

# Nonsteroidal anti-inflammatory drug hypersensitivity among children

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## ABSTRACT

**Background:** Nonsteroidal anti-inflammatory drugs (NSAID) are the second-most frequent drugs that cause hypersensitivity reactions among children. Studies related to NSAIDs hypersensitivity in children are limited. In this study, we aimed to evaluate children admitted with suspicion of NSAIDs reaction.

**Method:** Between January 1, 2011, and November 30, 2014, we included patients with suspicion of NSAIDs hypersensitivity in our clinic. For evaluation, skin tests and oral provocation tests with the drug (suspected or alternative) were proposed. Reactions were classified and defined according to the latest European Academy of Allergy and Clinical Immunology position paper on NSAID hypersensitivity.

**Results:** During the study period, 123 patients (with 136 drug reactions) were admitted to our clinic with suspected NSAID hypersensitivity. The mean (standard deviation) age of the patients, 67 female (55%), was  $83.10 \pm 56.05$  months. Thirteen patients described reactions to more than one chemically unrelated NSAID, and 110 patients described reactions with chemically similar drugs. Eight patients were not included because they did not have provocation tests. Thus, 115 patients were evaluated. A hundred and thirty provocations were performed. Twenty patients (17.4%) were diagnosed with NSAID hypersensitivity (13 patients diagnosed by provocation tests and 7 patients diagnosed according to their history). The most frequently encountered agent was ibuprofen (50% [10/20]). Eighty percent (16 patients) of the reactions were considered "non-cross-reactive type." Fifteen patients (75%) were classified as having single-NSAID-induced urticaria and/or angioedema, three patients were classified as having NSAID-induced urticaria and/or angioedema, one patient was classified as having NSAID-exacerbated respiratory disease, and the other patients were classified as having single-NSAID-induced delayed hypersensitivity reactions.

**Conclusion:** Detailed history and drug provocation tests are important to verify NSAID hypersensitivity. The most common type is the non-cross-reactive type, and, in our study, the most common responsible drug was ibuprofen.

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Nonsteroidal anti-inflammatory drugs (NSAID) are the second-most frequent drugs that cause hypersensitivity reactions in children.<sup>1</sup> The prevalence is estimated to be 0.6–5.7% in the general population.<sup>2</sup>

NSAIDs are frequently prescribed for their analgesic and antipyretic effects for children and also can be taken without prescription. This frequent use results in many adverse symptoms that are considered as true hypersensitivity without having performed any allergic evaluation. As a matter of fact, only a minority of these reactions are true hypersensitivity. For children who have a history compatible with hypersensitivity reactions, allergic evaluation should be done when

appropriate. The criterion for the diagnosis of drug hypersensitivity is the drug provocation test (DPT).<sup>3</sup>

After diagnosing NSAID hypersensitivity (NSAID-H), it has to be decided whether the reaction is *via* the cyclooxygenase (COX) pathway. If COX-1 enzyme inhibition is responsible, then an alternative COX-2 inhibitor must be defined by means of DPT. It is hard to find alternative COX-2 inhibitors because most of these drugs are not approved for children and many do not have liquid forms. Usually a low dose of paracetamol, a weak inhibitor of COX, is used, but the problem gets bigger when a strong alternative is needed.<sup>2</sup>

Although there are studies about NSAID-H that are conducted in adults, studies that included children are limited. Recently, the classification of NSAID-H was revised, and, as far as we could find, there is not any available study that used this new classification. In this study, we aimed to evaluate children admitted with a suspicion of a NSAID reaction and to define and classify proven allergies by DPTs.

## PATIENTS AND METHODS

This study was conducted in the pediatric allergy department of our hospital in Ankara. We included all

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patients with a suspicion of NSAID-H between January 1, 2011, and November 30, 2014. The local ethical committee approved the study design and protocols. The initial drug allergy workup started with the standardized European Network of Drug Allergy questionnaire on drug allergy.<sup>4</sup> A detailed history included the spectrum and timing of symptoms, dose and route of administration and a list of concomitant medications, history and timing of previous hypersensitivity reactions, and previously tolerated NSAIDs. The patients or their caregivers were asked whether they used aspirin and, if they did use aspirin, whether or not they experienced a reaction. Coexisting chronic diseases, especially asthma, chronic rhinosinusitis, nasal polyps, and chronic spontaneous urticaria and/or angioedema, and a family history of allergic diseases were also recorded.

