

ORIGINAL ARTICLE

EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Challenge-proven nonsteroidal anti-inflammatory drug hypersensitivity in children

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To cite this article: Yilmaz O, Ertoý Karagol IH, Bakirtas A, Topal E, Celik GE, Demirsoy MS, Turktaş I. Challenge-proven nonsteroidal anti-inflammatory drug hypersensitivity in children. *Allergy* 2013; DOI: 10.1111/all.12266.

Keywords

drug allergy; pediatrics.

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Accepted for publication 15 August 2013

DOI:10.1111/all.12266

Edited by: Marek Sanak

Abstract

Background: Few studies investigated hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) in children. The objective was to determine the frequency of true NSAID hypersensitivity (NSAID-H) and whether there were any parameters in the history of children that would predict NSAID-H. Secondly, an investigation was conducted into whether NSAID-hypersensitive children could tolerate safe alternatives. Differing from previous studies, the researchers followed the recent diagnostic algorithm proposed for acute reactions in NSAID-H.

Methods: Children with a history suggesting NSAID-H were evaluated by an allergist. The patients with a single NSAID in history were tested first with a skin prick test and if negative challenged with the culprit NSAID. The patients who had reactions with multiple NSAIDs were directly challenged with their culprit drugs. Safe alternatives in children with a confirmed NSAID-H were found by oral provocation tests (OPTs).

Results: Fifty-eight of 61 patients participated in the study. Thirty-eight patients (65.5%) described a reaction to a single NSAID and 20 mentioned reactions with ≥ 2 different NSAIDs. Single-drug-induced and cross-reactive NSAID-Hs were proven in 5 of 36 (14%) and 8 of 18 (44%) of patients, respectively. Acetaminophen and nimesulide were tolerated in 60% and 88.8% of the study patients as safe alternatives, respectively. Family history of NSAID-H was found as the only significant predictor of OPT (OR: 5.4; 95% CI: 1.02–28.6).

Conclusion: Histories of both single and multiple NSAID-Hs are poor predictors of actual drug hypersensitivity. Therefore, diagnostic tests should be performed in all children if no contraindication exists. Family history of NSAID-H is the only significant parameter predicting OPT results.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of medications with antipyretic and analgesic effects and are commonly used in children. Hypersensitivity to NSAIDs is among the top three drug-induced adverse reactions observed in children. NSAID-associated reactions are mainly divided into two types: acute (immediate reaction or reaction up to several hours after exposure) and delayed (more than 24 h after exposure). Acute reactions to NSAIDs may be single (possibly IgE-mediated) or multiple NSAID induced (cross-reactive). Skin prick/intradermal (ID) tests might be helpful in the diagnosis of possible IgE-mediated reactions (1). Single NSAID-induced reactions (the IgE-mediated reaction

mechanism) have largely been seen with pyrazolones (2). The oral provocation test (OPT) is the gold standard in the diagnosis of cross-reactive types of NSAID hypersensitivity (NSAID-H) (1).

The primary objective of this study was to determine the frequency of true NSAID-H and whether there were any parameters in the history of children admitted to a tertiary pediatric allergy center that would predict NSAID-H. As a secondary aim, an investigation was conducted into whether NSAID-hypersensitive children could tolerate safe alternatives. Differing from previous studies, the researchers followed the recent diagnostic algorithm proposed for acute reactions in NSAID-H (1–3).

Methods

Patients

The study group involved patients prospectively recruited between January 1, 2010, and September 30, 2012. Patients with a history of acute reactions such as urticaria/angioedema, bronchospasm, laryngeal edema, rhinitis, and systemic reactions involving hypotension, laryngeal edema, bronchospasm, and/or shock after use of any NSAID were included in the study (1). An allergist evaluated the patients, and an ENDA form for drug allergies was completed (4). Briefly, the culprit NSAID, reaction patterns and time, previous episodes in the past, improvement after drug removal, and presence of any individual risk factors, etc., were questioned in detail. The atopic status of the patients was also recorded from the patients' file. Atopy was determined with a panel of skin prick tests (SPTs) that included house dust mites, grass mix, cereal mix, weed mix, park trees, alternaria, animal dander, and histamine (10 mg/ml of histamine phosphate) as positive and 0.9% sterile saline as negative controls. The SPT was considered positive if the mean wheal diameter was ≥ 3 mm compared with the negative control. The Gazi University Hospital ethics committee approved the study, and written informed consent was obtained from all patients and/or their parents.

