The value of the clinical history for the diagnosis of immediate nonsteroidal anti-inflammatory drug hypersensitivity and safe alternative drugs in children

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ABSTRACT

Background: *Diagnosing hypersensitivity reactions that develop as a result of nonsteroidal anti-inflammatory drugs (NSAID) with a history is mostly misleading, and skin tests and/or provocation tests are needed for a definitive diagnosis.*

Objective: *To determine the frequency of actual NSAID hypersensitivity and whether there are any parameters in the history to predict NSAID hypersensitivity. In addition, to determine safe alternative drugs for children who are diagnosed with actual NSAID hypersensitivity.*

Methods: *Children with a history of NSAID hypersensitivity were evaluated by an allergist. Safe alternatives in children with a confirmed NSAID hypersensitivity were found by oral provocation tests.*

Results: *Sixty-four patients who were admitted with a suspicion of immediate-type reaction to NSAIDs were included in the study. The median age of the patients was 6 years old (range, 1–17 years), and 37 of the patients (57.8%) were boys. We performed skin tests for suspected NSAID in 35 patients (54.7%). Of these, two had positive results. Provocation tests were performed with 62 patients whose skin test results were negative or for whom skin tests were not available. During the provocation tests, 16 patients (25.8%) developed reactions. Low- and high-dose acetaminophen, nimesulide, and tolmetin sodium were used to find safe alternative drugs. Two patients developed reactions to high-dose acetaminophen but no reaction to nimesulide and tolmetin sodium. When statistically significant parameters were analyzed in a logistic regression model, the presence of multiple NSAIDs hypersensitivity in the patient history (odds ratio 26.6 [95% confidence interval, 1.47–481.63]; $p = 0.026$) and the emergence of a reaction within an hour (odds ratio 26.4 [95% confidence interval, 1.73–403.11]; $p = 0.019$) were found as the independent factors to predicted actual NSAID hypersensitivity.*

Conclusion: *The emergence of a reaction within an hour of taking the drug and the presence of multiple NSAIDs hypersensitivity history increased the possibility of actual NSAID hypersensitivity. Nimesulide, low-dose acetaminophen, and tolmetin sodium could be used as safe alternative drugs in patients with multiple NSAIDs hypersensitivity.*

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Nonsteroidal anti-inflammatory drugs (NSAID) are frequently used in children as antipyretics and analgesics. Hypersensitivity to NSAIDs is the second most common drug hypersensitivity, after β-lactam antibiotics.[1] The reported prevalence of NSAID hypersensitivity among healthy children is 0.3%, and the prevalence of aspirin sensitivity in children with asthma is ~5%, as assessed by provocation tests.[2,3] Most of the hypersensitivity reactions caused by these drugs presented as urticaria and/or angioedema.[4,5] During infections, NSAIDs are used in children, mostly as antipyretics. However, in the course of infections, especially viral infections, skin-localized symptoms, such as urticaria and angioedema, can also be seen. Thus, diagnosing hypersensitivity reactions that develop as a result of NSAID use by using history and physical examination is mostly misleading, and skin tests and/or provocation tests are needed for a definitive diagnosis. Previous studies[4,6,7] show a large range of positive oral challenges (14–68%).

NSAIDs-associated reactions are divided into two types: immediate (reaction ≤ 24 hours after exposure) and delayed (>24 hours after exposure). Immediate reactions to NSAIDs may be single (possibly immunoglobulin E [IgE] mediated) or multiple NSAIDs induced (cross-reactive). Single NSAID-induced immediate reactions are diagnosed with skin-prick and/or intradermal tests if the culprit drug is available or *via* oral provocation tests (OPT). In contrast, multiple (cross-reactive types) NSAIDs-induced immediate reactions are diagnosed with OPTs with potent cycloox-

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Table 1 **Drug dosages for oral provocation tests**

Drug	Provocation Doses, mg	Maximum Daily Dose, 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
Acetylsalicylic acid	10, 20, 50, 100, 200	40
Naproxen sodium	10, 20, 50, 150, 275	7
Ketoprofen	5, 10, 20	2
Safe alternative		
Acetaminophen, low dose	10, 30, 40	
Acetaminophen, high dose	30, 90, 120	
Nimesulide	25, 75, 100	
Tolmetin sodium	10, 50, 100	

ygenase (COX) 1 inhibitors, such as ibuprofen or acetylsalicylic acid.[8]

The primary objective of this study was to determine the frequency of actual NSAID hypersensitivity and whether there were any parameters in the history of children to predict NSAID hypersensitivity. The secondary aim was to determine safe alternative drugs for children diagnosed with actual NSAID hypersensitivity.

