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Severe Anaphylactic Reaction to Ibuprofen in a Child With Recurrent Urticaria

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ABSTRACT

An acute anaphylactic reaction after a conventional antipyretic dose of ibuprofen was diagnosed in a child with allergic rhinitis, recurrent idiopathic urticaria, and nonimmunologic cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs and acetaminophen. The patient reported several previous, mild (isolated cutaneous) hypersensitivity reactions after exposure to acetaminophen or ibuprofen. There was no evidence of an underlying inflammatory disease except as described above. Patients with chronic or recurrent idiopathic urticaria and those with atopic disease represent groups at increased risk of nonsteroidal antiinflammatory drug hypersensitivity. Mild hypersensitivity reactions to acetaminophen and/or ibuprofen may precede subsequent, more-severe adverse reactions. Risks and benefits of continued use of nonsteroidal antiinflammatory drugs in these children should be carefully considered.

IBUPROFEN, A PROPIONIC-ACID derivative nonsteroidal antiinflammatory drug (NSAID), is extensively used in children for analgesia and fever control. Its mechanism of action is the inhibition of prostaglandin production by blocking the cyclooxygenase enzymes known as COX-1 and COX-2, thus shunting arachidonic-acid metabolism, toward the 5-lipoxygenase pathway, resulting in increased production and release of cysteinyl leukotrienes.

Hypersensitivity reactions to NSAIDs are classified according to clinical reaction patterns^{1,2} and divided into 2 major classification groups. The first group comprises cross-reactive, most likely COX-inhibitor activity-related clinical syndromes. These syndromes span the spectrum from classical "aspirin triad" (aspirin-exacerbated respiratory disease) to isolated urticaria and/or angioedema reactions, which are more common in adults and children with chronic urticaria³ but also documented in otherwise healthy children and adults. The second classification group contains drug-specific, most likely immunologically mediated reaction types, from cellular-dependent delayed type hypersensitivity to classical type I immunoglobulin E-mediated anaphylaxis.

The true incidence of NSAID-hypersensitivity reactions in children is unknown and most likely shows a marked variability in genetically distinct populations. There is, however, a known increased incidence of the

cross-reactive type of reactions in children with allergic respiratory disease.⁴⁻⁶ By and large, the most common manifestations of NSAID hypersensitivity in children are angioedema and urticaria, but respiratory symptoms may appear as well.^{7,8}

Patients with chronic urticaria may have exacerbations of their urticaria symptoms after exposure to NSAIDs. In fact, in some cases, intolerance to NSAIDs is reported to precede by years the onset of chronic urticaria.⁹ However, most such reactions are confined to symptoms of facial angioedema and urticaria exacerbation, and most children with chronic urticaria can tolerate recommended doses of acetaminophen safely.

Here we report the case of a young Nepalese boy, born in Singapore, who presented with a severe anaphylactic reaction after ingestion of ibuprofen.

Key Words: nonsteroidal antiinflammatory drugs, acetaminophen, ibuprofen, child, allergy, chronic urticaria

Abbreviations: NSAID; nonsteroidal antiinflammatory drug; COX; cyclooxygenase

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CASE REPORT

A Nepalese boy who was born in Singapore presented at 12 years of age. He had had a significant history of recurrent urticaria/angioedema since the age of 5 years, with a frequency of urticaria/angioedema bouts of once or twice per month. The episodes were mostly unprovoked, but some reported triggers included egg ingestion, exercise, and acetaminophen ingestion. The patient has previously taken egg and acetaminophen with no apparent problems before the onset of these episodes.

With regards to the adverse drug reactions, there were encounters with acetaminophen on 3 separate occasions at 6, 8, and 12 years of age, with worsening of urticaria/angioedema symptoms approximately 1 hour postingestion of paracetamol. The child had also taken ibuprofen on a few occasions with similar but more-severe bilateral periorbital angioedema approximately 1 hour after ingestion.

In addition, the patient had had mild-persistent allergic rhinitis since 2 years of age and was treated with intermittent courses of nasal steroids. There was no history of previous bronchitis or wheezing episodes, and there was no significant family history of allergic or autoimmune disease or drug hypersensitivity.

Our patient presented to the KK Women's and Children's Hospital emergency department with fever and cough of 1 day's duration after receiving a 150-mg dose of ibuprofen (5 mg/kg) from his family physician. He developed a generalized rash, facial angioedema, and shortness of breath 1 hour after the ingestion.