If the history of suspected reaction was compatible with drug hypersensitivity, then skin tests (prick test and intradermal test) and oral provocation test with the drug (suspected or alternative) were proposed. These tests were performed at least 1 month after the initial reaction. Use of antihistamine medications and other drugs that could affect skin tests or drug provocations were ceased a week before the test. Written informed consent was taken from caregivers. Patients and caregivers who were diagnosed with NSAID-H were given written information, which included the list of forbidden and alternative NSAIDs.

### Skin Tests for Drugs

**Prick Intradermal.** Patients were subjected to prick and intradermal skin testing with the suspected drug (paracetamol 10 mg/mL, metamizole 0.1 mg/mL).<sup>5</sup> Isotonic saline solution was used for dilution. All the drugs were initially tested on the volar forearm skin with the prick method, and reactions were considered positive when a wheal diameter 3 mm larger than the negative control, with surrounding erythema, was present 20 minutes later.<sup>6</sup> When prick tests yielded negative 1 mg parenteral form of the drug was diluted with 9 mg isotonic sodium chloride to form a 1/10 dilution and 0.02 mL of this form was injected intradermally on volar forearm skin. Readings were made 20 minutes after injections. Results were considered positive when an increase of larger than 3 mm in the wheal diameter occurred, accompanied by erythema. Histamine at 10 mg/mL and 0.9% NaCl were used as positive and negative controls, respectively.<sup>6</sup>

**Drug Patch Test.** Paracetamol, 10% dilution in petrolatum by Finn chamber, was applied to the back and to the region of previously damaged skin of the patient.<sup>6</sup>

### DPTs

DPT was performed for three reasons: (1) to confirm hypersensitivity with the culprit drug, (2) to confirm or exclude cross-reactivity with aspirin, and (3) to determine a tolerated alternative drug. European Network of Drug Allergy guidelines for drug DPTs were carefully respected.<sup>7</sup> The suspected drug was administered at divided doses every 30 minutes, until a cumulative dose close to the age- and weight-adjusted daily dose of the drug was achieved. The test is discontinued in the event of any reaction. The provocation test was not blinded, and an open challenge was performed by a physician with full resuscitation backup. The DPT result was considered positive if any objective symptoms or signs were documented. After the last dose had been administered without a reaction, the patient was kept under surveillance for at least 2 hours. The patients were asked to contact the physician whether a reaction occurred in the day (24 hour) after the provocation test to identify delayed reaction. The tests were considered negative if no reaction occurred at the end of this time. Caregivers of patients who reported that they could use an alternative NSAID safely were not tested.

### Aspirin Provocation Test

Aspirin provocation was performed in two situations: (1) aspirin was the suspected drug, and (2) to confirm or exclude cross-sensitivity. On the first day, three placebo capsules were administered at 1.5-hour intervals. On the second day, four increasing doses (27 mg, 44 mg, 117 mg, and 312 mg) were given at 1.5-hour intervals until a maximum dose of 500 mg was reached or until the cumulative dose of 10 mg/kg was reached. Forced expiratory volume in 1 second was measured by spirometry at the beginning of the test and every 30 minutes during the provocation.<sup>8</sup>

### Skin-Prick Tests

Skin-prick tests (aeroallergen and/or food) were performed with mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), molds (*Alternaria*, *Cladosporidium*, and *Aspergillus*), cockroach, and cat and dog epithelia for the patients. Pollens (grass mix, cereal mix, weeds, and trees) (Stallergenes, Paris, France) were added for children older than 2 years of age, and food allergens were used for patients younger than 2 years.

### Definitions and Classification of NSAID Hypersensitivity

Reactions were classified and defined according to the latest European Academy of Allergy and Clinical Immunology position paper on NSAID-H.<sup>9</sup> Symptoms that occur within the first 24 hours are considered "acute reactions" and the ones that occur later are considered "delayed reactions."