METHODS

Patients and Study Design

We made a retrospective medical chart review in a two-year period between April 2013 and March 2015. The study included patients whose complete medical records were available. Cases referred to the pediatric allergy department of Inonu University and Ondokuz Mayıs University for hypersensitivity reactions to single or multiple NSAIDs were included in the study. Patients who were diagnosed with immediate reactions to NSAIDs, such as urticaria and/or angioedema, bronchospasm, and laryngeal edema, were included, and patients who were diagnosed with delayed reactions to NSAIDs, such as fixed drug eruptions, erythema multiforme, and Stevens-Johnson syndrome and/or toxic epidermal necrolysis complex, were excluded. In both allergy clinics, the diagnosis of NSAID hypersensitivity was carried out according to European Network for Drug Allergy.[8] The results of skin tests, if available, for culprit drugs, the results of provocation tests for culprit drugs, and safe alternative drugs were also obtained from patients' files. The Inonu University Hospital Ethics Committee approved the study, and written informed consent was obtained from all the patients and/or their parents.

Diagnostic Approach for Immediate Reactions to NSAIDs

The patients who had a history of immediate reactions to a single NSAID were assigned as having possible IgE-mediated hypersensitivity. These patients were first tested by skin-prick and/or intradermal test and, if negative results, were challenged with the culprit NSAID. Patients who had reactions with multiple NSAIDs were assigned as a possible cross-reactive group and were directly challenged with acetylsalicylic acid.[8]

Skin-Prick and Intradermal Tests

Skin-prick and intradermal tests were performed with acetaminophen, metamizole sodium, and diclofenac because their vials were available. Skin-prick tests with acetaminophen (Perfalgan, 10 mg/mL; Bristol-Myers Squibb, Itxassou, France), metamizole sodium (Novalgin, 1 g per 2 mL; Sanofi-Aventis, Milan, Italy), and diclofenac (Voltaren, 75 mg per 3 mL; Novartis Pharma AG, Basel, Switzerland) were performed at concentrations of 10 mg/mL, 0.4 g/mL, and 25 mg/mL, respectively. Intradermal tests were carried out in 1/10 dilutions.[9–11] The skin-prick test results were accepted as positive if a wheal diameter was ≥3 mm compared with the negative control and was accompanied by erythema 15 minutes after the test was performed.

OPTs

OPTs were carried out according to the European Network for Drug Allergy position paper on drug hypersensitivity.[12] During the OPTs, four or five escalating doses of the culprit NSAID were administered at intervals of 60 minutes up to the maximum single dose of the specific drug. The challenge doses were based on the recommendations of Messaad *et al.*[1] and were mod-

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ified according to the weight of the child when needed (Table 1). Test results were considered positive if any sign of hypersensitivity reactions, such as urticaria, angioedema, laryngeal edema, hypotension, dyspnea, nasal symptoms, anaphylaxis, or other rashes, was observed during or after the test. In the case of a positive reaction, the tests were stopped, the patients were treated symptomatically, and the patients were kept under medical observation until all symptoms were completely resolved.

OPTs Performed to Find Safe Alternative Drugs

OPTs were performed to find safe alternatives in the children with confirmed NSAID allergies. In children who were <12 years old, OPTs were first carried out with low-dose acetaminophen; if no reaction occurred, then provocation was carried out with high-dose acetaminophen. In children who were ≥12 years old, nimesulide was used to find a safe alternative. In patients younger than 12 years with reactions to acetaminophen or proven IgE-mediated reactions to other NSAIDs, tolmetin sodium was challenged as a safe alternative. The OPTs were stopped if any of the objective symptoms and/or signs specified above occurred.

