Original Article

Acetyl Salicylic Acid Challenge in Children with Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs Differentiates Between Cross-Intolerant and Selective Responders

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What is already known about this topic? In adults several phenotypes of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs are recognized. They can be cross-intolerant or selective. Within the cross-intolerant, 3 subtypes are well differentiated with respiratory or cutaneous manifestations.

What does this article add to our knowledge? Different phenotypes of cross-intolerant reactions in children are observed after confirmation by acetyl salicylic acid challenge. Following skin involvement, the most common association was respiratory plus cutaneous; isolated respiratory symptoms were infrequent.

How does this study impact current management guidelines? In children with a history of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs, the administration of acetyl salicylic acid is the most appropriate initial way to establish the diagnosis.

BACKGROUND: Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) in children are becoming a great concern. Most studies have focused on adults, with noted discrepancies observed in the classification of hypersensitivity reactions to NSAIDs in children when compared with adults.
OBJECTIVE: To phenotype a group of children with hypersensitivity reactions to NSAIDs, including paracetamol, and analyze the degree of agreement with the entities reported in adults and how they fit the proposed classifications.
METHODS: The study comprised 116 children aged 0.5 to 14 years, with a clinical history indicative of hypersensitivity reactions to NSAIDs. They all underwent a single-blind oral provocation test with acetyl salicylic acid, except in those cases when this was the suspected drug, in which case the challenge was done first with ibuprofen. If positive, cross-intolerance was established and if negative, an oral provocation test with the culprit drug was performed to establish a selective response or exclude allergy.
RESULTS: Of the 26% diagnosed as hypersensitive to NSAIDs, 83% were cross-intolerant and 17% selective reactors. The highest significant differences between reactors and nonreactors were observed in the time to reaction after drug intake and the clinical entity ($P < .0001$), followed by drug involved and age ($P < .01$).
CONCLUSIONS: From the total number of cases confirmed with NSAID hypersensitivity, 83% were cross-intolerant. In cross-intolerant reactions, both cutaneous and respiratory manifestations are common. Acetyl salicylic acid challenge as the first approach proved to be safe and useful to establish the diagnosis. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *NSAID hypersensitivity; Acetyl salicylic acid challenge; Cross-intolerant; Selective responder; Children*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs most frequently used all over the world.[1] NSAIDs can induce hypersensitivity reactions with cutaneous and/or respiratory symptoms, with sometimes life-threatening systemic manifestations.[2] Reactions can be induced by specific immunological mechanisms[3,4] or by the release of inflammatory mediators without any immunological recognition.[4] The first group is called allergic reactions and the second nonallergic hypersensitivity reactions. Together these comprise hypersensitivity reactions to NSAIDs (HR-NSAIDs).[2,5-7] Although the classical model of HR-NSAIDs has focused on respiratory airway involvement,[8] 5 major groups of HR-NSAIDs are recognized:

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Abbreviations used
ASA- Acetyl salicylic acid
CI- Cross-intolerant
ENDA- European Network for Drug Allergy
HR-NSAIDs- Hypersensitivity reactions to NSAIDs
IQR- Interquartile range
NSAIDs- Nonsteroidal anti-inflammatory drugs
OPT- Oral provocation test
SR- Selective responder

(1) NSAID-exacerbated respiratory disease, (2) NSAID-exacerbated cutaneous disease, (3) NSAID-induced urticaria and/or angioedema, (4) single NSAID-induced urticaria/angioedema or anaphylaxis, and (5) single NSAID-induced delayed reactions.[4,7] The first 3 belong to the cross-intolerance category, and the remaining to the selective response category.[9]

Most studies have focused on adults, including adolescents,[5,10-12] although some involve wide age ranges, from 2 to 80 years.[5,13,14] Because the number of subjects younger than 14 years is small, drawing conclusions regarding the differences in clinical entities and drugs involved is difficult.[5,12] Very few studies comprise only children[15-24] without focusing on the different entities recognized.[25-27] A recent study claimed to have evaluated the largest series of children but at the time of evaluation the age ranged from 11 to 25 years (mean age, 15 years).[28] Our study involved a large series of children younger than 14 years who were prospectively evaluated over 4 years (2011-2014) for a hypersensitivity reaction to 1 or more NSAID. After following an algorithm with a well-defined protocol, including acetyl salicylic acid (ASA) challenge, we classified the children as cross-intolerant (CI) if they responded to various nonchemically related NSAIDs, and as selective responders (SRs) if they responded to a single NSAID with good tolerance to ASA.

