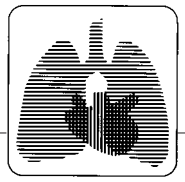

reviews

Acetaminophen and the Risk of Asthma*

The Epidemiologic and Pathophysiologic Evidence

Ihuoma Eneli, MD, MS; Katayoun Sadri, MD;
Carlos Camargo, Jr, MD, DrPH, FCCP; and R. Graham Barr, MD, DrPH

The prevalence of asthma has increased worldwide. The reasons for this rise remain unclear. Various studies have reported an association between acetaminophen, a widely used analgesic, and diagnosed asthma. In a prospective cohort study, the rate of newly diagnosed asthma was 63% higher among frequent acetaminophen users than nonusers in multivariate analyses. Studies of patients with asthma suggest that acetaminophen challenge can precipitate a decline in FEV_1 > 15% among sensitive individuals. Plausible mechanisms to explain this association include depletion of pulmonary glutathione and oxidative stress. This article reviews the existing literature and evaluates the epidemiologic and pathophysiologic evidence underlying a possible link between acetaminophen and asthma. ***(CHEST 2005; 127:604–612)***

Key words: acetaminophen; asthma; bronchoconstriction

Abbreviations: CI = confidence interval; ECHRIS = European Community Respiratory Health Survey; OR = odds ratio; ROS = reactive oxygen species; RR = relative risk

The prevalence of asthma in the United States has risen by 75% in the last 3 decades, with a particularly marked increase in children < 5 years of age (160%).[1] This rise transcends age, gender, ethnicity, and geographic location, but affects minority groups, the socioeconomically disadvantaged, and inner-city populations disproportionately. The reason for the surge in prevalence is unclear. A number of hypotheses have been proposed, including increased environmental exposures to "synthetic" materials and indoor allergens, decreased exposure to bacteria and childhood illnesses (the "hygiene" hypothesis), the increasing prevalence of obesity, changes in diet and antioxidant intake, increased exposure to cockroaches, changing meteorological patterns, and decreased use of aspirin.[2–9] In addition, cytokine imbalance or dysregulation occurring as a result of environmental exposures during infancy and early childhood is hypothesized to induce lifelong

For editorial comment see page 427

T-helper type 2 (allergic) dominance over T-helper type 1 (nonallergic) responses. T-helper type 2 dominance increases the risk for atopic diseases, including asthma.[4,6,10] While most studies[4,6,7] have focused on the effects of these factors after birth, some[6,10] have suggested sensitization *in utero*.

A link between acetaminophen and bronchoconstriction was originally suggested in a case report of an aspirin-intolerant patient as early as 1967 by Chafee and Settipane.[11] Recently, with the rise in asthma prevalence, there has been renewed interest in the role of acetaminophen. Acetaminophen, found frequently in combination with other drugs such as opiates and cold/cough formulations, is the most common form of analgesia used in the United States,

*From the Sparrow Hospital Pediatric Residency Program (Dr. Sadri) and Department of Pediatrics and Human Development (Dr. Eneli), Michigan State University, Lansing, MI; Department of Emergency Medicine (Dr. Camargo), Massachusetts General Hospital, Harvard Medical School, Boston, MA; and Department of Medicine (Dr. Barr), College of Physicians & Surgeons, Mailman School of Public Health, Columbia University, New York, NY.
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Correspondence to: Ihuoma Eneli, MD, MS, Department of Pediatrics and Human Development, Michigan State University, B220 Clinical Center Bldg, East Lansing, MI 48824-1313; e-mail: Eneli@msu.edu

particularly in children.[12] Kogan et al[12] estimated that approximately two thirds of analgesia used over a 30-day period by US preschool-aged children was acetaminophen. Concurrent with the use of acetaminophen, a large increase in asthma, particularly in the pediatric population, has been reported.[1] This review will summarize and evaluate the epidemiologic and pathophysiologic evidence underlying the hypothesis that acetaminophen is a risk factor for asthma and may have contributed to the recent increase in asthma prevalence.