Diagnostic approach

The patients who had a history of acute reactions to a single NSAID were assigned as having possible IgE-mediated hypersensitivity (Fig. 1). These patients were first tested by skin prick/intradermally and if negative challenged with the culprit NSAID. The patients who had reactions with multiple NSAIDs were assigned as a possible cross-reactive group and were directly challenged with their culprit drugs.

Skin prick and intradermal tests

Skin prick and intradermal tests were performed with acetaminophen and metamizole sodium to which IgE-mediated hypersensitivity reactions were reported. Skin prick tests with acetaminophen (Perfalgan[®], 10 mg/ml; Bristol-Myers Squibb, Ixassou, France) and metamizole sodium (Novalgin[®], 1 g/2 ml; Sanofi-Aventis, Milan, Italy) were performed at concentrations of 10 mg/ml and 0.4 g/ml, respectively. Intradermal tests were carried out in 1/10 dilutions (2, 5). The skin prick tests were accepted to be positive if a wheal diameter was ≥ 3 mm compared with the negative control and was accompanied by erythema 15 min after the test was performed.

Oral provocation tests

Oral provocation tests were performed under strict medical surveillance in the hospital setting and in a time period in which the children were in a good state of health. Antihistamines were stopped 7 days prior to the test; other drugs were also avoided according to the ENDA position paper on drug hypersensitivity (6). All patients were examined, and vital signs were recorded before the OPTs and each dose increase. An intravenous line was placed. OPTs were not performed in

patients with anaphylaxis confirmed by medical records or in those who experienced the reaction within the last 4–6 weeks, used a medication that could affect the test outcome such as antihistamines and oral steroids, exhibited active signs of underlying disease such as urticaria, uncontrolled asthma (forced expiratory volume in 1 s [FEV₁] value <80% of predicted), and suffered from uncontrolled cardiac, renal, or hepatic disease, or current upper airway infection (1).

