

Editorial

Acetaminophen and childhood asthma: Pill-popping at our peril?

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Give me the power to produce fever, and I will cure all disease.

—Parmenides, c. 500 BC

The notion that fever might have beneficial effects in combating infection has been around a long time. However, in the modern pharmaceutical age, there is a general reluctance by parents not to intervene with antipyretic treatment when their infant becomes febrile. More than 30 years ago, Schmitt¹ coined the term “fever phobia” to describe parents’ misconceptions and concerns about fever and their fear of not treating a fever in their infant or child. These beliefs have continued; survey data from the United States between 1998 and 2007 revealed that about a quarter of children less than 2 years of age had taken acetaminophen (paracetamol) in the previous week.² Yet in a randomized, double-blind placebo-controlled trial in young children with fever of presumed viral origin, when parents rated improvements in mood and comfort, acetaminophen was shown to be little better than placebo.³

The risk/benefit debate has been fueled in recent years by a body of epidemiologic evidence linking acetaminophen exposure in early life to childhood wheezing and asthma.⁴ However, it has been proposed that this link is noncausal and reflects the treatment of febrile respiratory tract infections in subjects who are more susceptible to infections and to having later asthma. In support of this, 2 birth cohort studies have reported that the association between infant acetaminophen use and later asthma was substantially attenuated on controlling for respiratory tract infections, but 3 other birth cohort studies have concluded that the association between infant acetaminophen use and asthma was not confounded by respiratory tract infections.^{4,5}

In this issue of the *Journal*, Sordillo et al⁶ report findings from the Project Viva birth cohort that contribute to this debate but do not resolve it. They show that associations between infant acetaminophen use and early childhood wheezing and asthma were substantially attenuated toward the null on controlling for respiratory tract and ear infections in infancy, but that adjusted

estimates suggested that infant acetaminophen exposure might be independently associated with an increased risk of asthma in midchildhood.

A strength of this latest study is that, unlike previous studies, information on use of ibuprofen was also available, enabling the specificity or otherwise of associations with acetaminophen to be examined. In fact, infant ibuprofen use was positively associated with early childhood asthma independent of acetaminophen use and after controlling for infant infection and other confounders, but was not associated with asthma in midchildhood. This study did not confirm a positive association between infant acetaminophen use and atopy reported previously.⁷

What should we conclude from these rather mixed findings on infant antipyretic use and asthma? The balance of evidence would appear to be split regarding whether the link between infant acetaminophen use and asthma is confounded by infection, although the possibility of residual confounding cannot be ruled out. The latest findings for ibuprofen use have raised new questions about possible detrimental effects of this antipyretic. On the basis of the evidence to date, we cannot dismiss the possibility that acetaminophen use in infancy might contribute to the persistence of wheezing, perhaps in synergy with viral infection. Nor should we ignore clues suggesting that infant exposure might interfere with immune development; a randomized controlled trial showed that prophylactic use of acetaminophen at vaccination was associated with impaired vaccine responses.⁸

In contrast to the muddled waters surrounding infant acetaminophen use, there is more convincing epidemiologic evidence implicating prenatal acetaminophen exposure in the inception of childhood wheezing and asthma, although mechanisms remain speculative. The majority of birth cohort studies that have investigated this association have confirmed a positive relation,⁴ including this latest study, which also showed that ibuprofen use in pregnancy was not a risk factor.⁶ Sordillo et al⁶ rightly point out that detailed information on indications for taking acetaminophen during pregnancy has been lacking from these studies, raising the theoretical possibility of confounding by indication. However, the association between prenatal acetaminophen exposure and asthma has been shown to be robust to adjustment for maternal asthma, migraine, and infections and antibiotic use in pregnancy.⁷ Furthermore, the major indications for acetaminophen during pregnancy are likely to be nonmigrainous headache and musculoskeletal pain; as far as we know, these conditions have not been linked to the risk of asthma in offspring and therefore are unlikely to be confounders. In addition, demonstration of plausible interactions between prenatal exposure and maternal antioxidant gene polymorphisms on asthma risk has strengthened causal inference.⁷ Of note, acetaminophen use in pregnancy has recently been under the spotlight for reasons other than asthma. For example, birth cohort

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studies in Norway and Denmark have also reported associations with childhood neurodevelopmental outcomes⁹ and behavioral disorders.¹⁰

It is 14 years since the first report of an association between acetaminophen exposure and asthma.¹¹ Will this conundrum ever be solved? Given the high prevalence of asthma and acetaminophen use in the West, this is a puzzle that needs a solution. However, further observational studies probably have little more to contribute. Although there have been calls for placebo-controlled randomized trials, I would argue that a primary prevention trial in infancy would be difficult to justify, given the strong possibility that the observational link with infant acetaminophen use might be confounded. It would also be difficult to design with respect to choice of comparator treatments, and maintaining a sufficiently long follow-up with high compliance and low contamination between treatment arms would be unfeasible. Given the more compelling evidence for a causal link with prenatal exposure, I believe there is a stronger case for a trial in pregnancy, although such a study would also be challenging because acetaminophen is the recommended analgesic for pregnant women. Even if a causal link could be established, the choice of alternative analgesics, especially in late pregnancy, is limited.

In contrast, secondary prevention trials to investigate whether acetaminophen affects asthma severity are more feasible. Although there is little epidemiologic evidence to suggest a relation between acetaminophen and severity, a *post hoc* analysis of trial data suggested that the drug might worsen short-term asthma morbidity.¹² Therefore results from the Acetaminophen Versus Ibuprofen in Children with Asthma multicenter trial in the United States (<http://clinicaltrials.gov/ct2/show/NCT01606319>) are eagerly awaited. This trial is investigating whether preschool children with asthma who are randomized to take acetaminophen as required for fever or pain will have more exacerbations than children randomized to take ibuprofen. Although there is no placebo arm, the trial could still answer the following important clinical question: Which of these commonly used antipyretics should children with asthma preferably be given? Meanwhile, what should parents and pregnant women be advised? We live in a pill-popping culture in

the West, and where acetaminophen is concerned, it seems likely that there is scope for a reduction in use without ill effects. There is clearly little to be lost by advocating a higher threshold for using antipyretics in infancy and for taking acetaminophen in pregnancy; avoidance of excessive, unnecessary, or inappropriate use would seem prudent.

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