

The Frequency of Nonsteroidal Anti-Inflammatory Drug Hypersensitivity in Children with Asthma

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Keywords

Asthma · Children · Drug provocation test · Hypersensitivity · Nonsteroidal anti-inflammatory drugs

Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are the second-most frequent drug type to cause hypersensitivity reactions in children. Asthma is one of the risk factors for NSAID hypersensitivity (NSAID-H) in adult patients. There are limited number of studies evaluating NSAID-H among children with asthma. Our aim was to assess the frequency of confirmed NSAID-H and evaluate the classification of NSAID-H in children with asthma. **Methods:** Patients followed with a diagnosis of asthma in our Pediatric Allergy Clinic were evaluated for NSAID-H. Patients were questioned whether they had used NSAIDs, and if they experienced any reaction with these drugs. A control group was also questioned for reactions to NSAID use. **Results:** 976 children with asthma and 2,000 healthy children as a control group were included in this study. The mean age of the patients with asthma was 10.61 ± 4.21 years and 59.5% were

male. Ten (1%) had a reaction history to NSAIDs. NSAID-H was confirmed in 9 (0.9%) who were tested with the suspected drugs. Six of these were classified as "single NSAID-induced urticaria/angioedema or anaphylaxis" and 3 were classified as "NSAIDs-exacerbated respiratory disease." In the control group, only 1 subject had a reaction history to acetylsalicylic acid and no reaction developed in the provocation test. **Conclusions:** In our study, NSAID-H was found more frequent in children with asthma than in the control group. Children with asthma should be evaluated for reactions to NSAIDs during hospital visits. © 2018 S. Karger AG, Basel

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for their analgesic and antipyretic effects among children [1]. They are frequently prescribed and can be taken without prescription. NSAIDs are the sec-

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ond-most frequent type of drug to cause hypersensitivity reactions in children [2].

The overall prevalence of NSAID hypersensitivity (NSAID-H) has been reported as being between 0.6 and 5.7% in the general population [3]. A questionnaire-based frequency of NSAID-induced reactions reported a frequency of 0.3% in children [4]. However, in risky populations (such as asthma or chronic urticaria sufferers) NSAID-H prevalence is higher. In adult patients with asthma, in particular, the prevalence of NSAID-H is higher than in the general population [5]. The prevalence of acetylsalicylic acid (ASA) hypersensitivity is 14–29% in adults with asthma [6].

There are only a limited number of studies evaluating NSAID-H in children with asthma. Most of the data belong to reports published before the 1980s that evaluated children with asthma who had undergone ASA provocation; there is a frequency of 0–28% positivity [7–11]. None of these studies evaluated patients who reported a reaction to NSAIDs or according to the most recent European Academy of Allergy and Clinical Immunology (EAACI) classification which involves clinical manifestations and suspected mechanisms.

The aim of our study was to assess the frequency of confirmed NSAID-H and evaluate the classification of NSAID-H in children with asthma.

Methods

Patients followed with a diagnosis of asthma in our Pediatric Allergy Clinic were evaluated for NSAID-H between October 2015 and May 2016. The study was approved by the local ethics committee and the parents provided written informed consent.

Patients Group

The diagnosis of bronchial asthma was made according to the Global Initiative for Asthma (GINA) criteria [12]. The patients or their caregivers were asked whether they used ASA and NSAIDs, and, if so, whether or not they experienced a reaction. If they claimed they did have a reaction, they were evaluated for hypersensitivity. The initial drug allergy workup started with the standardized European Network of Drug Allergy (ENDA) questionnaire on drug allergy [13]. A detailed history included the spectrum and timing of symptoms, the dose, the route of administration, a list of concomitant medications, a history and timing of previous hypersensitivity reactions, and previously tolerated NSAIDs. In addition, the demographic and clinical features of the patients and coexisting chronic diseases, especially chronic rhinosinusitis, nasal polyps, and chronic spontaneous urticaria/angioedema, and any family history of allergic disease and NSAID allergy were recorded. According to the GINA criteria, the levels of asthma symptom control and asthma severity were also recorded [12].