The patient was noted to be tachypneic on presentation, with a respiratory rate of 54 breaths minute and an oxygen saturation of 89%. He was also noted to be bradycardic (heart rate from 40 to 60 beats per minute) and hypotensive (blood pressure trough of 60/40 mm Hg). Other physical findings included generalized urticaria and bilateral periorbital and perioral angioedema.

Resuscitation was commenced immediately, and his vital signs stabilized after intravenous adrenaline, hydrocortisone, fluid boluses, nebulized salbutamol, and supplemental oxygen. He was subsequently transferred to our children's ICU for additional management.

The patient's subsequent progress was uneventful, with no further progression or recurrence of symptoms. The investigations performed included a full septic workup, which was unremarkable. The results of investigations for chronic urticaria, including measuring the erythrocyte sedimentation rate, running renal- and liver-function tests, obtaining complement component 3 and 4 levels, performing mycoplasma serology, and measuring levels of autoimmune antibodies, were normal. Results of an examination of a stool sample for ova, cysts, and parasites were negative. His total immunoglobulin E level was elevated at 1140 IU/L.

A skin-prick test (SPT) to food allergens, aeroaller-

gens, and ibuprofen was performed in our outpatient clinic. The syrup ibuprofen solution consumed by the patient was used in the SPT. We diluted 1 mL of the syrup solution with 9 mL of normal saline 0.9% before application to the skin. The patient had positive SPT reactions to house dust mites (Der P and Der F mix, and *Blomia tropicalis*) and cockroach mix. Results of the ibuprofen SPT were negative, and results of the pulmonary-function tests were normal.

An acute anaphylactic reaction to ibuprofen was diagnosed in this child with nonimmunologic cross-reactive hypersensitivity to NSAIDs and acetaminophen. An oral provocation test with a selective COX-2 inhibitor is currently being considered.

DISCUSSION

Here we have described a case of severe anaphylactic reaction to ibuprofen in a Nepalese boy with recurrent urticaria and angioedema, persistent allergic rhinitis, and previous mild hypersensitivity reactions to acetaminophen and ibuprofen.

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 relatively recently discovered COX-3, found only in the brain and spinal cord.¹⁰ Thus, although acetaminophen has almost no antiinflammatory effects even at high doses and, therefore, is not an NSAID, strictly speaking, it is an inhibitor of prostaglandin synthesis, similar to aspirin and the NSAIDs.

Our patient presented with a severe anaphylactic reaction including hypotension, respiratory distress, and cutaneous symptoms and required significant resuscitation at the emergency department after a conventional antipyretic dose of ibuprofen (5 mg/kg). This occurred in the background of previously mild (isolated cutaneous) but progressively more severe hypersensitivity reactions to acetaminophen and ibuprofen. The drug-hypersensitivity reactions developed after the onset of allergic rhinitis and recurrent urticaria in our patient. 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.⁷

An underlying autoimmune disease may be an additional risk factor. A severe anaphylactoid reaction with ibuprofen has been reported as the first manifestation of systemic lupus erythematosus in adolescence.¹¹ Our patient has a history of recurrent idiopathic urticaria that may also be secondary to an as-yet-undiagnosed autoimmune mechanism. Therefore, patients who present with such severe reactions to NSAIDs may need an evaluation for an autoimmune inflammatory disease.

A cross-reactive hypersensitivity reaction to NSAIDs and acetaminophen is the likely explanation for our

patient. We have noted that NSAID cross-reactive hypersensitivity reactions are more common than previously reported, especially in Asian children who present with facial angioedema and urticaria.^{4,7} In addition, we have observed that the majority of these children under 6 years of age with NSAID hypersensitivity have cross-reactive hypersensitivity reactions to paracetamol.¹²

We postulate that there may be increased susceptibility to prostaglandin inhibition in this population, and genetic markers could possibly be identified and serve to abrogate the need for diagnostic oral provocation tests in the future. Selective COX-2-specific medications may be appropriate alternatives for some of the older children.

CONCLUSIONS

There are many facets to NSAID hypersensitivity, and patients with chronic or recurrent idiopathic urticaria and those with atopic disease represent groups with increased risk. Mild hypersensitivity reactions to acetaminophen and/or ibuprofen may precede subsequent, more-severe adverse reactions. Continued use of NSAIDs in patients with previous hypersensitive reactions may result in increasingly severe responses including systemic anaphylactoid reactions.

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