

Original Article



Tolerability to paracetamol and preferential COX-2 inhibitors in patients with cross-reactive nonsteroidal anti-inflammatory drugs hypersensitivity

OPEN ACCESS

Received: Sep 23, 2019

Accepted: Jul 6, 2020

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Conflict of Interest

The authors have no financial conflicts of interest.

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ABSTRACT

Background: Acetylsalicylic acid/aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used drugs that may cause hypersensitivity reactions in a substantial proportion of patients. Physicians ought to be aware of these situations.

Objective: We aimed to present the clinical characteristics and rates of tolerability to cyclooxygenase (COX)-2 inhibitor analgesics in patients who had admitted due to multiple cross-reactive type of NSAID hypersensitivity.

Methods: The files of the patients who had admitted with multiple NSAIDs-induced symptoms were investigated retrospectively. Age, sex, underlying diseases, clinical manifestation, skin test results, and drug provocation test results were analyzed.

Results: In 105 patients with multiple cross-reactive type of NSAID hypersensitivity, we found the rate of cross-reactivity to any of the relatively safe alternatives including paracetamol, meloxicam, and nimesulide to be 16.1%. The rate of cross-reactivity to these relatively safe drugs was significantly higher in patients with a history of anaphylaxis induced by NSAID intake ($p = 0.006$).

Conclusion: The diagnosis of COX-1-mediated multiple NSAID hypersensitivity can be often established with a detailed history. Although rare, severe hypersensitivity reactions may be observed in these patients. Undesired situations for both patients and physicians may be avoided by testing relatively safe paracetamol and COX-2 inhibitors in experienced centers.

Keywords: Cyclooxygenase-2 inhibitors; Hypersensitivity; Nonnarcotic analgesics; Nonsteroidal anti-inflammatory agents; Paracetamol

Author Contributions

Conceptualization: Kadriye Terzioğlu, Raziye Tülümen Öztürk. Data curation: Kadriye Terzioğlu, Özgür Sancar. Formal analysis: Kadriye Terzioğlu, Raziye Tülümen Öztürk, Hasan Çetin Ekerbiçer. Methodology: Özgür Sancar, Hasan Çetin Ekerbiçer. Project administration: Kadriye Terzioğlu. Visualization: Kadriye Terzioğlu. Writing - original draft: Kadriye Terzioğlu, Kürşat Epöztürk. Writing - review & editing: Kadriye Terzioğlu, Kürşat Epöztürk.

INTRODUCTION

Acetylsalicylic acid/aspirin (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been used in various branches of medicine because of their analgesic, antipyretic, and anti-inflammatory properties; yet, they are the second most common cause of drug-related hypersensitivity reactions. The estimated prevalence of hypersensitivity to NSAIDs was reported to be around 0.6%–2.5% in general population and up to 20% among patients with asthma or chronic urticaria. European Network for Drug Allergy (ENDA) and Global Allergy and Asthma European Network (GA²LEN) interest group prepared a special classification as an approach to NSAID-induced hypersensitivity reactions and divided them as allergic and nonallergic [1, 2].

Immunologically mediated reactions to NSAIDs are induced by a single NSAID or chemically related NSAIDs and these patients can receive chemically unrelated NSAIDs. These reactions are IgE-mediated and diagnosed with skin tests.

Nonimmunologic mechanism of NSAID hypersensitivity involves cross-reactivity to various NSAIDs in different subgroups via inhibition of cyclooxygenase-1 (COX-1). Skin tests have no diagnostic value and, although selective COX-2 inhibitors (e.g., celecoxib) are considered as better options, most of the patients can receive safely paracetamol (a weak COX-1 inhibitor) and preferential COX-2 inhibitors (nimesulide or meloxicam). NSAID hypersensitivity reactions mediated by COX-1 inhibition are divided to subtypes according to presenting symptoms and underlying disorders. In NSAIDs-exacerbated respiratory disease (NERD), formerly known as Samter's triad, there is underlying respiratory disease such as asthma, rhinitis, and nasal polyposis; moreover, NSAID intake induces various symptoms and clinical pictures including rhinorrhea, sneezing, coughing, dyspnea, urticaria/angioedema, and anaphylaxis. Its prevalence is about 4.3%–20%. In NSAIDs-exacerbated cutaneous disease (NECD), there is underlying chronic urticaria with exacerbations due to NSAID intake. In NSAIDs-induced urticaria/angioedema (NIUA), there is no underlying disease and urticaria/angioedema appears only due to NSAID intake. Blended reactions (BRs) are mixed reactions induced by various NSAIDs, such as anaphylactic reactions induced by multiple NSAIDs or BRs in patients with both asthma/chronic rhinosinusitis and chronic urticaria; they cannot be categorized properly into any of the proposed groups [3-5]. This classification is important for management and follow-up.