Statistical Analysis

Statistical analysis was performed by using the Statistical Package for Social Sciences 15.0 software (SPSS Inc., Chicago, IL). Descriptive statistics were expressed as frequencies and percentages for categorical variables, whereas quantitative data were expressed as medians for non-normally distributed data. Univariate analysis to identify variables associated with provocation results (positive/negative) was conducted by using the Pearson χ^2 test and the Fisher exact test when appropriate; they were compared by using a χ^2 test for categorical variables. Quantitative variables were compared by using the Mann-Whitney U test. A logistic regression model was constructed by including statistically significant parameters to determine the factors that predict the actual NSAID hypersensitivity. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Demographic

Sixty-four patients who were admitted with a suspicion of immediate-type reactions to NSAIDs were included in the study. The median age of the patients was 6 years old (range, 1–17 years), and 37 of the patients (57.8%) were boys. Although 52 of the patients (81.2%) had reactions against only one NSAID group, 12 patients (18.8%) had reactions against multiple NSAIDs groups. Twenty patients (31.3%) had a history of NSAID hypersensitivity before being referred to the allergy department. The drug group that developed the most-frequent hypersensitivity reaction in etiology was ibuprofen (30 [46.9%]) and acetaminophen (28 [43.8%]). Thirty-two patients (50%) developed reactions to NSAID within the first hour. The most-frequent reactions were urticaria (38 [59.4%]) and angioedema (35 [54.7%]). NSAIDs that caused reactions were given orally in 58 patients (90.8%). Twenty of the patients (31.3%) had an allergic comorbidity (food allergy in nine patients [14.1%], asthma in eight patients [12.5%], allergic rhinitis in eight patients [12.5%], and chronic urticaria in three patients [4.7%]). Ten parents (15.6%) had a history of hypersensitivity to NSAIDs.

Diagnostic Tests and Safe Alternatives

We performed skin tests for the suspected NSAID with 35 patients (54.7%). Of these, two had positive results (one to immediate-reading intradermal tests with acetaminophen and one to immediate-reading intradermal tests with metamizole sodium). OPTs were performed with 62 patients whose skin test results were negative or for whom skin tests were not available. Whereas provocation tests were performed on 12 patients with acetylsalicylic acid because they had a history of multiple NSAIDs hypersensitivity, provocation tests were performed on the remaining patients with a suspicion of NSAID hypersensitivity. As a result of the provocation tests, 16 patients (25.8%) developed reactions (Fig. 1). To find safe alternative drugs for patients who were found to have NSAID hypersensitivity, provocation tests were performed on seven patients younger than 12 years old with low-dose acetaminophen first, and none of them developed reactions. Later, provocation was performed on them with high-dose acetaminophen, and reactions developed in two patients. Tolmetin sodium was given to these two patients and no reactions occurred. OPTs were performed with nimesulide on nine patients older than 12 years old. None of these patients developed reactions. In addition, provocation tests with tolmetin sodium were performed with acetaminophen and metamizole sodium on two patients whose intradermal test results were positive. Neither developed a reaction (Table 2).

The Factors in History to Predict the Actual NSAIDs

When the patients who were found to have NSAIDs hypersensitivity as a result of provocation tests and the patients who were not found to have NSAID hypersensitivity were compared, the rates of a patient being older than 10 years old ($p = 0.007$), a history of having a reaction to multiple NSAIDs ($p = 0.008$), a history of hypersensitivity with the same drug ($p = 0.038$), acetylsalicylic acid hypersensitivity in history ($p = 0.034$), a reaction developing within an hour of taking the

