

# 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 2018;6:1226-35)

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

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

#### 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.<sup>4,7</sup> The first 3 belong to the cross-intolerance category, and the remaining to the selective response category.<sup>9</sup>

Most studies have focused on adults, including adolescents,<sup>5,10-12</sup> although some involve wide age ranges, from 2 to 80 years.<sup>5,13,14</sup> Because the number of subjects younger than 14 years is small, drawing conclusions regarding the differences in clinical entities and drugs involved is difficult.<sup>5,12</sup> Very few studies comprise only children<sup>15-24</sup> without focusing on the different entities recognized.<sup>25-27</sup> 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).<sup>28</sup> 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 contra-indicating 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.<sup>29</sup>

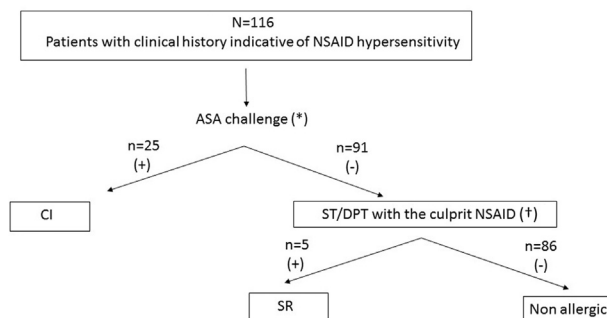


**FIGURE 1.** Diagnostic algorithm for evaluating the children. \*If ASA was the culprit NSAID, a challenge with ibuprofen was done. †In cases in which dipyrone was the culprit, ST was done before DPT. DPT, Drug provocation test; ST, skin testing.

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<sup>4</sup> 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 intra-dermal testing, as described.<sup>3</sup> We did not perform skin testing with other NSAIDs because they have not been validated.<sup>28</sup>

### 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.<sup>4</sup> 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.

TABLE I. Clinical characteristics of the confirmed cases (group A)

| Patient | Age (y) | Sex | Drug          | No. of episodes | Clinical entities (no. of episodes)*                                                       | TID-S   |
|---------|---------|-----|---------------|-----------------|--------------------------------------------------------------------------------------------|---------|
| 1       | 6       | F   | Ibuprofen     | 2               | Facial angioedema after treating fever (2)                                                 | 1-6 h   |
| 2       | 8       | M   | Ibuprofen     | 1               | Facial angioedema, generalized urticaria, and asthma after treating headache               | ≤1 h    |
| 3       | 13      | F   | Ibuprofen     | 3               | Bilateral eyelid angioedema after treating pharyngitis (3)                                 | 1-6 h   |
| 4       | 13      | M   | Ibuprofen     | 1               | Facial and lip angioedema after treating pharyngitis                                       | ≤1 h    |
| 5       | 11      | F   | Paracetamol   | 1               | Urticaria after treating respiratory infection with fever                                  | ≤1 h    |
| 6       | 12      | M   | ASA           | 1               | Urticaria after treating respiratory infection                                             | 1-6 h   |
| 7       | 8       | M   | Ibuprofen     | 1               | Bilateral eyelid angioedema after treating fever                                           |         |
| 8       | 5       | M   | Ibuprofen     | 3               | Facial angioedema and asthma after treating tonsillitis with fever (3)                     | ≤1 h    |
| 9       | 14      | M   | Ibuprofen     | 2               | Facial angioedema and asthma after treating headache (2)                                   | ≤1 h    |
| 10      | 9       | M   | Ibuprofen     | 2               | Facial angioedema and asthma after treating pharyngitis with fever (2)                     | ≤1 h    |
| 11      | 7       | M   | Ibuprofen     | 5               | Urticaria after treating laryngitis (5)                                                    | 1-6 h   |
| 12      | 12      | F   | Ibuprofen     | 4               | Unilateral eyelid angioedema after treating respiratory infection (4)                      | ≤1 h    |
| 13      | 9       | F   | Ibuprofen     | 2               | Facial angioedema after treating fever (2)                                                 | ≤1 h    |
| 14      | 12      | F   | Ibuprofen     | 2               | Facial angioedema, erythema on chest and abdomen plus rhinitis after treating headache (2) | ≤1 h    |
| 15      | 4       | M   | Ibuprofen     | 3               | Urticaria after treating respiratory infection (4)                                         | ≤1 h    |
|         |         |     | Dipyrone      | 1               | Urticaria after treating omphalocele (1)                                                   |         |
|         |         |     | Paracetamol   | 1               |                                                                                            |         |
| 16      | 12      | M   | Ibuprofen     | 3               | Urticaria and angioedema after treating headache (3)                                       | ≤1 h    |
| 17      | 7       | M   | Ibuprofen     | 1               | Facial angioedema after treating headache                                                  | ≤1 h    |
| 18      | 11      | F   | Ibuprofen     | 2               | Facial angioedema after treating respiratory infection (2)                                 | ≤1 h    |
| 19      | 13      | F   | Ibuprofen     | 2               | Facial angioedema after treating tonsillitis (2)                                           | 1-6 h   |
|         |         |     | Dipyrone      | 1               | Facial angioedema after treating headache                                                  | 1-6 h   |
| 20      | 11      | F   | Ibuprofen     | 1               | Generalized pruritus and facial angioedema after treating respiratory infection            | ≤1 h    |
| 21      | 9       | M   | Ibuprofen     | 1               | Rhinitis plus asthma after treating fever                                                  | ≤1 h    |
| 22      | 6       | M   | Ibuprofen     | 1               | Anaphylaxis after treating respiratory infection                                           | ≤1 h    |
| 23      | 14      | M   | Ibuprofen     | 2               | Facial angioedema and asthma after treating headache (2)                                   | ≤1 h    |
| 24      | 13      | M   | Dipyrone      | 1               | Anaphylaxis after treating toothache                                                       | ≤1 h    |
| 25      | 9       | M   | Dexketoprofen | 1               | Facial angioedema and asthma after treating toothache                                      | Unknown |
|         |         |     | Ibuprofen     | 1               | Facial angioedema and conjunctivitis after treating fever                                  |         |
|         |         |     | Dipyrone      | 1               | Facial angioedema and conjunctivitis after treating headache                               |         |
| 26      | 7       | M   | Ibuprofen     | 1               | Urticaria and facial angioedema after treating respiratory infection with fever            | Unknown |
| 27      | 5       | M   | Ibuprofen     | 2               | Urticaria and facial angioedema after treating respiratory infection with fever (2)        |         |
| 28      | 9       | M   | Ibuprofen     | 1               | Urticaria, facial angioedema, rhinitis, and asthma after treating fever                    | ≤1 h    |
| 29      | 10      | M   | Dipyrone      | 1               | Generalized urticaria after treating viral infection                                       | ≤1 h    |
| 30      | 8       | M   | Ibuprofen     | 1               | Generalized urticaria after treating pain                                                  | ≤1 h    |