Materials and Methods

A computerized search of the English-language literature of PUBMED, the IOWA Databases, and the Cochrane Clinical Trial Database between 1966 and 2002 was conducted using the terms *asthma*, *wheezing*, *cough*, *analgesia*, *acetaminophen*, and *paracetamol*. Various combinations of the terms were used to maximize the results. Bibliographies of original research, commentaries, textbooks, and symposia were reviewed for additional relevant references. These publications were abstracted and compiled into tabular form under types of study design. An article was included if it fulfilled the following criteria: (1) clinical study design, (2) human subjects, (3) acetaminophen use, and (4) outcome involved respiratory symptoms (cough, dyspnea, wheezing, or lung function changes). Two of the authors (I.U.E., K.S.) reviewed each article independently. Twenty-two articles met the inclusion criteria and were selected for critical review. Disagreements regarding inclusion were resolved by consensus. Of the articles excluded, most were letters to the editors or case reports that described anaphylactic reactions such as angioedema and urticaria, but without respiratory symptoms.[13–28]

Clinical Studies Examining the Relationship Between Acetaminophen and Asthma

Various epidemiologic and quasiexperimental studies have suggested a link between both therapeutic and overdose ingestion of acetaminophen and bronchoconstriction in certain individuals. Table 1 lists these studies by research design.

Across European countries, asthma rates have been ecologically associated with acetaminophen use.[29] This study by Newson et al[29] was the first large epidemiologic study to suggest a link between asthma and acetaminophen. Using data from the International Study of Asthma and Allergies in Childhood and the European Community Respiratory Health Survey (ECHRIS), the authors observed a positive correlation between acetaminophen sales and asthma symptoms, eczema, and allergic rhinoconjunctivitis at the country level. For each gram increase in per capita paracetamol sales in 1994/1995, the prevalence of wheeze increased by 0.52% among 13- to 14-year-old subjects in the International Study of Asthma and Allergies in Childhood study. Similarly, wheezing rose by 0.26% ($p = 0.0005$) per gram increase among young adults surveyed in ECHRIS. The results parallel comparative prevalence trends of asthma noted since acetaminophen became the primary over-the-counter analgesic. While ecologic findings such as these are helpful for the description of group-level (in this case, country-level) patterns of association, inferences about individuals (or patients) cannot be surmised.

The association between asthma and acetaminophen has also been seen at the individual level. In a large population-based, case-control study[30] of young adults ($n = 1,574$), daily and weekly use of acetaminophen was strongly associated with asthma. Acetaminophen exposure was defined only by frequency of intake. There was a significant trend comparing acetaminophen users: never users, infrequent users (less than monthly), monthly users, weekly and daily users ($p = 0.0002$), and self-reported history of asthma. In a multivariate regression analysis controlling for sex, age, social class, type of accommodation, employment and parental status, other analgesic use, and smoking and passive smoke exposure, acetaminophen use was positively associated with asthma (odds ratio [OR], 1.79; 95% confidence interval [CI], 1.21 to 2.65). The relationship was much stronger for severe asthma (OR, 8.2; 95% CI, 2.8 to 23). Aspirin avoidance did not appear to account for the positive results, as the association was found in those taking only acetaminophen as well as in those taking both analgesics. Limitations in the study included an overall response rate of 50%, with lower enrollment in younger persons, current smokers, and men, hence introducing selection bias, as acetaminophen use may differ among these groups. The study did not account for factors such as headaches and respiratory tract infections, which may lead to increased use of acetaminophen among asthmatic patients. Furthermore, given the cross-sectional design of the study, it is unclear if acetaminophen contributed to asthma or *vice versa*.

A recent report from the Nurses' Health Study,[31] a prospective cohort study of 121,700 women (age range, 30 to 55 years) in 1976, found that increased frequency of acetaminophen use in 1990 to 1992 was associated with a subsequent risk of physician diagnosis of new-onset asthma diagnosed between 1990 and 1996 (adjusted relative risk [RR], 1.63; 95% CI, 1.11 to 2.39; $p = 0.006$ for trend). The positive association remained unchanged whether the participants used or did not use aspirin. In multivariate analysis adjusting for a variety of potential confounders including body mass index, osteoarthritis, and frequency of physician visits, aspirin was inversely associated with newly diagnosed asthma ($p = 0.03$ for trend), but no association was seen with nonsteroidal antiinflammatory drugs ($p = 0.12$ for trend).