

Acetaminophen Use: A Risk for Asthma?

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A growing number of studies show that regular use of acetaminophen (paracetamol) carries a dose-dependent risk of developing allergies in general and asthma in particular and of worsening other respiratory diseases and lung function. The most disturbing finding has come from the population-based Avon Longitudinal Study of Parents and Children, in which use of paracetamol—but not aspirin—in late pregnancy was positively associated with asthma when comparing children whose mothers took paracetamol “sometimes” and “most days/daily” with those whose mothers never took it. Assuming a causal relationship, the percentage of asthma attributable to paracetamol use in late pregnancy was 7%. In this review, we present data from the most important studies published since 2000. Although the pathophysiology remains unclear, the available data justify a warning to the general public that the uncritical use of over-the-counter acetaminophen can lead to the development of allergies and asthma, even in utero.

Introduction

Over the past 8 years, a growing number of published studies have indicated that regular use of acetaminophen (paracetamol) carries a dose-dependent risk of developing allergies in general—asthma in particular—and of worsening other respiratory diseases and lung function (Table 1). In this review, we present data from the most important studies published since 2000.

Epidemiologic Studies

In 2000, Shaheen and coworkers [1] first reported a correlation between the use of acetaminophen and asthma

in a case-control study of adults. Of the study's 1700 respondents in 1997, 1574 (664 cases, 910 controls) had complete information on analgesic use and potential confounding factors and were included in analyses. Of these individuals, 787 reported taking paracetamol only, 98 were taking aspirin only, 536 were taking both analgesics, and 153 reported taking neither. Frequent (daily/weekly) paracetamol use was reported more commonly by women and unemployed individuals, and frequent aspirin use was reported more commonly by single parents. Aspirin use was similar among individuals with asthma and controls. Increasing paracetamol use was strongly associated with asthma. Compared with those who never used paracetamol, the odds ratios (ORs) in weekly and daily users were 1.79 (95% CI, 1.21–2.65) and 2.38 (95% CI, 1.22–4.64), respectively. When comparing the effect of frequent (daily/weekly) paracetamol use with less frequent use (including never users) in all individuals, the OR for asthma was 1.73 (95% CI, 1.29–2.31; $P < 0.001$). When restricting this analysis to 634 individuals who were also taking aspirin, the OR was 2.24 (95% CI, 1.30–3.89; $P = 0.004$). The adjusted OR for daily users of acetaminophen compared with never users was 2.4 (95% CI, 1.2–4.6).

In an analysis of the Nurses' Health Study, a prospective cohort study of 121,700 women (age range, 30–55 years) beginning in 1976 and published by Barr et al. [2] in 2004, 346 participants reported a new physician diagnosis of asthma. Increasing frequency of acetaminophen use was positively associated with newly physician-diagnosed asthma ($P = 0.006$ for trend). The multivariate rate ratio for asthma for participants who received acetaminophen for more than 14 days per month (compared with nonusers) was 1.63 (95% CI, 1.11–2.39; $P < 0.006$ for trend). 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 NSAIDs ($P < 0.12$ for trend).

Using the population-based Avon Longitudinal Study of Parents and Children in 2005, Shaheen et al. [3] determined associations of paracetamol and aspirin use in late pregnancy (20–32 weeks) with asthma, hayfever, eczema

Table 1. Studies investigating the association between acetaminophen use and respiratory diseases