F, Female; M, male; P, patient; TID-S, time interval between drug administration and symptom appearance.

\*In the parentheses of the column "clinical entities" are shown the number of episodes with the entity described.

2. This was done if the first step was negative. One week after step 1, an OPT with the culprit drug was done, adjusted for body weight (Figure 1). Challenge was also made at least 4 weeks after the OPT with ASA.

### Statistical analysis

Descriptive analysis was done for all the variables, first in the total group and then in the separate groups. Data were expressed as mean, SD, median and interquartile ranges (IQRs), and proportions. Quantitative variables were compared by Student test, and categorical variables by chi-square test. Analysis of all the variables was done by univariate and multivariate logistic regression.<sup>20</sup> A *P* value of less than .05 was considered statistically significant.

### RESULTS

The study included 116 children (67 [58%] boys and 49 [42%] girls) evaluated for a reaction attributed to 1 or more

NSAID. The mean and median ages were 7.15 and 7.5 years, the youngest being 6 months and the oldest 14 years. The indications for NSAIDs were fever (44%), headache (19%), pharyngitis (16%), respiratory infection (14%), pain (4%), and otitis (3%). The clinical entities reported were urticaria with/without angioedema (46%), isolated angioedema (29%), exanthema (14%), facial angioedema plus asthma and/or rhinitis (5%), anaphylaxis (3%), rhinitis plus asthma (2%), and asthma (1%). The cases with respiratory airway involvement accounted for 8%. The clinical history showed that the drugs involved were ibuprofen (83%), paracetamol (10%), ASA (4%), dipyrone (2%), and dexketoprofen (1%). In 69% only 1 episode was reported, in 19% 2 episodes and in 13% 3 or more. The time interval between NSAID intake and symptom appearance was within 1 hour in 51%, between 1 and 6 hours in 34%, between 7 and 12 hours in 13%, and longer than 12 hours in only 2%. In 4 cases the parents could not give the time interval. None of the