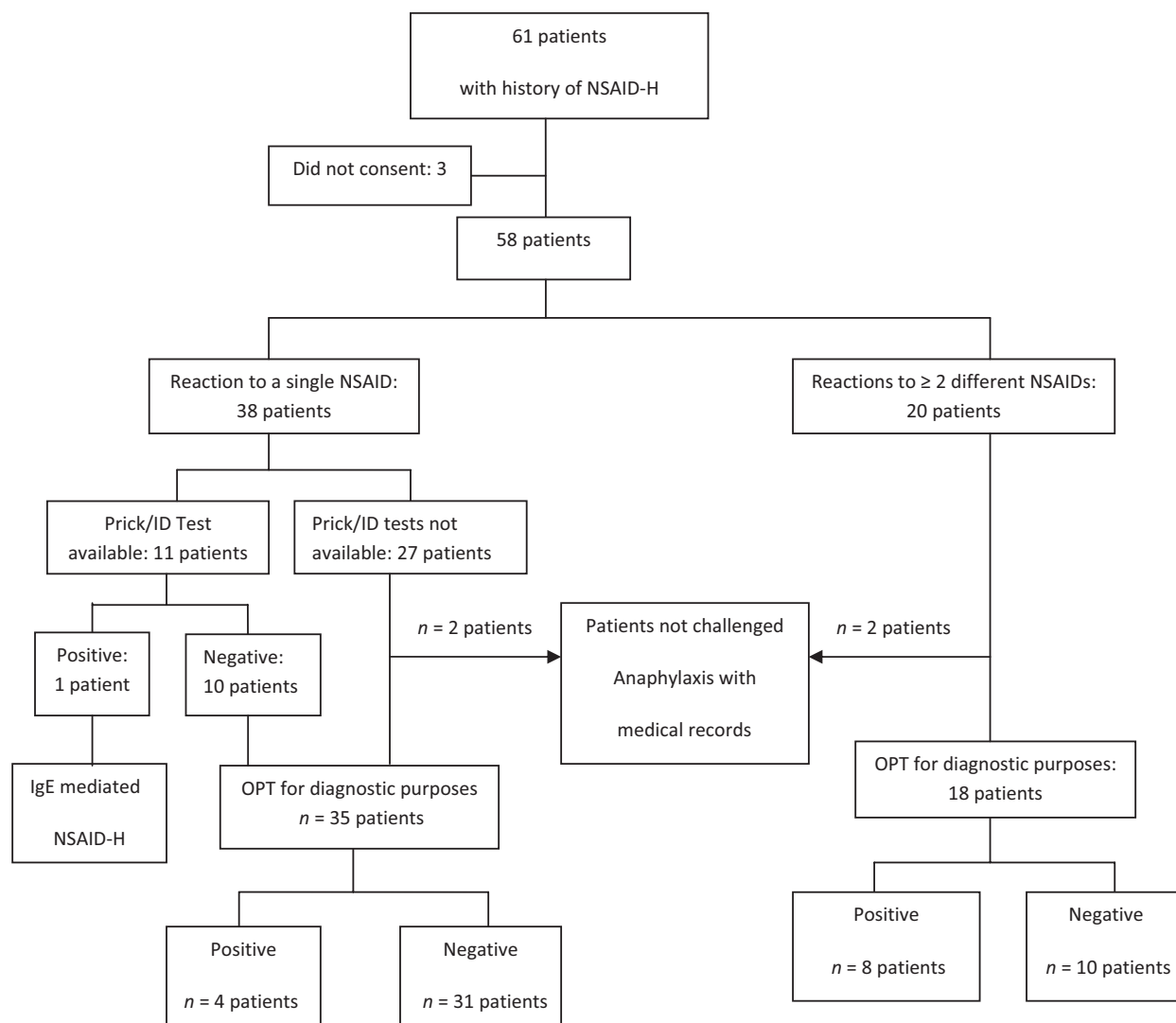
During the OPT, four or five escalating doses of the culprit NSAID were administered at intervals of 60 min up to the maximum single dose of the specific drug. The challenge doses were based on the recommendations of Messaad et al. (7) and were modified according to the weight of the children when needed (Table 1). The patients were kept under strict medical observation for up to 2 h after completing the test in cases of a negative test. If the maximum daily dose (MDD) allowed for the specific drug was not reached, the patients continued to take additional doses at specified intervals at home. A written plan for the doses was given to the parents. If no reaction occurred, all challenges were continued for 2 days to diagnose delayed responses. The patients were interviewed by telephone. In case of a suspected reaction, the child was brought back to the clinic and examined by the investigators for confirmation of the reaction. The tests were considered negative if no adverse reaction occurred at the end of 24 h after administration of the last dose. Tests were considered positive if any sign of hypersensitivity reaction such as urticaria, angioedema, laryngeal edema, hypotension, dyspnea, nasal symptoms, a 20% fall in FEV₁ value, anaphylaxis, or other rashes was observed during or after the test. In the case of a positive reaction, the tests were stopped, and the patients were treated symptomatically and were kept under medical observation until all symptoms were completely resolved. The reaction-eliciting dose was calculated as the cumulative dose given to the patient up until the reaction. Reaction time was defined as the period between the last administered dose and the appearance of the clinical reaction.

OPTs performed to find safe alternatives

Oral provocation tests performed to find safe alternatives were performed in children with confirmed NSAID-H. Acetaminophen and nimesulide/meloxicam were challenged as safe alternatives in children <12 years and ≥ 12 years, respectively. In patients <12 years with a cross-reactive type of hypersensitivity who were also reactive to acetaminophen, tolmetin sodium was challenged as a safe alternative (Table 1). In patients ≥ 12 years, nimesulide was tested as the first drug for a safe alternative because it is approved for children as young as 12 years. Meloxicam, however, is approved for children ≥ 15 years. The general rules for diagnostic OPTs as stated above were followed to find safe alternatives. The OPTs were stopped if any of the objective symptoms/signs specified above occurred.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 15.0 software (SPSS, Inc.,



NSAID-H: Nonsteroidal anti-inflammatory drug hypersensitivity; OPT: Oral provocation test

Figure 1 Diagnostic algorithm of patients with histories suggesting NSAID-H.

