

## Acetaminophen and Asthma in Children: Association or Causality?

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Use of acetaminophen and increasing risk of asthma have been reported in the epidemiological studies. Despite lack of controlled prospective clinical trials evaluating these associations in children, avoidance of acetaminophen in children with asthma has become controversial. This review presents data from observational studies and a recent prospective clinical trial investigating the association with use of acetaminophen in children with mild asthma and on asthma control.

**Keywords:** asthma, pediatrics, acetaminophen

**A**N ASSOCIATION BETWEEN asthma and acetaminophen exposure has been investigated in several ways: prenatal exposure to acetaminophen and risk of asthma development in children, exposure during infancy and risk of asthma in children, frequent use of acetaminophen and increased asthma symptoms.

Acetaminophen (also known as paracetamol in the United Kingdom) is widely used for fever in children. Acetaminophen is a nonopioid analgesic and antipyretic that was approved by the U.S. Food and Drug Administration (FDA) in 1955 as a prescription medication and was approved as an over-the-counter medication in 1959. Acetaminophen is the most commonly used medication in children <12 years of age in the United States with a weekly prevalence use of 26% in children <2 years old, and 10% weekly prevalence use in children 2–11 years old.<sup>1</sup> The exact mechanism of antipyretic and analgesic effect of acetaminophen is not defined; it seems to have a weak anti-inflammatory effect by inhibition of cyclooxygenase (COX), which leads to lowering hypothalamic set-point to fever. The analgesic effect is caused by activation of descending inhibitory serotonergic pathways.<sup>2–5</sup> Acetaminophen is metabolized in the liver by cytochrome P450 enzymes, which may result in glutathione depletion in the lungs. Reduced glutathione in the lungs may impair respiratory defense mechanisms against oxidative stress, causing damage to epithelial cells.<sup>6,7</sup> The association between asthma and acetaminophen remains controversial as a majority of the reports are observational studies with confounding factors.

Prenatal exposure to acetaminophen and wheezing in early childhood has been investigated and showed inconsistent

results. In the population-based Avon Longitudinal Study of Parents and Children, frequent use of acetaminophen in late pregnancy was associated with an increased risk of wheezing at 30–42 months of age<sup>8</sup> and asthma at 6–7 years of age compared with those who did not use acetaminophen.<sup>9</sup> As it was noted by the authors, this effect only explains 1% of the prevalence of wheezing in childhood and 7% of the prevalence of asthma in children of school age.<sup>8</sup> A similar association was reported from the Danish National Birth Cohort.<sup>10</sup> In a population-based birth cohort study of Dominican Republic and African American children in New York, exposure to acetaminophen prenatally was predictive of wheezing at age 5, and the risk of wheezing was increased by a functional polymorphism in the glutathione S transferase Pi gene.<sup>11</sup> In an epidemiological survey from Spain, asthma in the mother was reported to modify the risk; a significant association was reported between the nonasthmatic mothers who took acetaminophen at least once a month during pregnancy and children with wheezing at preschool age.<sup>12</sup>

In the International Study of Asthma and Allergies in Childhood (ISAAC) program, use of acetaminophen for the first year of life was associated with an increased risk of asthma at age 6–7.<sup>13</sup> However, in a birth cohort study, acetaminophen exposure between ages 5 and 6 showed a dose-dependent association with asthma at age 6 but not for the exposure before age of 15 months.<sup>14</sup> Current use of acetaminophen in children 6 and 13–14 years of age has been associated with a dose-dependent increase in risk of asthma symptoms in the ISAAC program.<sup>13,15</sup> *Post hoc* analyses of previous clinical trials had shown similar results.<sup>16,17</sup> In a

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randomized, double-blind, controlled trial, children 6 months to 12 years of age with febrile illness were randomly assigned to acetaminophen or ibuprofen and followed for 4 weeks.<sup>16</sup> A *post hoc* analysis of children with asthma showed that the rate of hospitalization did not differ significantly by treatment groups; interestingly, the risk of an outpatient visit was significantly lower for the ibuprofen group than for acetaminophen group. In a cross-sectional study at emergency department, association between wheezing and use of acetaminophen or ibuprofen in children 6 months to 6 years of age with current febrile illness was investigated.<sup>17</sup> Parents provided information regarding use of the antipyretics before admission to the emergency room and wheezing was diagnosed by a trained study physician. About 14% of the patients were diagnosed with wheezing with a negative association between ibuprofen use and wheezing and no association between acetaminophen use and wheezing.