## Acute Reactions

NSAID-exacerbated respiratory disease (NERD): Hypersensitivity reactions manifesting with bronchial obstruction, dyspnea, nasal congestion in a person who has an underlying chronic airway respiratory disease.

NSAID-exacerbated cutaneous disease: Reactions manifesting with urticaria, angioedema and/or anaphylaxis with several chemically unrelated NSAIDs in a person who has underlying chronic urticaria. If there is not underlying chronic urticaria, then the state is defined as NSAIDs-induced urticaria and/or angioedema (NIUA).

Single-NSAID-induced urticaria and/or angioedema or anaphylaxis (SNIUAA): Urticaria and/or angioedema and/or anaphylactic reactions with a single NSAID.

## Late Reactions

Single-NSAID-induced delayed hypersensitivity reactions: Delayed reactions with a single NSAID.

## Classification of Reaction According to Immunologic Mechanism

Nonimmunologically mediated cross-reactive type (caused by COX-1 enzyme inhibition): Reactions caused by more than one chemically unrelated COX-1 inhibitor.

Immunologically mediated non-cross-reactive type (caused by immunoglobulin E or T-cell-mediated pathways): Reactions caused by drugs only from a chemically related group and manifesting as urticaria, angioedema, and/or anaphylaxis.

To classify the reactions as cross-reactive or non-cross-reactive, we performed DPT with aspirin. DPT with aspirin was not performed with patients who claimed that they used aspirin safely. Paracetamol was considered as an independent group of NSAIDs.

## Statistical Analysis

Statistical analyses were performed by using the SPSS-22 Statistical Software Package (SPSS, Inc., Chicago, IL) for Windows. The definitions were provided as number and percentage for discrete variables and mean and standard deviation (SD) for continuous variables.

## RESULTS

During the study period, 123 patients (with 136 drug reactions) were admitted to our clinic with suspected NSAID-H. The mean age  $\pm$  SD of the patients was  $83.10 \pm 56.05$  months (range, 2–203 months), and the median interquartile range (IQR) was 73 months (range, 36–172 months). Sixty seven (55%) of the patients were female.

At presentation, a history was compatible with immediate reaction for 122 patients (except one patient) and with anaphylaxis for 9 patients (7.3%) (5, paracetamol; 1,

Table 1 The characteristics of patients and reactions ( $n = 123$ )

| Characteristics                              | Patients, no. (%) |
|----------------------------------------------|-------------------|
| Reactions in history with single NSAID       | 110 (89.4)        |
| Paracetamol                                  | 45 (36.6)         |
| Ibuprofen                                    | 44 (35.8)         |
| Metamizole                                   | 7 (5.8)           |
| Aspirin                                      | 5 (4)             |
| Ketoprofen                                   | 4 (3.3)           |
| Naproxen                                     | 3 (2.4)           |
| Naproxen + ketoprofen                        | 1 (0.8)           |
| Naproxen + flurbiprofen                      | 1 (0.8)           |
| Reactions in history with 2 different NSAIDs | 13 (10.6)         |
| Ibuprofen + paracetamol                      | 6 (4.9)           |
| Paracetamol + aspirin                        | 2 (1.6)           |
| Ibuprofen + aspirin                          | 1 (0.8)           |
| Ibuprofen + aspirin + metamizole             | 1 (0.8)           |
| Ketoprofen + aspirin                         | 1 (0.8)           |
| Paracetamol + naproxen                       | 1 (0.8)           |
| Paracetamol + metamizole                     | 1 (0.8)           |
| Reaction in history                          |                   |
| Skin reactions                               | 123 (100)         |
| Urticaria and angioedema                     | 51 (41.4)         |
| Urticaria                                    | 35 (28.5)         |
| Maculopapular exanthema                      | 30 (24.4)         |
| Isolated angioedema                          | 6 (4.9)           |
| Fix drug eruption                            | 1 (0.8)           |
| Anaphylaxis                                  | 9 (7.3)           |
| Atopic disease                               | 22 (18)           |
| Allergic rhinitis                            | 16 (13)           |
| Asthma                                       | 9 (7.3)           |
| Chronic urticaria                            | 2 (1.6)           |
| Atopic dermatitis                            | 1 (0.8)           |
| Family history for allergic disease          | 32 (26)           |
| Drug allergy                                 | 10 (8.1)          |
| NSAID                                        | 4 (3.3)           |
| Antibiotic                                   | 6 (4.9)           |
| Skin prick test                              |                   |
| Atopy                                        | 17 (14.9)         |

