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Hypersensitivity to Ibuprofen: Real-Life Experience in Children with History of Suspected Immediate Reactions

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Keywords
Children · Drug provocation test · Hypersensitivity · Ibuprofen · Nonsteroidal anti-inflammatory drugs

Abstract
Introduction: Ibuprofen is the most common culprit drug causing nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity in children. We aimed to evaluate the frequency, clinical characteristics, and risk factors of confirmed ibuprofen allergy in children presenting with a history of suspected immediate type ibuprofen-induced hypersensitivity reactions. ***Methods:*** We evaluated 50 (35 M, 15 F) children with a median age of 7 years, who were referred to our clinic with suspected immediate ibuprofen hypersensitivity. Patients were subjected to a diagnostic work up including drug provocation tests (DPTs) with the culprit drug. Reactions were classified according to the European Academy of Allergy and Clinical Immunology Task Force recommendations for pediatric patients. Proven ibuprofen allergic patients underwent DPT to find a safe alternative drug. ***Results:*** Ibuprofen allergy was confirmed in 34% (*n*: 17) of children; 9 patients were diagnosed by DPTs and 8 patients diagnosed based on their histories. Angioedema was the most common clinical manifestation (*n*: 30, 60%). Among patients with proven ibuprofen allergy, 7 of them were classified as cross-intolerant. Cross-intolerance reactions were further classified as NSAID-exacerbated cutaneous disease (*n* = 1) and NSAID-induced urticaria/angioedema/anaphylaxis (*n* = 6). As an alternative drug, paracetamol was safely tolerated, whereas 1 patient developed angioedema and urticaria with nimesulide. Older age and male gender were identified as independent risk factors for immediate-type ibuprofen allergy. ***Conclusion:*** DPTs should be performed to confirm or exclude ibuprofen allergy in children and to find safe alternative drugs. Male gender and older age are risk factors for ibuprofen allergy. NSAID-induced hypersensitivity reactions in the pediatric population cannot be well defined using the adult classification system.

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Introduction

Ibuprofen is the most commonly used nonsteroidal anti-inflammatory drug (NSAID) at all age ranges as analgesic and antipyretic agent, and its mechanism of action is based on the inhibition of cyclooxygenase enzymes

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(COX) [1, 2]. In line with its widespread use, it has been found to be the most common culprit drug in confirmed NSAID-hypersensitive children [3]. The estimated prevalence of NSAID hypersensitivity has been reported between 0.6 and 5.7% of the general population. The results vary significantly depending on the ethnic and genetic differences of the study population and the method of diagnostic assessment [4–6]. Although the number of patients presenting with the complaints of hypersensitivity reactions due to ibuprofen is high, those whose diagnosis is confirmed are much less [7]. Ibuprofen-induced hypersensitivity reactions can be classified clinically as early and delayed. Based on Drug Allergy/Global Allergy and Asthma European Network (ENDA/GA^{2}LEN) classification, an immediate reaction was considered as the appearance of a reaction within the first 24 h after the drug consumption; whereas others were defined as delayed hypersensitivity reactions [8]. Early type reactions can occur in a wide clinical spectrum from mild urticaria to severe anaphylaxis [9].

Hypersensitivity (H) reactions to NSAIDs are classified as selective hypersensitivity reaction (SR, immunologic) and cross-intolerance reaction (CI, nonimmunologic) according to the underlying mechanisms [10]. SRs are induced by a single or multiple NSAIDs in the same subclass, and these selective responders tolerate other chemically unrelated drugs. CIs which are induced by different chemically nonrelated NSAIDs occur due to COX enzyme inhibition. These cross-intolerant patients do not tolerate strong COX-1 inhibitor NSAIDs such as aspirin [9]. The ENDA/GA^{2}LEN classification has allocated CIs and SRs into subgroups according to the underlying mechanisms and the presence of concomitant allergic diseases as NSAID-exacerbated respiratory disease, NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema (AO), single NSAID-induced urticaria/AO and/or anaphylaxis, and single NSAID-induced delayed reactions [8, 9]. However, pediatric patients cannot always fit properly into this classification, since NSAID-H may present with different characteristics in this age group [3, 11, 12]. Besides, the European Academy of Allergy and Clinical Immunology (EAACI) has published a consensus document in which a new classification for children and adolescents was proposed [13]. In this classification, anaphylactic reactions in cross-intolerant patients which are not included in ENDA/GA^{2}LEN classification [8] are defined as NSAID-induced urticaria/AO/anaphylaxis (NIUAA).

