

Retrospective Evaluation of Children with Non-Steroidal Anti-Inflammatory Drug Allergy

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Abstract

Aim: Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs and are among the drug-related hypersensitivity reactions after antibiotics. There are limited studies evaluating nonsteroidal drug reactions in children. In this study, we aimed to evaluate the concomitant atopic diseases, admission clinic, laboratory findings and drug provocation test results of children with a pre-diagnosis of nonsteroidal drug reaction and who underwent allergy tests, retrospectively.

Methods: In this study, patients who applied to the pediatric allergy outpatient clinic due to nonsteroidal drug reaction were included. In this group of patients, age, gender, fx5 (nutrient mix specific IgE), phadiatop (inhalant allergen mix specific IgE), skin prick tests and drug provocation tests were recorded from their files. Demographic and clinical features of the cases were compared.

Results: 61 patients with suspected NSAIDs allergy were included in the study. When the admission clinics of the patients were evaluated, 54% (n:33) had urticaria, 22.9% (n:14) had isolated angioedema, 6.5% (n:4) had urticaria angioedema, 14.7% (n:9) had maculopapular eruption. Only 1 patient presented with anaphylaxis. NSAIDs allergy was confirmed in 16.3% (n:10) of the patients.. Single ibuprofen sensitivity was detected in 13.1% of patients (n:8), both paracetamol and ibuprofen sensitivity were detected in 1 patient (1.6%), and single paracetamol sensitivity was detected in 1 patient (1.6%).

Conclusions: It is usually not easy to detect drug allergies in patients. These patients may usually be misdiagnosed as NSAIDs allergy. In our study, it was revealed that drug provocation tests should be performed to confirm the diagnosis in case of suspected NSAIDs allergy.

Keywords: Non-steroidal anti-inflammatory drug allergy, isolated angioedema, drug provocation test

1. Introduction

The WHO (World Health Organization) describes adverse drug reaction as noxious and unintended events which occurs at the appropriate doses of medicines used for diagnosis/treatment¹. Unexpected and not dose-related effects in only susceptible individuals are classified as drug hypersensitivity reactions². Drug hypersensitivity reactions that occur through immunologic mechanisms constitute drug allergies³. The incidence of drug hypersensitivity events is not clearly known, but it is reported that these reactions result in significant public health problems in terms of morbidity, mortality, and socioeconomic burden^{4,5}. Drug allergies account for 6-10% of adverse drug reactions.

Beta-lactam antimicrobial agents and NSAIDs are the most common causes of drug allergy. The clinical presentation of drug allergies is frequently associated with skin involvement including maculopapular erythematous rash and urticaria⁶. A number of diagnostic tests are performed in cases with a preliminary diagnosis of drug allergy based on the detailed clinical history and physical examination⁷. Among these tests, the drug provocation test is considered as the gold standard method and is the controlled administration of the suspected drug to the patient.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the second most common cause of drug-related hypersensitivity reactions following antibiotics. It causes hypersensitivity reactions that occur with varying courses in reaction time, organ involvement, and severity in individuals who develop sensitivity.

The reported prevalence of hypersensitivity reaction to NSAIDs is 0.3% both in adult and childhood population⁸. Hypersensitivity reactions to NSAIDs have been classified based on clinical findings, the presence of comorbidities and cross-reaction history with other cyclooxygenase-1 (COX-1) inhibitors⁹. In patients with a history of hypersensitivity to NSAIDs, allergic reaction through type 1 IgE-mediated mechanism is rarely observed. In this group of patients, a hy-

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Received: 01.02.2023, Accepted: 22.04.2023, Available Online Date: 31.08.2023

Cite this article as: Aydogdu AK, Akcam NY. Retrospective evaluation of children with non-steroidal anti-inflammatory drug allergy. J Cukurova Anesth Surg. 2023;6(2):215-9. doi: 10.36516/jocass.1246401