ibuprofen; 1, flurbiprofen; 1, naproxen; and 1, metamizole). Paracetamol was the most common cause of drug reaction (40.5% [55/136]). The mean (SD) duration between drug intake and reaction was  $201.80 \pm 295.59$  minutes (minimum, maximum: 5, 1440 minutes); median (IQR), 90 minutes (30–240 minutes). Thirteen patients (10.5%) described reactions to more than one chemically unrelated COX-1 inhibitor NSAIDs, 110 patients with chemically similar drugs (89.5%). Characteristics of patients and reactions are given in Table 1.

Eight patients were not included because they did not attend for DPTs and 115 patients were evaluated.

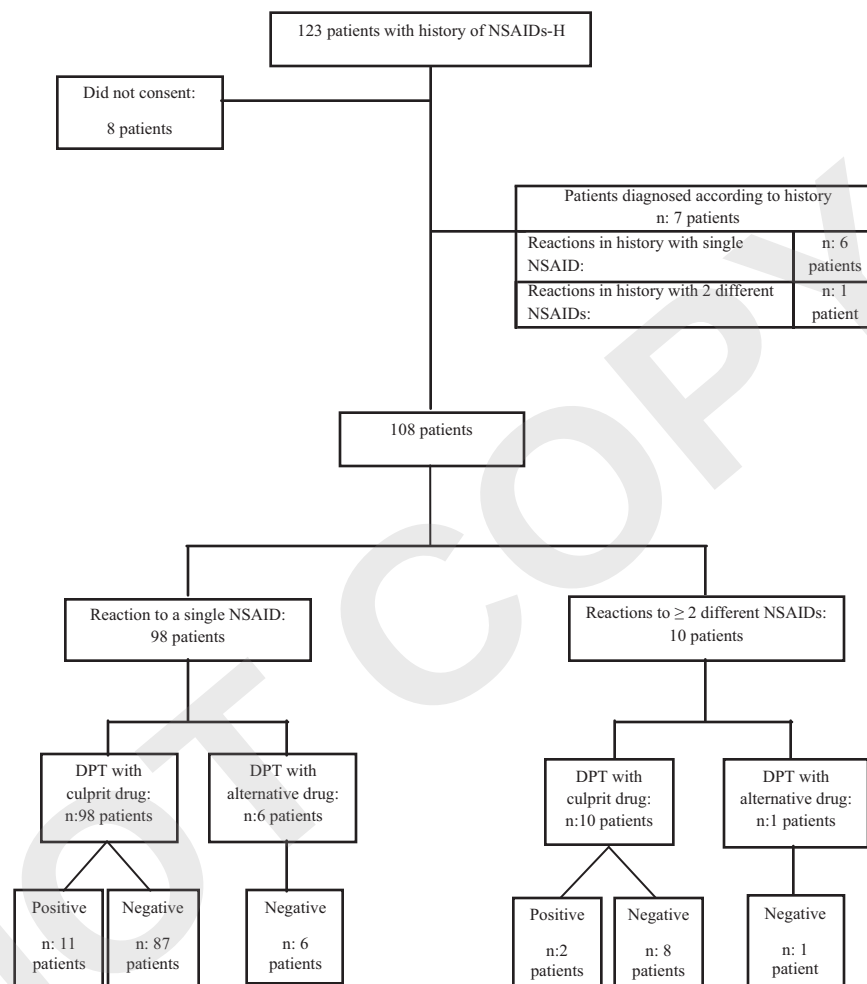


Figure 1. Algorithm of study.

Seven patients were diagnosed as NSAIDs-H based on clinical history. DPTs were performed for 108 patients. Algorithm of the study is shown in Fig. 1.

