EDITORIALS

Acetaminophen and Asthma — A Small Sigh of Relief?

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Acetaminophen is the drug of choice for fever in young children. Pediatricians, parents, and caregivers consider it to be safe for most children when it is administered in accordance with the manufacturer's directions for use. In 2000, however, concern was raised about the safety of acetaminophen as a result of the findings of a case–control study by Shaheen et al.[1] that suggested that frequent use of acetaminophen (also known as paracetamol in the United Kingdom) among adults was associated with asthma, and among those who already had asthma, with more severe disease. The mechanism for this association was thought to be the depletion of glutathione in the lung, leading to greater oxidative stress. This concern led to more than a decade of observational research on acetaminophen use and asthma in adults,[2] as well as in children and in pregnant women. The three main questions that the studies attempted to answer were whether frequent acetaminophen use (either prenatal or postnatal) leads to asthma in children who would otherwise be asthma-free, whether frequent acetaminophen use in children and adults who already have asthma worsens symptoms, and whether ibuprofen is safer than acetaminophen with respect to these asthma-related issues.

The limitation of observational studies in assessing the risk associated with these common over-the-counter medications is confounding by indication[3] (i.e., people who use a drug more frequently differ in key characteristics from those who use the drug less frequently or who do not use the drug at all). In the case of studies evaluating an association between acetaminophen use and asthma in children, viral respiratory illnesses are the most common causes of wheezing among children with asthma, but because these illnesses also cause fever and aches (two potential indications for acetaminophen), it is difficult to determine a causal association. Therefore, there have been calls for well-performed clinical trials to settle the issue of causation.[2,4]

The Acetaminophen versus Ibuprofen in Children with Asthma (AVICA) trial, reported by Sheehan et al. in this issue of the *Journal*,[5] attempts to provide some answers. The AVICA trial was a 48-week randomized, double-blind, parallel-group trial that compared the as-needed use of acetaminophen with that of ibuprofen for fever or pain in 300 children 12 to 59 months of age at enrollment who had mild persistent asthma and were receiving treatment with asthma-controller therapies. After a run-in period, the children were randomly assigned to receive acetaminophen or ibuprofen, as needed, as antipyretic, analgesic therapy; the study design also included another randomization in a simultaneous, factorially linked trial that aimed to study the asthma-controller regimens, but those outcomes are not considered in the current report. Because acetaminophen and ibuprofen are commonly available over the counter, the investigators also assessed additional open-label intake of these medications. The investigators did not find any significant difference in the primary outcome of asthma exacerbations leading to treatment with systemic glucocorticoids or in any of the secondary outcomes between the two treatment groups over the course of 48 weeks.

What do the results of the AVICA trial mean for patients? First, the AVICA trial did not ad-

dress whether acetaminophen use can lead to the development of asthma in otherwise healthy children; a different study will have to be designed to answer that question. Next, the results indicated that in usual, as-needed doses (participants used a median of 5.5 doses of study medication over the course of 48 weeks), the use of acetaminophen, as compared with ibuprofen, did not worsen asthma or wheezing in children. Thus, caregivers of young children who are receiving treatment with asthma-controller medications may be reassured by this result that the use of acetaminophen in usual, as-needed doses will not worsen asthma symptoms in their children and that acetaminophen and ibuprofen can be used similarly in situations for which they are indicated.

The finding that children who had more asthma exacerbations leading to treatment with systemic glucocorticoids also had greater use of acetaminophen or ibuprofen probably supports the notion that these children have a greater predisposition to both fever and wheezing exacerbations; however, no definitive statement can be made because this was not a placebo-controlled study. Thus, the AVICA trial does not directly answer the question of whether the use of acetaminophen or ibuprofen, as compared with no drug use, can worsen asthma. As stated by the authors, the inclusion of a placebo group would have been unethical in this case, and thus this question may never be answered definitively. However, the outcome rates over the course of this trial (0.81 asthma exacerbations per participant in the acetaminophen group and 0.87 asthma exacerbations per participant in the ibuprofen group) appear to be approximately the same as the outcome rates in other trials involving children in this age group,[6,7] which suggests that there is no significant increase in symptoms associated with the use of either acetaminophen or ibuprofen. Given the difficulties of designing a trial with a true placebo group, this may be the best answer we can get in this age group.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Primary Biliary Cholangitis — A New Name and a New Treatment

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Primary biliary cholangitis, previously called primary biliary cirrhosis, is a cholestatic autoimmune liver disease that is marked by the progressive lymphocytic destruction of the smallest intralobular bile ducts.[1,2] In the absence of effective therapy, it progresses inexorably to cirrhosis and liver failure.

Ursodiol, a hydrophilic bile acid with an excellent safety profile, was approved by the Food and Drug Administration (FDA) in 1988 for the dissolution of gallstones. On the basis of early promising data in the management of primary biliary cholangitis and the unmet clinical need, the FDA granted ursodiol orphan status in 1991 for the management of primary biliary cholangitis.[3] Ursodiol gained full FDA approval in 1997, supported by a pivotal placebo-controlled trial.[4] This trial was deemed to be critical by the FDA reviewers because it showed the superiority of ursodiol over placebo with regard to important clinical end points, including death and the need for liver transplantation.