

Anaphylaxis to Over-the-Counter Flurbiprofen in a Child

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Key Words

Anaphylaxis · Child · Over-the-counter flurbiprofen

Abstract

Non-steroidal anti-inflammatory drugs are suspected to cause drug hypersensitivity very frequently in paediatric patients. In this article, we describe the first case of anaphylaxis to flurbiprofen in a child and provide insight into the possibility of severe reactions and even anaphylaxis to over-the-counter flurbiprofen. Finally, the importance of a rigorous allergy work-up in reaching a confident diagnosis and providing the patient with a safe alternative is shown.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) rank second among drugs that are suspected to cause drug hypersensitivity in paediatric patients [1–5]. Respiratory and cutaneous reactions are the most frequent manifestations [6], but anaphylaxis may even occur [7]. Flurbiprofen (1,1'-biphenyl-4-acetic acid, 2-fluoro- α -methyl) is a prostaglandin synthetase inhibitor with anti-inflammatory activity. It is usually administered orally because of its almost complete and rapid absorp-

tion through this route. Due to its good tolerance, flurbiprofen is also very commonly used as a topical preparation and is present as a component in widely used over-the-counter (OTC) drugs. Here, we describe the first paediatric case of anaphylaxis to OTC flurbiprofen.

Case Report

A 10-year-old girl was admitted to the Anna Meyer Children's Hospital Emergency Department because of a feeling of numbness in the mouth with swelling of the lips and tongue, swelling of the eyelids and of the glottis. Upon physical examination, she appeared in good general condition, but had difficulty speaking due to a partial obstruction of the airway caused by tongue oedema. Her oxygen saturation was 93% in ambient air. Her other vital signs were normal: a heart rate of 90 bpm, rhythmic peripheral pulses, blood pressure of 113/63 mm Hg, refill time <2 s, no preload signs and a Glasgow coma scale score of 15. Her symptomatology developed approximately 1 h after the consumption of an OTC tablet containing 8.75 mg of flurbiprofen for a sore throat. Blood tests were performed and they showed normal blood count, normal C-reactive protein levels, and a tryptase level of 3 μ g/l (normal value <12 μ g/l). The negative reaction was treated with intravenous chlorphenamine (0.25 mg/kg/dose), hydrocortisone (10 mg/kg/dose) and saline solution. The clinical symptoms resolved in 4–5 h, and the girl was discharged after 7 h with a home therapy consisting of prednisone (1 mg/kg/day) and 10 mg cetirizine for one additional day. After 1 month, she was evaluated at the Allergy Unit of Anna Meyer Children's Hospital. With regard to family history, she revealed that she had a paternal uncle with

