

The Association of Acetaminophen and Asthma Prevalence and Severity

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KEY WORDS

asthma, asthma epidemic, acetaminophen

ABBREVIATIONS

CI—confidence interval

PAR—population-attributable risk

Dr McBride takes full responsibility with regard to the contents and opinions expressed in this article.

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abstract

FREE

The epidemiologic association between acetaminophen use and asthma prevalence and severity in children and adults is well established. A variety of observations suggest that acetaminophen use has contributed to the recent increase in asthma prevalence in children: (1) the strength of the association; (2) the consistency of the association across age, geography, and culture; (3) the dose-response relationship; (4) the timing of increased acetaminophen use and the asthma epidemic; (5) the relationship between per-capita sales of acetaminophen and asthma prevalence across countries; (6) the results of a double-blind trial of ibuprofen and acetaminophen for treatment of fever in asthmatic children; and (7) the biologically plausible mechanism of glutathione depletion in airway mucosa. Until future studies document the safety of this drug, children with asthma or at risk for asthma should avoid the use of acetaminophen. *Pediatrics* 2011;128:1181–1185

A growing number of studies have documented such a strong association between acetaminophen exposure and asthma that it is possible that much of the dramatic increase in childhood asthma over the past 30 years has been related to the use of acetaminophen. Although this possibility has been widely acknowledged,^{1–6} commentators have been reluctant, without a randomized clinical trial, to conclude that acetaminophen causes asthma and, with rare exception,^{7–9} have not recommended changes in practice. As a pediatric pulmonologist, I am entrusted with the care of many asthmatic children and, at some level, with the respiratory health of all children in my area. Given this role, I must decide when and how to act on the possibility that acetaminophen is detrimental to asthmatic children. Considering currently available data, I now recommend that any child with asthma or a family history of asthma avoid using acetaminophen.

Many observations suggest that the epidemiologic association between acetaminophen and asthma is causative: (1) the strength of the association^{10–15}; (2) the consistency of the association across geography,^{10–14,16} culture,^{9–11,16} and age^{9–17}; (3) the dose-response relationship between acetaminophen exposure and asthma^{10–17}; (4) the coincidence in the timing of increasing asthma prevalence and increasing acetaminophen use¹⁸; (5) our inability to identify any other abrupt environmental change that could explain this increase in asthma morbidity; and (6) the relationship between per-capita sales of acetaminophen and asthma morbidity across countries.¹⁹ Furthermore, the metabolism of acetaminophen provides a biologically plausible explanation for causation: depletion in airway mucosal glutathione that could contribute to vulnerability to oxidant stress.²⁰

Although studies of acetaminophen and asthma have been covered previously in thoughtful reviews^{1,2,4-7} and a meta-analysis,³ little has appeared in the pediatric literature, so this brief review might be helpful in providing the rationale for my recommendation. Studies have addressed 2 hypotheses regarding possible ways that acetaminophen might contribute to the severity or prevalence of asthma. First is the possibility that taking acetaminophen increases airway inflammation in people with asthma or a predisposition to asthma contributing to the severity and frequency of symptoms. Second is the possibility that those exposed to acetaminophen in utero^{3,21,22} or in the first year of life might be more likely to develop asthma later in childhood. My decision to discourage acetaminophen use in children with asthma is based on data that support the first of these 2 possibilities. The hypothesis that exposure early in life increases the prevalence or severity of asthma subsequently is important, but these data do not affect my recommendations regarding acetaminophen use by children with asthma. The literature can be confusing in this regard; although most studies address one or the other of these 2 hypotheses, some have addressed both.^{11,16,23,24}

Studies published through October 2008 with data on current acetaminophen use and asthma symptoms in children and/or adults have been systematically reviewed.³ Since that time, 4 additional studies can be identified through a PubMed search of “acetaminophen” (or “paracetamol”) and “asthma”: 3 of children^{10,16,24} and 1 of adults.²⁵ Here I review the epidemiologic studies in children and adults, some reservations about these epidemiologic data, the 2 prospective trials pertaining to this issue, and the clinical implications of these data and the

possible relationship between acetaminophen and the asthma epidemic.