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persensitivity reaction to a single drug or drugs in the same chemical group develops, while drugs with different chemical structures are well tolerated. This type of reaction is caused by an immunological mechanism and is called an allergic reaction. The most described hypersensitivity reaction mechanism is related to the inhibition of COX-1 which is involved in the mechanism of action of NSAIDs, characterized by cross-reactions to different NSAIDs. This reaction occurs through a non-immunologic mechanism. COX-1 inhibition decreases prostaglandins, which are regulators of mediator release from mast cells, and increases cysteinyl leukotrienes, leading to an allergic drug reactions. This increase may cause clinical signs of urticaria, angioedema, rhinitis, and bronchospasm. Although the primary goal is to determine whether the clinical findings develop due to drug allergy in patients who present with suspected allergy after drug use, it is also necessary to determine a alternative drug that will not cause an allergic reaction to the patient in case the allergy is confirmed. It is essential to make a definitive diagnosis of patients with suspected NSAID allergy in children, because the new COX-2 inhibitors, which are frequently used as an alternative in the diagnosis of cross-reactive NSAID allergy in adults, have not been approved for pediatric use, and these drugs are not available in syrup form. Detailed patient history, physical examination, and evaluation of the patient with standardized diagnostic tests are recommended for the diagnosis. An oral drug provocation test is recommended for the definitive diagnosis of NSAID reaction under appropriate settings and conditions^{8,9}. In a drug provocation test, a drug suspected of causing allergy is administered in a controlled manner gradually. There have been limited number of publications evaluating non-steroidal drug reactions worldwide and from our country. In this study, we aimed to retrospectively analyze the comorbid atopic diseases, clinical presentation at the admission, laboratory findings and drug provocation tests of children who were admitted to our clinic with a prediagnosis of non-steroidal drug reactions, and underwent allergy tests.

2. Materials and methods

The medical records of 61 patients admitted to the Pediatric Allergy-Immunology Clinic of Mersin City Hospital between May 2020 and May 2022 due to non-steroidal drug reactions were retrospectively investigated. Date of birth, gender, presence of concomitant allergic conditions, physical examination findings, fx5 (food mix specific IgE), phadiatop (inhalant allergen mix specific IgE), skin prick tests, and drug provocation tests were evaluated from the records of the patients. Eosinophilia was defined when the eosinophil level was above 4% in the complete blood count. Total IgE levels greater than 100 KU/L were considered positive. ImmunoCAP method was used for serum specific IgE levels. Food and inhalant specific IgE values ≥ 0.35 kU/l were considered positive. Skin prick test was performed by epidermal application with Dermatophagoides pteronyssinus, Dermatophagoides farinae, alternaria, cat and dog epithelium, meadow and cereal pollen mix, weed mix, tree pollen mix, olea, milk, egg, wheat, soy, peanut, hazelnut, beef, chicken meat, fish mix (alk) antigens. In skin prick test, histamine was used as positive control and sterile saline as negative control. Histamine was considered positive when >5 mm edema accompanied by erythema appears and was considered as the criterion for the test validation. The presence of erythema with edema diameter ≥ 3 mm compared to the negative control was considered positive for allergens applied for the skin prick test¹⁰.

Testing for the diagnosis of NSAID allergy was scheduled 6 weeks after the onset of allergic symptoms. Patients were asked not to use antihistamines in the week before the allergy test if they were receiving any. If the skin prick test with the suspected drug was negative, an intradermal test was performed. The test result was evaluated at the 20th minute of the intradermal administration of the

drug and the resulting edema diameter 3 mm or more compared to the negative control was considered positive. Drug provocation test (DPT) was performed to confirm drug allergy in patients with negative skin tests. Written informed consent was obtained from parents. The test was performed by starting with a dose calculated between 1/1000 and 1/10 of the targeted drug dose, considering the severity of allergic symptoms. After the initial dose, the test was gradually maintained by administering the drug every 30-60 minutes until reaching the targeted drug dose. If objective findings were detected during or after the test, the test was considered positive and terminated. If no reaction was observed in the patients followed during this period of time, they were considered to have no allergies to NSAIDs¹¹.

The study was approved by the University of Toros Ethics Committee (September 2022/156). Statistical analysis was performed using SPSS 26.0 (Statistical Package for the Social Sciences Version 26.0) package program.

3. Results

Sixty-one patients with suspected NSAID allergy were included in the study. 59% (n:36) were boys with 1.44 boy/girl ratio. The mean age of the patients was 5.2 years ($P^{25}-P^{75}:2.5-8$). The evaluation of clinical presentations at the admission demonstrated that 54% (n:33) presented with urticaria, 22.9% (n:14) with isolated angioedema, 6.5% (n:4) with urticaria-angioedema and 14.7% (n:9) with maculopapular eruption. Only 1 patient presented with anaphylaxis.