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

All patients with asthma who were identified as having NSAID-H were evaluated for nasal polyps.

Control Group

Two thousand children, similar to the study group regarding age and gender, with no physician-diagnosed asthma and admitted to the hospital for acute problems, comprised the control group. All children in the control group were questioned for an allergic reaction to ASA and NSAIDs. If the history of a suspected reaction was compatible with drug hypersensitivity, then an SPT, IDT, and/or OPT with the suspected drug were proposed.

Study Measurements

Skin Tests for Drug Hypersensitivity

Patients were subjected to an SPT (diclofenac 25 mg/mL and metamazole 0.4 mg/mL) and an IDT (0.1 mg/mL) with the suspected drug [14]. Isotonic sodium chloride was used for dilution. All drugs were initially tested on the volar forearm skin with the prick method, and reactions were considered positive when a wheal diameter was 3-mm larger than in a negative control, with surrounding erythema that had developed 20 min later. When the SPT was negative, 1 mL of the parenteral form of the drug was diluted with 9 mL isotonic sodium chloride to form a 1:10 dilution, and 0.02 mL of this was injected intradermally into the skin of the volar forearm. Readings were made 20 min after injection. Results were considered positive when an increase of >3 mm in wheal diameter occurred, accompanied by erythema. Histamine at 10 mg/mL and isotonic sodium chloride were used as positive and negative controls, respectively [15].

SPT for Aeroallergens

SPTs were performed on the patients with pollens (grass mix, cereal mix, weeds, and trees), mites (*Dermatophagoides pteronyssinus* and *D. farinae*), molds (*Alternaria*, *Cladosporium*, and *Aspergillus*), cockroach, and cat and dog epithelia (ALK-Abello, Hørsholm, Denmark).

Drug Provocation Tests with NSAIDs

ENDA guidelines for drug provocation tests were carefully respected [16]. The suspected drug was administered at divided doses every 30 min, until a cumulative dose close to the age- and weight-adjusted daily dose of the drug was achieved. The test was discontinued in the event of any reaction. The OPT was not blinded, and an open challenge was performed by a physician with full resuscitation back-up. Forced expiratory volume in 1 s (FEV₁) was measured by spirometry at the beginning of the test and every 30 min during testing. The OPT result was considered positive if any objective symptoms or signs were documented. After the last dose was administered without a reaction, the patient was kept under surveillance for at least 2 h. The patients were asked to contact the

Table 1. Characteristics of all asthmatic children ($n = 976$)

Median age, years (IQR)	10.5 (7.02–14.0)
Gender, male	575 (59)
Atopic dermatitis	89 (9.1)
Allergic rhinitis	492 (50.5)
Atopy to aeroallergens	524 (53.7)
Asthma severity	
Mild intermittent	167 (17.1)
Mild persistent	532 (54.6)
Moderate persistent	251 (25.8)
Severe persistent	24 (2.5)
Level of asthma control	
Controlled	735 (75.5)
Partially controlled	201 (20.6)
Uncontrolled	38 (3.9)
A family history of allergic disease	272 (27.9)
Asthma	197
Allergic rhinitis	71
Drug allergy	2
Penicillin	1
NSAID hypersensitivity	1

Values express n (%), unless otherwise specified.

physician if a reaction occurred in the 24 h after the provocation test, to identify a delayed reaction. The tests were considered negative if no reaction had occurred by the end of this time.

ASA provocation was performed in 2 situations, i.e., when it was the suspected drug, and to confirm or exclude cross-sensitivity. On the first day, 3 placebos were administered at 1.5-h intervals. On the second day, 4 increments (27, 44, 117, and 312 mg) were given at 1.5-h intervals until a maximum dose of 500 mg was reached, or until the cumulative dose of 10 mg/kg was reached. FEV₁ was measured by spirometry at the beginning of the test and every 30 min thereafter. A positive OPT was defined by ≥ 1 of the following: an upper respiratory reaction (rhinorrhea, nasal congestion, sneezing, or increased lacrimation), bronchospasm (coughing, wheezing, chest tightness, or dyspnea), laryngospasm (stridor or dysphonia), and/or a decrease in FEV₁ of $\geq 15\%$ [17].