A suitable approach to NSAID hypersensitivity requires special knowledge and training. Although NSAIDs are utilized commonly in almost every branch of medicine, lack of appropriate approach to NSAID hypersensitivity by some physicians can be observed in clinical practice. On this matter, we believe that the awareness and knowledge of physicians other than allergists should be increased. In this study on patients with cross-reactive NSAID hypersensitivity mediated by COX-1 inhibition, we aimed to present the frequency, clinical presentation, rate of tolerability to alternative analgesics, and related risk factors.

MATERIALS AND METHODS**Subjects**

The files of 105 patients who had admitted to the adult allergy and immunology outpatient clinic of Sakarya University Training and Research Hospital, between the years 2016 and 2018

due to cross-reactive types of hypersensitivity to NSAIDs were analyzed retrospectively. The diagnosis of NSAID hypersensitivity was established with a positive ASA provocation test and/or with a history of multiple reactions against NSAIDs of various groups. Exclusion criteria were delayed-type cutaneous reactions and a history of reaction against sole group of NSAIDs.

The patients were categorized according to ENDA/GA²LEN classification as NSAIDs-exacerbated respiratory disease, NSAIDs-exacerbated cutaneous disease, NSAIDs-induced urticaria/angioedema, and BRs.

Age, sex, accompanying diseases, type of reaction related to NSAID intake, skin prick test with inhalant allergens, and drug provocation tests with paracetamol, nimesulide, and meloxicam were analyzed. Selective COX-2 inhibitors were not available in our country at the time.

Drug provocation tests

The patients with suspected cross-reactive types of hypersensitivity to NSAIDs underwent oral provocation test (OPT) with ASA. Short-acting bronchodilators (for 8 hours), long-acting bronchodilators and inhaled steroids (for 48 hours), antihistamines (for 3 days), systemic steroids and leukotriene antagonists (for 7 days) were discontinued before the test. All OPTs were performed in hospital and under sufficient emergency action measures. Before the test, vital findings and peak flow meter values of the patients were recorded. Those patients with a history of anaphylaxis received an intravenous line. In the patients with high level of anxiety, the test was commenced with a placebo pill. In ASA provocation test, aspirin was administered in increasing doses as 50, 100, 350, and 500 mg with 30-minute intervals. Therefore, the total aspirin challenge dose was 1,000 mg. The test was considered positive if urticaria/angioedema, rhinitis symptoms, dyspnea, arterial blood pressure alteration, nausea, vomiting, or palpitation occurs; in that case, the test was stopped and appropriate symptomatic treatment was administered. The diagnosis of cross-reactive types of hypersensitivity to NSAIDs was considered, thus, as substantiated.

To determine a safely utilizable alternative analgesic for patients with cross-reactive types of hypersensitivity to NSAIDs verified by medical history and/or ASA provocation test, OPT with paracetamol (500 mg tablet) and/or preferential COX-2 inhibitor (meloxicam 7.5-mg tablet and/or nimesulide 100-mg tablet) was performed. During OPT, a quarter of the single dose of the tested drug was administered at first and the remaining three-fourths of the drug were administered 30 minutes later if no symptoms occurred at the first step. At the end of 1 hour, test was considered as negative if no symptoms occurred and peak flow meter values were stable; thus, safety of the administration of the tested drug was demonstrated [6].

Skin tests

Histamine (10 mg/mL) was used as positive control and sterile saline solution (0.9%) as negative control. Rhinitis and asthma patients underwent skin prick test with standardized inhalant allergens including pollens, house dust mites, cockroach, molds, cat, and dog (Allergopharma, Reinbek, Germany).

Statistics

Age, being a continuous variable, was presented as mean \pm standard deviation. To compare the age variable between groups, Kolmogorov-Smirnov and Mann-Whitney *U* tests were utilized. Categorical variables were presented as frequency and relevant percentage values. For comparisons between groups, Fisher exact test or chi-square test was performed. The

analyses of the study were executed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). program. A *p* value ≤ 0.05 was considered statistically significant.