**TABLE II.** Clinical characteristics of negative testing (group B)

| Patient | Age (y) | Sex | Drugs                           | No. of episodes | Clinical entities (no. of episodes)*                                                                                                           | TI D-S           |
|---------|---------|-----|---------------------------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 1       | 6       | F   | Ibuprofen                       | 1               | Eyelid and facial angioedema after treating respiratory infection                                                                              | 1-6 h            |
| 2       | 1.5     | M   | Ibuprofen                       | 1               | Generalized wheals with facial angioedema after 7-d treatment of respiratory infection with fever                                              | 1-6 h            |
| 3       | 1.6     | M   | Ibuprofen                       | 1               | Generalized exanthema in trunk 24 h after treatment initiation for otitis                                                                      | 1-6 h            |
| 4       | 1.2     | F   | Ibuprofen                       | 2               | Generalized maculopapular exanthema after treating tonsillitis with fever<br>Generalized exanthema after treating respiratory infection        | 6-12 h<br>6-12 h |
| 5       | 6       | M   | Ibuprofen                       | 1               | Wheals with pruritus with lip angioedema after treating pharyngitis                                                                            | ≤1 h             |
| 6       | 11      | F   | Ibuprofen                       | 2               | Nonpruriginous maculopapular exanthema on chest and abdomen after treating pharyngitis (2)                                                     | Unknown          |
| 7       | 2       | M   | Ibuprofen                       | 1               | Wheals on legs and abdomen after 3 d of treatment for hip synovitis                                                                            | 1-6 h            |
| 8       | 8       | F   | Ibuprofen                       | 3               | Generalized wheals with pruritus and erythema for otitis and fever (3)                                                                         | ≤1 h             |
| 9       | 1.2     | M   | Ibuprofen                       | 1               | Generalized erythema followed by wheals and pruritus after treating fever                                                                      | ≤1 h             |
| 10      | 3       | F   | Ibuprofen                       | 3               | Eyelid angioedema after treating cephalaea (2)<br>Eyelid angioedema after treatment for pharyngitis                                            | ≤1 h             |
| 11      | 3       | M   | Ibuprofen                       | 1               | Maculopapular exanthema after treating fever                                                                                                   | 1-6 h            |
| 12      | 1.1     | F   | ASA<br>Ibuprofen<br>Paracetamol | 1<br>2<br>1     | Unilateral eyelid angioedema after treating fever (4)                                                                                          | 1-6 h            |
| 13      | 9       | M   | Paracetamol                     | 1               | Erythema on ears with pruritus on the skull and wheals on the abdomen after treating gastroenteritis with fever                                | ≤1 h             |
| 14      | 2       | M   | Ibuprofen                       | 1               | Facial erythema after treating fever. First time administration                                                                                | ≤1 h             |
| 15      | 1.2     | M   | Paracetamol                     | 1               | Facial angioedema, ear erythema with generalized wheals after treating fever                                                                   | 1-6 h            |
| 16†     | 5       | M   | Ibuprofen + paracetamol         | 1               | Generalized wheals with systemic pruritus after treating respiratory infection and fever. Good tolerance to paracetamol after the episode      | ≤1 h             |
| 17      | 4       | M   | Ibuprofen                       | 2               | Generalized wheals and pruritus after taking ibuprofen for fever (2)                                                                           | 6-12 h           |
| 18      | 10      | F   | Ibuprofen                       | 4               | Generalized wheals with pruritus and facial angioedema after treatment with ibuprofen for fever (4)                                            | 1-6 h            |
| 19      | 1       | F   | Paracetamol                     | 1               | Maculopapular exanthema on chest with pruritus after treatment for toothache                                                                   | 6-12 h           |
| 20      | 1.1     | F   | Ibuprofen                       | 1               | Maculopapular exanthema after treatment of cranial trauma. Worsening after repeating the dose                                                  | 6-12 h           |
| 21      | 2.5     | F   | Ibuprofen                       | 1               | Several episodes of disseminated wheals with pruritus after treatment for fever                                                                | 6-12 h           |
| 22      | 14      | M   | Ibuprofen                       | 1               | Facial and lip angioedema followed by wheals on chest, hands, and feet after treating chest pain                                               | 1-6 h            |
| 23      | 13      | F   | Ibuprofen                       | 1               | Systemic pruritus with generalized erythema and wheals on chest and abdomen after treating otitis                                              | ≤1 h             |
| 24      | 4       | M   | Ibuprofen                       | 1               | Facial and eyelid angioedema at age 8 mo after treating respiratory infection                                                                  | 1-6 h            |
| 25      | 5       | M   | Ibuprofen                       | 1               | Facial and lip angioedema after treating fever                                                                                                 | 1-6 h            |
| 26      | 10      | F   | Ibuprofen                       | 2               | Facial angioedema after treating ankle pain<br>Facial angioedema after treating pharyngitis                                                    | 1-6 h<br>1-6 h   |
| 27      | 12      | F   | Ibuprofen                       | 1               | Generalized exanthema after treating fever and cough                                                                                           | 1-6 h            |
| 28      | 13      | F   | Ibuprofen                       | 1               | Facial and lip angioedema after treating headache                                                                                              | 1-6 h            |
| 29      | 12      | M   | Paracetamol<br>Ibuprofen        | 1<br>1          | Lip angioedema after treating respiratory infection<br>Systemic pruritus with wheals on chest and abdomen after treating respiratory infection | ≤1 h<br>≤1 h     |
| 30      | 2.5     | M   | Paracetamol                     | 1               | Facial and lip angioedema after treating dysphagia                                                                                             | ≤1 h             |
| 31      | 13      | M   | Ibuprofen                       | 1               | Generalized wheals and angioedema 10 y previously after treating fever                                                                         | ≤1 h             |
| 32      | 2       | M   | Ibuprofen                       | 1               | Rhinorrhoea with nasal obstruction, eye erythema with eyelid angioedema after treating respiratory infection                                   | ≤1 h             |
| 33      | 0.4     | M   | Ibuprofen                       | 2               | Wheals and erythema on legs and arms after treating fever (2)                                                                                  | 6-12 h           |
| 34      | 8       | F   | Paracetamol                     | 2               | Facial and eyelid angioedema after treating fever (2)                                                                                          | 6-12 h           |
| 35      | 10      | M   | Ibuprofen                       | 1               | Palpebral angioedema after treating fever                                                                                                      | 1-6 h            |
| 36      | 13      | F   | Ibuprofen                       | 1               | Generalized wheals with pruritus and lip angioedema after treatment for headache                                                               | ≤1 h             |

(continued)