Patients who were identified as having NSAID-H underwent an OPT with paracetamol and/or meloxicam (for patients >12 years of age) in order to find an alternative NSAID. The caregivers of patients who reported that they could use an alternative NSAID safely were not tested.

Definition and Classification of NSAID-H

According to the latest EAACI position paper, NSAID-H can be classified in 2 groups, i.e., induced by: nonspecific immunological mechanisms (nonallergic or cross-intolerance [CI] reactions), or specific immunological mechanisms (allergic or selective reactions [SR]) [18].

NSAID-H reactions have been classified into 5 main groups: (i) NSAIDs-exacerbated respiratory disease (NERD); (ii) NSAIDs-exacerbated cutaneous disease (NECD); (iii) NSAIDs-induced urticaria/angioedema (NIUA); (iv) single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA); and (v) single NSAID-induced delayed reactions (SNIDRs) [18].

Power Analysis

Since no similar studies have been conducted previously on the frequency of NSAID-H in children with asthma, the case/control ratio was planned as 1:2. For the case group of 976 children with asthma, 2,000 healthy children were included in the control group. The power analysis of the study was retrospectively done with OpenEpi, v3, an open-source calculator, and the power was found to be 94.5%.

Statistical Analysis

Statistical analyses were performed using SPSS v22.0 (IBM, Chicago, IL, USA). Descriptive statistics were expressed as mean $\pm$ SD or median (interquartile range [IQR]) for continuous variables, and n (%) for nominal variables. The Shapiro-Wilk test was used to investigate whether the distribution of continuously measured variables was close to normal. The χ^2 test was performed to compare nonparametric data and the Mann-Whitney U test for non-normally distributed data. A p value of <0.05 was considered statistically significant.

Results

Nine hundred and seventy-six patients with asthma (59% males; a median age of 10.5 years, IQR 7.02–14.0) and 2,000 healthy children (60% male; aged 11.58 years, IQR 3.52–14.53) were evaluated. There was no statistical difference between the asthmatic group and the control group regarding age and gender ($p = 0.84$ and $p = 0.61$, respectively).

The characteristics of children with asthma are seen in Table 1. There was a reaction history to NSAID in 10 (1%) children in the asthmatic group and 1 (0.05%) child in the control group ($p < 0.001$). Of the 976 children with asthma, 86 were <5 years of age, and none of them had a history of NSAID allergy.

At presentation, 10 patients (1%) reported an immediate reaction to NSAID use (3 to ibuprofen, 2 to flurbiprofen, 1 to diclofenac potassium, 2 to ibuprofen + ASA, and 1 to ibuprofen + metamizole + ASA). Four patients had angioedema, 3 had angioedema + dyspnea + cough, 2 had urticaria + angioedema, and 1 had a maculopapular eruption (MPE) in their history. Three patients described reactions to >1 chemically unrelated NSAID, and 6 patients had reactions to chemically similar NSAIDs. One patient who had a history of MPE with ibuprofen had a negative OPT. Characteristics of patients and reactions are presented in Table 2. SPT and IDT with suspected NSAIDs (metamizole and diclofenac potassium) were negative in 2 patients. As a result of OPTs performed for diagnostic purposes, 9 patients (0.9% of all patients; 33.3% males; median age 14.83 years, IQR 9.62–17.03) were defined as “NSAID-H.”