### Diagnostic workup

Skin-prick and intradermal tests were performed with 55 patients (50 paracetamol and 5 metamizole). All skin tests were negative. The patch test was performed on 1 patient who had fixed drug eruption, and it was negative. A hundred and thirty provocations were performed: 118 with the suspected drug and 12 with an alternative drug. The mean (SD) age of the patients at the time of provocations was  $78.61 \pm 50.46$  months (minimum, maximum: 12, 190 months); median (IQR), 72.5 months (36–127 months). The mean duration  $\pm$  SD between reaction duration to the drug and the DPT was  $18.19 \pm 30.34$  months (range, 1–141 months) and median IQR was 4 months (2–15.5 months).

### Results of DPT With the Suspected Drugs

A total of 118 DPTs were performed with the suspected drug for 108 patients. There was a reaction

during 14 of 118 DPTs (11.8%) in 13 of 108 patients (12%) (1 patient had positive DPT result with two different NSAIDs). One of the six patients who had a history of anaphylaxis had a reaction during DPT. Characteristics of patients are given in Table 2. The most frequently proven hypersensitivity reaction was to ibuprofen (50%, [10/20]). Patients with negative provocation results and those with positive provocation results were not statistically different in terms of age during DPT, time between reaction and DPT, concomitant atopic disease, and family history of drug allergy. Patients who were diagnosed with NSAID-H were older (median, 113.50 months; IQR, 45.75–174 months) than patients who had negative allergic work-up for drug hypersensitivity (median, 70 months; IQR, 36–119 months;  $p = 0.029$ ).

### Results of DPT for Alternative Drugs

Twelve DPTs were performed to determine alternative drugs (Table 2). Four of these tests were done with paracetamol and two with meloxicam. All DPTs were negative.