There are few clinical studies regarding ibuprofen-H in both pediatric and adult population, and late reactions have also been included in most of the reported series [7, 14, 15]. In this study, we aimed to investigate the frequency, clinical characteristics, and risk factors of proven ibuprofen allergy in children presenting with a history of suspected ibuprofen-induced immediate-type hypersensitivity reactions. Our secondary aim was to classify ibuprofen allergy based on the EAACI recommendations [13].

Materials and Methods

Patients

Children who were referred to our outpatient clinic with suspected immediate ibuprofen-H between January 2015 and February 2020 were evaluated. Demographic and clinical data were retrieved according to the ENDA questionnaire [16]. The characteristics of reactions, history of drug allergy, previously tolerated NSAIDs, and presence of allergic diseases were recorded. Assessments of atopy were based on serum total immunoglobulin E (IgE) level/skin prick test (SPT) results with major inhalant and food allergens. Patients with any suspected unprovoked reaction, patients younger than 1 year of age, and patients whose families refused diagnostic drug provocation tests (DPTs) with ibuprofen were excluded from the study.

Diagnostic Evaluation and Patient Classification

Skin Tests

We could not perform skin tests with ibuprofen in any patients, since there was no i.v. preparation of ibuprofen available in our country at the time of the study, and pediatric skin test concentrations for ibuprofen have not been confirmed yet [13]. However, SPT with metamizole could not be performed to the patient who had a history of confirmed anaphylaxis with metamizole as well as ibuprofen. In patients with a history of reaction to paracetamol in addition to ibuprofen, skin tests were applied with paracetamol. SPT with paracetamol was performed with a concentration of 10 mg/mL and was considered positive when the wheal diameter was at least 3 mm or larger than the negative control with surrounding erythema after 20 min. In the case of negative SPT, intradermal test (IDT) was performed on volar forearm skin and considered positive if the mean diameter of the bleb increased by 3 mm or more with surrounding erythema [17].

Drug Provocation Tests

Diagnostic evaluations including DPTs were performed in patients with a history of suspected hypersensitivity reactions to ibuprofen as well as those with a history of additional hypersensitivity to other NSAIDs. Drug provocation tests with culprit drugs were performed as open challenge procedures following ENDA recommendations [18] and at least 4 weeks after the last allergic reaction in all patients. After obtaining informed consent forms from families, four escalating doses of the culprit drug were administered by oral route with 30 min intervals until a cumulative dose was achieved without any symptoms. The patients were kept under medical observation during and for up to 2 h after the tests. The test was considered positive if an objective symptom was observed. The cumulative doses were 10 mg/kg/dose and 15 mg/kg/