TABLE II. (Continued)

| Patient | Age (y) | Sex | Drugs                    | No. of episodes | Clinical entities (no. of episodes)*                                                                                                        | TI D-S  |
|---------|---------|-----|--------------------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 37      | 10      | M   | Ibuprofen                | 1               | Eyelid angioedema with pruritus, facial and hand angioedema after treating headache                                                         | 1-6 h   |
| 38      | 2       | F   | Paracetamol              | 1               | Facial angioedema after taking 1.7 mL for respiratory infection and fever. This was followed by generalized wheals after repeating the dose | ≤1 h    |
| 39      | 14      | F   | Ibuprofen                | 1               | Pruriginous wheals on abdomen, chest, and neck after treating respiratory infection with fever                                              | 1-6 h   |
| 40      | 1.2     | M   | Paracetamol              | 1               | Generalized pruritus plus wheals on buttocks, abdomen, and arms after treating fever                                                        | ≤1 h    |
| 41      | 6       | M   | Ibuprofen                | 2               | Generalized wheals with pruritus after treating fever (2)                                                                                   | 1-6 h   |
| 42      | 0.6     | M   | Ibuprofen                | 1               | Facial, leg, and thorax erythema after treatment for a respiratory infection with fever                                                     | ≤1 h    |
| 43      | 3       | M   | Ibuprofen                | 1               | Generalized wheals with pruritus after treatment for abdominal pain and fever                                                               | 1-6 h   |
| 44      | 2.5     | F   | Ibuprofen                | 1               | Maculopapular pruriginous exanthema with facial angioedema after treating pharyngitis with fever                                            | 1-6 h   |
| 45      | 1.4     | M   | Ibuprofen                | 1               | Nonpruriginous maculopapular exanthema after treating bronchitis with fever                                                                 | 1-6 h   |
| 46      | 1.5     | M   | Ibuprofen                | 1               | Generalized wheals with pruritus on chest, abdomen, and legs after treating fever                                                           | ≤1 h    |
| 47      | 3       | F   | Ibuprofen                | 1               | Wheals on buttocks, arms, and legs after treating fever                                                                                     | 1-6 h   |
| 48      | 0.6     | M   | Ibuprofen                | 1               | Maculopapular exanthema on chest and after treatment for respiratory infection                                                              | ≤1 h    |
| 49      | 9       | M   | Ibuprofen                | 1               | Eyelid angioedema after treatment for headache                                                                                              | ≤1 h    |
| 50      | 8       | M   | Ibuprofen                | 1               | Facial angioedema after treatment for fever and headache                                                                                    | 1-6 h   |
| 51      | 4       | F   | Ibuprofen                | 1               | Facial erythema with perinasal angioedema treatment for respiratory infection with fever                                                    | ≤1 h    |
| 52      | 1       | M   | Paracetamol              | 1               | Generalized pruriginous wheals including abdomen, chest, and face after treating bronchiolitis with fever                                   | ≤1 h    |
| 53      | 11      | F   | Paracetamol              | 1               | Wheals on chest, abdomen, and legs in the course of taking 650 mg/8 h; fourth day, give for respiratory infection and fever                 | 1-6 h   |
| 54      | 6       | F   | Ibuprofen                | 1               | Pruriginous wheals on face, abdomen, and chest after treating otitis                                                                        | 1-6 h   |
| 55      | 1       | M   | Ibuprofen                | 2               | Generalized wheals with eyelid angioedema after treating respiratory infection (2)                                                          | ≤1 h    |
| 56      | 0.7     | M   | Paracetamol              | 2               | Pruriginous maculopapular exanthema after treating fever (2)                                                                                | 1-6 h   |
| 57      | 8       | M   | Ibuprofen                | 1               | Lip angioedema and wheals on chest and abdomen after treating flu with fever                                                                | 1-6 h   |
| 58      | 6       | M   | Ibuprofen                | 1               | Hands with lip and tongue angioedema followed by wheals on chest, abdomen, and neck after treating pharyngitis                              | ≤1 h    |
| 59      | 5       | M   | Ibuprofen                | 1               | Generalized wheals after treating respiratory infection                                                                                     | ≤1 h    |
| 60      | 5       | F   | Ibuprofen                | 1               | Generalized pruritus and wheals with lip and eyelid angioedema after treating scarlet fever                                                 | 1-6 h   |
| 61      | 12      | M   | Paracetamol<br>Ibuprofen | 1<br>1          | Lip angioedema and generalized wheals with cutaneous pruritus after treating respiratory infection (2)                                      | ≤1 h    |
| 62      | 12      | F   | Paracetamol              | 1               | Generalized erythema and wheals after treating headache                                                                                     | ≤1 h    |
| 63      | 4       | F   | Paracetamol<br>Ibuprofen | 1<br>1          | Wheals on legs and arms with facial angioedema after treating fever (2)                                                                     | Unknown |
| 64*     | 12      | F   | Paracetamol+ ibuprofen   | 1               | Eyelid angioedema after treating fever                                                                                                      | 1-6 h   |
| 65      | 8       | M   | Ibuprofen                | 1               | Facial angioedema after treating fever                                                                                                      | ≤1 h    |
| 66      | 6       | M   | Ibuprofen                | 2               | Micropapular generalized exanthema after treating respiratory infection with fever (2)                                                      | 6-12 h  |
| 67      | 4       | F   | Ibuprofen                | 2               | Wheals on thorax, arms, and legs after treating otitis (2)                                                                                  | ≤1 h    |
| 68      | 9       | F   | Ibuprofen                | 3               | Eyelid and lip angioedema after treating fever (3)                                                                                          | 6-12 h  |
| 69      | 5       | F   | Paracetamol<br>Ibuprofen | 2<br>3          | Generalized wheals and lip angioedema after treating respiratory infection with fever (5)                                                   | 1-6 h   |
| 70      | 11      | M   | Ibuprofen                | 2               | Lip angioedema after treating headache (2)                                                                                                  | ≤1 h    |
| 71      | 12      | F   | Ibuprofen                | 1               | Maculopapular exanthema after treating respiratory infection with fever                                                                     | >12 h   |