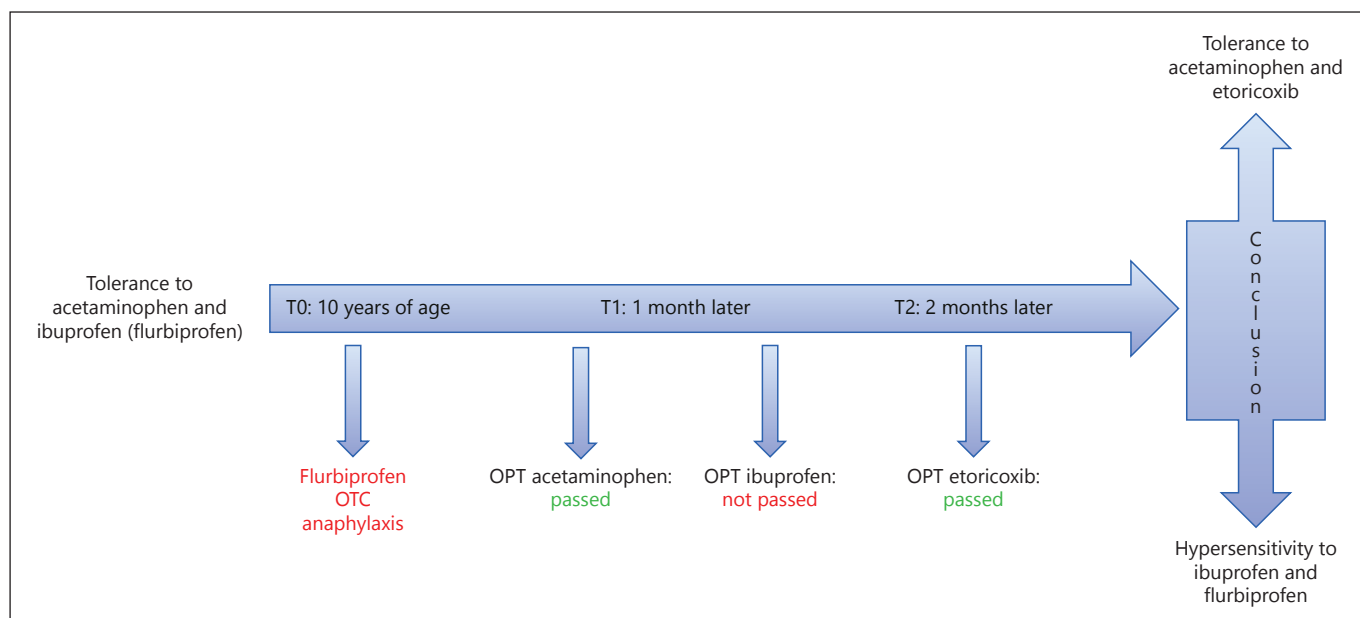


Fig. 1. Allergy work-up.

asthma and allergic reaction (anaphylaxis) to unspecified drugs. At physiological anamnesis, she had nothing to report except an Apgar score of 6 at the first minute and a neonatal diagnosis of transient tachypnoea of the infant. Regarding medical history, the girl had controlled asthma through cross-therapy with fluticasone and salmeterol/fluticasone in the winter months and an admission to the intensive care unit for a severe episode of bronchospasm 2 years prior to this incident. At drug history, it was reported that she had previously used and tolerated ibuprofen, acetaminophen and possibly OTC tablets containing flurbiprofen on one occasion. Because of the severity of the reaction, flurbiprofen was not investigated using a drug provocation test but with a skin prick test, with the full strength oral suspension [8] testing negative. To provide the patient with a safe drug alternative in case of clinical need, an oral provocation test (OPT) with acetaminophen was conducted in a three-step grading challenge at a dose of 10 mg/kg (e.g., 1/10th, 2/10th and 7/10th of the therapeutic dose at 30 min intervals). The girl was observed for 2 h after the administration of the last dose of the drug (cumulative dose of 500 mg), and she did not develop any reaction. Therefore, the factor of becoming hypersensitive to oral acetaminophen was excluded. Before undergoing any OPT, the girl's parents signed a written informed consent. Because of the discrepancy between the reaction and the girl's drug history, an OPT with ibuprofen was conducted in a three-step grading challenge at a dose of 10 mg/kg (e.g., 1/10th, 2/10th and 7/10th of the therapeutic dose at 30 min intervals) in the same month. In this case, there was a reaction characterized by facial erythema, bilateral periocular angioedema, a tingling sensation and mild angioedema of the lips approximately half an hour after the administration of the last dose of the drug (cumulative dose 500 mg). Her cardiovascular and respiratory parameters remained stable. Corticosteroids and antihistamines were administered, with almost complete recovery except for the persistence of a mild angioedema of the upper eyelids. Therefore, the girl was diagnosed to be hyper-

sensitive to flurbiprofen and ibuprofen. After 1 month, an OPT with etoricoxib (off label in children under 12 years of age) was conducted in fractional doses (1/3 + 2/3) to a cumulative dose of 60 mg, without the appearance of any reaction after 2 h of observation. Therefore, hypersensitivity to etoricoxib was ruled out, and it was indicated that the drug could be taken along with acetaminophen as necessary (fig. 1).

Discussion

Although an Italian meta-analysis detected an increased risk of allergic reaction to propionic acid derivatives compared with other NSAIDs [9], case reports of real allergic reactions to flurbiprofen are rare in the literature.

There are some reports of drug eruptions such as contact dermatitis [10], cutaneous vasculitis [11], generalized bullous fixed drug eruption [12], toxic epidermal necrolysis, exfoliative dermatitis [13] and lichenoid eruption [14] related to the use of flurbiprofen. A rare case of myocarditis due to a hypersensitivity reaction caused by oral flurbiprofen has also been described [15].

The case of a patient who developed a maculopapular rash 48 h after beginning oral therapy with flurbiprofen and angioedema and hypotension 2 days after was reported by Romano and Pietrantonio [16]. However, the clinical and allergic features that were reported strongly suggested a type IV hypersensitivity reaction; in fact, patch

tests 48 and 72 h after application resulted positive for flurbiprofen. Sendur et al. [17] described a case of isolated unilateral eyelid angioedema upon the use of flurbiprofen. Another case of a hypersensitivity reaction to a single oral dose of flurbiprofen, characterized by itching and swelling around the eyes, redness and increased lacrimation, was reported by Mehra et al. [18].