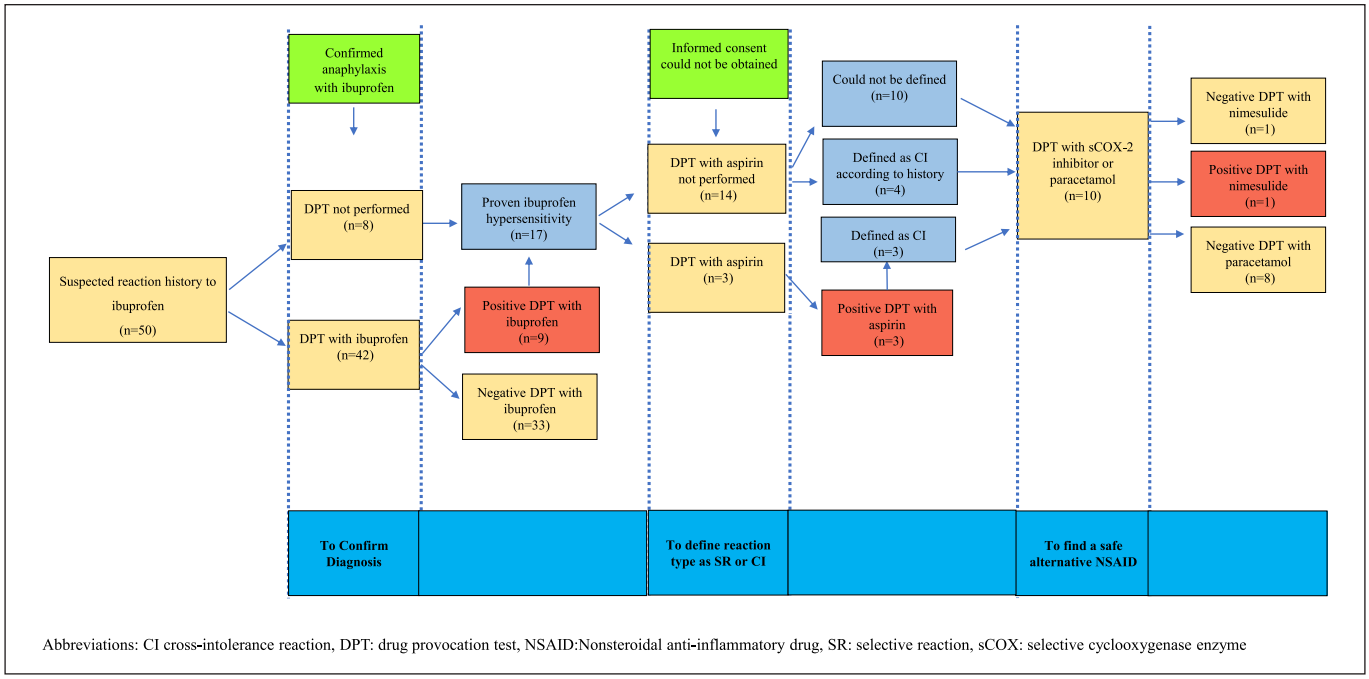


Fig. 1. Study design. Drug provocation tests with ibuprofen were performed for diagnostic purposes if there was no history of confirmed anaphylaxis. In patients with proven ibuprofen allergy, DPTs with aspirin were performed to define the reaction type. Additional DPTs with selective COX-2 inhibitor or paracetamol were performed to find out a safe alternative.

dose for ibuprofen and paracetamol, respectively, with the maximal dose determined for age and weight [3]. Patients with a positive DPT with the culprit drug or with a history of confirmed anaphylaxis after the intake of the culprit drug were accepted as "ibuprofen-hypersensitive."

DPT was performed to find a safe alternative NSAID in proven ibuprofen-hypersensitive patients if needed. In all proven ibuprofen-hypersensitive children, DPTs were performed with paracetamol to find a safe alternative drug, except for those who had already used it. Additionally, DPTs with selective COX-2 inhibitors were performed in patients with proven ibuprofen and paracetamol hypersensitivity or in patients who required an NSAID with potent anti-inflammatory effects. The general rules for DPTs as stated above were also followed to find safe alternatives. The study design is shown in Figure 1.

Drug Provocation Tests with Aspirin

DPTs with aspirin were performed to classify confirmed hypersensitivity reactions as CIs or SRs [8]. SRs and CIs were further categorized according to the EAACI classifications [13]. Drug provocation tests with aspirin were performed according to the EAACI/GA^{2}LEN guideline [19]. The cumulative dose of aspirin was 20 mg/kg/dose with the maximal dose determined for age and weight [3].

Statistical Analyses

IBM Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 statistics package program (IBM SPSS Corp.; Armonk, NY, USA) was used for data evaluation and analysis. Categorical variables were presented as frequency (n) and percentage (%), and numeric variable were presented as mean ± standard deviation, median (interquartile range) value. χ^2 and Fisher's exact test were applied for the comparison of categorical variables between two independent groups. Independent samples t test and Mann-Whitney U test were used for comparison of continuous variables between two independent groups. Logistic regression analysis was performed to determine the risk factors for ibuprofen-H. Multivariate analysis included the variables which have $p < 0.250$ in univariate analysis, providing they did not show multicollinearity (i.e., correlation needed to be <0.40). Enter method was used for multivariate logistic regression. The results were given as odds ratios and 95% CIs. The statistical significance level was set at $p < 0.05$.

The Ethics Committee of our university hospital approved the study protocol (2018/197). Written informed consent from parents/legal guardians for all participants aged under 18 years was obtained.

Results

The study included 50 (35 M, 25 F) children with a median age of 7 years (interquartile range, 1–15) with suspected ibuprofen-H. All suspected hypersensitivity re-

Table 1. Clinical characteristics of patients with suspected ibuprofen hypersensitivity ($n = 50$)

Characteristics	*n* (%)
Drug involved	
History of single NSAID (ibuprofen)	36 (72.0)
History of multiple NSAIDs	14 (28.0)
Ibuprofen + paracetamol	11 (78.5)
Ibuprofen + metamizole	2 (14.3)
Ibuprofen + aspirin	1 (7.2)
Clinical presentation	
Urticaria	24 (48.0)
Angioedema	30 (60.0
Anaphylaxis	9 (18.0)
Concomitant allergic disease	
Yes	22 (44.0)
No	28 (56.0)
Allergic disease	
Asthma	8 (16.0)
Allergic rhinitis	6 (12.0)
Asthma and allergic rhinitis	2 (4.0)
Chronic urticaria	4 (8.0)
Food allergy	1 (2.0)
Atopic dermatitis	1 (2.0)
Serum total IgE, IU/mL	
Median (IQR)	102.5 (36–270.3)
Serum eosinophilia, *n* (%)	
Median (IQR)	2.2 (1–3.5)
Skin tests with paracetamol	
Negative	17 (34.0)
Not applied	33 (66.0)
Ibuprofen allergy	
Yes	17 (34.0)
No	33 (66.0)
Type of the reaction	
Selective hypersensitivity reaction	0 (0.0)
Cross-intolerance reaction	7 (41.2)
Unclassified	10 (58.8)