Table 1
Demographic and Clinical Characteristics of the Patients

	Frequency(n)	Percentage(%)
Age(year)*	2.5-8*	0-16*
Gender		
Female	25	41
Male	36	59
Existence of Allergic diseases		
No	46	75.4
Allergic rhinitis	10	16.3
Asthma	3	4.9
Recurrent urticaria	2	3.2
Symptoms		
Urticaria	33	54
Urticaria angioedema	4	6.5
Angioedema	14	22.9
Maculopapular exanthema	9	14.7
Anaphylaxis	1	1.6
Eosinophil		
$<4\%$	51	83.6
$\geq 4\%$	10	16.4
Total IgE		
≤ 100	34	65.4
>100	18	34.6
FX5		
Negative	44	97.7
Positive	1	2.3
Phadiatop		
Negative	35	77.7
Positive	10	22.3

* $P^{25}-P^{75}:2.5-8$

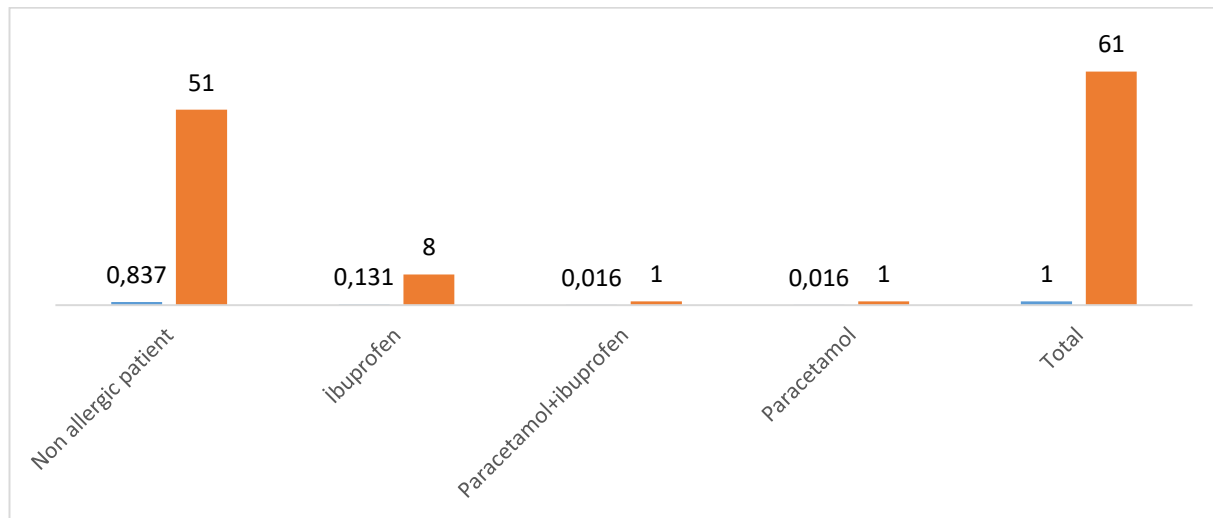


Figure 1
Confirmed drug allergies

There was no history of atopic disease in 75.4% (n:46) of the patients. Among the patients with atopic disease, 16.3% (n:10) had allergic rhinitis, 4.9% (n:3) had asthma, and 3.2% (n:2) had recurrent urticaria. Fx5 and phadiatop were examined in 45 patients, and fx5 was positive in only 1 patient, whereas phadiatop was positive in 16.3% (n:10). Total IgE was analyzed in 52 patients and found to be elevated in 18 patients (34.6%; min-max 18-1280; mean:146). Eosinophil elevation was detected in 10 patients (16.4%; min-max:0.1-7.7, mean: 2.37). (Table1) NSAID allergy was confirmed in 16.3% (n:10) of the patients. There were 5 patients with urticaria, 3 patients with urticaria angioedema, and 2 patients with angioedema in proven NSAID allergy. Ibuprofen-induced sensitivity was detected in 13.1% (n:8) of the patients, while 1 patient (1.6%) had both paracetamol and ibuprofen sensitivity and 1 patient (1.6%) had only paracetamol sensitivity (Figure 1).

4. Discussion

In this study, drug allergy was commonly observed to ibuprofen among suspected non-steroidal drug reactions.