Table 2. Characteristics of asthmatic patients who had confirmed NSAID hypersensitivity

Patient No.	Age, years	Gender	Asthma control	Atopy	A history of NSAID-H	Reactions in the history	Reaction during OPT to suspected NSAIDs	Reaction during OPT with ASA	OPT with an alternative NSAID	Classification of NSAID-H
1	17.41	female	uncontrolled	–	ibuprofen metamizole ^a ASA	angioedema dyspnea cough	wheezing, dyspnea, and 20% decrease in FEV ₁ with ibuprofen and metamizole	dyspnea, and 25% decrease in FEV ₁	positive with paracetamol and meloxicam (25 and 35% decrease in FEV ₁ , respectively)	NERD
2	10.25	male	uncontrolled	pollen and mold	ibuprofen ASA	angioedema dyspnea cough	wheezing, dyspnea, and 25% decrease in FEV ₁ with ibuprofen	dyspnea, and 20% decrease in FEV ₁	negative with paracetamol	NERD
3	9	female	partially controlled	pollen and house dust mite	ibuprofen ASA	angioedema dyspnea cough	wheezing, dyspnea, and 20% decrease in FEV ₁ with ibuprofen	dyspnea, and 25% decrease in FEV ₁	negative with paracetamol	NERD
4	19	female	controlled	–	flurbiprofen	urticaria angioedema	angioedema with flurbiprofen	negative	negative with paracetamol and meloxicam	SNIUAA
5	14.83	male	partially controlled	pollen and mold	flurbiprofen	angioedema	urticaria and angioedema with flurbiprofen	negative	negative with paracetamol and meloxicam	SNIUAA
6	14.86	female	partially controlled	pollen	ibuprofen	angioedema	angioedema with ibuprofen	negative	negative with paracetamol and meloxicam	SNIUAA
7	12.2	male	controlled	pollen and mold	ibuprofen	angioedema	angioedema with ibuprofen	n.d.	negative with paracetamol and meloxicam	SNIUAA
8	6.9	female	partially controlled	–	ibuprofen	urticaria angioedema	urticaria and angioedema with ibuprofen	n.d.	negative with paracetamol	SNIUAA
9	16.66	female	controlled	pollen	diclofenac ^a	angioedema	angioedema with diclofenac	n.d.	negative with naproxen	SNIUAA

ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drug; NSAID-H, NSAID hypersensitivity; NERD, NSAIDs-exacerbated respiratory disease; n.d., not done; OPT, oral provocation test; SNIUAA, single NSAID-induced urticaria/angioedema or anaphylaxis.

^a Skin tests with metamizole and diclofenac were negative.

Only 1 out of 2,000 children in the control group had a history of suspected allergic reaction to NSAIDs. This patient had a history of MPE after ASA use. An OPT with ASA was negative. As a result, no NSAID allergy was confirmed in the control group.

Classification and Definition of Patients Diagnosed with NSAID-H

According to the results of the drug provocation tests and the self-reported use of ASA, 66.7% (6/9) of the patients had a “non-cross reactive type” and 33.3% (n : 3/9) had a “cross-reactive type” of hypersensitivity.

Six patients (66.7%) had a reaction with only 1 NSAID. In 3 patients, OPT with ASA was negative. The parents of 3 patients did not consent to OPT with ASA, but reported that their children could use ASA at home without a reaction; these children were thus classified as having SNIUAA.

Three patients (33.3%) had a reaction to ASA as well as to the culprit drug. They had dyspnea, cough, and urticaria and/or angioedema, and a $\geq 15\%$ decrease in FEV₁ during OPT, so they were classified as having NERD.

All children with asthma who were diagnosed with NSAID-H were evaluated by an ENT specialist for nasal polyps with rhinoscopy. Only 1 was found to have nasal polyps. This patient was in the NERD group.

Discussion

There are limited data on the frequency of NSAID-H in children with asthma. In this study, the prevalence of confirmed NSAID-H in children with asthma was 0.9% (9/10). Six of these patients were classified as SINUAA and 3 as NERD. There were no patients with confirmed NSAID-H in the control group.

