CASE REPORT

Anaphylaxis to ibuprofen in a 12-year-old boy

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SUMMARY

Non-steroidal anti-inflammatory (NSAIDs) drugs are a group of medications acting through cyclooxygenase (COX-1) and cyclooxygenase (COX-2) enzymes inhibition. Hypersensitivity reactions to NSAIDs, although not rare, are poorly characterised and often go undiagnosed especially in children. We present in this paper a case of ibuprofen anaphylaxis that exemplifies the challenges involved in diagnosis and management of hypersensitivity reactions to NSAIDs.

BACKGROUND

Non-steroidal anti-inflammatory (NSAIDs) drugs are a group of medications acting through cyclooxygenase (COX-1) and cyclooxygenase (COX-2) enzymes inhibition. This inhibition leads to reduced prostaglandin production from arachidonic acid and increased shunting of arachidonic acid towards the 5-lipoxygenase pathway.¹ The latter results in higher production of cystenil leukotrienes. Hypersensitivity reactions to NSAIDs may involve immunological and non-immunological mechanisms.² Immune-mediated reactions are particularly rare and may be IgE or non-IgE mediated. Symptoms associated with immune-mediated reactions are usually drug specific and include: bronchospasm, rhinitis and conjunctivitis; angioedema and urticaria; and anaphylaxis as well as aseptic meningitis and hypersensitivity pneumonitis. Non-immune-mediated reactions are likely related to disequilibrium in the arachidonic acid degradation pathway. These reactions are characterised by a high level of cross reactivity between different NSAIDs and may result in NSAID induced asthma and rhinitis in asthmatic patients, NSAID induced urticaria/angioedema in patients with chronic urticaria, Asthma or urticaria in otherwise normal individuals and blended reactions in otherwise normal individuals.³ Despite the widespread use of NSAIDs, hypersensitivity reactions to NSAIDs, although not rare, are poorly characterised and often go undiagnosed especially in children. Furthermore, the heterogeneous clinical presentation patterns may contribute to the complexity of diagnosis and treatment of these reactions. We present in this paper a case of ibuprofen hypersensitivity that highlights challenges in the diagnosis and management of patients presenting with NSAID hypersensitivity.

CASE PRESENTATION

A 12-year-old boy with a history of mild intermittent asthma (no asthma exacerbations in the last 2 years) and known environmental sensitivities (grass, trees and dust mite) presented with anaphylaxis to the emergency department. Fifteen minutes after eating a hotdog and taking 200 mg ibuprofen

for mild headache he had developed urticaria, a burning sensation in his eyes, conjunctivitis, peri-orbital swelling, sensation of tightness in his throat and shortness of breath (figure 1). Intramuscular epinephrine was administered in the emergency room with improvement within minutes in his respiratory symptoms and resolution of angioedema over the following 4 h. He was prescribed an epinephrine autoinjector. Over the next 3 months he had four similar episodes. Each episode was treated promptly with an epinephrine autoinjector (twice at the emergency department and twice at home) with gradual improvement of his symptoms. Three episodes occurred 15 min after eating (macaroni and cheese and mustard; a chicken sandwich with mayonnaise; and salmon with mustard, dried green onion, coriander and vegetable seasoning mix, respectively) and within 1 h after taking 200 mg of ibuprofen for headache. The fifth episode occurred within 1 h after taking 400 mg of ibuprofen for headache with no known food exposure. He did not exercise for 2–3 h preceding his reactions nor was he exposed to cold, latex, venom or other medications. Prior to the first episode of anaphylaxis the patient had taken ibuprofen multiple times without adverse reactions.

Figure 1 A 12-year-old boy presenting to the emergency department with angioedema and shortness of breath following ingestion of ibuprofen.

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INVESTIGATIONS

Skin prick test was negative for hotdog, mozzarella cheese, mustard; dried green onion, coriander and vegetable seasoning mix. These foods constituted all foods eaten immediately prior to an episode of anaphylaxis that were not part of the patient's regular diet. An oral challenge to the same brand of hotdog associated with his first reaction was also negative.

Given his recurrent episodes of angioedema and difficulty in breathing, blood was drawn for levels of tryptase, C1 esterase inhibitor and C4 levels. All tests results were within the normal range.

After the initial work-up outlined above, strict avoidance of ibuprofen and all other NSAIDs was implemented. An oral celecoxib challenge was performed and 100 mg of celecoxib was tolerated well. During the following 6 months the patient did not have any allergic reactions.

DIFFERENTIAL DIAGNOSIS

Involvement of two organ systems after exposure to a potential allergen is consistent with the diagnosis of anaphylaxis.⁴ Foods and food additives, medications, insect stings, latex, exercise, cold and transfusions are the most common causes of anaphylaxis.⁵ Our patient had negative skin tests to the infrequently consumed foods he ate prior to anaphylaxis, making foods and food additives unlikely causes. He was not exposed to venom, latex, exercise or cold at the time of anaphylaxis. The differential diagnosis of recurrent angioedema and difficulty in breathing include hereditary and acquired angioedema as well as idiopathic anaphylaxis and systemic mastocytosis.⁵ However, given the lack of family history of angioedema, normal levels of C4 and C1 esterase inhibitor during an attack and given the lack of skin lesions and normal tryptase levels, these diagnostic options are highly unlikely.