EPIDEMIOLOGIC STUDIES IN CHILDREN

Phase 3 of the International Study of Allergy and Asthma in Childhood was a large cross-cultural study that involved 122 centers in 54 countries. Each study site enrolled at least 1000 children. The investigators rigorously identified children with wheezing and asthma symptoms and also collected data on acetaminophen exposure and other environmental factors that potentially contribute to the pathogenesis or severity of asthma. Data were available for 200 000 children aged 6 to 7 years¹¹ and for 320 000 children aged 13 to 14 years.¹⁰ Nearly 30% of all 13- to 14-year-olds reported taking acetaminophen at least once per month. In both age groups there was an acetaminophen dose-dependent increase in the prevalence and severity of asthma. For 6- to 7-year-olds, the risk of current asthma was increased 1.61-fold (95% confidence interval [CI]: 1.46–1.77) for those who took acetaminophen more than once per year but less than once per month and 3.23-fold (95% CI: 2.91–3.60) for those who took acetaminophen at least once per month. For 13- to 14-year-olds the risks were 1.43 (95% CI: 1.33–1.53) and 2.51 (95% CI: 2.33–2.70), respectively. In both age groups, the association of asthma and acetaminophen was identified at almost all sites regardless of geography, culture, or stage of economic development. For each age cohort, the investigators calculated a population-attributable risk (PAR) for acetaminophen exposure. This parameter estimates the reduction in incidence of asthma or asthma symptoms that would occur in the entire population if exposure to acetaminophen were eliminated, assuming that acetaminophen does exacerbate asthma. For 6- to 7-year-olds the PAR for severe

asthma symptoms related to acetaminophen exposure was 38%; for 13- to 14-year-olds, the PAR for current wheeze was 41% and for severe asthma symptoms was 43%.

A meta-analysis of 6 other epidemiologic studies in children published before November 2008³ calculated a pooled odds ratio for wheezing in the previous year of 1.97 (95% CI: 1.51–2.56) related to acetaminophen use in a total of nearly 27 000 subjects. An Ethiopian population-based cohort study¹⁶ revealed that a high rate of acetaminophen use among 1- and 3-year-olds (36% and 42%, respectively) and an association between acetaminophen use and wheeze are not limited to urban/industrial environments. In a group of 5- to 6-year-old children in New Zealand,²⁴ use of >10 doses of acetaminophen per year was associated with an increased risk of current asthma (odds ratio: 2.83 [95% CI: 1.63–4.88]).

EPIDEMIOLOGIC STUDIES IN ADULTS

An association between asthma and acetaminophen usage was first demonstrated in adults in England¹³ in 2000. In a meta-analysis³ of 6 adult studies with a total of nearly 90 000 subjects, an odds ratio for asthma was calculated in adults with acetaminophen use of 1.74 (95% CI: 1.36–2.23). Of the publications included, a careful multicenter case-control study organized by the Global Allergy and Asthma European Network¹⁴ is typical. Weekly use of acetaminophen was associated with an increased risk of asthma of 2.87 times (95% CI: 1.49–5.37), an association that was not found for other analgesics. Another of these studies, an analysis of the third National Health and Nutrition Examination Survey in the United States,¹² found a dose-response relationship between acetaminophen use and both chronic ob-

structive pulmonary disease and asthma and an inverse relationship to lung function. Recent analysis of asthma symptoms and analgesic use in a relatively small group of adult survivors of childhood cancer, the results of which were published in a letter,²⁵ failed to support an association of acetaminophen use and asthma. This study, which included only 76 subjects with asthma, found an association between asthma and analgesic use, but the association was similar for acetaminophen and nonsteroidal anti-inflammatory drugs.