NSAID, nonsteroidal anti-inflammatory drug; IQR, interquartile range.

actions were immediate type and developed within the first hour in 54% of patients. AO was the most common clinical manifestation affecting more than half of the ($n =$ 30, 60%) patients. Twenty-two patients (44%) had concomitant allergic diseases, 16 (32%) had a history of drug allergy. While there were 36 (72%) patients who only reacted to ibuprofen, 11 (22%) patients had a history of reactions to both paracetamol and ibuprofen, 2 (4%) had a history of reactions to both ibuprofen and metamizole, and 1 (2%) had a history of reactions to both ibuprofen and aspirin. The demographic and clinical characteristics of the patients are presented in Table 1.

Results of the Diagnostic Evaluation

Skin Tests

Skin tests were performed with paracetamol in 9 patients with suspected reactions to paracetamol-H in addition to ibuprofen and in 8 patients with confirmed ibuprofen allergy to find a safe alternative drug; all of the tests were negative.

Drug Provocation Tests

Fifty-two DPTs were performed and resulted positive in 9 patients (shown in Fig. 2). All of them developed immediate allergic reaction during DPT with ibuprofen. Urticaria and AO developed in 6 of these patients, AO alone in 2 patients, and anaphylaxis in 1 patient. The patient who experienced anaphylaxis during DPT developed respiratory symptoms immediately after urticaria and AO, and he recovered quickly with epinephrine shot. Overall, ibuprofen allergy was confirmed in 17 (34%) patients, in 9 patients with positive DPTs and 8 patients with a history of confirmed ibuprofen-induced anaphylaxis. The clinical characteristics of ibuprofen-hypersensitive patients are presented in Table 2.

Ibuprofen-Hypersensitive Patients with a Reaction History Only to Ibuprofen

Of the 36 patients with a history of reaction to ibuprofen alone, 32 underwent DPT with the offending drug, and 7 of them had positive results. We did not perform DPTs in 4 patients who had a history of ibuprofen-induced anaphylaxis. Ultimately, "ibuprofen hypersensitivity" was confirmed in 11 (30.5%) patients with a history of reaction only to ibuprofen (shown in Fig. 2).

Ibuprofen-Hypersensitive Patients with Reaction Histories to Multiple NSAIDs

The most common culprit drug reported to accompany ibuprofen was paracetamol (78.6%) among the patients with a reaction history of multiple NSAIDs. A total of 20 DPTs were performed on 11 patients (ibuprofen and paracetamol [$n = 9$ patients]; paracetamol [$n = 1$ patient]; and ibuprofen [$n = 1$]). DPT with ibuprofen alone was positive in 1 patient, and DPT with both ibuprofen and paracetamol was positive in 1 patient. Besides, 4 patients with a history of physician-diagnosed anaphylaxis (ibuprofen and metamizole = 2, ibuprofen and paracetamol = 1, ibuprofen alone = 1) were considered "NSAID-hypersensitive" without DPT (patient No. 1, 5, 7, and 16, Table 2). In conclusion, "ibuprofen hypersensitivity" was confirmed in 6 (42.8%) out of 14 patients with a history of multiple NSAID reactions (shown in Fig. 2). However,