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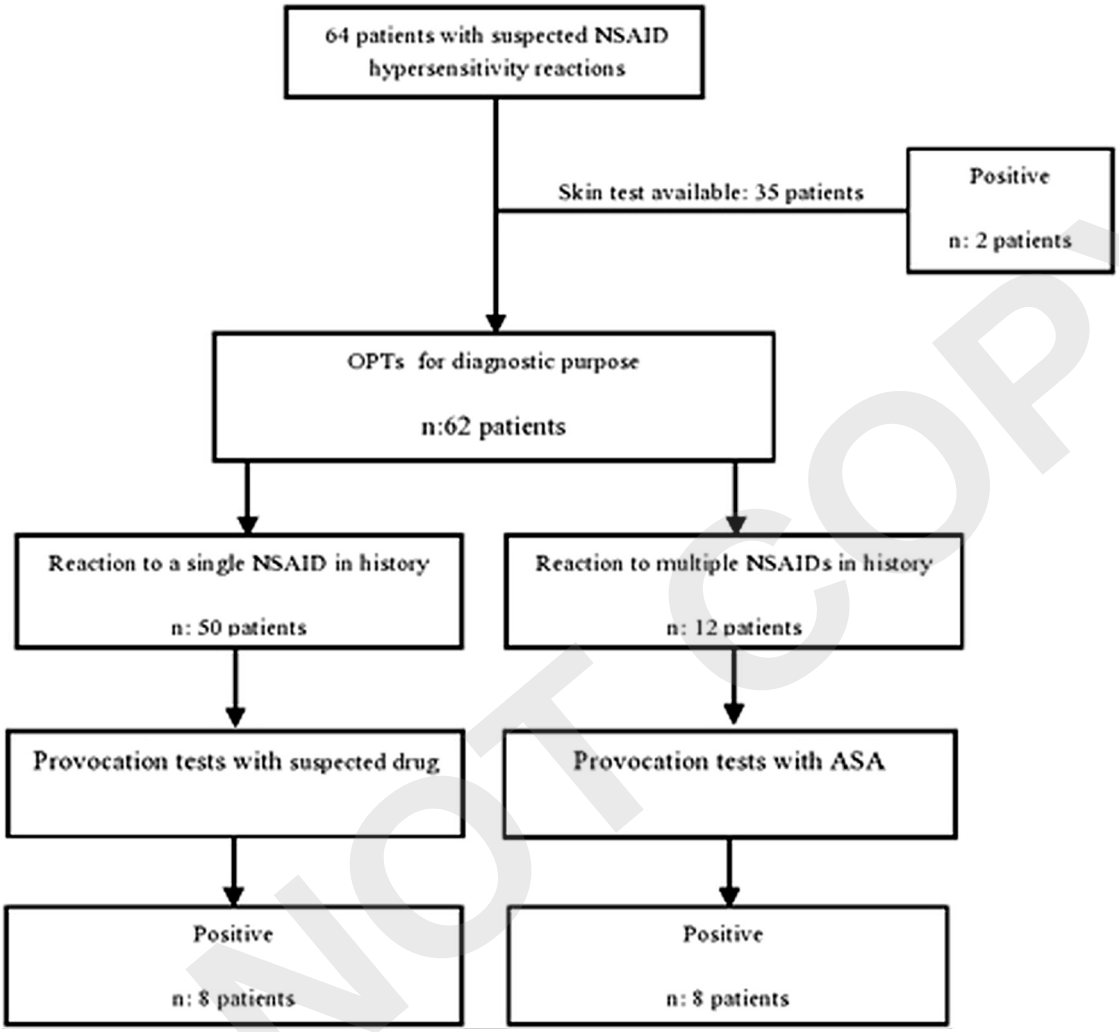


Figure 1. *Flow chart of the study.*

drug ($p = 0.029$), NSAID hypersensitivity in the family ($p = 0.014$), and the presence of peripheral eosinophile ($p = 0.039$) were higher in patients who had NSAID hypersensitivity proven with provocation tests (Table 3). When statistically significant parameters were analyzed in a logistic regression model, the presence of multiple NSAIDs hypersensitivity (odds ratio 26.6 [95% confidence interval, 1.47–481.63]; $p = 0.026$) and the emergence of a reaction within an hour (odds ratio 26.4 [95% confidence interval, 1.73–403.11]; $p = 0.019$) were found as the independent factors to predicted actual NSAID hypersensitivity.

DISCUSSION

Our study showed that only approximately one-fourth of the patients with NSAID hypersensitivity in their history had actual NSAID hypersensitivity. The presence of multiple NSAIDs hypersensitivity and the emergence of the reaction within the first hour of taking the drug in the history were the independent factors that predicted actual NSAID hypersensitivity. In addition, our study found that low-dose acetaminophen or tolmetin sodium in children younger than 12 years old and nimesulide in children older than 12 years old could be used as safe alternative drugs.

Diagnosing or excluding NSAID hypersensitivity based on patient history and/or as a result of skin tests is mostly misleading. This is because COX-1 inhibition or TH lymphocyte mediated, rather than IgE-mediated immune mechanisms, is held responsible for hypersensitivity to NSAIDs. Thus, in most patients, the results of skin-prick and/or intradermal test results are negative, and provocation tests are needed for diagnosis. A few studies conducted with children have shown that 14–68.2% of children who had a history of NSAID hypersensitivity had true NSAID hypersensitivity.[4,7,13] In our study, it was found that only one-fourth of the patients who described NSAID hypersensitivity in their history had actual NSAID hypersensitivity. Thus, a NSAID hypersensitivity diagnosis should not to be made based on history and the results of skin tests; a

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Table 2 **The patients with proven NSAID hypersensitivity (N = 18)**