RESULTS

Demographical and clinical characteristics of study subjects

We evaluated 105 patients with aspirin and/or NSAID hypersensitivity. The mean age was 39.9 ± 13.3 years and the female/male ratio was 76 (72.4%)/29 (27.6%). Almost all of the patients had a strong medical history substantiating aspirin and/or NSAID hypersensitivity; only 2 patients with a suspicious history underwent ASA provocation test that gave positive results in both cases. As underlying diseases, 22 patients (21%) had asthma, 40 (38.1%) had chronic rhinosinusitis, 28 (26.7%) had chronic idiopathic urticaria, and 20 (19%) had comorbid asthma and rhinitis.

OPT was performed in 42 (40%) patients with paracetamol, in 104 (99%) with meloxicam, and in 72 (68.6%) with nimesulide. Of the patients, 33 (31.4%) were classified in NERD group, 47 (44.8%) in NIUA group, 21 (20%) in NECD group, and 4 (3.8%) in BRs group (Table 1).

Cross-reactivity to paracetamol

At initial admission to hospital, 59 patients (56.2%) were able to use paracetamol safely and 4 (3.8%) were avoiding the drug due to previous hypersensitivity reaction. The remaining 42 patients (40%) underwent OPT with paracetamol; 2 (1.9%) had reaction with a quarter dose in the form of urticarial lesions. In total, 6 out of 105 patients (5.7%) had cross-reaction to paracetamol.

Cross-reactivity to COX-2 inhibitors

OPT with meloxicam was performed in 104 patients; 97 (93.3%) could receive the drug safely but 3 (2.9%) had reaction with a quarter dose and 4 (3.8%) with full dose. In total, 7 (6.7%) patients had cross-reactivity to meloxicam. Out of them, 3 had systemic reaction and 4 had urticarial lesions only.

OPT with nimesulide was performed in 72 patients; 65 (90.3%) could receive the drug safely but 3 (4.2%) had reaction with a quarter dose and 4 (5.5%) with full dose. In total, 7

Table 1. Some descriptive and demographical statistics of the study group (n = 105)

Characteristic	Value
Age (yr)	39.9 \pm 13.3
Female sex	76 (72.4)
Atopy (n = 44)	26 (59.1)
Underlying disease	
Asthma	22 (21.0)
Chronic rhinosinusitis	40 (38.1)
Chronic idiopathic urticaria	28 (26.7)
Diagnosis of NSAIDs hypersensitivity	
ASA provocation test	3 (2.9)
Convincing clinical history	102 (97.1)
Classification of NSAIDs hypersensitivity	
NSAIDs-exacerbated respiratory disease	33 (31.4)
NSAIDs-induced urticaria/angioedema	47 (44.8)
NSAIDs-exacerbated cutaneous disease	21 (20.0)
Blended reactions	4 (3.8)

Values are presented as mean \pm standard deviation or number (%).

NSAIDs, nonsteroidal anti-inflammatory drugs; ASA, acetylsalicylic acid/aspirin.

Table 2. Distribution of drug hypersensitivities within the clinical groups (n = 21)

Reaction-inducing drugs	NERD	NIAU	NECD	BRs	Total, n (%)
Paracetamol	1	4	1	0	6 (5.7)
Meloxicam	3	1	2	1	7 (6.7)
Nimesulide	5	2	0	1	8 (10.9)
Total	9	7	3	2	21 (20.0)

NSAIDs, nonsteroidal anti-inflammatory drugs; NERD, NSAIDs-exacerbated respiratory disease; NIAU, NSAIDs-induced urticaria/angioedema; NECD, NSAIDs-exacerbated cutaneous disease; BRs, blended reactions.

patients (9.7%) had cross-reactivity to nimesulide. Out of them, 1 had systemic reaction and remaining 6 had urticarial lesions only. One patient had a history of reaction to nimesulide at initial admission. In total, 8 patients (10.9%) were cross-reactive to nimesulide.