Chicago, IL, USA). Univariate analysis to identify variables associated with provocation results (positive/negative) was conducted using the Pearson's chi-square test, Fischer's exact test where appropriate. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the logistic regression analysis to determine independent predictors of patient outcome. A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Patients

Fifty-eight of 61 children with suspicion of NSAID-H agreed to participate in the study. The mean age was 8.9 ± 4.8 years (min–max: 4 months–17.8 years), and there was no gender

predominance (Table 2). Thirty-eight patients (65.5%) described a reaction to a single NSAID, whereas 20 mentioned reactions with ≥ 2 different NSAIDs (Table 2) (Fig. 1).

There were 27 patients who had multiple reactions on different occasions (2–6 times) with the same ($n = 7$) or different NSAIDs ($n = 20$); sixteen of these patients developed no reaction during the OPT (six of seven with the same NSAID and ten of 20 with different NSAIDs).

Reaction to a single NSAID ($n = 38$ patients)

Four patients described anaphylaxis (metamizole sodium: 2; acetaminophen: 1; and ibuprofen: 1) and 34 patients described urticaria and/or angioedema. The most common NSAID suspected in patient histories was ibuprofen (Table 2).

Table 1 Drug dosages for oral provocation tests

Drug	Provocation doses (mg)	MDD (mg/kg/day)
Diagnostic purposes		
Acetaminophen	10, 50, 250, 500	60
Ibuprofen	10, 20, 80, 150, 300	40
Metamizole sodium	62.5, 125, 250	66
Acetyl salicylic acid	10, 20, 50, 100, 200	40
Naproxen sodium	10, 20, 50, 150, 275	7
Tolmetin sodium	10, 50, 100, 200	30
Ketoprofen	5, 10, 20	2
Safe alternative		
Acetaminophen	30, 90, 120†	
Nimesulide	25, 75, 100	
Meloxicam	2, 6, 7.5	
Tolmetin sodium	10, 50, 100	

MDD, Maximum daily dose.

†For children ≥ 12 years-old: 60, 180, 250.*Prick and intradermal tests:*

Skin prick and ID tests were performed on 11 patients (seven patients with acetaminophen and four patients with metamizole sodium). One patient with a history of anaphylaxis had a positive reaction on the SPT performed with metamizole sodium (5×6 mm at 1 : 1 concentration, Table 3, Patient 16). The other skin tests were negative.

OPTs for diagnostic purposes

Thirty-five patients were challenged with the culprit NSAID. Three patients with a history of anaphylaxis were not challenged (confirmed with medical records: 2; skin test positivity: 1; Table 3, Patient No. 14, 15, and 16, respectively). Another patient with a history of anaphylaxis from metamizole sodium responded with a negative SPT with the culprit drug and was therefore challenged with no reaction. During the OPT, four patients (three patients with ibuprofen and one patient with acetyl salicylic acid (ASA)) developed angioedema and/or urticaria, which were treated with antihistamines (Table 3, Patient No. 5, 6, 9, and 11). Finally, excluding two patients, single NSAID-induced hypersensitivity was proven in 5 of 36 patients (14%).

Reaction with ≥ 2 different NSAIDs (n: 20 patients)

Five patients described anaphylaxis and 15 patients described urticaria and/or angioedema with multiple NSAIDs.

OPT for diagnostic purposes

Two patients with histories of anaphylaxis were not challenged (confirmed with medical records: 2; Table 3, Patient No. 12 and 13). Finally, 18 patients were challenged with the culprit NSAID. The OPT was positive in eight patients (44%) (Table 3). Four of the patients (50%) also developed urticaria and/or angioedema with acetaminophen.