RESERVATIONS REGARDING EPIDEMIOLOGIC STUDIES

Cross-sectional epidemiologic studies can document an association between acetaminophen exposure and asthma, but they cannot prove that acetaminophen causes asthma. Commentators have suggested that part or all of the epidemiologic association between acetaminophen exposure and asthma might be explained by confounding factors.^{2–4} Of these factors, the most frequently cited are (1) confounding by indication (increased viral illnesses or fever²⁶ in asthmatic people that lead to both asthma and acetaminophen exposure), (2) confounding by reverse causation (asthma itself causing pain or fever resulting in increased acetaminophen exposure), or (3) preferential use of acetaminophen by children at greatest risk for asthma because of the fear that alternative treatments (aspirin or other anti-inflammatory agents) might increase asthma symptoms. These possibilities can only be laid completely to rest by a well-designed controlled trial. In the meantime, the clinician is left to consider how likely it is that these confounders singly or in concert could explain (1) the strength and consistency of the observed relationship between acetaminophen and asthma, (2) the repeatedly demonstrated acetaminophen dose-

response dependency, and (3) the lack of similarly close associations to the use of other antipyretics/analgesics. In this regard, the results of 2 prospective trials relating to current acetaminophen exposure and asthma are particularly pertinent.

PROSPECTIVE TRIALS

The results of 2 prospective studies of acetaminophen and asthma support the possibility that the association between acetaminophen exposure and asthma severity seen in epidemiologic studies represents causation. Between 1991 and 1993 the Boston University Fever Study¹⁷ randomly assigned nearly 84 000 febrile children aged 6 months to 12 years to receive, as necessary, low-dose ibuprofen, high-dose ibuprofen, or acetaminophen (12 mg/kg per dose) in a double-blind fashion. Of these children, 1879 with preexisting asthma were nearly evenly assigned among the 3 groups. For asthmatic children with a respiratory infection, the subsequent need for an outpatient asthma visit was 2.3 times higher in those treated with acetaminophen (95% CI: 1.26–4.16), and the risk was dose-dependent. Because there was no placebo control, it is theoretically possible that this outcome was a result of a protective action of ibuprofen, but the acetaminophen dose dependence, the lack of dose dependence for ibuprofen, and the availability of other evidence that acetaminophen exacerbates asthma make this explanation unlikely.

In 1990 and 1992, >73 000 female nurses who were enrolled in the Nurses' Health Study¹⁵ were asked about their use of acetaminophen and similar medications as well as known diagnoses. By 1996, 346 women who did not report a diagnosis of asthma at enrollment had a new physician diagnosis of asthma. There was a dose-dependent increase in the risk of de-

veloping asthma among women exposed to acetaminophen and little relationship to aspirin or nonsteroidal anti-inflammatory agents. Women who took acetaminophen >14 days/month, were 1.63 times as likely (95% CI: 1.11–2.39) to have developed asthma as those who did not take acetaminophen.

ACETAMINOPHEN AND THE ASTHMA EPIDEMIC

The possibility that acetaminophen causes asthma is of particular importance because of the coincidence of the asthma epidemic^{18,27} and the increased use of acetaminophen that followed recognition of the association of Reye syndrome with the use of aspirin. Between 1980 and 2003, the prevalence of pediatric asthma in the United States increased from 3.6% to 5.8%, and similar increases were observed throughout the world. Asthma prevalence leveled off in the 1990s at a time in which acetaminophen had already become the most commonly used analgesic/antipyretic for children. Although other changes in the environment have been suggested that might explain an increase in childhood asthma, including the "hygiene hypothesis,"²⁷ none so easily explains the rapid increase in asthma in the 1980s and the subsequent leveling off of asthma prevalence over the last 15 years. Furthermore, the prevalence of childhood wheezing in 36 countries around the world is predicted by each country's per-capita sales of acetaminophen.¹⁹

