Cross-Reactive Hypersensitivity to COX Inhibitors in a Child with Mild Allergic Rhinitis

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Key words: non-steroidal anti-inflammatory drugs, preschool, child, allergy

IMAJ 2005; 7: 790–791

Non-steroidal anti-inflammatory drugs, mainly ibuprofen, are extensively used in children as analgesics and antipyretics. Their mechanism of action is the inhibition of prostaglandin production by blocking the cyclo-oxygenase enzymes known as COX-1 and COX-2. Acetaminophen, the most ubiquitously used antipyretic medication for children worldwide, has no significant action on peripheral COX-1 and COX-2, but its antipyretic effect is consistent with a central nervous system-mediated activity on a new, previously unknown cyclo-oxygenase enzyme, COX-3, found in the brain and spinal cord [1]. Despite having almost no anti-inflammatory effects, even at high doses, and so strictly speaking not an NSAID, acetaminophen is therefore an inhibitor of prostaglandin synthesis. This may explain the reported incidence of cross-sensitivity to acetaminophen – on average around 7% (0–16%) – in patients with NSAID hypersensitivity [2].

Classically, NSAID hypersensitivity is diagnosed in non-atopic adults with severe chronic difficult-to-control asthma, persistent sinusitis and nasal inflammatory polyps. Termed the aspirin triad or aspirin-exacerbated respiratory disease, it has been extensively studied and characterized. Diagnosis is made using standardized protocols for oral or inhalation provocation tests. The incidence of aspirin-exacerbated respiratory disease established by using such tests is approximately 21% in adults and 0%–5% in children with asthma [2]. Significant controversy exists regarding the importance of these challenge-derived findings in selected groups of patients to the routine treatment of children with asthma.

Other types of adverse reactions to members of the NSAID family have been documented, but all such reactions are rare in the pediatric age group. The incidence of facial angioedema and NSAID hypersensitivity in atopic children was studied by Capriles-Behrens et al. [3] in a 10 year retrospective random chart review of patients attending an allergy clinic for asthma and/or allergic rhinitis. In this group of children 41 of 1007 (4.1%) had documented facial angioedema in response to NSAIDs, with the reaction being quite rare in early childhood and increasing sharply with age. In a recent retrospective study from Singapore, a group of relatively young Asian children (mean age 7.4 years, 25% under 5 years old) was diagnosed with cross-reactive dose-dependent angioedema/urticaria after recurrent reactions with multiple NSAIDs and/or aspirin oral challenge. More than half of these patients had significant immediate bronchospasm as part of their adverse drug reaction and more than a third showed challenge-positive cross-reactivity with acetaminophen [4].

We report the case of a young Israeli girl presenting with severe immediate bronchospasm, facial angioedema and generalized urticaria after the ingestion of ibuprofen and acetaminophen. As a referral service for children with both allergic and rheumatologic complaints, we are following a significant number of children requiring anti-inflammatory medications. Similar to the United States, in Israel, liquid ibuprofen preparations are increasingly popular as antipyretics in the pediatric age group. To the best of our knowledge, this is the first documented case in a child in Israel.

Patient Description

Our patient is a 6 year old female of Jewish Iraqi-Moroccan ancestry, with allergic rhinitis and a previous history of juvenile rheumatoid arthritis. At age 4 she received a prolonged course of anti-inflammatory doses of naproxen, with no apparent problems. In the past year, she has had increasingly bothersome symptoms of daily watery rhinorhea, sneezing, nasal blockage and itch. In recent months, episodes of fever, arthralgia and recurrent oral ulcers were treated intermittently with ibuprofen. She presented to our clinic with a history of four episodes of increasing severity of facial swelling and respiratory distress immediately following the ingestion of ibuprofen (three doses) and acetaminophen (single dose) for fever. A diagnosis of NSAID hypersensitivity was made, using a modified oral provocation test, as previously published [4]. Repeated doses of 2.5 mg/kg aspirin were administered orally at 60 minute intervals until a clinical reaction was elicited or a maximal cumulative dose of 10 mg/kg achieved. Atopy was evaluated clinically and tested using a standard panel of skin prick tests.

The patient showed a significant positive response to skin prick tests with standardized mite extracts and a clinical diagnosis of mild persistent allergic rhinitis. A family history positive for allergic rhinitis and asthma was elicited on the maternal side. Our patient also had a positive history of familial Mediterranean fever on the paternal side as well as a known carrier

NSAID = non-steroidal anti-inflammatory drugs

state for the *MEFV* mutation at location 694. There were no complaints of respiratory distress other than within the context of a drug reaction, and on physical examination there was no evidence of nasal polyps or sinus disease. The patient had no reported episodes of unprovoked or chronic urticaria.

The oral provocation test with aspirin produced a significant reaction of periorbital angioedema and moderate-severe bronchospasm at a cumulative dose of 5 mg/kg. Symptoms resolved after 2 to 3 hours with a bronchodilator and oral steroids. An oral challenge with etodolac, a relatively selective COX-2 inhibitor, was scheduled.

Comment

We describe a mixed reaction (angioedema-urticaria-bronchospasm) with multiple cross-sensitivities to aspirin, ibuprofen and acetaminophen in a 6 year old Israeli girl without the classical symptoms of aspirin-exacerbated respiratory disease. This dose- and potency-dependent reaction severely limits the options for antipyretic/anti-inflammatory treatment if needed. It seems obvious that our patient developed this sensitivity only recently, most likely in association with the development of overt atopic disease. Although atopy is not considered a risk factor for most drug allergic reactions, NSAID hypersensitivity seems to be directly related to atopy and allergic disease [5]. A selective COX-2-specific medication may be an appropriate alternative, but no approved preparations suitable for use in a 6 year old are available even if one overlooks the problems of off-label use of these drugs.

Conclusion

Facial angioedema and urticaria with or without respiratory distress is another facet of dose- and potency-dependent, cross-reactive reactions to NSAIDs in individual atopic children. Concomitant reactions to acetaminophen severely limit the options for antipyretics/anti-inflammatory treatment in these patients.

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