(continued)

TABLE II. (Continued)

| Patient | Age (y) | Sex | Drugs     | No. of episodes | Clinical entities (no. of episodes)*                                                        | TI D-S |
|---------|---------|-----|-----------|-----------------|---------------------------------------------------------------------------------------------|--------|
| 72      | 13      | M   | Ibuprofen | 2               | Lip angioedema after treating respiratory infection with fever (2)                          | 1-6 h  |
| 73      | 13      | M   | Ibuprofen | 1               | Wheals on face after treating respiratory infection                                         | ≤1 h   |
| 74      | 14      | F   | Ibuprofen | 1               | Facial angioedema and throat tightness after treating otitis                                | 1-6 h  |
| 75      | 2       | F   | Ibuprofen | 3               | Wheals on thorax after treating fever (3)                                                   | 6-12 h |
| 76      | 14      | F   | Ibuprofen | 1               | Eyelid angioedema and wheals on the neck after treating fever                               | 1-6 h  |
| 77      | 8       | F   | Ibuprofen | 1               | Facial and thorax exanthema after treating respiratory infection with fever                 | >12 h  |
| 78      | 5       | F   | Ibuprofen | 1               | Facial and arm exanthema after treating urinary infection with fever                        | 1-6 h  |
| 79      | 2       | F   | Ibuprofen | 1               | Facial angioedema and generalized wheals with pruritus after treating respiratory infection | ≤1 h   |
| 80      | 8       | M   | Ibuprofen | 1               | Generalized wheals and pruritus after treating knee pain                                    | ≤1 h   |
| 81      | 3       | M   | Ibuprofen | 1               | Generalized wheals and pruritus after treating viral infection                              | ≤1 h   |
| 82      | 6       | M   | Ibuprofen | 1               | Palpebral angioedema after treating muscular pain                                           | 1-6 h  |
| 83      | 2       | F   | Ibuprofen | 1               | Generalized exanthema after treating respiratory infection with fever                       | 1-6 h  |
| 84      | 8       | F   | Ibuprofen | 1               | Generalized wheals and pruritus after treating tonsillitis                                  | 6-12 h |
| 85      | 11      | F   | Ibuprofen | 1               | Bilateral palpebral angioedema after treating fever                                         | ≤1 h   |
| 86      | 3       | M   | Ibuprofen | 1               | Palpebral angioedema after treating fever                                                   | 1-6 h  |

F, Female; M, male; TI D-S, time interval between drug administration and symptom appearance.

\*In the parentheses of the column "clinical entities" are shown the number of episodes with the entity described.

†This patient developed the reaction after taking the combination of paracetamol and ibuprofen.

patients reported episodes indicative of chronic spontaneous urticaria in the clinical history.

### Group A

Following the workup (Figure 1), 30 cases (26%) were considered hypersensitive or allergic to NSAIDs (group A) (Table I). Of the 30 cases, 25 (83%) were classified as CI and 5 (17%) as SRs. Most were male (70%). The mean age was  $9.5 \pm 2.89$  years and the median 9 years (IQR<sub>25-75</sub>, 7-12). A total of 59 episodes occurred in group A, with ibuprofen involved in 84.7%, dipyrone in 8.4%, paracetamol in 3.3%, and ASA and dextetopfen in 1.6% each; 46.6% of the patients reported just 1 episode, 26.6% reported 2 episodes, and 26.6% reported 3 or more episodes. In 90% of the cases, only 1 drug was involved and in 6% 2 non-chemically related NSAIDs, with 3 different NSAIDs involved in 1 child (Table I). The time interval between drug intake and symptom appearance was less than 1 hour in 76.6% of cases and 1 to 6 hours in 16.6%, with no patient reporting symptoms after 6 hours. In 2 cases the parents could not give the time interval. Regarding atopy, 80% were positive to at least 1 inhalant allergen by prick testing, with pollens being the most important (70.8%), followed by house dust mite (62.5%), animal dander (58.3%), and moulds (50%).

On classifying the clinical entities in the positive cases (group A, Table I) according to the proposed ENDA classification,<sup>4</sup> we found that NSAID-induced urticaria and/or angioedema occurred in 56.6% of cases, NSAID-exacerbated respiratory disease in 3.3%, and single NSAID-induced urticaria/angioedema and/or anaphylaxis in 16.6%. However, 23.5% of cases did not fit the ENDA classification properly because they had involvement of 2 or more organs and were therefore classified as mixed reactions (5 cases with facial angioedema plus asthma and 3 with anaphylaxis presenting respiratory symptoms plus generalized urticaria and facial angioedema). Only 1 case concerned isolated respiratory symptoms (rhinitis plus asthma). If we consider facial angioedema plus asthma as a distinct entity from

anaphylaxis and we include this as an NSAID-exacerbated respiratory disease, the percentage of this category increases to 24% and that of mixed reactions decreases to 12%.