Table 2 The characteristics of patients who were diagnosed with NSAID-H

| Patient no.                                           | Reaction Age, mo | Sex  | Culprit Drug in History    | Reaction in History  | Atopic Disease            | Skin-Prick Test       | Administered Drug Provocation | Provocation Age, mo | Between the Reaction and Provocation Time, mo | Reaction Drug Provocation | Reaction Time and Eliciting Dose During Provocation | Reaction with Aspirin | Alternative NSAID |
|-------------------------------------------------------|------------------|------|----------------------------|----------------------|---------------------------|-----------------------|-------------------------------|---------------------|-----------------------------------------------|---------------------------|-----------------------------------------------------|-----------------------|-------------------|
| Patients diagnosed according to drug provocation test |                  |      |                            |                      |                           |                       |                               |                     |                                               |                           |                                                     |                       |                   |
| 1                                                     | 148              | Boy  | Ibuprofen ASA              | Urticaria angioedema | None                      | No atopy              | Ibuprofen                     | 150                 | 2                                             | Urticaria angioedema      | 45 min after the 5th dose (200 mg)                  | +                     | Paracetamol*      |
| 2                                                     | 60               | Boy  | Ibuprofen                  | Urticaria angioedema | None                      | No atopy              | Ibuprofen                     | 154                 | 94                                            | Urticaria angioedema      | 30 min after the 5th dose (300 mg)                  | -                     | Paracetamol       |
| 3                                                     | 72               | Girl | Ibuprofen                  | Urticaria angioedema | Chronic urticaria         | No atopy              | Ibuprofen                     | 74                  | 2                                             | Urticaria                 | 30 min after the 4th dose (100 mg)                  | -                     | Paracetamol*      |
| 4                                                     | 149              | Boy  | Ibuprofen                  | Urticaria angioedema | None                      | House-dust mite atopy | Ibuprofen                     | 161                 | 12                                            | Urticaria angioedema      | 30 min after the 5th dose (300 mg)                  | -                     | Paracetamol       |
| 5                                                     | 92               | Girl | Ibuprofen                  | Urticaria angioedema | None                      | No atopy              | Ibuprofen                     | 95                  | 3                                             | Urticaria angioedema      | 20 min after the 5th dose (200 mg)                  | -                     | Paracetamol*      |
| 6                                                     | 19               | Boy  | Ibuprofen                  | Urticaria angioedema | None                      | ND                    | Ibuprofen                     | 22                  | 3                                             | Urticaria angioedema      | 55 min after the 4th dose (80 mg)                   | -                     | Metamizole*       |
| 7                                                     | 19               |      | Paracetamol                | Urticaria angioedema |                           |                       | Paracetamol                   | 22                  | 3                                             | Urticaria angioedema      | 1440 min after the 4th dose (80 mg)                 |                       |                   |
| 8                                                     | 83               | Girl | Ibuprofen, metamizole, ASA | Urticaria angioedema | Asthma                    | ND                    | Ibuprofen                     | 89                  | 6                                             | Urticaria, cough, dyspnea | 10 min after the 1st dose (10 mg)                   | (+)                   | Paracetamol       |
| 9                                                     | 135              | Girl | ASA                        | Urticaria angioedema | None                      | No atopy              | ASA                           | 139                 | 4                                             | Urticaria angioedema      | 90 min after the 3rd dose (117 mg)                  | (+)                   | Paracetamol       |
| 10                                                    | 41               | Boy  | Ibuprofen                  | Urticaria            | None                      | No atopy              | Ibuprofen                     | 13                  | 2                                             | Urticaria                 | 180 min after the 5th dose (100 mg)                 | -                     | Paracetamol*      |
| 11                                                    | 148              | Boy  | Paracetamol                | Urticaria            | None                      | No atopy              | Paracetamol                   | 151                 | 3                                             | Urticaria                 | 15 min after the 2nd dose (125 mg)                  | -                     | Ibuprofen*        |
| 12                                                    | 12               | Girl | Paracetamol                | MPE                  | None                      | No atopy              | Paracetamol                   | 37                  | 25                                            | Urticaria angioedema      | 600 min after the 5th dose (200 mg)                 | -                     | Ibuprofen         |
| 13                                                    | 177              | Boy  | Paracetamol                | Anaphylaxis          | Allergic rhinitis         | Pollen and mold atopy | Paracetamol                   | 194                 | 17                                            | Urticaria                 | 10 min after the 2nd dose (50 mg)                   | -                     | Meloxicam*        |
| 14                                                    | 165              | Girl | Metamizole                 | Urticaria angioedema | Asthma, chronic urticaria | No atopy              | Alternative drug              | 166                 | 1                                             |                           |                                                     | -                     | Paracetamol*      |
| 15                                                    | 72               | Boy  | Ibuprofen                  | Urticaria            | None                      | No atopy              | Alternative drug              | 74                  | 2                                             |                           |                                                     | -                     | Paracetamol*      |
| 16                                                    | 184              | Girl | Ketoprofen, ASA            | Angioedema           | None                      | No atopy              | Alternative drug              | 208                 | 12                                            |                           |                                                     | +                     | Meloxicam*        |
| 17                                                    | 187              | Girl | Naproxen, ketoprofen       | Anaphylaxis          | None                      | No atopy              | Alternative drug              | 188                 | 1                                             |                           |                                                     | -                     | Paracetamol*      |
| 18                                                    | 203              | Girl | Flurbiprofen, naproxen     | Anaphylaxis          | None                      | No atopy              | Alternative drug              | 204                 | 1                                             |                           |                                                     | -                     | Paracetamol*      |
| 19                                                    | 193              | Boy  | Paracetamol                | Anaphylaxis          | None                      | No atopy              | Alternative drug              | 195                 | 2                                             |                           |                                                     | -                     | Meloxicam*        |
| 20                                                    | 120              | Boy  | Paracetamol                | Fixed drug eruption  | None                      | No atopy              | —                             | —                   | —                                             |                           |                                                     | -                     | Ibuprofen         |

ASA = acetylsalicylic acid; ND = not done; MPE = maculopapular eruption.

\*Confirmed with a DPT.

| Immunologically mediated (non-cross-reactive) hypersensitivity reactions to NSAIDs |        | Non-immunologically mediated (cross-reactive) hypersensitivity reactions to NSAIDs |      |
|------------------------------------------------------------------------------------|--------|------------------------------------------------------------------------------------|------|
| SNIDR                                                                              | SNIUAA | NERD                                                                               | NIUA |
| n:1                                                                                | n:15   | n:1                                                                                | n:3  |

SNIDR: Single NSAID-Induced Delayed Reactions SNIUAA: Single NSAID-Induced Urticaria/Angioedema and Anaphylaxis NERD: NSAIDs-Exacerbated Respiratory Diseases NIUA: NSAIDs-Induced Urticaria/Angioedema

Figure 2. Classification of NSAID hypersensitivity.