Given that each episode occurred within an hour after ibuprofen exposure and given the complete absence of episodes after ibuprofen avoidance in the following 6 months, the most likely diagnosis is ibuprofen hypersensitivity.

TREATMENT

Strict avoidance of ibuprofen and all (NSAIDs), with the exception of celecoxib, was advised. He was also advised that acetaminophen may be used if needed for pain or fever.

OUTCOME AND FOLLOW-UP

Skin prick testing and patch testing for ibuprofen were not conducted as there are no published protocols and their sensitivity and specificity are not known. An ibuprofen challenge was not considered ethical due to risk of anaphylaxis. The patient used acetaminophen and celecoxib for pain control in the following 6 months with no adverse reaction.

DISCUSSION

Anaphylaxis is defined when symptoms involving two organ systems or hypotension develop in response to an allergen. Mast cell degranulation and basophil activation play a major role in the pathogenesis of anaphylaxis. Cellular mediators released following mast cell degranulation cause vasodilatation, fluid extravasation, smooth muscle contraction and increased mucosal secretions.⁵ Anaphylaxis may be IgE and non-IgE mediated. Ibuprofen is a non-steroidal anti-inflammatory drug commonly used to treat fever and pain in adults and children. Ibuprofen use can be associated with hypersensitivity reactions that are both IgE mediated and non-IgE mediated.⁶ Diagnosis of

ibuprofen hypersensitivity is considerably difficult. There are no reliable in vitro confirmatory tests and there is a wide clinical variety of reactions. The only effective way to establish the diagnosis is through a provocative challenge test.⁷

Only a few cases of ibuprofen induced anaphylaxis were described in the medical literature.⁸⁻⁹ Our patient met clinical criteria for anaphylaxis. All five episodes of anaphylaxis occurred within 1 hour of ibuprofen ingestion and his reaction involved both the coetaneous and respiratory systems. None of the other common triggers for anaphylaxis were present. It is extremely difficult to differentiate between IgE and IgE-mediated anaphylaxis to ibuprofen. Our patient did not present with asthma symptoms in recent years and had previously taken ibuprofen without asthma exacerbation. Furthermore, the current reactions were not associated with wheezing or cough. Hence, his reaction cannot be defined as NSAID exacerbated asthma and rhinitis in an asthmatic patient.

Given prior exposure to ibuprofen and severity of reaction he could have had an IgE-mediated reaction. This is also in line with his prompt response to epinephrine. A recent review of medical literature on adverse reactions to NSAIDs in children in the years 1980 and 2005 reveals that the most common clinical presentation of NSAID hypersensitivity in children is angioedema with or without hives. These reactions were not drug specific, hence non-IgE mediated.³ A prospective study involving 55 785 children with acute febrile illness who were given either 5 or 10 mg/kg of ibuprofen did not observe a single case of anaphylaxis, suggesting anaphylaxis is very rare in children exposed to ibuprofen.¹⁰ However, given the severity of reaction in our case and the availability of efficacious COX-2 inhibitors, we elected to present a challenge with a COX-2 antagonist rather than with a different COX-1 antagonist. The patient passed the challenge successfully.

Regardless of the mechanisms leading to NSAID sensitivity the best management strategy is avoidance of re-exposure. The use of COX-2 specific medications, such as celecoxib, is appropriate in both IgE and non-IgE mediated hypersensitivity reactions to NSAIDs and should be considered as the first line option when the risk of anaphylaxis is high.

Learning points

- ▶ Consider ibuprofen as a trigger for anaphylaxis in children.
- ▶ Currently, skin prick and patch testing cannot be used to reliably rule in or out IgE-mediated ibuprofen allergy.
- ▶ Patients who have anaphylaxis to ibuprofen may tolerate selective cyclooxygenase COX-2 inhibitors. Tolerance can be determined by an oral challenge.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Kidon MI, Kang LW, Chin CW, *et al.* Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children. *Pediatrics* 2005;116:e675–80.
- 2 Caimmi S, Caimmi D, Bousquet PJ, *et al.* How can we better classify NSAID hypersensitivity reactions?—validation from a large database. *Int Arch Allergy Immunol* 2012;159:306–12.

- 3 Kidon MI, Kang LW, Chin CW, *et al.* Nonsteroidal anti-inflammatory drug hypersensitivity in preschool children. *Allergy Asthma Clin Immunol* 2007;3:114–22.
- 4 Sampson HA, Munoz-Furlong A, Campbell RL, *et al.* Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006;47:373–80.
- 5 Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. *Allergy* 2010; 66:1–14.
- 6 Stevenson DD. Aspirin and NSAID sensitivity. *Immunol Allergy Clin North Am* 2004;24:491–505, vii.
- 7 Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001;87:177–80.
- 8 Hassani A, Ponvert C, Karila C, *et al.* Hypersensitivity to cyclooxygenase inhibitory drugs in children: a study of 164 cases. *Eur J Dermatol* 2008;18:561–5.
- 9 Kang LW, Kidon MI, Chin CW, *et al.* Severe anaphylactic reaction to ibuprofen in a child with recurrent urticaria. *Pediatrics* 2007;120:e742–44.
- 10 Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* 1995;273:929–33.

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