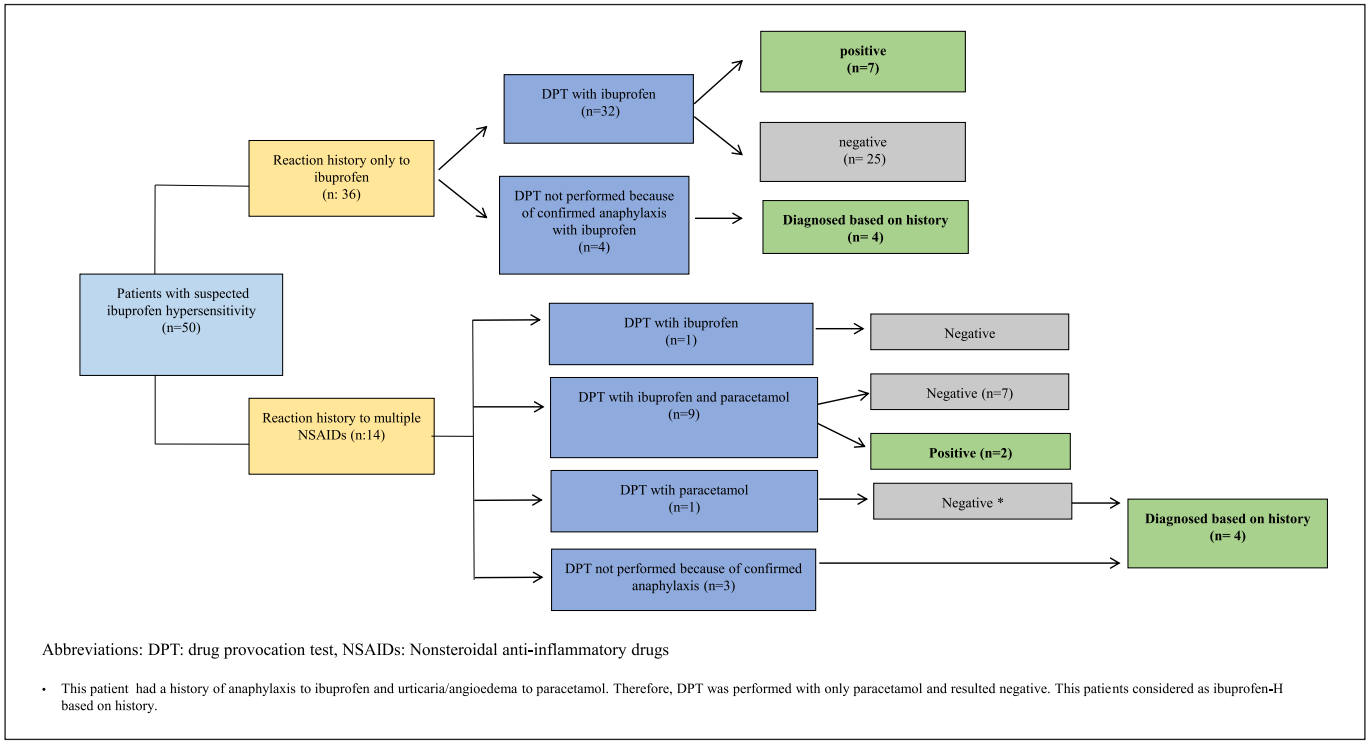


Fig. 2. Diagnostic evaluation of patients. Fifty children with suspected ibuprofen hypersensitivity were evaluated. While 36 patients had reacted only to ibuprofen, 14 patients had reacted to multiple NSAIDs. Ibuprofen hypersensitivity was confirmed by DPTs in 9 patients. Additionally, diagnosis was confirmed in 8 patients based on history of confirmed anaphylaxis without performing DPT.

"multiple NSAID-induced hypersensitivity" was confirmed in only 4 patients (28.6%).

Classification of Patients with Ibuprofen Hypersensitivity

We classified 7 (41.2%) of 17 patients with proven ibuprofen-H as cross-intolerant. Two patients with a history of reaction only to ibuprofen were classified as cross-intolerant since they developed anaphylaxis during DPT with aspirin. DPT with aspirin was performed only in 1 of the patients with a history of reactions to multiple NSAIDs, and it resulted as positive. The rest 4 patients, who did not give informed consent for DPT with aspirin, were classified as cross-intolerant due to their history of reactions induced by NSAIDs from different chemical groups. The remaining 10 patients with a history of reactions to ibuprofen could not be classified as CI or SR, since parents did not give consent for DPT with aspirin. After all, no patient could be classified as selective responder (Table 2).

We also classified cross-intolerants according to EAACI position paper. One of the cross-intolerant patients without any underlying allergic disease developed urticaria/AO during DPT with ibuprofen and was classified as NIUAA (patient No. 11, Table 2). The other cross-intolerant patient with underlying chronic urticaria developed urticaria/AO with ibuprofen and paracetamol during DPTs and was classified as NECD (patient No. 17, Table 2). The remaining 5 patients had a history of confirmed anaphylaxis with ibuprofen and classified as NIUAA (patient No. 1, 5, 7, 9, and 16, Table 2). Consequently, CIs were further classified as NECD (n = 1) and NIUAA (n = 6) according to the recent recommended classification of EAACI for pediatric patients [11].

Results of the DPTs for Finding Alternative Drugs

DPTs with paracetamol (n = 8) and nimesulide (n = 2) were performed in 10 patients to find a safe alternative NSAID. All patients tolerated paracetamol. AO and urticaria with nimesulide developed in 1 of the patients (patient No.: 11) during DPTs (Table 2).

