Nonsteroidal anti-inflammatory drug administration in children with history of wheeze

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Abstract

Question A child in my clinic who recently sprained his ankle is experiencing pain and having trouble bearing weight on the affected leg. His mother has been giving him acetaminophen, as she was told never to use nonsteroidal anti-inflammatory drugs (NSAIDs) because of his pharmacologically controlled asthma. Is asthma in children a contraindication to giving NSAIDs? Is NSAID-exacerbated respiratory disease (NERD) a real entity?

Answer Nonsteroidal anti-inflammatory drugs are effective analgesic and antipyretic medications. While described in adults with some predisposing conditions, NERD has not been clearly described in a large number of children. Nonsteroidal anti-inflammatory drugs can be recommended to children with known wheeze who do not have a history of NERD reaction.

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The use of various nonsteroidal anti-inflammatory drugs (NSAIDs) among children has increased considerably over the past few decades, partially owing to avoidance of acetylsalicylic acid (ASA), an NSAID that was found to be associated with Reye syndrome.[1-3]

Nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (NERD) is a known hypersensitivity reaction in adults.[2] Nonsteroidal anti-inflammatory drugs inhibit the cyclooxygenase-1 enzyme, resulting in increased levels of arachidonic acid metabolism, which therefore increases the levels of pro-inflammatory cysteinyl leukotrienes. This inflammatory process results in reduced anti-inflammatory effects of prostaglandins (ie, prostaglandin E_2) and bronchoconstriction.[1,3-7]

In adults, prevalence of NERD ranges between 8% and 20% among individuals exposed to an oral provocation test (OPT), and between 3% and 5% among patients who self-report that they have NERD.[3-5,8] A recent systematic review suggests that regardless of the method used to obtain prevalence, the prevalence is 7% among adults.[9] Szczeklik and colleagues collected data from 10 European countries using a questionnaire and reported a progressive pattern of symptoms. Among 500 patients over several years, these symptoms resulted in ASA and NSAID intolerance.[8] Persistent rhinitis or congestion appeared first; asthma, ASA and NSAID intolerance, and nasal polyps were diagnosed subsequently. Only 6% of these patients had a family history of ASA intolerance. In an article by a panel of experts from the European Academy of Allergy and Clinical Immunology Task Force on NSAIDs Hypersensitivity, acute clinical manifestations of NERD included bronchial obstruction, dyspnea, nasal congestion, and rhinorrhea. Onset was reported as being immediate or several hours after ingestion.[5] While a detailed clinical hypersensitivity history is important, the criterion standard for diagnosis of NERD is an OPT, which involves slowly titrating an ASA or NSAID dose to see if it elicits a reaction.[5,6,10]

Occurrence of NERD in children

To date, NERD has not been clearly described in children and is likely to be different than in adults.[1,11,12] First, children have less comorbid precursor conditions, such as nasal polyps.[1,11] Furthermore, different acute clinical manifestations such as hives, angioedema, flushing, gastric pain, and hypotension have been described in childhood NERD-like reactions.[1,11]

A chart review of 1298 children, based on history alone, suggested a prevalence of 2% (95% CI 1.2% to 2.6%), but no definition for a positive response was provided.[13] The report was limited by the use of pooled data from studies with heterogeneous populations, methodology, and clinical outcomes.

In a recent retrospective study of 10 adolescents with previous history of NSAID reaction, an OPT was conducted with at least 2 different NSAIDs to confirm NERD.[11] Comorbidity of chronic rhinosinusitis was reported in 2 participants; 5 participants had a reaction to both NSAIDs after exposure, and symptoms included a drop in forced expiratory volume in 1 second (FEV_1) of 15% to 57%, rhinorrhea, dyspnea, wheezing, hives, angioedema, hypotension, and flushing. Participants had mild to moderate asthma symptoms at baseline, compared with severe

asthma reported in adults. Most reactions were skin related and included urticaria or angioedema combined with lower airway compromise; in adults cutaneous symptoms are often reported as isolated and atypical. The small number of patients and inconsistent NSAID exposure makes generalizability of these findings very difficult.

A systematic review, aiming to describe the prevalence of NERD, summarized 15 adult and 6 pediatric studies.[4] The pooled prevalence among adults was 21% (95% CI 14% to 29%). Three studies included analysis of cross-sensitivity reaction to other NSAIDs among those with ASA-induced asthma, showing a pooled incidence of 98% for ibuprofen, 100% for naproxen, and 93% for diclofenac. Pooled cross sensitivity to acetaminophen was only 7% among individuals who underwent an oral challenge. In 6 studies including children 9 to 13 years of age, almost 200 children underwent OPT, with a reported prevalence of ASA-induced asthma of 5% (95% CI 0% to 14%).[4]

A recent meta-analysis explored the prevalence of NERD and the mean provocation dose of ASA to trigger a respiratory event.[3] Of the 18 studies, 14 were among adults: 11 were observational, population-based studies and 3 were oral provocation studies that used various values to document fall in FEV_1 as an outcome representing respiratory reaction. Prevalence of respiratory reactions from the 14 adult studies was 9% (95% CI 6% to 12%) with a mean provocation dose of 85.5 mg of ASA. Results also revealed that those who had NERD were twice as likely to have uncontrolled asthma as those with NSAID-tolerant asthma were, with 60% suffering more severe asthma and requiring 80% more emergency department visits. Four of the provocation dose studies were in the pediatric population; they were not randomized and were published in the 1970s and 1980s. These studies reported the prevalence of NERD was 11% (95% CI 5% to 17%). One study reported that provocation doses of 15 to 37.5 mg of ASA induced reactions.[14] Overall, there was considerable heterogeneity among the 4 pediatric studies; selection bias was present by including children with more severe asthma, as well as selecting ASA as the only provocation agent.

There has only been one randomized, double-blind, placebo-controlled, crossover trial among the pediatric population; in this 2005 study, children aged 6 to 8 with mild to moderate persistent asthma were exposed to both ibuprofen and placebo on 2 separate visits.[1] Clinical parameters and spirometry findings were recorded to account for a clearly defined primary outcome of ibuprofen sensitivity. Of 100 children tested, 2 developed bronchospasms with decreases of FEV_1 to 35% and 25% within 1 hour after ingestion of ibuprofen. Both children responded well to albuterol therapy. No other symptoms were reported as associated with the reaction. The 2 patients were described as having moderate asthma and allergic rhinitis at baseline, as well as being ibuprofen naïve before the study. The authors suggested that the low prevalence might be a result of exclusion of children with severe asthma and those who had had previous NSAID-induced reactions.

Conclusion

Although pediatric-specific NERD literature is sparse, it is apparent that this hypersensitivity reaction can rarely occur in this population. Prevalence of NERD among children appears to be 2% to 28%. Risk factors associated with NERD in adults, such as chronic rhinosinusitis, nasal polyps, and more severe asthma, are not common precursors in children who have developed NSAID reactions. Along with respiratory function decline, NERD might present in children with more cutaneous symptoms.

Overall, children with a known NERD reaction should avoid further exposure to NSAID-related products. With no known reaction, children can proceed with a recommendation to take NSAIDs even if they have asthma. More caution and monitoring might be required in children who have chronic rhinosinusitis or nasal polyps.

Competing interests
None declared

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Child Health Update is produced by the Pediatric Research in Emergency Therapeutics (PRETx) program (**www.pretx.org**) at the BC Children's Hospital in Vancouver, BC. **Dr Sih** is a member and **Dr Goldman** is Director of the PRETx program. The mission of the PRETx program is to promote child health through evidence-based research in therapeutics in pediatric emergency medicine.

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