METHODS

Patient evaluation

Children aged 14 years or younger referred to our service were evaluated prospectively for HR-NSAIDs over 4 years (2012-2015). After the workup (Figure 1) they were classified as hypersensitive to NSAIDs (group A, cases) or tolerant (group B). Challenge with ASA was made in all cases and if good tolerance occurred challenge was made with the culprit drug. Children with positive skin test results to dipyrone were not challenged. Informed written consent was obtained before the allergological study.

Inclusion criteria

Children younger than 14 years with a clinical history suggestive of HR-NSAIDs were included.

Exclusion criteria

Patients with acute infections and/or underlying diseases contraindicating oral provocation test (OPT) and patients with suspicion or evidence of a severe delayed reaction were excluded.

Clinical entities

After taking the clinical history, the clinical entities were defined as follows:

1. Urticaria, with or without angioedema, if there were large pruriginous wheals elevated over the skin, with or without flare and angioedema.[29]

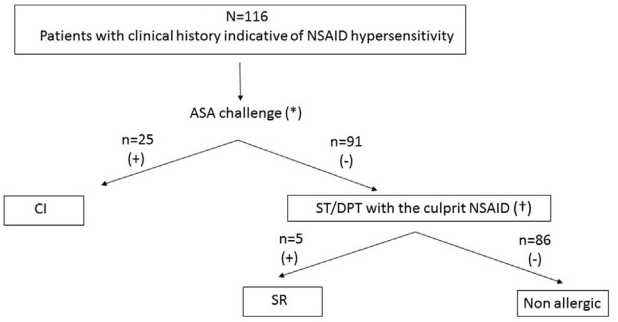

FIGURE 1. Diagnostic algorithm for evaluating the children. *If ASA was the culprit NSAID, a challenge with ibuprofen was done. †In cases in which dipyrone was the culprit, ST was done before DPT. *DPT,* Drug provocation test; *ST,* skin testing.

2. Isolated angioedema, in the absence of any other skin manifestation.
3. Anaphylaxis: symptoms involving 2 or more organs.
4. Asthma: wheezing with chest tightness and difficulty breathing requiring inhaled B2 and/or corticoids.
5. Rhinitis: nasal obstruction with itching and rhinorrhea.
6. Rhinitis plus asthma: a combination of the previous 2 entities.
7. Facial angioedema plus asthma/rhinitis: a combination of the 2.
8. Exanthema: small maculae or maculopapular rash.

These entities were then grouped following the ENDA classification[4] and if they (alone or in combination) did not fit properly they were analyzed independently.

Time interval between drug intake and symptom appearance

The time intervals considered were (1) less than 1 hour, (2) 1 to 6 hours, (3) 6 to 12 hours, and (4) more than 12 hours.

Assessment of atopy

This was done by skin prick testing with a panel of prevalent inhalant allergens including pollens, house dust mite, animal dander, and moulds (ALK-Abelló, Madrid, Spain). Patients with at least 1 positive test result were considered as atopic.

Skin testing with NSAIDs

This was done only with dipyrone by prick followed by intradermal testing, as described.[3] We did not perform skin testing with other NSAIDs because they have not been validated.[28]

Oral provocation test

Following the protocol (Figure 1), OPT was done with ASA to assess CI. If ASA was the culprit drug, ibuprofen was used. OPT was administered by a single-blind procedure according to the guidelines.[4] In all cases, OPT was done at least 4 weeks after the reaction. When symptoms appeared the procedure was stopped and patients were evaluated and treated. OPT was done in 2 steps:

1. Incremental doses of ASA at intervals of 90 minutes administered on 2 consecutive days. The first day, after single-blind placebo administration, 3 incremental doses of ASA were given till reaching half the therapeutic dose adjusted for body weight (15-20 mg/kg/dose). If negative, the following day 2 doses of ASA were administered till the full therapeutic dose.