### Patients Diagnosed According to History

Seven patients were diagnosed with NSAID-H based on clinical history. Three patients had severe anaphylaxis (with paracetamol, flurbiprofen plus naproxen, and ketoprofen plus naproxen), therefore, DPT was not used. Three patients had recurrent urticaria and/or angioedema with the same drug (ibuprofen, metamizole, and aspirin plus ketoprofen), but their parents did not consent for a provocation with the culprit drug. DPT was performed with these six patients to determine an alternative NSAID. One patient who had fixed drug eruption could not be tested because his parents did not consent for DPT with the culprit drug. He was using an alternative NSAID (ibuprofen) without reaction (Table 2).

### Classification and Definition of Patients Diagnosed With NSAID-H

Twenty patients who were diagnosed with NSAID-H (13 patients diagnosed by using DPTs and 7 patients diagnosed according to history) were classified. According to the results of DPTs and self-reported use of aspirin, 80% (16 patients) of the reactions had a “non-cross-reactive type” and 20% (4 patients) had a “cross-reactive type.” Fifteen patients (75%) had a reaction with only one drug and were shown to tolerate aspirin, so they were classified as having SNIUAA. Four patients had a reaction with aspirin as well as the culprit drug. Three of these patients (15%) had urticaria and/or angioedema, and anaphylaxis, and they were classified as having NIUA. One of these patients (5%) had underlying asthma, and had dyspnea, cough, and urticaria and/or angioedema during provocation, so this patient was classified as having NERD. One patient (5%) had a delayed reaction with only paracetamol and was classified as having SNIDR (Fig. 2).

### DISCUSSION

In this study, the ratio of patients diagnosed with NSAID-H was 17.4%. Eighty percent of the reactions were considered “non-cross-reactive type.” The most common type of reaction was SNIUAA, and the most common drug was ibuprofen. In our study, only 17.4% of the suspected patients were diagnosed with NSAID-H. This result supports the data in the litera-

ture that most self-reported reactions with NSAIDs are not true drug hypersensitivity. In studies conducted with adults, only 22–55% of patients suspected to have NSAID-H were found to have confirmed hypersensitivity.<sup>10,11</sup> Zambonino *et al.*<sup>12</sup> evaluated children and confirmed the diagnosis of NSAID-H in 68.2% of patients. Two other studies were performed on this subject in Turkey. One of them found the frequency of confirmed reactions as 9.8% and the other reported a frequency of 29.3%.<sup>13,14</sup> The lower frequency of NSAID-H in our study may be the result of the younger age of our study group. It has been reported that the frequency of NSAID-H is lower in the younger age group.<sup>15,16</sup> NSAIDs other than paracetamol are not widely used for younger patients; most NSAIDs are not permitted in this age group and they do not have liquid forms. Furthermore, infectious eruptions are more common in this age group, and these eruptions may be confused with drug reactions.

In accordance with previous studies,<sup>13,17</sup> in our study, the most commonly proven cause of confirmed NSAID-H was ibuprofen. Paracetamol was the most commonly suspected agent and the second most common proven cause of NSAID-H. Kidon *et al.*<sup>18</sup> also reported that paracetamol hypersensitivity was more common among children younger than 6 years of age. Zambonino *et al.*<sup>12</sup> found paracetamol as the most infrequently encountered drug. The types of NSAIDs that cause hypersensitivity reactions may vary among countries due to the preference of drug utilization. Paracetamol and ibuprofen are the most commonly used NSAIDs in our country. Zambonino *et al.*<sup>12</sup> found aspirin as the second most common agent, and paracetamol was reported as the most infrequently encountered drug. This difference may be the result of the infrequent use of aspirin among children in Turkey. Due to concern of Reye syndrome, aspirin is not prescribed for children in our country, unless the patient undoubtedly needs the drug (*e.g.*, in case of acute rheumatic fever).