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Table 2. Characteristics of the patients with confirmed ibuprofen allergy (*n* = 17)

Patient	Age, years	Allergic disease	Culprit drug	Presenting complaints	DPT	Reaction during DPT	SR/CI	Classification according to the EAACI	DPT for safe alternative
1	10	Asthma	Paracetamol Ibuprofen	U+AO Anaphylaxis	Paracetamol Aspirin	Negative U+AO	CI	NIUAA	ND
2	8.5	No	Ibuprofen	Anaphylaxis	ND	ND	Unclassified	Unclassified	Paracetamol
3	16	Asthma Allergic rhinitis	Ibuprofen	U+AO	Ibuprofen	U+AO	Unclassified	Unclassified	Paracetamol
4	14	No	Ibuprofen	AO	Ibuprofen	U+AO	Unclassified	Unclassified	Paracetamol
5	9	Asthma	Ibuprofen Metamizole	Anaphylaxis Anaphylaxis	ND	ND	CI	NIUAA	Paracetamol
6	14	Asthma	Ibuprofen	AO	Ibuprofen	U+AO	Unclassified	Unclassified	Paracetamol
7	13	Allergic rhinitis	Ibuprofen Metamizole	Anaphylaxis Anaphylaxis	ND	ND	CI	NIUAA	Paracetamol
8	5.5	No	Ibuprofen	AO	Ibuprofen	AO	Unclassified	Unclassified	ND
9	16	Allergic rhinitis	Ibuprofen	Anaphylaxis	Aspirin	Anaphylaxis	CI	NIUAA	Paracetamol
10	14	No	Ibuprofen	Anaphylaxis	ND	ND	Unclassified	Unclassified	Paracetamol
11	13	No	Ibuprofen	AO	Ibuprofen Aspirin	U+AO Anaphylaxis	CI	NIUAA	Nimesulide
12	8	No	Ibuprofen	Anaphylaxis	ND	ND	Unclassified	Unclassified	ND
13	13.5	Asthma	Ibuprofen	AO	Ibuprofen	Anaphylaxis	Unclassified	Unclassified	ND
14	9	CU	Paracetamol Ibuprofen	U AO	Paracetamol Ibuprofen	Negative AO	Unclassified	Unclassified	ND
15	12	Asthma	Ibuprofen	AO	Ibuprofen	U+AO	Unclassified	Unclassified	ND
16	13	Asthma Allergic rhinitis	Paracetamol Ibuprofen	Anaphylaxis Anaphylaxis	ND	ND	CI	NIUAA	Nimesulide
17	17.5	CU	Paracetamol Ibuprofen	U+AO U+AO	Paracetamol Ibuprofen	U+AO U+AO	CI	NECD	ND

AO, angioedema; CI, cross-intolerance reaction; CU, chronic urticaria; DPT, drug provocation test; ND, not done; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; NIUAA, NSAID-induced urticaria/angioedema/anaphylaxis; SNIUAA, single NSAID-induced urticaria/angioedema and/or anaphylaxis; SNIDR, single NSAID-induced delayed-type hypersensitivity reaction; SR, selective reaction; U, urticaria.

Table 3. Characteristics of the ibuprofen-hypersensitive and ibuprofen-tolerant patients

	Ibuprofen-hypersensitive (*n*: 17), *n* (%)	Ibuprofen tolerant (*n*: 33), *n* (%)	*p* value
Gender			
Male	Gender	20 (60.2)	**0.043**[a]
Female	Male	13 (39.4)	
Age, years			
Median (IQR)	13 (9–14)	6 (3.5–12)	**0.001**[b]
Serum total IgE, IU/mL			
Median (IQR)	182 (58–499)	77.5 (29.9–238.5)	**0.032**[c]
Serum eosinophilia, %			
Median (IQR)	1.4 (0.35–3.7)	2.2 (1.3–3.5)	0.873[c]
Personal history of drug allergy			
Yes	7 (41.2)	9 (27.3)	0.318[a]
No	10 (58.8	24 (72.7)	
Family history of drug allergy			
Yes	3 (17.6)	6 (18.2)	1[d]
No	14 (82.4)	27 (81.8)	
Timing of the reaction			
Within first hour	14 (82.4)	13 (39.4)	0.118[a]
After 1 h	3 (17.6)	20 (60.6)	
Atopic sensitization			
Yes	12 (70.6)	18 (54.5)	0.273[a]
No	5 (29.4)	15 (45.5)	
Allergic disease			
Yes	11 (64.7)	11 (33.3)	**0.034**[a]
No	6 (35.3)	22 (66.7)	
Drug(s) involved			
Single NSAID	11 (64.7)	25 (75.8)	0.511[a]
Multiple NSAIDs	6 (35.3)	8 (24.2)	

NSAID, nonsteroidal anti-inflammatory drug; IQR, interquartile range. [a] χ^2 test was applied. [b] Mann-Whitney U test was applied. [c] Student's test was applied. Analysis conducted after the natural log (ln) has taken. [d] Fisher's exact test was applied.