### Group B

A total of 86 children (74%) tolerated ASA and the culprit NSAID (group B) (Table II); 53% were boys. The mean age was  $6.3 \pm 4.39$  years and the median 5.5 years (IQR<sub>25-75</sub>, 2-10). A total of 120 episodes were reported, with ibuprofen involved in 81.6%, paracetamol in 17.5%, and ASA in 0.8%. No cases were reported of reactions with dipyrone or other NSAIDs. In the clinical history most patients (73.2%) reported only 1 episode, 18.6% reported 2, and 8.1% reported 3 or more episodes. As shown in Table II, 2 patients experienced the reaction after taking 2 different NSAIDs simultaneously (cases 16 and 64). The time interval between drug intake and symptom appearance was less than 1 hour in 39.5% of the cases, 1 to 6 hours in 43%, 6 to 12 hours in 12.7%, and longer than 12 hours in 2.3%. In 2 cases the parents could not give this interval. The atopic status was positive in 68.9% of this group, with 80% being positive to pollens, 20% to house dust mite, 40% to animal dander, and 10% to moulds.

### Oral provocation tests

Table III presents the clinical results of the ASA challenge in group A. Of 30 children diagnosed with HR-NSAIDs, 24 were positive to ASA and considered as CI. Case number 6, because ASA was the culprit drug, was challenged first with ibuprofen, with a positive response to this drug and was also considered as CI. Five subjects who tolerated ASA but responded to the culprit drug were considered SRs (described below).

Regarding CI, the median cumulative dose of ASA after OPT was 300 mg (IQR<sub>25-75</sub>, 162-437 mg). The time interval between drug challenge and symptom appearance was within 30 minutes in 24%, 30 to 60 minutes in 16%, 1 to 2 hours in 20%, 2 to 6 hours in 28%, and longer than 6 hours in 12%.

TABLE III. Results of challenge with ASA in group A

| Patient | OPT | ASA cumulative dose (mg) | TI D-S     | Symptoms                                                                                                                                     |
|---------|-----|--------------------------|------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| 1       | +   | 200                      | 30 min     | Facial erythema, lip and eyelid angioedema, wheals on abdomen and neck                                                                       |
| 2       | +   | 150                      | 15 min     | Conjunctival hyperemia with eye pruritus, palpebral angioedema, repetitive cough, and FEV <sub>1</sub> % decrease of 18%%                    |
| 3       | +   | 500                      | 2 h        | Bilateral eyelid angioedema                                                                                                                  |
| 4       | +   | 500                      | 2.5 h      | Lip and eye angioedema                                                                                                                       |
| 5       | —   | 500                      |            | None                                                                                                                                         |
| 6*      | +   | 400 (ibuprofen)          | 5 h        | Skin pruritus followed by wheals on chest, abdomen, and legs                                                                                 |
| 7       | +   | 250                      | 5 h        | Eyelid angioedema with ocular pruritus                                                                                                       |
| 8       | +   | 150                      | 30 min     | Unilateral eyelid angioedema                                                                                                                 |
| 9       | +   | 375                      | 90 min     | Eyelid angioedema                                                                                                                            |
| 10      | +   | 175                      | 45 min     | Pruritus on eyes and nose, conjunctival hyperemia followed by itching and rhinorrhoea and lip angioedema. FEV <sub>1</sub> % decrease of 18% |
| 11      | +   | 500                      | 8 h        | Wheals on chest, legs, and abdomen                                                                                                           |
| 12      | +   | 500                      | 8 h        | Eyelid angioedema                                                                                                                            |
| 13      | +   | 150                      | 60 min     | Conjunctival hyperemia with eyelid angioedema                                                                                                |
| 14      | +   | 250                      | 1 h 15 min | Nasal obstruction and rhinorrhea, plus facial angioedema                                                                                     |
| 15      | +   | 25                       | 10 min     | Pruriginous wheals on chest and neck with eyelid angioedema                                                                                  |
| 16      | +   | 375                      | 90 min     | Conjunctival hyperemia with pruritus                                                                                                         |
| 17      | +   | 25                       | 50 min     | Conjunctival hyperemia with eyelid angioedema                                                                                                |
| 18      | +   | 300                      | 50 min     | Eyelid angioedema with facial erythema and pruritus                                                                                          |
| 19      | +   | 375                      | 6 h        | Facial angioedema                                                                                                                            |
| 20      | +   | 250                      | 24 h       | Lip angioedema                                                                                                                               |
| 21      | +   | 500                      | 6 h        | Cough, difficulty breathing (decrease of 25% in FEV <sub>1</sub> )                                                                           |
| 22      | —   | 300                      |            | None                                                                                                                                         |
| 23      | +   | 375                      | 90 min     | Eyelid angioedema                                                                                                                            |
| 24      | —   | 500                      |            | None                                                                                                                                         |
| 25      | +   | 375                      | 5 min      | Lip and eyelid angioedema, conjunctivitis, and difficulty breathing (decrease of 60% in FEV <sub>1</sub> )                                   |
| 26      | +   | 250                      | 4 h        | Eyelid angioedema                                                                                                                            |
| 27      | +   | 25                       | 30 min     | Eyelid angioedema                                                                                                                            |
| 28      | +   | 500                      | 6 h        | Nasal obstruction with rhinorrhoea, cough, and difficulty breathing with wheezing                                                            |
| 29      | —   | 500                      |            | None                                                                                                                                         |
| 30      | —   | 500                      |            | None                                                                                                                                         |

TI D-S, Time interval between drug administration and symptom appearance.

\*This patient, because ASA was the culprit drug, underwent a DPT with ibuprofen.

