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THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN ACADEMY OF PEDIATRICS

AAP News

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AAP News 2011;32;1

DOI: 10.1542/aapnews.20113212-1a

The online version of this article, along with updated information and services, is located on the
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American Academy of Pediatrics

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Focus On Subspecialties

Is acetaminophen the best choice of analgesic for children with asthma?

by Julie P. Katkin, M.D., FAAP,
and John McBride, M.D.

An association between asthma and acetaminophen use was first reported in a 2000 study from England. Since then, more than 15 studies have confirmed that both adults and children who take acetaminophen are more likely to have a diagnosis of asthma or exhibit asthma symptoms.

Still, epidemiologists have been reluctant to conclude that acetaminophen causes asthma and generally have not recommended changes in practice. A few have recommended that asthmatics limit acetaminophen use until the relationship between this common analgesic/antipyretic and asthma is clarified by a randomized clinical trial.

This article focuses on the possibility that acetaminophen might increase airway inflammation in individuals with asthma or a predisposition to asthma, thereby contributing to the severity and frequency of symptoms. (See related article in the December issue of *Pediatrics*, <http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2011-1106>.)

Epidemiologic studies

Six studies in adults published since 2000 involving 90,000 subjects have a pooled increased odds ratio for asthma of 1.74. A multicenter study organized by the Global Allergy and Asthma European Network is typical. Individuals who used acetaminophen at least once a week were 2.9 times as likely to have asthma as controls. An increased asthma risk was not found for aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Similarly, six pediatric studies published prior to 2009 showed that children who used acetaminophen were nearly twice as likely as controls to wheeze.

The epidemiologic association of asthma and acetaminophen has been confirmed recently by two publications from Phase Three of the International Study of Allergy and Asthma in Childhood. The study included data on 200,000 children ages 6-7 years and 320,000 children 13-14 years old from more than 40 countries. In both age groups, there was an acetaminophen dose-dependent increase in the prevalence and severity of asthma. Children who took acetaminophen at least monthly were more than three times as likely to report asthma at 6-7 years of age and more than twice as likely at ages 12-14 years.

The epidemiologic association between acetaminophen and asthma has been so strong that if acetaminophen actually causes asthma, an estimated 20%-40% of asthma morbidity in childhood could be

related to the use of this common analgesic.

Causation or confounding?

Many epidemiologists are concerned by the possibility that the association between acetaminophen and asthma does not reflect causation but is due to confounding factors. They point out that asthmatics may have more febrile viral illnesses than controls so that their increased use of acetaminophen may be due to their asthma. Alternatively, asthmatics may be more likely to take acetaminophen because of the concern that aspirin and NSAIDs might exacerbate asthma. They argue that the only way to be sure that acetaminophen causes asthma is a randomized controlled trial.

Bradford Hill criteria

In the 1960s, English epidemiologist Austin Bradford Hill proposed nine criteria to evaluate the likelihood that an epidemiologic association reflects causation. Five of these clearly support the possibility that acetaminophen causes asthma: the **strength** of the association is impressive; the association has been demonstrated **consistently** across ages, geography and cultures; the **timing** of the effect is reasonable (acetaminophen use precedes asthma symptoms); the association is **specific** for acetaminophen as opposed to other analgesics; and there is a pronounced **dose-response relationship** in nearly all of the studies.

The sixth criterion is the presence of **experimental data** consistent with causation. Although most studies have been observational, cross-sectional and epidemiologic, the Boston University Fever Study (1991-'93) prospectively compared ibuprofen and acetaminophen given in a double-blind fashion to 2,000 febrile children with pre-existing asthma. Those with apparent respiratory viral illness who received acetaminophen were twice as likely as children taking ibuprofen to have a subsequent acute visit for asthma.

The seventh criterion is **biologic plausibility**. It has been demonstrated that acetaminophen at therapeutic doses decreases the levels of glutathione in pulmonary cells; this could decrease the resistance to oxidant injury and thereby increase the intensity of airway inflammation. If this is the case, the fact that acetaminophen is most likely to be taken at the time of respiratory viral infections that are initiating airway inflammation is unfortunate.

The eighth criterion is the extent to which causation is **coherent** with

other current phenomena/observations. In this regard, the coincidence of the relatively abrupt onset of the asthma epidemic around 1980 and the increased use of acetaminophen in children is interesting. If the strength of the association between asthma and acetaminophen does reflect causation, it is theoretically possible that the asthma epidemic reflects acetaminophen use.

The final criterion is the **consideration of alternate explanations**. As mentioned earlier, some epidemiologists believe the relationship between viral infections and asthma might explain the association between acetaminophen and asthma in observational studies. Investigators continue to consider whether environmental changes such as those potentially underlying the “hygiene hypothesis” might explain the abrupt onset of the asthma epidemic as well as a change in analgesic preferences.

Acetaminophen has become a staple of the home remedy arsenal around the world, with a track record of safety and utility for most users. But for children with a history or family history of asthma, there is mounting evidence that the balance between the likely risks and benefits of acetaminophen need to be considered carefully. Until further studies are available, pediatricians must decide whether it is prudent to guide children at risk for asthma to other NSAIDs or nonpharmacologic interventions for the treatment of mild to moderate pain or fever.

Dr. Katkin is chair-elect of the AAP Section on Pediatric Pulmonology Executive Committee. Dr. McBride is professor of pediatrics, Northeast Ohio Medical University, and vice chair, Department of Pediatrics, Akron Children's Hospital.

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