Table 4. Risk factors related to ibuprofen hypersensitivity

	Univariate logistic regression			Multivariate logistic regression[a]		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Gender (male)	4.875	0.953–24.939	0.057	24.375	1.800–330.045	**0.016**
Age	12.805	2.320–70.685	**0.003**	1.461	1.126–1.895	**0.004**
Serum total IgE	1.676	1.021–2.751	**0.041**	1.003	0.997–1.009	0.300
Reaction within the first hour of drug intake	3.033	0.727–12.665	0.128	7.518	0.806–70.122	0.077
Allergic disease history	3.667	1.072–12.547	**0.038**	1.555	0.227–10.665	0.653

Enter method: Nagelkerke R2: 0.593. Hosmer-Lemeshow test *p* value: 0.428. Prediction percentage: 80%. [a] Variables included in the enter method: gender, age, IgE, reaction within the first hour of drug intake, and allergic disease history.

Risk Factors Related to NSAID Hypersensitivity

When we compared the possible risk factors between ibuprofen-tolerant and nontolerant patients, we observed that ibuprofen allergy was more frequently confirmed in the male gender ($p = 0.043$). Also, the median age of children ($p = 0.001$), history of other allergic diseases ($p = 0.034$), and the median serum total IgE level ($p = 0.032$) were significantly associated with ibuprofen allergy (Ta-

ble 3). Multivariate logistic regression analysis revealed that male gender (adjusted OR: 24.4, 95% CI: 1.8–330, $p = 0.016$) and older age were the independent risk factors for confirmed ibuprofen-H (Table 4).

Discussion

Ibuprofen is the most common culprit drug in NSAID-induced hypersensitivity reactions in children [13, 20]. Our study is one of the studies specifically investigating immediate-type ibuprofen-induced hypersensitivity in children [3, 14, 15]. Moreover, this is the first pediatric study in which ibuprofen-H was classified as CI or SR.

In our study, ibuprofen-H was confirmed in 34% of patients based on DPT results and history. In a recent pediatric study, the prevalence of ibuprofen-H was reported as 22.73% [7]. This difference can be explained by the ethnic and genetic characteristics of different populations, as well as by different diagnostic procedures.

Reactions to NSAIDs may be either based on immunologic or nonimmunological mechanisms. Allergic (selective) reactions induced by NSAIDs are mediated by specific immunologic mechanisms such as IgE or T-lymphocyte dependent, whereas nonallergic (cross-intolerance) reactions are mediated by mediators which can be released in the absence of any specific immunologic recognition [9]. It should be kept in mind that evaluation of a patient according to clinical history only may lead to overdiagnosis. Therefore, a patient must be evaluated with a DPT which is considered as the gold standard for the diagnosis of NSAID-H [7]. However, it may be difficult to perform a DPT due to the lack of appropriate clinical settings or failure to obtain consent from parents. In this study, we could perform a total of 52 DPTs with culprit drugs. However, we did not perform DPTs in 8 patients due to a history of confirmed anaphylaxis.

Various risk factors for NSAID-H have been identified in the previous studies [3, 7, 11, 12, 14]. In our study, older age was identified as an independent risk factor for ibuprofen-H. Also, we found that 1 year increase in age resulted in a 1.46-fold increase in the risk of ibuprofen-H. Similarly, ibuprofen-H was found to be more likely in older patients in a recent study performed by Gaffar et al. [7]. Additionally, our results were consistent with the literature reporting that NSAID-H frequency was found higher among older children [6, 20–24]. This finding can be explained by the fact that viral infections, which are the most common cause of skin rashes, are more common in the younger age group. Thus, this result supports the hypothesis that skin rashes due to viral infection may lead to misdiagnosis of NSAID-H in younger children, as previously suggested by Mori et al. [6]. Moreover, this result can be attributed to the lower consumption of NSAIDs, especially those other than paracetamol, in younger children [22]. Consequently, diagnostic evaluation in addition to reaction history is essential to confirm or rule out ibuprofen allergy, especially in young children. Although female gender was found to be a risk factor for NSAID-H in previous studies, male gender was identified as an independent risk factor for ibuprofen-H in our study [25, 26]. This finding may be explained by the increased prevalence of atopic diseases in male gender and the association between atopy and NSAID-H, as proposed in the previous studies [5, 20]. Although a history of other atopic diseases was found as a significant risk factor in the univariate analysis, it disappeared in the multivariate analysis.