Table 2 Clinical characteristics of patients evaluated for NSAID-H (n = 58)

Characteristics	n (%) of patients
Reactions in history	
With single NSAID	38 (65.5)
Ibuprofen	20 (52.6)
Acetaminophen	6 (15.8)
Metamizole sodium	4 (10.5)
Acetyl salicylic acid	2
Ketoprofen	1
Naproxen sodium	1
Tolmetin sodium	1
Acetaminophen+ibuprofen	3
With ≥ 2 different NSAIDs†	20 (34.5)
Presenting complaints	
Isolated angioedema	36 (62)
Periorbital	15
Lips	8
Multiple sites	13
Anaphylaxis	9 (15.6)
Urticaria	8 (13.9)
Urticaria and angioedema	5 (8.5)
Atopic sensitization	26 (44.8)
Atopic disease	30 (51.7)
Allergic rhinitis	18 (31)
Asthma	6 (10.3)
Chronic urticaria	3 (5.2)
Atopic dermatitis	2 (3.5)
Food allergy	1 (1.7)
Family history of drug allergy	13 (22.3)
NSAID	10 (17.2)
Antibiotic	2 (3.4)
Contrast medium	1 (1.7)

NSAID-H, Nonsteroidal anti-inflammatory drug hypersensitivity.

†The patients who had multiple reactions with different NSAIDs were not presented as many combinations existed.

The median (min–max) cumulative reaction-eliciting doses for ibuprofen and acetaminophen were 11.4 mg/kg (0.49–27.3 mg/kg) and 22.3 mg/kg (11.7–31.2 mg/kg), respectively. The reaction-eliciting doses of other NSAIDs are shown in Table 3.

Reactions to the OPTs were treated with oral antihistamines in patients with urticaria/angioedema and with adrenaline in patients with anaphylaxis. There were no patients requiring more than one dose of adrenaline during the OPTs. No hospitalization was needed.

Predictors in history

Gender, atopic status, presence of atopic disease, history of anaphylaxis, angioedema, reaction time, history of multiple reactions with the same NSAID, and safe use of a similar group of NSAID were not associated with OPT results in the univariate analysis ($P > 0.05$ for each). A history of NSAID-H in the family and having reactions with ≥ 2 different NSAIDs were found to be associated with provocation results ($P = 0.02$ and 0.013, respectively). Logistic regression analysis revealed that only a family history of NSAID-H

Table 3 The patients with proven NSAID-H (*n* = 17)

Patient	Age	Atopic Disease	Culprit drug in history	Reaction in history	Reaction during provocation	Reaction eliciting dose (mg/kg)	Reaction time†	Safe alternative
1	3 ^{2/12}	Allergic rhinitis	Ketoprofen Ibuprofen	Lip edema Lip, hand, foot edema Lip edema	Lip edema Lip edema	1.95 11.4	12 h 30 min	Tolmetin‡
			Metamizole	Lip edema	Lip edema	41.1	3 h	
			Acetaminophen	—	Lip edema	11.7	1 h	
			Tolmetin	—	No reaction			
2	12 ^{11/12}	Allergic rhinitis	Ibuprofen Metamizol	— Periorbital edema	Anaphylaxis Anaphylaxis	10.76 18	30 min 30 min	Nimesulide
			Acetaminophen	Periorbital edema	Periorbital edema No reaction	15.57	30 min	
			Nimesulide	—				
3	14	No	Ibuprofen	Lip edema	Lip, hand edema	9.04	1 h	Acetaminophen‡
			Nimesulide	Lip edema	NC			
4	3 ^{9/12}	No	Acetaminophen	Urticaria	Forehead edema, urticaria	29	30 min	Ibuprofen (Low dose)
			ASA	Hand edema	NC			
5	9 ^{4/12}	No	ASA	Lip edema	Hand edema	4.9	1 h	Acetaminophen
6	6 ^{11/12}	No	Ibuprofen	Lip edema, urticaria	Periorbital edema, urticaria	23.3	3 h	Acetaminophen
7	17 ^{10/12}	Chronic urticaria	Acetaminophen	Periorbital, lip edema, urticaria	Hand and finger edema, urticaria	31.2	1 h	Nimesulide
			Ibuprofen	Urticaria	Lip edema	11.57	12 h	
			Flurbiprofen	Lip edema, urticaria	NC			
			Metamizole	Lip edema, urticaria	NC			
			Nimesulide	—	No reaction			
8	1 ^{1/12}	Asthma, allergic rhinitis	Ibuprofen	Periorbital, lip edema	Urticaria	20.2	1 h	Acetaminophen Nimesulide
			Naproxen	Lip edema	NC	—		
			Nimesulide	—	No reaction	—		
9	4 ^{1/12}	Allergic rhinitis	Ibuprofen	Lip edema	Lip edema	1.2	1 h	Acetaminophen
			Acetaminophen	—	No reaction			
10	2 ^{1/12}	No	Ibuprofen	Urticaria	Urticaria	27.3	10 h	Acetaminophen
			Acetaminophen	—	No reaction	60		
11	15	Asthma, allergic rhinitis	Ibuprofen	Periorbital, lip, hand edema, urticaria	Hand edema, pruritus on face	0.49	1 h	Acetaminophen Nimesulide
			Acetaminophen	—	No reaction			
			Nimesulide	—	No reaction			
12	16	Asthma	Naproxen	Anaphylaxis	NE	—	—	Acetaminophen
			ASA	Anaphylaxis	NE	—	—	Meloxicam
			Nimesulide	—	Urticaria	1.63	1 h	
			Meloxicam	—	No reaction			
13	14 ^{1/12}	Asthma, allergic rhinitis	Naproxen sodium	Anaphylaxis	NE	—	—	Acetaminophen
			Diclofenac	Periorbital, lip edema, urticaria	NC	—		Nimesulide
			Metamizole	Urticaria	NC			
			Nimesulide	—	No reaction			