Eighty percent of the reactions were “non-cross-reactive type” in our study. These data are quite different when compared with previous studies in adults in which the most common reaction type was cross reactive.<sup>19</sup> As far as we could find, there are only two studies on the subject that are conducted in children. In

another study from our country, 65.5% of patients reported reaction with a single NSAID. However, after provocation, 11.4% of patients who reported a reaction history with a single NSAID and 44.4% of patients who had a reaction with two or more drugs have been confirmed as having true hypersensitivity. Whether or not patients had aspirin hypersensitivity was not specified in this study, and children were not specifically grouped as “cross reactive” or “non-cross reactive.”<sup>13</sup> Zambonino *et al.*<sup>12</sup> performed a DPT with acetylsalicylic acid with all the patients who had a positive DPT with the culprit drug and reported that the reaction was cross reactive in 58.1% and selective in 41.9% of the patients.

One of our patients (patient no. 6) with a reaction to paracetamol had a reaction with another NSAID (ibuprofen), but, interestingly, this patient could tolerate aspirin and metamizole. Kidon *et al.*<sup>17</sup> evaluated 24 children and reported that 25% of their patients with NSAID-H also had reactions with paracetamol. In some of the previous studies, the patients were considered as “cross reactive” when they had a reaction to both paracetamol<sup>17</sup> and another NSAID, but, in other reports, they were considered as single agent.<sup>13</sup> Paracetamol is a low inhibitor of COX and is classified as an independent group in recent studies.<sup>17,20</sup> Thus, we classified these patients as being cross reactive in our study.

In our study, 75% (15/20) of confirmed cases of NSAID-H were classified as SNIUAA, 15% (3/20) as NIUA, 5% (1/20) as NERD, and 5% (1/20) as SNIDR. In the literature, up to 30% of the NSAID-induced skin reactions are the non-cross-reactive type (SNIUAA). Less commonly, it can be seen as a late-type reaction (SNIDR) induced by a single drug use. Cross-reactive-type NSAIDs-H can be seen as respiratory disease induced by NSAID (NERD) (4.3–20%) or cutaneous disease induced by NSAIDs (NSAID-exacerbated cutaneous disease and NIUA) (10–30%).<sup>3,9,19</sup>

In our study, one patient was diagnosed as having SNIDR. This patient had fixed drug eruption with repeated use of paracetamol. A patch test result with paracetamol was negative. Fixed drug eruption accounts for 10% of the hypersensitivity reactions induced by drugs, of which NSAIDs are the most frequently involved.<sup>3,21</sup>

One of our patients (patient no. 8) had urticaria and angioedema with aspirin three times at home, and this reaction was confirmed by DPT in our clinic. However, this patient could use ibuprofen and paracetamol without any reaction. It is generally accepted that patients with hypersensitivity to aspirin have a COX-related reaction and that they are assumed to have a reaction with other NSAIDs. Although it is very rare, it has been shown that patients may have an immunologic reaction to aspirin.<sup>22,23</sup>

A safe alternative drug must be found for patients with NSAID-H. If a reaction is a selective-reactive type, then DPT with NSAIDs from another chemical class must be performed. If a reaction is a cross-reactive type, then DPT with COX-2 inhibitors must be performed.<sup>3</sup> We performed DPT with paracetamol for eight patients, with meloxicam for three, with ibuprofen for one, and with metamizole for one patient to find alternative drugs. Five patients were already using paracetamol, and three were using ibuprofen without reaction. Because the use of COX-2 inhibitors is not approved for those younger than 12 years old, usually low-dose paracetamol is used in this condition. Tolmetin can be an alternative for patients who need a more-effective NSAID.<sup>13</sup>

Allergic diseases (*e.g.*, asthma allergic rhinitis) and atopic sensitization is reported to be common in patients with NSAID-H.<sup>24</sup> In our study, only 18% of children had an allergic disease and 13.8% had atopic sensitizations. The low frequency may be the result of younger age and also may be related to the frequent occurrence of a non-cross-reactive type reaction. It has been reported that no association with atopy was established in patients with SNIUAA and that most of our patients were classified in this group.<sup>3</sup>

One of the limitations of this study is that we could not perform DPT with aspirin for all the patients and relied on self-reporting for some. In conclusion, a detailed history should be taken from patients with suspected NSAID-H and DPTs should be performed. The most common type is non-cross-reactive NSAID-H, and the most common drug is ibuprofen in our study.

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