The case of a fatal hypersensitivity reaction to an oral flurbiprofen spray was described by Calapai et al. [19]. Immediately after administering the spray, the patient underwent a severe reaction with serious dyspnoea followed by death. Upon post-mortem examination, the reported cause of death was heart failure with acute asphyxia from oedema of the glottis. Although this case was described in an adult and occurred after the use of a spray instead of a tablet, it notes the possibility of severe reactions or even anaphylaxis to OTC drugs and indicates that

health professionals should be aware of potential adverse reactions to OTC preparations.

Moreover, ibuprofen and flurbiprofen are both phenylpropionic acid derivatives. Cross reactivity between these two drugs is known and occurs because the drugs are biochemically related.

In conclusion, this is the first paediatric report of anaphylaxis to OTC flurbiprofen. This case shows the importance of a rigorous allergy work-up, in particular the OPT, especially when skin tests are not standardized and have a poor sensitivity, to provide the patient with a safe alternative in case of clinical need.

Disclosure Statement

All authors disclose any conflicts of interest.

References

- 1 Erkokoglu M, Kaya A, Civelek E, Ozcan C, Cakir B, Akan A, et al: Prevalence of confirmed immediate type drug hypersensitivity reactions among school children. *Pediatr Allergy Immunol* 2013;24:160–167.
- 2 Rebelo Gomes E, Fonseca J, Araujo L, Demoly P: Drug allergy claims in children: from self-reporting to confirmed diagnosis. *Clin Exp Allergy* 2008;38:191–198.
- 3 Lange L, Koningsbruggen SV, Rietschel E: Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in German children. *Pediatr Allergy Immunol* 2008;19:634–638.
- 4 Orhan F, Karakas T, Cakir M, et al: Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren. *Pediatr Allergy Immunol* 2008;19:82–85.
- 5 Tan VA, Gerez IF, Van Bever HP: Prevalence of drug allergy in Singaporean children. *Singapore Med J* 2009;50:1158–1161.
- 6 Gomes ER, Brockow K, Kuyucu S, et al: Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy* 2016;71:149–161.
- 7 Torres MJ, Barrionuevo E, Kowalski M, Blanca M: Hypersensitivity reactions to non-steroidal anti-inflammatory drugs. *Immunol Allergy Clin North Am* 2014;34:507–524.
- 8 Wickern GM, Nish WA, Bitner AS, et al: Allergy to beta-lactams: a survey of current practices. *J Allergy Clin Immunol* 1994;94:725–731.
- 9 Salvo F, Polimeni G, Cutroneo PM, et al: Allergic reactions to oral drugs: a case/non-case study from an Italian spontaneous reporting database (GIF). *Pharmacol Res* 2008;58:202–207.
- 10 Kawada A, Aragane Y, Maeda A, Yudate T, Tezuka T: Contact dermatitis due to flurbiprofen. *Contact Dermatitis* 2000;42:167–168.
- 11 Wei N: Flurbiprofen and cutaneous vasculitis. *Ann intern Med* 1990;112:550–551.
- 12 Balta I, Simsek H, Simsek GG: Flurbiprofen-induced generalized bullous fixed drug eruption. *Hum Exp Toxicol* 2014;33:106–108.
- 13 Roth DE, Spencer LV, Ahrens EM: Cutaneous reactions to drugs used for rheumatologic disorders. *Med Clin North Am* 1989;73:1275–1298.
- 14 Hamburger J, Potts AJ: Non-steroidal anti-inflammatory drugs and oral lichenoid reactions. *Br Med J (Clin Res Ed)* 1983;287:1258.
- 15 Uzkeser M, Emet M, Aslan S, et al: Myocarditis due to oral flurbiprofen use. *Am J Emerg Med* 2009;27:132.e3–e5.
- 16 Romano A, Pietrantonio F: Delayed hypersensitivity to flurbiprofen. *J Intern Med* 1997;241:81–83.
- 17 Sendur MA, Aksoy S, Ozdemir NY, Yaman S, Zengin N: Flurbiprofen-induced unilateral eyelid angioedema. *Cutis* 2014;94:E12–E13.
- 18 Mehra KK, Rupawala AH, Gogtay NJ: Immediate hypersensitivity reaction to a single oral dose of flurbiprofen. *J Postgrad Med* 2010;56:36–37.
- 19 Calapai G, Imbesi S, Cafeo V, et al: Fatal hypersensitivity reaction to an oral spray of flurbiprofen: a case report. *J Clin Pharm Ther* 2013;38:337–338.

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