Table 3 (Continued)

Patient	Age	Atopic Disease	Culprit drug in history	Reaction in history	Reaction during provocation	Reaction eliciting dose (mg/kg)	Reaction time†	Safe alternative
14	12 ^{9/12}	Allergic rhinitis	Ibuprofen Nimesulide	Anaphylaxis —	NE No reaction	— 1.6		Acetaminophen Nimesulide
15	6	No	Acetaminophen Nimesulide	Anaphylaxis —	NE No reaction	— 4.16		Ibuprofen§ Nimesulide
16	11	Allergic rhinitis	Metamizole Acetaminophen	Anaphylaxis —	—	—	—	Acetaminophen Ibuprofen
17	13 ^{11/12}	Asthma, allergic rhinitis	Naproxen sodium Dexketoprofen Acetaminophen Nimesulide	Anaphylaxis Anaphylaxis — —	Anaphylaxis NE No reaction No reaction	— —	— —	Acetaminophen Nimesulide

NC, no consent; NE, not ethical; ASA, acetyl salicylic acid.

Diagnosis of anaphylaxis on medical records.

†Reaction time: The period between the last administered dose and the appearance of clinical reaction.

‡We expected him to had reaction with acetaminophen. But parents did not give consent for OPT for a safe alternative.

§She said she could use ibuprofen. The challenge could not be performed. Because she died due to neuroblastoma.

increases the odds of a positive OPT with a NSAID by 5.4 (95% CI: 1.02–28.6).

OPT to find a safe alternative (n: 17 patients)

Five patients had already been using a safe alternative (Table 3, Patient No. 3, 4, 5, 6 and 16). One of these five patients (Table 3, Patient No. 4) was using a possible reaction-eliciting NSAID at a low dose (ibuprofen: 5 mg/kg/day), but this patient's parents did not consent to the OPT. The other 12 patients were challenged for a safe alternative (6 patients with nimesulide, two patients with acetaminophen, two patients with acetaminophen and nimesulide, one patient with nimesulide and meloxicam, and one patient with acetaminophen and tolmetin).

Two patients developed isolated angioedema and urticaria with acetaminophen and nimesulide (treated with oral antihistamine) during the OPT for a safe alternative. Tolerability rates for acetaminophen and nimesulide were 60% and 88.8%, respectively.