Case numbers 5, 22, 24, 29, and 30 of Table III were considered SRs. Two cases were diagnosed as SRs to dipyrone after positive intradermal skin testing at 4 mg/L. Another 2 cases were diagnosed as SRs to ibuprofen, one after a positive OPT at a cumulative dose of 200 mg and in the other the diagnosis was made from the clinical history because of the severity of the reaction reported (anaphylaxis). The fifth child was diagnosed as SR to paracetamol after a positive OPT result at a cumulative dose of 300 mg.

### Differences between groups

Group A was significantly ( $P < .001$ ) older ( $9.5 \pm 2.89$  years) than group B ( $6.3 \pm 4.39$  years). Although there were more males in group A (70%) than in group B (53%), the difference was not significant ( $P = .086$ ).

Figure 2 compares the clinical entities between groups A and B according to the clinical history. Urticaria, with or without angioedema, was less frequent in group A, while isolated angioedema was similar in both groups. Anaphylaxis was 10 times more frequent in group A than in group B. Rhinitis occurred in both groups. Facial angioedema with asthma

appeared only in group A and exanthema appeared only in group B ( $P < .0001$ ).

The time interval between drug intake and symptom appearance also differed markedly ( $P < .0001$ ) (Figure 3). In group A, almost 80% reported symptoms within 1 hour, 20% between 1 and 6 hours, and no cases after 6 hours. In group B, symptoms occurred within 1 hour in 37%, between 1 and 6 hours in 38%, and longer than 6 hours in 22%.

The drugs involved also differed significantly ( $P < .01$ ). Although ibuprofen was implicated equally in both groups, more group A cases involved ASA and dipyrone and more group B cases involved paracetamol.

The multivariate logistic regression included as dependent variable the probability of being hypersensitive to NSAIDs and as independent variables age, age, number of episodes, clinical entity induced, time interval between drug intake and symptom appearance, drug involved, indication for treatment, and the atopic status. However, the only variable that showed significance ( $P < .01$ ) was the time interval between drug intake and symptom appearance, with an odds ratio of 5.6 (95% CI, 1.4-20.8) for 1 hour or less versus more than 1 hour.

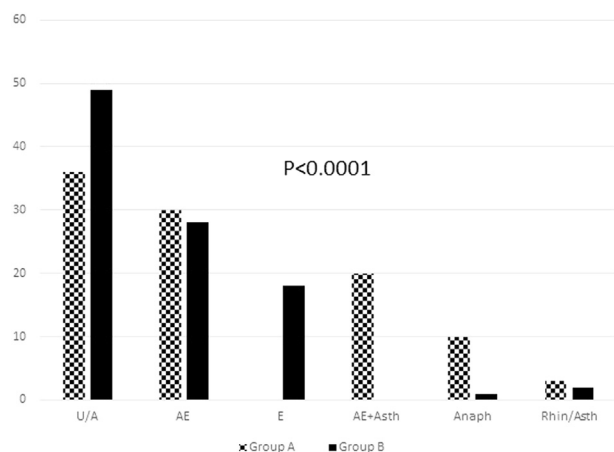


**FIGURE 2.** Comparison of the clinical entities between group A and group B. *AE*, Isolated angioedema; *AE + Asth*, angioedema plus asthma; *Anaph*, anaphylaxis; *E*, exanthema; *Rhin/Asth*, rhinitis and/or asthma; *U/A*, urticaria with or without angioedema.

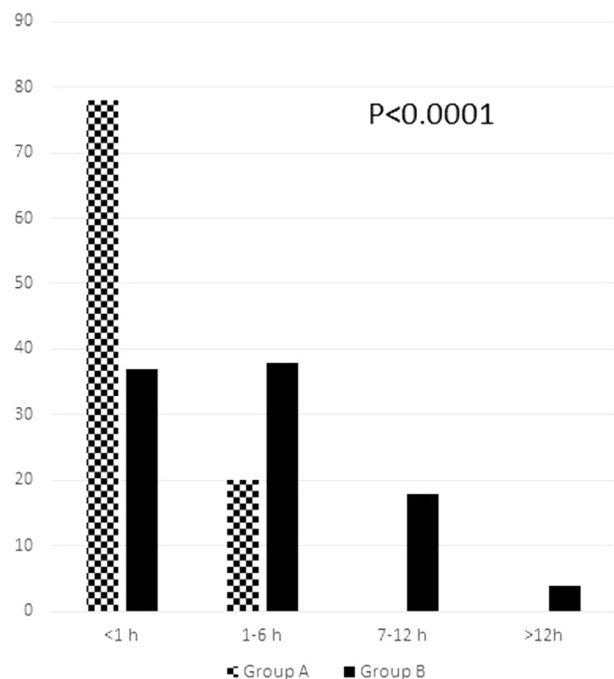


**FIGURE 3.** Time interval between drug intake and appearance of reactions in group A and group B.

## DISCUSSION

We evaluated 116 children aged 14 years or younger who reported symptoms after intake of NSAIDs, with 26% having confirmed NSAID sensitivity. In the remaining cases, although they reported similar symptoms in the clinical history, hypersensitivity was ruled out. Many children often develop urticaria during acute infectious (frequently viral) episodes, with these reactions often being falsely attributed to the NSAID. This is the largest series evaluating confirmed cases with the youngest group of children (IQR<sub>25-75</sub>, 3-11 years). Cavkaytar et al<sup>20</sup> reported a

series of 121 cases with an IQR<sub>25-75</sub> of 4.7 to 10.8, with 22% confirmed. Alves et al<sup>21</sup> included children with an IQR<sub>25-75</sub> of 5 to 14, though this was a retrospective study and the number of confirmed cases was 7.6%. Another study claimed to be the largest pediatric cohort with 635 cases, but the mean age at the time of the evaluation was 15 years (11-22.5 years). This may explain why in this study subjects with NSAID-exacerbated cutaneous disease were identified but not in our study.<sup>28</sup>

