this effect. It is also possible that an inactive ingredient (eg, a coloring or flavoring agent) in the study drug given to children in the acetaminophen arm of the trial could have increased the risk. It is widely known that coloring agents commonly used in foods (eg, tartrazine) can occasionally induce bronchoconstriction, especially in sensitive patients with asthma. However, none of the medications used in this study contained tartrazine or other ingredients known to cause bronchospasm. The observation that risk was increased only among children who received the highest dose of acetaminophen per kilogram of body weight is compatible with a dose-related effect.

It is important to note that the original study from which these data are derived was not designed to investigate this question, and only the observed relative risk for outpatient visits was statistically significant. Therefore, the possibility that this represents a chance finding must be considered as one explanation for these results. Because outpatient visits for

asthma were obtained by parental report and were not a primary endpoint of the original study, our data concerning this outcome may be incomplete, and no objective measures of pulmonary function are available to assess the nature and severity of these outcomes. However, it is unlikely that the difference in risk between the 2 treatment groups is attributable to biased assessment because physicians and patients were blinded with respect to which drug was administered. Furthermore, a similar difference in risk was observed for hospital admissions for asthma, an outcome verified by medical record review. Although some children with mild or episodic asthma were not included in this analysis, we do not believe that this introduced any material bias. Children who receive asthma medication daily are likely to be the most severely affected by asthma and are at the greatest risk for an adverse reaction to medication. Because children with a known sensitivity to either drug were ineligible, the results cannot be extended to these groups. Because the study population involved only a small number of minority children, it was not possible to perform race-specific analyses. However, there is no reason to believe that the results would vary by race.

These data provide reassurance about the risk of acute bronchospasm after short-term use of ibuprofen. No increase in risk, measured by either outpatient visit or hospitalization, was apparent. The observed difference in risk for the treatment groups is intriguing, but whether it is attributable to an increased risk after acetaminophen use or a decrease after ibuprofen remains to be determined.

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