There are also limited data about NSAID-H in children. Zambonino et al. [19] evaluated children with a history of reactions to NSAID, reporting the rate of NSAID-H confirmation in children to be 68.2%. This frequency is lower in the studies designed in our country (9.8–29.3%) [20–23]. It has been reported in the literature that NSAID-H is more common in patients with asthma, but pediatric data are limited. Jenkins et al. [6] analyzed data from early studies, using a weighted average of the incidence rates, and reported an incidence of 5% of ASA hypersensitivity for children with asthma. Accordingly, in our study, 1% of children with asthma and 0.05% of the control group reported a reaction to NSAIDs, and 90% of the reactions in the asthmatic group and no reactions in

the control group were confirmed by an OPT in our study.

As far as we know, no study in the literature has evaluated children with asthma for symptoms of NSAID-H and examined them for confirmed allergy according to the most recent EAACI classification. Previous studies evaluated children with asthma who did not report symptoms with NSAIDs, and looked for bronchial obstruction after OPT with ASA. They reported a frequency of positive OPT in a range of 0–28% [7–11]. Rachelefsky et al. [11] evaluated 50 children with atopic asthma, aged 6–18 years, and reported that 28% had a reaction during OPT with ASA. Schuhl and Pereyra [7] evaluated 32 children with asthma, aged 6–14 years, and did not report any positive OPT with ASA. Towns and Mellis [10] reported that 21% (6/29) of children with asthma had a positive OPT with ASA. Vedanthan et al. [9] examined 54 children with asthma, and reported that 2 (3.7%) experienced respiratory symptoms with ASA and 5 (9%) had a positive OPT.

There are only a limited number of studies related to bronchial obstruction due to NSAIDs other than ASA among children with asthma. Debley et al. [8] performed OPT with ibuprofen in 100 children with asthma, and reported that 2 had a positive OPT. Soferman et al. [24] compared the pulmonary function of 42 children with asthma before and after paracetamol and placebo use, reporting that they had similar FEV₁ results. None of these children had reported a reaction to NSAID use before the study, and they were not evaluated for phenotypes of NSAID-H.

The latest EAACI position paper on NSAID-H classified patients according to cross-intolerance, clinical symptoms, and underlying allergic disease. Cross-intolerance is associated with COX-1 inhibition, whereas single reactions are mediated by a specific IgE or T cell response. When COX inhibition is seen in patients with asthma, the situation is called NERD [18]. In children, the general approach to categorizing NSAID reactions would be similar to that for adults, with the main difference being that NERD is not common in children [25]. If we consider previous studies on children with asthma in the light of this classification, patients were only evaluated for NERD. In our study, we evaluated children with asthma not only for NERD but also for other phenotypes of NSAID-H. In our study, 3 children with asthma had respiratory symptoms during OPT with both the suspected drug and with ASA, and were thus classified as NERD (33.3%). The other 6 patients had urticaria and/or angioedema with the suspected drug during OPT and did not

have a reaction with ASA; they were thus classified as SNIUAA (66.7%). In previous studies from our country, 3.7–5% of confirmed NSAID-H in children was classified as NERD and 25–48% as SINUUA [21, 22].

Data on risk factors for NSAID-H among patients with asthma are also limited. In adult studies, female gender is shown as a risk factor [26]. Rachelefsky et al. [11] evaluated children with asthma and reported that bronchial obstruction with ASA is more frequent in females. In our study, 66.7% of patients with confirmed NSAID-H were female. Another risk factor identified as influencing NERD frequency in adult asthma studies is disease severity [26, 27]. A meta-analysis undertaken by Rajan et al. [27] showed that the prevalence of NERD was higher in patients with severe asthma (14.89%). In agreement with their study, we found that 78% ($n = 7/9$) of patients with confirmed NSAID-H had partially controlled or uncontrolled asthma. The presence of atopy to aeroallergens is also associated with NERD in previous studies [26]. In our study, 66.7% of patients with confirmed NSAID-H had atopy to aeroallergens.