Patient No.	Sex	Age, y	Culprit Drugs in History	Proven IgE Mediated Reaction (skin-prick/ intradermal tests)	Provocation Drug	Reaction During Provocation	Safe Alternative			
							Low-dose Acetaminophen	High-dose Acetaminophen	Nimesulide	Tolmetin sodium
1	Female	6	Ibuprofen	NA	Ibuprofen	Urticaria, angioedema, itching	No reaction	Reaction positive	NP	No reaction
2	Female	7	ASA, ibuprofen	NA	ASA	Angioedema	No reaction	No reaction	NP	NP
3	Female	6	Acetaminophen	Intradermal positive	NP		NP	NP	NP	No reaction
4	Male	5	Ibuprofen	NA	Ibuprofen	Urticaria, angioedema, itching	No reaction	No reaction	NP	NP
5	Female	12	Ibuprofen	NA	Ibuprofen	Angioedema	NP	NP	No reaction	NP
6	Female	16	Ketoprofen	NA	Ketoprofen	Urticaria, itching	NP	NP	No reaction	NP
7	Female	15	Diclofenac sodium	Negative	ASA	Angioedema	NP	NP	No reaction	NP
			Ketoprofen	NA						
8	Female	12	Acetaminophen	Negative	Acetaminophen	Urticaria, angioedema, itching	NP	NP	No reaction	NP
9	Male	3	Metamizole sodium	Intradermal positive	NP		No reaction	No reaction	NP	NP
10	Male	16	Diclofenac sodium	Negative	ASA	Urticaria	NP	NP	No reaction	NP
			Ketoprofen	NA		Flushing				
11	Female	15	Acetaminophen	Negative	Acetaminophen	Urticaria	NP	NP	No reaction	NP
12	Male	10	ASA	NA	ASA	Urticaria, angioedema	No reaction	No reaction	NP	NP
13	Female	17	Acetaminophen	Negative	ASA	Urticaria	NP	NP	No reaction	NP
			Diclofenac sodium	Negative						
14	Male	16	Acetaminophen	Negative	ASA	Angioedema	NP	NP	No reaction	NP
			Ibuprofen	NA						
15	Male	10	ASA	NA	ASA	Urticaria	No reaction	Reaction positive	NP	No reaction
16	Male	11	Metamizole sodium	Negative	Metamizole sodium	Angioedema	No reaction	No reaction	NP	NP
17	Male	9	Metamizole sodium	Negative	Metamizole sodium	Angioedema	No reaction	No reaction	NP	NP
18	Female	12	Acetaminophen	Negative	ASA	Angioedema	NP	NP	No reaction	NP
			Diclofenac sodium	Negative						

NSAID = nonsteroidal anti-inflammatory drug; IgE = immunoglobulin E; NA = not available; NP = not provocated; ASA = acetylsalicylic acid.

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Table 3 **Comparison of patients with proven NSAID hypersensitivity and patients with proven non-NSAID hypersensitivity**

Variable	Patient with Proven NSAID Hypersensitivity, no. (%) (n = 16)	Patient with Proven Non-NSAID Hypersensitivity, no. (%) (n = 46)	p Value
Sex, male	7 (43.8)	29 (63)	0.292
Age > 10 y	9 (56.3)	8 (17.4)	**0.007**
Reactions in history			
With single NSAID			
Acetaminophen	5 (31.3)	22 (47.8)	0.390
Ibuprofen	7 (43.8)	23 (50)	0.888
Metamizole sodium	2 (12.5)	5 (10.9)	1.0
Acetylsalicylic acid	4 (25)	2 (4.3)	**0.034**
Ketoprofen	3 (18.8)	0	NC
Etodolac	0	1 (2.2)	NC
Diclofenac	4 (25)	0	NC
With ≥2 different NSAIDs	7 (43.8)	5 (10.9)	**0.008**
≥2 reactions in history with culprit NSAID	9 (56.3)	11 (23.9)	**0.038**
Reaction time after NSAID intake, ≤1 hr	12 (75)	18 (39.1)	**0.029**
Route of NSAID, p.o.	14 (87.5)	44 (95.7)	0.272
Generalized reaction with NSAID	6 (37.5)	26 (56.5)	0.307
Presenting concern			
Urticaria	7 (43.8)	30 (65.2)	0.226
Angioedema	11 (68.8)	24 (52.2)	0.390
Itching	5 (31.3)	24 (52.2)	0.248
Flushing	4 (25)	0	NC
Anaphylaxis	0	2	NC
Concomitant allergic disease	7 (43.8)	13 (28.3)	0.406
Asthma	2 (12.5)	6 (13)	1.0
Allergic rhinitis	3 (18.8)	5 (10.9)	0.414
Food allergy	2 (12.5)	7 (15.2)	1.0
Chronic urticaria	3 (18.8)	0	NC
Family history of NSAID	6 (37.5)	4 (8.7)	**0.014**
Eosinophilia	5 (55.6)	7 (18.9)	**0.039**
Serum total IgE level, median (minimum-maximum)	293 (99–373)	88.9 (2.14–758)	0.060

NSAID = nonsteroidal anti-inflammatory drug; p.o. = by mouth; NC = non-calculated; IgE = immunoglobulin E. The data in bold is statistically significant.

definitive diagnosis in children should be made based on provocation tests.