Discussion

In this study, the recent diagnostic algorithm for acute reactions to NSAIDs was applied, depending on the number of drugs in the patient's history. Similar to adults, children can reveal histories of reactions to NSAIDs, particularly to ibuprofen (8). However, 86% of single reactors and 56% of double cross-reactors avoid NSAIDs for no reason. It is believed that comorbid conditions such as infections, fever, or concomitant use of other drugs might be playing a role in causing symptoms in these patients (9–12).

The diagnosis of NSAID-H was confirmed by OPTs in a few childhood studies (7, 11, 13). In some publications, children with a history of anaphylaxis/reactions to multiple NSAIDs were accepted as hypersensitive without performing an OPT (14–16). However, neither anaphylaxis nor reactions

to multiple NSAIDs were associated with OPT results in this study. This points to the importance of performing OPTs to diagnose true NSAID-H.

A history of parents who reacted to one of the NSAIDs was reported to be between 11% and 17% in only two studies (15, 16). In the present study, this was the only parameter increasing the odds of a positive challenge by fivefold, a finding that may deserve an investigation of the role of genetics in NSAID-H. The number of children, however, with true NSAID-H was small, a fact that may limit a generalization of this result.

Acetaminophen hypersensitivity in cross-reactive patients was documented in 0–25% of patients in pediatric studies (5, 11, 14, 15). In this study, half of the cross-reactors were allergic to acetaminophen. The higher ratio may be associated with the MDD administered in the OPT. In children, acetaminophen may be needed several times a day as an antipyretic/analgesic. It is therefore important to reach the MDD of the drug before labeling it as safe.

Provocation with an ASA challenge is the screening test in adults for detecting cross-reactive-type NSAID-H (1). However, ASA is not widely used in children because of the risk of Reye syndrome. In our challenge-proven NSAID-H children, ibuprofen was the most frequent drug responsible for the cross-reactive type of NSAID-H. In addition, ibuprofen was found to be positive in all patients challenged with the drug. It is believed, therefore, that instead of ASA, ibuprofen may be used to detect the cross-reactive type of NSAID-H in children.

In the present study, all children with confirmed NSAID-H were challenged to find a safe alternative. Nimesulide and meloxicam are shown to be well tolerated in patients with NSAID-H in several studies performed in adults (16–19). For children <12 years with acetaminophen hypersensitivity, we used tolmetin sodium, which is the only drug approved for this age group for use as an anti-inflammatory, antipyretic, and analgesic (20). Our results showed good tolerability rates for all safe alternatives. There are, however, patients who

react to safe alternatives, and these drugs should not be prescribed without an OPT.

We think that challenging the cases with all of the culprit NSAIDs is one of the strengths of our study. Although this was much more time-consuming, it enabled us to be sure that all negative results were true negatives and that positive results were true positives. Another strength of the study was the provocation of all cases until the MDD of the culprit NSAID was reached if no reaction occurred. It is important not to miss patients who react only at high doses (Patient No. 4, 7, and 10 in Table 2) as these patients could be under-diagnosed if challenged with therapeutic doses.

The cross-reactive type of NSAID-H could not be excluded in the study group in patients with a reaction to a single NSAID where the OPT was performed only with the culprit drug. We could not perform a second challenge with ASA or ibuprofen in these cases. Another limitation of the study was the small number of subjects being analyzed. However, considering the rarity of NSAID-H in children, it is believed that the data in the study have provided some important preliminary results about the frequency of this condition in a tertiary care clinic in Turkey.

In conclusion, like adults, few children with suggested relevant histories have true hypersensitivity to NSAIDs. Histories of both single and multiple NSAID-induced hypersensitivity are poor predictors of proven diagnosis, and family history may increase the probability of true NSAID-H. It is therefore necessary to have diagnostic tests performed in all children with suspected NSAID-H if no contraindication exists. These tests should be carried out under the supervision of allergists in a hospital setting equipped with emergency care facilities.

Acknowledgments

We thank all children and their parents who participated in the study. The article has been checked for spelling, punctuation, sentence structure, and grammar by a native English speaker, Emine Mizyal.

Conflict of interest

The authors declare no conflict of interest.

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