Paracetamol is not a frequent cause of NSAID-H, and low doses of paracetamol are usually used as an alternative drug for patients with NSAID-H [21–23]. However, 1 of our patients had a reaction to paracetamol during OPT. This patient also had a reaction to meloxicam.

One of the limitations of our study was that we could not perform OPT for 3 of the patients with ASA. However, the parents of these patients have reported that their children have used ASA at home without a reaction. Another limitation is the low number of confirmed NSAID-H cases, which disables performing a statistical analysis for comparing patients with and without NSAID-H and determining the risk factors. However, we evaluated a large patient and control group, and we think that our data are important for future research.

In conclusion, NSAID allergy is more common in children with asthma. Thus, children with asthma, especially those with poor asthma control, should be evaluated for reactions to NSAIDs during hospital visits. There is a need for studies involving more patients for the frequency of NSAID-H in children with asthma and to determine the characteristics of patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

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1	17.41	female	uncontrolled	-	ibuprofen, metamizole* ASA	angioedema, dyspnea, cough	wheezing, dyspnea, and 20% decrease in FEV ₁ with ibuprofen and metamizole	dyspnea, and 25% decrease in FEV ₁	positive with paracetamol and meloxicam (25 and 35% decrease in FEV ₁ , respectively)	NERD
2	10.25	male	uncontrolled	pollen and mold	ibuprofen ASA	angioedema, dyspnea, cough	wheezing, dyspnea, and 25% decrease in FEV ₁ with ibuprofen	dyspnea, and 20% decrease in FEV ₁	negative with paracetamol	NERD
3	9	female	partially controlled	pollen and house dust mite	ibuprofen ASA	angioedema, dyspnea, cough	wheezing, dyspnea, and 20% decrease in FEV ₁ with ibuprofen	dyspnea, and 25% decrease in FEV ₁	negative with paracetamol	NERD
4	19	female	controlled	-	flurbiprofen	urticaria, angioedema	angioedema with flurbiprofen	negative	negative with paracetamol and meloxicam	SNTUAA
5	14.83	male	partially controlled	pollen and mold	flurbiprofen	angioedema	urticaria and angioedema with flurbiprofen	negative	negative with paracetamol and meloxicam	SNTUAA
6	14.86	female	partially controlled	pollen	ibuprofen	angioedema	angioedema with ibuprofen	negative	negative with paracetamol and meloxicam	SNTUAA
7	12.2	male	controlled	pollen and mold	ibuprofen	angioedema	angioedema with ibuprofen	n.d.	negative with paracetamol and meloxicam	SNTUAA
8	6.9	female	partially controlled	-	ibuprofen	urticaria, angioedema	urticaria and angioedema with ibuprofen	n.d.	negative with paracetamol	SNTUAA
9	16.66	female	controlled	pollen	diclofenac*	angioedema	angioedema with diclofenac	n.d.	negative with naproxen	SNTUAA

ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drug; NSAID-H, NSAID hypersensitivity; NERD, NSAIDs-exacerbated respiratory disease; n.d., not done; CPT, oral provocation test; SNTUAA, single NSAID-induced urticaria/angioedema or anaphylaxis.

* Skin tests with metamizole and diclofenac were negative.

Median age, years (IQR)	10.5 (7.02–14.0)
Gender, male	575 (59)
Atopic dermatitis	89 (9.1)
Allergic rhinitis	492 (50.5)
Atopy to aeroallergens	524 (53.7)
Asthma severity	
Mild intermittent	167 (17.1)
Mild persistent	532 (54.6)
Moderate persistent	251 (25.8)
Severe persistent	24 (2.5)
Level of asthma control	
Controlled	735 (75.5)
Partially controlled	201 (20.6)
Uncontrolled	38 (3.9)
A family history of allergic disease	272 (27.9)
Asthma	197
Allergic rhinitis	71
Drug allergy	2
Penicillin	1
NSAID hypersensitivity	1

Values express *n* (%), unless otherwise specified.