Editorial

Reactions to Nonsteroidal Anti-Inflammatory Drugs in Children

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According to various epidemiological studies, hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common cause of drug-induced hypersensitivity in children.[1] In spite of their frequent use in early life, the medical literature dealing specifically with adverse reactions to analgesics and anti-inflammatory drugs in childhood is relatively sparse.

The classical reported prevalence rate of aspirin hypersensitivity in the general population of children is 0.3%.[2] However, approximately 12.5% of pooled reports of adverse drug reactions suspected of causing serious or fatal outcomes in infants and children under the age of 2 years are caused by indomethacin, paracetamol, or ibuprofen.[3] In a multinational study carried out in Latin America, NSAIDs were the most common cause of drug reactions in both adults and children, and accounted for almost 50% of reactions observed in the pediatric age group.[4] A relatively high rate of adverse drug reactions due to NSAIDs, between 18.6% and 26%, was also observed in Singaporean children, by Kidon and See[5] and Tan et al.[6] These significant variations can be explained by both ethnic and environmental factors and also by differences in classification and diagnostic criteria. Interestingly, when children with a history suggesting NSAID hypersensitivity are submitted to confirmatory provocation tests with aspirin or other NSAIDs, only between 16.9% and 31.1% experience reactions.[1,7] The rate of "true" reactions seems to increase with age.

Various risk factors have been associated with reactions to NSAIDs in childhood, including chronic urticaria,[8] atopy (personal and family history of atopic diseases), and allergic rhinoconjunctivitis.[9,10]

Facial angioedema is the most frequent clinical manifestation of NSAID HS in children,[11] followed closely by the combination of acute respiratory symptoms with facial angioedema.[12] These previously called "blended" reactions are not currently included in the classification of hypersensitivity reactions to NSAIDs.[13]

Hypersensitivity reactions to NSAIDs are classified according to the drugs eliciting the reactions as selective (reactions to one drug or more than one chemically similar compounds) and cross-intolerant (CI; reactions to multiple chemically unrelated cyclooxygenase [COX] inhibitors). Five phenotypes of NSAID hypersensitivity, 3 cross-reactive putatively mediated by non-immunological mechanisms and 2 selective (allergic), have been identified by the task force on NSAID Hypersensitivity of the European Academy of Allergy and Clinical Immunology (EAACI).[13]

In this issue of the *JACI In Practice*, Blanca-Lopez et al[14] present their observations on 116 children with a clinical history suggestive of NSAID hypersensitivity who were submitted to single-blinded oral provocation tests with aspirin. NSAID hypersensitivity was confirmed in 26% of the patients. According to the history and results of drug challenges, allergic patients were classified as CI (83%) or selective reactors (17%). The clinical patterns of elicited reactions were NSAID-induced urticaria and angioedema (56.6%), NSAID-exacerbated respiratory disease (3.3%), and single-NSAID-induced urticaria, angioedema, and/or anaphylaxis (16.6%). However, 23.5% did not fit the current EAACI categories and were classified as mixed reactions, a combination of respiratory and cutaneous manifestations. This mixed (or blended) group of reactions to NSAIDs had been proposed years ago by Stevenson et al,[15] but was not included in the recent versions of the classification.[13]

Nonetheless, increasing evidence suggests that this type of reaction is common in childhood, may be driven by different pathophysiological mechanisms, and should be added to the classification of CI NSAID hypersensitivity reactions in this age group.[1,8,10] In Cousin et al's study, 40.2% of patients could not be completely classified in the EAACI classification and 3.7% were designated as "not possible to classify." These authors proposed 3 groups of reactions: group I—nonallergic, CI NSAID hypersensitivity (corresponding to EAACI 1, 2, and 3 phenotypes but also including the "mixed" reactions), group II—single NSAID-induced urticaria/angioedema or anaphylaxis (EAACI 4), and group III—single NSAID-induced delayed reactions (EAACI 5).[1] By definition, an allergic reaction causing 2 or more systems' involvement is considered an anaphylactic reaction, and Cavkaytar et al,[8] Kidon et al,[10] and Blanca-Lopez et al[14] all observed a significant number of CI children who developed NSAID-induced anaphylaxis.

It is generally accepted that for the nonallergic CI reactions, the relative COX-1 inhibitory efficacy of the drugs can predict the *in vivo* challenge results. The management of fever, pain, and

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inflammation in children with confirmed cross-reactive NSAID hypersensitivity is restricted to the utilization of acetaminophen, a weak COX-1 inhibitor,[16] which may be tolerated by many patients. However, reactions may still occur, especially when increased doses are administered, and in a high-risk subpopulation of children as documented in previous studies.[12,17] In this regard, a high-risk subset of NSAID hypersensitive patients who cannot tolerate weak COX-1 inhibitors has been proposed.[18,19] A related paper by Kidon et al[12] observed that children with early onset NSAID hypersensitivity appear to have a significantly increased likelihood of reacting to paracetamol when compared with children with later onset NSAID hypersensitivity.

Collectively, these observations support the need for a change in the classification of NSAID-induced hypersensitivity reactions in children and are a current focus of the EAACI's task force on pediatric drug hypersensitivity review.

In the current work, Blanca-Lopez et al propose that because the diagnosis of NSAID hypersensitivity is currently based on the performance of observed provocation tests, performing an aspirin challenge as the first of such tests is a safe and effective screening method, capable of immediately classifying allergic children into one of 2 major categories as CI or single drug allergy. In 86% of hypersensitivity children described in their work, the aspirin challenge was indeed enough to establish the diagnosis. However, in their entire studied group, with a majority of nonallergic patients, when the aspirin study was negative, a second provocation test with the culprit drug was required to rule out hypersensitivity. This suggests that the effectiveness of an aspirin provocation as the first recommended study in the diagnosis of NSAID hypersensitivity in children will depend on the frequency of "true reactions" in the population studied. These recommendations are also one of the focuses of the EAACI's task force on pediatric drug hypersensitivity review.

In conclusion, because of the large population of children who are exposed to NSAIDs, hypersensitivity to such drugs should always be considered as a possible drug-induced adverse effect that needs to be properly assessed and managed. Because NSAID hypersensitivity phenotypes may differ between adult and pediatric patients, further studies and new consensus documents are needed for better patient classification, diagnosis, and management. The current study[14] is an important contribution for the clarification of pediatric NSAID hypersensitivity, and novel phenotypes such as the mixed group of reactions (cutaneous plus respiratory) and anaphylactic reactions induced by different NSAIDs in cross-reactor patients should be included in these new recommendations.

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