The use of acetaminophen in otherwise healthy children and adults with asthma has also been investigated. Bronchoconstriction and airway inflammation did not alter with a single dose of acetaminophen in children with asthma compared with placebo.<sup>18</sup> Similarly, daily use of acetaminophen (1 g, twice daily) for 12 weeks in adult patients with mild-to-moderate asthma did not have any effect on bronchial hyperresponsiveness and asthma control.<sup>19</sup> However, the potential causality of the previous noted associations appeared to warrant further investigation of acetaminophen in the potential increased risk of asthma or asthma symptoms in well-designed prospective clinical trials rather than observational studies or *post hoc* analyses.

Recently, the first prospective, randomized clinical trial in children evaluated the risk of asthma symptoms and exacerbations with use of acetaminophen compared with ibuprofen. The acetaminophen versus ibuprofen in children with asthma (AVICA)<sup>20</sup> trial was a parallel trial to the individualized therapy for asthma in toddlers (INFANT)<sup>21</sup> trials. After 2–8 weeks of run-in period, children underwent randomization in 2 steps; INFANT trial: sequence of asthma controller medications that included daily inhaled corticosteroids (fluticasone propionate, 44 µg/puff, 2 inhalations twice daily), oral leukotriene-receptor antagonist (montelukast, 4 mg, once daily at bed time), and as-needed use of inhaled corticosteroids (fluticasone propionate, 44 µg/puff, 2 inhalations) with each use of albuterol sulfate; AVICA trial: acetaminophen (15 mg/kg every 6 h as needed) or ibuprofen (9.4 mg/kg every 6 h as needed) in a blinded manner on an as-needed basis. Children 12 to 15 months old with mild persistent asthma and on step 2 asthma controller therapy, as defined by the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR 3)<sup>22</sup> were enrolled. Eighteen sites in the United States screened 443 children and randomized 300 children to be followed for the 48-week duration of the study. The primary outcome was the number of asthma exacerbations per child, defined by use of systemic corticosteroids. A total of 226 children completed the trial and there was no significant difference in baseline clinical characteristics and demographics of the participants. The rate of asthma exacerbation did not differ in the acetaminophen and ibuprofen groups for the follow-up period; 0.81 exacerbation [confidence interval (95% CI) 0.65–1.02] versus 0.87 exacerbation (95% CI 0.69–1.1), respectively. There were no significant differences in time to first exacerbation, asthma control days, use of rescue albuterol, and unscheduled healthcare utilization for asthma.

Although use of acetaminophen and ibuprofen was significantly associated with the number of asthma exacerbations ( $P < 0.001$ , Kruskal–Wallis test), there was no significant differences between acetaminophen group and ibuprofen group. A median of 5.5 doses were used with no difference between acetaminophen and ibuprofen groups. No interaction was detected between asthma control therapy and treatment groups. The authors concluded no significant difference in the frequency of asthma exacerbations or in asthma control between acetaminophen- and ibuprofen-treated groups. As the authors pointed out, use of placebo in this trial was unethical, hence the comparison of the most commonly used antipyretic/analgesic medicines for the age group. As a result, one may conclude that acetaminophen and ibuprofen showed similar association with an increase in the rate of asthma exacerbation and decreased asthma control. It may well be that the primary cause of exacerbations viral respiratory infections caused the increased use of the antipyretics. As always it is important to keep in mind the patient population in this study that had persistent asthma on controller medications; the result may or may not be applicable to others with different levels of asthma severity.

It is important to note that the AVICA study does not address development of asthma with use of acetaminophen prenatally or during infancy. The result can be reassuring that use or recommendation of as needed use of acetaminophen as antipyretic/analgesic in preschool children with asthma will not increase asthma exacerbations or symptoms.

## Author Disclosure Statement

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