CLINICAL IMPLICATIONS

The clinical relevance of a putative causative role for acetaminophen in asthma can hardly be exaggerated. Various studies have estimated a PAR of acetaminophen exposure for the prevalence and severity of asthma of 20% to 40%.^{10,11,16} These estimates reflect not only that a clinical effect

seems to occur with relatively modest doses of acetaminophen but also that so many children throughout the world are exposed to such doses. This estimated PAR for asthma associated with acetaminophen use is similar to PARs estimated for the contributions of atopy²⁸ and residential exposures²⁹ to asthma, factors that are not so easily modified as acetaminophen exposure. The possibility that a measure as simple as limiting acetaminophen use might result in so great a decrease in the suffering of children throughout the world (and a reduction in the cost of their medical care) is both sobering and exciting. The situation could recapitulate experience with the “Back to Sleep” campaign, during which the estimated PAR of prone sleeping for sudden infant death syndrome was confirmed by the resulting reduction in its incidence.

What considerations can guide a clinician faced with the possibility that acetaminophen exposure is detrimental to children with asthma when caution has not been incontrovertibly

established? The ethical principle of nonmaleficence, often expressed as “primum non nocere,” can be helpful: in considering the balance between the likelihood of benefit and the risk of harm of any therapy, physicians should give particular weight to avoiding harm. Acetaminophen is a moderately effective treatment for fever and pain. The main argument for its use, however, has not been its effectiveness but, rather, its safety from the point of view of Reye syndrome and lack of effects on coagulation, the kidney, and the gastrointestinal tract. For the majority of children in most situations, nonpharmacologic interventions for short-term management of fever or modest pain or the use of ibuprofen³⁰ are reasonable alternatives. For asthmatic children with dehydration, renal disease, or coagulation disorders, assessing the risks and benefits of using acetaminophen or ibuprofen might be more difficult.

In my opinion, the balance between the likely risks and benefits of acetamino-

phen has shifted for children with a history or family history of asthma. I can understand how those responsible for regulation or policy statements of professional organizations might be more comfortable waiting for incontrovertible evidence. There remains a possibility that confounding variables might explain some or all of the association between acetaminophen and asthma. For this reason we need further studies. At present, however, I need further studies not to prove that acetaminophen is dangerous but, rather, to prove that it is safe. Until such evidence is forthcoming, I will recommend avoidance of acetaminophen by all children with asthma or those at risk for asthma and will work to make patients, parents, and primary care providers aware of the possibility that acetaminophen is detrimental to children with asthma.

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500 WORDS: *“It is 513 words long. I have to cut something,” lamented my third son. He was applying early action to two colleges and was trying to finish his Common Application admissions essay. The deadline for submission was three days away and after a day of work he had shown the essay to my wife and me. “The essay has to be 500 hundred words or less” he told us. He wanted to know if he should cut out descriptions of the field, the turmoil he felt, or something from his plans for the future. Evidently, our son is not alone in his struggles. As reported in The New York Times (Education: October 28, 2011), this week many high school seniors are fine-tuning their college admission essays to ensure they meet the new word limit guidelines. After four years with no upper limit length, new guidelines state the essay should be 250–500 words long. The restriction was in response to a general feeling that essays had become too long. However, unlike in other parts of the online application where a strict character limit exists, essays longer than 500 words are still uploaded in their entirety. Moreover, colleges are not told if the essay is longer than 500 words. In theory, a student could still write an essay of any length. While most college admission officers report they will continue to read all essays regardless of length, they do point out that students exceeding the established guidelines are taking a substantial risk. Without a true fixed word limit, however, many argue that not much difference exists between an essay of 520 and 500 words and that forcing students to chop an essay to conform with an arbitrary limit puts too much pressure on them. As for my son, he re-worded his opening lines dropping some descriptions of the field and happily filed a 496-word essay.*

Noted by WVR, MD

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