Cross-reactivity comorbidities

According to initial history at admission and in the light of the test results, 21 out of 105 patients (20%) in total were defined as cross-reactive to paracetamol and/or meloxicam and/or nimesulide. One patient had reaction to both paracetamol (quarter dose) and meloxicam (full dose); OPT with nimesulide was not performed in this patient. Another patient had reaction with paracetamol (quarter dose) and nimesulide (full dose) but tolerated meloxicam. Another patient had previous history of hypersensitivity reactions to paracetamol and nimesulide; the patient reacted to full dose of meloxicam as well. Remaining 14 patients (13.3%) had cross-reactivity to only one drug tested. The distribution of the patients was shown in **Table 2**.

Risk factors for cross-reactivity

Age, sex, and presence of atopy posed no significant risk for cross-reactivity with paracetamol, meloxicam, or nimesulide; conversely, the cross-reactivity was frequent in patients with a history of anaphylaxis due to NSAID intake and it was shown to be a significant risk factor ($p = 0.006$).

DISCUSSION

We presented a series of 105 adult patients with a suggestive history of multiple NSAID hypersensitivity. In general, drug allergies are more frequent among women [7, 8]; moreover, several studies reported that female/male ratio was even higher among patients with NSAID hypersensitivity [9-11]. In our study, the female/male ratio was 76 (72.4%)/29 (27.6%), showing that NSAID hypersensitivity was more prevalent among women.

Cross-reactive types of hypersensitivity to NSAIDs are elicited by nonallergic mechanisms via inhibition of COX-1 and subsequent alteration in eicosanoid biosynthesis, most prominently cysteinyl leukotriene overproduction. Generally, patients with aspirin intolerance are also sensitive to all NSAIDs that preferentially inhibit COX-1 [12-14]. Paracetamol, a weak COX inhibitor, and nonselective COX-2 inhibitors (meloxicam, nimesulide) are known to be relatively safe therapeutic alternatives for patients with aspirin intolerance [15].

In the present study, we found that paracetamol, meloxicam, and nimesulide, which have been recognized as relatively safe drugs, also induced adverse reactions in 5.7%, 6.7%, and 9.7% of the patients with NSAID hypersensitivity, respectively. A recent review of European Academy of Allergy and Clinical Immunology/ENDA and GA²LEN/HANNA classified NSAIDs

into 3 separate groups: A, those cross-reacting in the majority of hypersensitive patients (60%–100%); B, those cross-reacting in the minority of hypersensitive patients (2%–10%); and C, those that are well tolerated in all hypersensitive patients. Paracetamol, meloxicam, and nimesulide are classified into group B in which cross-reactions are reported in a minority of hypersensitive patients at the rates of 2%–10% [2]. Our results were within this range. We found 16 patients with cross-reactivity to paracetamol and/or meloxicam and/or nimesulide, 4 of them having systemic reactions. Although they are considered as relatively safe within group B, our findings stress that the first dose of the recommended drugs should be administered in an equipped medical center by experienced personnel.

Classifications of NSAID hypersensitivity according to clinical presentation, cross-reactivity among NSAIDs, and underlying diseases were made by Quiralte et al. [16] in 1996 and by Stevenson et al. [17] in 2001. Sánchez-Borges et al. [18] revised this classification in 2004 and included the term "blended." The final revision of the classification was made by ENDA/GA²LEN, in which BRs included those unclassified into other groups [2]. Kim et al. [19] and Demir et al. [20] noted that anaphylaxis cases induced by chemically different multiple NSAIDs in 8.9% and 1.6% of their patients, respectively, could not fit into any group. Among our patients, 3.8% showed BRs and were not classified into classical groups.

A previous study showed anaphylaxis and presence of atopy to be risk factors for cross-reactivity to paracetamol and COX-2 inhibitors [21]. In our study, anaphylaxis due to NSAID intake was found to be the sole risk factor for intolerance to paracetamol and preferential COX-2 inhibitors ($p = 0.006$); the presence of atopy was not shown to be risk factor.

The comorbidity between NSAID hypersensitivity and a clinical picture including asthma/rhinitis/urticaria is usually overlooked by patients and physicians other than allergists and clinical immunologists. This study aimed to emphasize the strong association between these 2 entities and show that this is a special group of patients. Sometimes the underlying diseases are so subtle that they are diagnosed incidentally by the physicians when the patients admit for NSAID hypersensitivity. Creating awareness about multiple NSAID hypersensitivity in physicians prescribing NSAIDs frequently in their daily practice and consulting allergists and clinical immunologists in order to diagnose and treat underlying diseases and to determine relatively safe drugs are important for follow-up and subsequent treatments of the patients.

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