Reference	Study design	Study objective	Population	Results
Newson et al. [19]	Ecologic	To examine the rate of asthma and aggregate consumption of acetaminophen in 1994–1995	English-speaking countries in the ECHRIS study	Prevalence of wheeze increased by 0.52% for 13- to 14-year-olds and by 0.26% for young adults for each gram increase in per capita paracetamol (acetaminophen) sales
Shaheen et al. [1]	Case-control	To determine whether frequent acetaminophen use is a risk factor for asthma	Adults 16–51 y old in South London; cases ($n = 720$), 51% response rate; controls ($n = 980$), 49% response rate	Never users: OR, 1.06 (95% CI, 0.77–1.45); monthly users: OR, 1.22 (95% CI, 0.87–1.72); weekly users: OR, 1.79 (95% CI, 1.21–2.65); daily users: OR, 2.38 (95% CI, 1.22–4.64); $P = 0.0002$ for trend
Shaheen et al. [18]	Prospective cohort	To examine the relationship between prenatal acetaminophen use and wheezing in offspring at 6 mo	9400 women	Frequent acetaminophen use over 20–32 wk prenatally increased risk for wheezing in offspring before 6 mo (OR, 2.34; 95% CI, 1.24–4.40)
Barr et al. [2]	Analysis using the Nurses' Health Study	To examine the relationship between acetaminophen use and new-onset asthma	73,321 female nurses in the United States (44–69 y old)	Increased risk of diagnosis of new-onset asthma with frequency of use ($P = 0.006$ for trend [adjusted risk ratio, 1.63; 95% CI, 1.11–2.39])
Shaheen et al. [3]	Avon Longitudinal Study of Parents and Children	To examine the relationship between acetaminophen use in late pregnancy and asthma, wheezing, and other atopic outcomes in school-aged children	Mothers of 8511 children and their offspring	Use of acetaminophen—but not aspirin—was positively associated with asthma when comparing children whose mothers took acetaminophen “sometimes” and “most days/daily” with never-user mothers. Asthma ORs were 1.22 (95% CI, 1.06–1.41) and 1.62 (95% CI, 0.86–3.04; $P = 0.0037$ for trend), respectively. Wheezing ORs were 1.20 (95% CI, 1.02–1.40) and 1.86 (95% CI, 0.98–3.55; $P = 0.011$ for trend), respectively
McKeever et al. [4]	Cross-sectional analysis using NHANES III	To investigate the associations between use of pain medication, asthma, COPD, and FEV ₁ in adults	6303 males, 7189 females, ages 20–80 y (mean age, 44.9 y)	Dose–response association of acetaminophen use and asthma (adjusted OR, 1.20; 95% CI, 1.12–1.28; $P = 0.001$ for trend). Dose-dependent association with COPD (adjusted OR for increasing category of intake, 1.16; 95% CI, 1.09–1.24; $P = 0.001$ for trend)
Davey et al. [6]	Cross-sectional survey	To determine the relationship between acetaminophen use and asthma and to explore potential biases in acetaminophen use in a developing country population	7649 adults and children from Butajira, Ethiopia	Allergic symptoms increased significantly with frequency of acetaminophen use; ORs in those using > 3 tablets in the past month relative to none were 1.89 for wheeze (95% CI, 1.51–2.36), 2.14 for nocturnal shortness of breath (95% CI, 1.72–2.67), and 2.52 for rhinitis (95% CI, 1.99–3.20)
Shaheen et al. [7•]	Case-control study	To determine the relationship between analgesic use and asthma in European adults	12 European centers recruited 521 individuals with asthma and 507 controls between May 2005 and May 2007	Weekly acetaminophen use was positively associated with asthma after controlling for confounders (adjusted OR, 2.87 [95% CI, 1.49–5.37]; $P = 0.002$)

COPD—chronic obstructive pulmonary disease; ECHRIS—European Community Respiratory Health Survey; FEV₁—forced expiratory volume in 1 second; NHANES III—Third National Health and Nutrition Examination Survey; OR—odds ratio.
(Adapted from Shaheen et al. [3] and Allmers [20].)

($n = 8511$), and wheezing ($n = 8381$) in offspring at 69 to 81 months, and with atopy ($n = 6527$) and blood total IgE ($n = 5148$) at 7 years. Use of paracetamol, but not aspirin, in late pregnancy was positively associated with asthma when investigators compared children whose mothers took paracetamol “sometimes” and “most days/daily” with those whose mothers never took it. ORs were 1.22 (95% CI, 1.06–1.41) and 1.62 (95% CI, 0.86–3.04; $P = 0.0037$ for trend), respectively. Wheezing ORs were 1.20 (95% CI, 1.02–1.40) and 1.86 (95% CI, 0.98–3.55; $P = 0.011$ for trend), respectively. For total IgE, geometric mean ratios were 1.14 (95% CI, 1.03–1.26) and 1.52 (95% CI, 0.98–2.38; $P = 0.0034$ for trend), respectively. No association was detected for hayfever, eczema, or skin test positivity. The percentage of asthma attributable to paracetamol use in late pregnancy—assuming a causal relationship—was 7%.

McKeever et al. [4] published a study in 2005 analyzing the Third National Health and Nutrition Examination Survey (NHANES III) data [5]. Increased acetaminophen use was associated with increased prevalence of asthma in a dose-dependent manner. OR for increasing category of intake was 1.20 (95% CI, 1.12–1.28; $P < 0.001$ for trend). Although no association between acetaminophen use and atopic asthma existed (OR for trend, 1.02; 95% CI, 0.85–1.21), a significant association between acetaminophen use and nonatopic asthma (OR for trend, 1.41; 95% CI, 1.06–1.86) could be shown.

The study also looked at risk of developing chronic obstructive pulmonary disease (COPD) with acetaminophen use and found it to be associated with an increased prevalence of COPD. The OR for increasing category of intake was 1.16 (95% CI, 1.09–1.24; $P < 0.001$ for trend).

Even when taking into account smoking, the risk of reporting COPD was significantly increased in people using acetaminophen at least daily compared with never users. Adjusted OR was 1.72 (95% CI, 1.36–2.18). No such trend could be detected for aspirin or ibuprofen use. The same was true for asthma, with an adjusted OR of 1.75 (95% CI, 1.34–2.28).

The 2005 paper by Davey et al. [6] added an important facet to the growing number of reports pointing toward a dose–response relationship between use of acetaminophen and development of allergic and respiratory diseases. Because most studies were conducted in economically developed countries, the authors assumed that there might be biases arising from the medical contraindication to use of aspirin or other NSAIDs in asthma. They also argued that reverse causation, such as treatment of headache caused by asthma therapy, is much less likely to have a strong influence in developing countries, in which awareness of adverse effects of aspirin and use of medication to treat asthma are relatively low. Their hypothesis was that acetaminophen use was associated with increased risk of allergic symptoms and sensitization in a cross-sectional survey of children and adults in Ethiopia.