In patients diagnosed with NSAID hypersensitivity, avoiding the culprit drug should be recommended and therapeutic options can be found, such as the administration of alternative drugs, *e.g.,* weak COX-1 inhibitors and/or preferential or highly selective COX-2 inhibitors, or desensitization to the culprit. In studies of adults and a few studies made with children, meloxicam or nimesulide was used, and the studies gave successful results.[4,14,15] In our study, in children older than 12 years old, the preferential selective COX-2 inhibitor nimesulide was used; whereas in children younger than 12 years old, low and high doses of the weak COX-1 inhibitor acetaminophen were used. Although no patient developed reactions to nimesulide and low doses of acetaminophen, two of the eight patients who were given high doses of acetaminophen developed reactions. This result showed that nimesulide and low doses of acetaminophen could be used as safe alternatives. However, these drugs should be used by patients after provocation.

In patients younger than 12 years old who had multiple NSAIDs hypersensitivity, the use of preferential or highly selective COX-2 inhibitors as safe alternatives was not approved. In this age group, the weak COX-1

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inhibitor acetaminophen was used. However, for patients who develop reactions to acetaminophen, there is no choice left for safe alternative drugs. Recently, a case study showed that tolmetin sodium can be used as safe alternative in this age group.[16] Tolmetin sodium is a pyrrole-derivative anti-inflammatory drug that possesses an antipyretic effect,[17] but the mode of action is not known exactly. It is shown that it inhibits prostaglandin synthesis *in vitro* and lowers prostaglandin E levels in man.[16] Although it might have a potential to cause similar reactions, the absence of a direct effect on the COX enzyme may not be able to change the leukotriene to prostaglandin ratio dramatically, which may explain the low incidence of a clinically detectable event. In our study, two patients who developed reactions against high-dose acetaminophen used as a safe alternative drug did not develop reactions to tolmetin sodium. This result showed that tolmetin sodium should be considered among safe alternative drugs.

It is sometimes misleading to diagnose NSAID hypersensitivity based on history. In a few studies conducted so far, factors that predict that actual NSAID hypersensitivity may occur based on clinical history have been examined.[4,5] In their study on adults, Blanca-Lopez *et al.*[5] reported that being a female, the emergence of a reaction within an hour of taking the drug, and a history of multiple NSAIDs hypersensitivity were the factors that predicted NSAID hypersensitivity. In their study on children, Ylmaz *et al.*[4] reported that a family history of NSAID hypersensitivity predicted the actual NSAID hypersensitivity. In our study, the emergence of a reaction within an hour of taking the drug increased the possibility of actual NSAID hypersensitivity 26.4 times, and multiple NSAIDs hypersensitivity in the patient history increased the possibility of actual NSAID hypersensitivity 26.6 times. Thus, multiple NSAIDs hypersensitivity history and the emergence of a reaction within an hour of taking the drug should bring to mind the fact that the reaction may be actual NSAID hypersensitivity.

There were some limitations to our study. First, the cross-reactive type of NSAID hypersensitivity could not be excluded in the study group in patients with a reaction to a single NSAID when the OPTs were performed only with the culprit drug. We could not perform a second challenge with acetylsalicylic acid in these cases. Second, a small number of subjects were analyzed in the study. Thus, studies that include higher numbers of patients are required to be able to generalize the results.

CONCLUSION

The diagnosis of NSAID hypersensitivity should not be made based on history; provocation tests should be conducted for definitive diagnosis when necessary. The emergence of a reaction within an hour of taking the drug and the presence of multiple NSAIDs hypersensitivity in the patient history increases the possibility of actual NSAID hypersensitivity. In patients with multiple hypersensitivity, nimesulide or low-dose acetaminophen can be used as safe alternative drugs. In addition, tolmetin sodium can be used as a safe alternative drug in children who develop hypersensitivity to acetaminophen.

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