In our study, approximately half of the proven ibuprofen-H patients had a history of confirmed anaphylaxis. In a pediatric study involving 104 children with a history of drug hypersensitivity reactions, authors reported that ibuprofen was the second most common culprit drug (75%) after dipyrone as the responsible drug for anaphylactic reactions in children [27]. In another study from Singapore, which evaluated 485 children with a mean age of 8.4 years who presented with anaphylaxis, it was found that ibuprofen-induced anaphylaxis was the most common cause (47.6%) of drug-induced anaphylactic reactions in children [28].

CIs are more common in our study group (41.2%), consistent with the previous reports [3, 13]. Besides, we could not classify any reaction as SR contrary to the literature reporting ibuprofen is one of the most common culprit drugs in children with SRs [15, 29]. These results can be explained by the limited number of patients in the study group and the few numbers of DPTs with aspirin. Although it has been recommended that DPT with aspirin should be performed for the diagnosis of CIs in adults [9], it may be difficult to perform in the pediatric population. As this is a real-life experience, we preferred to confirm or exclude ibuprofen hypersensitivity in the first step, then perform DPT with aspirin. However, it was difficult to get permission from the families for a second DPT with aspirin.

The ENDA experts proposed a classification in 2013 [9]; nevertheless, several studies have emphasized that these recommendations are not suitable for the pediatric population since they were focused on the adult population [11, 21, 27]. In previous studies, co-existence of cutaneous and respiratory symptoms was categorized as

"blended or mixed reaction" [5, 30]. However, such reactions involving at least two different systems at the same time, which must be considered anaphylaxis, are not included in the ENDA/GA^{2}LEN classification [8] but are differently defined as NIUAA in the modified classification of EAACI [14]. In line with this recommendation, 5 cross-intolerant patients in our study group were classified as NIUAA since they had a history of confirmed anaphylaxis after consumption of the culprit drugs. In this regard, our study is a real-life validation of the pediatric classification.

DPTs should be performed in all proven NSAID allergic patients to find a safe alternative drug [9]. Although paracetamol is generally considered a safe alternative in cross-intolerant patients [3], paracetamol-H has been reported to be up to 25% in children with CI reactions [31, 32]. These results may be due to the fact that paracetamol may inhibit the COX-1 enzyme at high doses (15 mg/kg), as stated by Cavkaytar et al. [33]. In contrast, we performed DPTs with paracetamol at high doses on 3 cross-intolerant patients, and none of the patients developed a reaction. COX-2 inhibitors may be safe alternative drugs for children with NSAID-H; however, 6–25% of children have been reported to react to this group [29]. In our study, 1 of the two patients who underwent DPT with nimesulide developed AO and urticaria.

The limitations of this study were that it was a retrospective investigation based on clinical chart reviews and our study group consisted of a small number of subjects. Also, one of the limitations was drug provocation test with aspirin was performed in a small group of patients. However, our study had several strengths such as providing major information regarding the clinical characteristics and risk factors of proven immediate-type ibuprofen allergy. Additionally, our findings highlight the importance of DPTs in the pediatric population for definitive diagnosis of ibuprofen allergy.

In conclusion, DPT should be performed to confirm NSAID-H, if no contraindication exists, as well as to find a safe alternative drug. Male gender and older age are risk factors for ibuprofen-H in children with immediate-type reactions. In addition, NSAID-induced hypersensitivity reactions in the pediatric population cannot be well defined using the adult classification system.

Statement of Ethics

Written informed consent from parents/legal guardians for all participants aged under 18 years was obtained. The Ethics Committee of Istanbul University, Istanbul Faculty of Medicine approved the study protocol (No. 2018/197). The study was performed according to the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare no conflict of interests.

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Author Contributions

Sevgi Sipahi Cimen: conceptualization (lead); writing – original draft (lead); formal analysis (lead); and writing – review and editing (equal). Esra Yucel, Ayse Suleyman, Zeynep Hizli Demirkale, and Deniz Ozceker: conceptualization (supporting); writing – original draft (supporting); and writing – review and editing (equal). Ugurcan Sayili: formal analysis (lead) and writing – review and editing (equal). Nermin Guler: conceptualization (equal); writing – original draft (supporting); and writing – review and editing (equal). Zeynep Tamay: conceptualization (equal); writing – original draft (equal); and writing – review and editing (equal).

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author (S.S.C.).

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