The prevalence of all investigated outcomes rose in relation to increasing acetaminophen use, with the exception of cockroach sensitization, which was increased only in the highest dose category. After adjustment for age, gender, area of residence, presence of any parasite, smoking status, and educational level, statistically significant dose–response relationships were observed for wheeze, shortness of breath at night, eczema, and rhinitis ($P < 0.001$ for trend). ORs for more than three tablets taken in the past month compared with none ranged from 1.89 for wheeze to 2.52 for rhinitis. The adjusted OR of cockroach sensitization also significantly increased in those consuming more than three tablets of acetaminophen per month relative to none—by a ratio of 1.40 (95% CI, 1.10–1.79)—but there was no significant adjusted association between acetaminophen use and self-reported asthma or dust mite sensitization. Restriction of analysis to individuals without self-reported asthma resulted in similar or slightly stronger associations with acetaminophen use. Adjusted ORs for more than three tablets taken per month compared with none were as follows: 1.88 for wheeze (95% CI, 1.47–2.40), 2.25 for shortness of breath (95% CI, 1.78–2.86), 1.93 for eczema (95% CI, 1.37–2.70), 2.81 for rhinitis (95% CI, 2.16–3.67), and 1.38 for cockroach sensitization (95% CI, 1.07–1.79).

The study results are consistent with previous research demonstrating a positive association between acetaminophen use and prevalence of respiratory diseases. The study shows statistically significant dose–response associations between acetaminophen use and a range of allergic symptoms and sensitizations in a population of a developing country. The results are similar to those reported in developed country populations, making it probable that these associations reflect an influence on the etiology of allergic disease.

The most recent published study was a European multicenter case-control study carried out between 2005 and 2007 [7•]. Shaheen et al. [7•] have confirmed a positive association between frequent use of paracetamol and adult asthma. Weekly paracetamol use (compared with less frequent use) was positively associated with asthma, and the overall effect estimate became stronger after controlling for confounders (adjusted OR, 2.87 [95% CI, 1.49–5.37]; $P = 0.002$). No significant heterogeneity existed between centers ($P = 0.61$), and no significant relationship was observed between use of other analgesics and asthma.

Pathophysiology

Three mechanisms have been suggested as explanations for the increased morbidity caused by regular acetaminophen use [4,8]. Oxidative stress appears to play an important role in the development and progression of respiratory diseases. Glutathione, an endogenous antioxidant, is found in the respiratory tract–lining fluid, of which 95% is present in the reduced form as an antioxidant [9]. Evidence suggests that decreased glutathione levels are

associated with oxidant damage in the lung [10,11]. Furthermore, glutathione plays a role in drug detoxification, particularly in the metabolism of acetaminophen [12]. High doses of acetaminophen reduce levels of glutathione in animal lung tissue [13]. Therefore, regular users of acetaminophen may, through depletion of glutathione, be at an increased risk of lung tissue damage and, ultimately, respiratory disease [14].

Cyclooxygenase-2 activity and an increase of prostaglandin E₂ production may be stimulated by way of acetaminophen-promoting T2 allergic pathways [15].

The fewest data are available for the theory that suggests an IgE-mediated mechanism with acetaminophen as the antigenic agent [16,17]. The pathologic mechanisms that lead to the increases in allergic and respiratory diseases when ingesting acetaminophen regularly need to be better understood. It is still not clear how sensitization via the suggested acetaminophen-directed, IgE-mediated mechanism may occur.

Conclusions

In their review in *Chest*, Eneli and coworkers [8] argue that physicians need to be cognizant of analgesia intolerance in some asthmatic patients but that it is premature to recommend any change in current analgesic-prescribing patterns for adults and children with asthma.

However, data from the NHANES III analysis [4,5], results derived from the Nurses' Health Study [2], and data from Davey et al. [6] seem to be sufficient to justify giving a word of caution to the huge number of people who regularly use acetaminophen as an over-the-counter medication without a physician's advice. Furthermore, data from Shaheen and coworkers [18] suggest that acetaminophen exposure late in gestation may cause asthma, wheezing, and elevated IgE levels in school-aged children. The latest published multicenter case-control data from Europe [7•] also have confirmed a positive association between frequent use of acetaminophen and adult asthma.

It is not known how well this association has been recognized by primary care physicians and pharmacists, who have the most intensive contact with patients using over-the-counter medication. However, we can assume that the general population is not aware of any danger, except liver damage in cases of overdosing. Even more disturbing is that many pregnant women see acetaminophen as an unproblematic substance that can be taken without the dangers known to be associated with taking aspirin. The data available warrant a warning that uncritical ingestion of acetaminophen increases the risk of developing asthma, even in unborn children, and thus should be avoided.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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