Although literature on NSAID allergy in childhood is limited¹², beta-lactam antibiotics have been found to be the most common causative agents in drug-induced anaphylaxis in France and Portugal. In both studies, NSAIDs were the second most common causative agents^{13,14}. Similarly, the most common causative agents in the US are beta-lactam antibiotics, followed by NSAIDs¹⁵. A recent study reported that beta-lactam antibiotics were the most common causative agents with a rate ranging from 35.5-66.6%¹⁶. In the same study, NSAIDs followed beta-lactam antibiotics with a rate of 21.5-28.5%.

In population-based prevalence screening studies, NSAID allergy was reported to be 0.3% in children and 5% in children with asthma¹⁷. In our study, we found NSAID allergy at a rate of 16%. Different rates have been reported in the literature. Ibuprofen allergy was 14.7% and paracetamol allergy was 3.2% in our study. The majority (90%) of the cases were due to ibuprofen, while paracetamol sensitivity was detected in 20% of allergic patients. Our results seem to be consistent with the literature^{8,13,17}. In our study, ibuprofen was detected most frequently both as a suspected drug and as an NSAID to which

allergy was confirmed. Similar reports were observed in previous studies^{17,18,19}. Reactions with paracetamol in patients with NSAID allergy have been reported at rates between 0-25%^{20,22}. It was 3.2% in our study.

Several studies have shown an association between NSAID allergy and allergic diseases (asthma, rhinitis)^{19,20,21}. Similarly, in our study, 50% (n:5) of patients with confirmed NSAID allergy had allergic rhinitis and 10% (n:1) had asthma, whereas in the group with negative NSAID allergy result, 10% (n:5) had allergic rhinitis and 4% (n:2) had asthma. 59% of our participants were male (n:36). There is a male dominance (n:8, 80%) among patients with NSAID allergy. Similar findings were reported in previous studies^{18,20}. The most common clinical presentation was urticaria. It was observed that 54% of the patients presented with urticaria and 6.5% with urticaria angioedema and this was consistent with the literature^{20,22}.

Isolated angioedema is a common presentation in patients who develop NSAID allergy. This requires the meticulous differential diagnosis of hereditary angioedema, another cause of isolated angioedema. Because both diagnostic and therapeutic approaches are completely different²³. Different prevalence rates have been reported in previous studies^{9,24,25}. In our study, isolated angioedema developed in 22.9% of the patients. Patient number 22 was admitted to the emergency department with a clinical presentation of viral infection. Renal function, total protein and albumin values were examined to understand underlying etiology of edema. Since findings were normal, pediatric allergy consultation was obtained, and detailed patient history revealed that the symptoms developed after non-steroidal drug intake and the patient was treated accordingly. This case suggests that emergency and family physicians should have increased awareness of diseases that may cause edema in patients presenting with isolated angioedema, as they are usually the first physicians to see patients.

Although history, physical examination and skin prick tests are performed in the investigation of drug allergy, drug provocation tests are considered as the gold standard^{26,27,28}. Drug provocation tests are important to prevent unnecessary diagnosis of drug allergy. Indeed, drug allergy was reported as 17.7% in a study conducted by Tuğcu et al.²⁹. In a study by Yılmaz et al.³⁰, NSAID allergy was 14%. Alves et al.¹⁸ confirmed the drug allergy in 7.6% of patients evaluated for suspected NSAID allergy. In our study, NSAID allergy was confirmed

in 16.4% of patients.

5. Conclusions

Investigation of patients with suspected drug allergy is challenging. Confirmation of suspected cases require a detailed medical history, physical examination and specific tests. Tests to detect the presence of drug allergy should be performed by trained personnel, in an appropriate clinical setting, and are contraindicated in some cases. They are, therefore, not widely performed. This issue not only causes patients to be misdiagnosed as having drug allergy, but also leads to administration of drugs that are less effective or have more side effects as an alternative to patient's treatment. In addition, it has been observed that some of the patients who are allergic to NSAIDs present with isolated angioedema signs and it is crucial to differentiate it from other isolated angioedema diseases such as hereditary angioedema. Our study revealed that drug provocation tests should be performed to confirm the diagnosis in case of suspected NSAID allergy.

Acknowledgements

None.

Statement of ethics

The study was approved by the University of Toros University Ethics Committee (September 2022/156) and was conducted in accordance with the Declaration of Helsinki.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the design and writing of the study. All authors reviewed and accepted the final version of the study.

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