In our study, ibuprofen accounted for 83% of the drugs involved, followed by a few cases of dipyrone and paracetamol, with ASA contributing in a very few cases. This agrees with other studies.<sup>15,17,19-22</sup> In our study, paracetamol was involved in 10% of cases, slightly more than in another Spanish study (7.9%).<sup>19</sup>

Not all children are diagnosed using similar criteria in studies of HR-NSAIDs. In some studies, more than 60% were diagnosed by clinical history,<sup>15,16,22</sup> with 2 limitations: reactions were imputed to the culprit drug in cases taking 1 single NSAID<sup>15</sup> and no ASA or alternative strong COX-1 inhibitor was given to all cases evaluated.<sup>16,22</sup>

Considering CI versus SRs, most of our cases were CI, as reported.<sup>28</sup> These data contrast with others where the percentage of SRs varied from 50% to 75%. One explanation is that the older the patient the higher the possibility of an SR, as in adult populations.<sup>10</sup> Another explanation for the difference in SRs is that in other studies not all cases were challenged with ASA.<sup>20,22</sup>

Cases belonging to the NSAID-exacerbated respiratory disease category are rather infrequent, although children with nasal polyposis and asthma have been reported.<sup>30</sup> In our study, only 12% developed respiratory symptoms after challenge while in other studies the percentage varied from 4.3% to 10%.<sup>21,22</sup>

Mixed reactions with both respiratory and skin (urticaria accompanied or not by facial angioedema) involvement occurred in 12% of our cases. This increases to 23.3% if we include facial angioedema plus upper and/or lower respiratory symptoms, this being the second most frequent entity after NSAID-induced urticaria/angioedema and/or anaphylaxis. Some authors have claimed that a different phenotype may exist in children, with the appearance of cutaneous and respiratory symptoms combined.<sup>24</sup>

Different studies put the rate of anaphylaxis at 7% to 42%.<sup>15-17,20-22</sup> Although in the ENDA classification this entity is included within SRs, it may also occur in patients having NSAID-induced urticaria/angioedema and/or anaphylaxis within the CI category. Other studies have also reported anaphylaxis within the CI category, although the possibility of being a multiple SR also exists.<sup>15,31</sup>

Group A was significantly older than group B, as has been reported.<sup>19,22</sup> The clinical entities also differed significantly ( $P < .0001$ ), with more anaphylaxis in group A, facial angioedema plus asthma appearing only in group A, and exanthema appearing only in group B. Urticaria, either alone or with angioedema, was more frequent in group B.

Different approaches have been used for OPT so data cannot be compared. Although ASA is not usually given in children, different studies have used this NSAID for diagnosing HR-NSAIDs in pediatric populations.<sup>15,20</sup> Our approach consisted of administering ASA as a first choice to discriminate among CI, SRs, or tolerant. Accordingly, the total number of OPTs required to diagnose the positive cases was much lower than in other studies in which more than 50% of cases required 2 or more challenges.<sup>28</sup> Furthermore, because patients who have a positive challenge usually refuse to continue the study, the risk for

noncompletion of the study by giving the culprit drug is higher.<sup>28</sup> In other studies, ASA challenge was not performed and only the culprit drug was given. This may represent a selection bias in favor of SRs.<sup>15,20</sup>

The time interval between drug intake and symptom appearance was also highly significant ( $P < .0001$ ); 80% in group A reported the symptoms within just 1 hour, in contrast to group B, where 60% had reactions after 1 hour.

Atopy may be an important risk factor.<sup>10,29,32,33</sup> In our study, although there were differences they were not significant. When we compared the association with each allergen the only association in group A was with alternaria ( $P < .05$ ), with the association with house dust mite approaching significance ( $P = .06$ ). These data showed that the association is not exclusively with house dust mite,<sup>33</sup> and other associations may exist in areas with other prevalent allergens.

ASA is currently not prescribed in children because side effects or complications, like Reye syndrome, are a concern. This effect is seen only after repeated administration of high doses and with a certain predisposition like rheumatic disease,<sup>34</sup> not the case in our study.

Multivariate logistic regression analysis showed that the only significant risk factor was the time interval between drug intake and symptom appearance, with patients who reacted within 1 hour having a 5.6 times higher risk of developing a reaction. Although a positive association with respiratory involvement has been reported,<sup>22</sup> this was not confirmed by us. Another study in adults also found that this variable did not contribute with a significant risk.<sup>12</sup> The number of drugs involved and sex have also been reported to contribute as risk factors.<sup>23,35</sup> As mentioned above, we could not confirm these findings in a childhood population.

Summarizing, we report for the first time a series of children younger than age 14 years, with the youngest less than 1 year, who were diagnosed with NSAID hypersensitivity that was confirmed by challenge with ASA in all cases except 1, where this was the culprit drug. Although CI cases with cutaneous manifestations were the most frequent, cases also appeared with respiratory manifestations. However, because cases with both cutaneous and respiratory manifestations appeared as well as anaphylactic reactions within the CI category, the current ENDA classification should be modified to consider these phenotypes.

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