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Characteristics and Contributing Factors Related to Nonsteroidal Anti-Inflammatory Drugs Hypersensitivity

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Keywords
Nonsteroidal anti-inflammatory drugs · Hypersensitivity · Self-reported · Predisposing factors · Drug allergy

Abstract
Introduction: Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is reported to be the most common drug hypersensitivity. The aim of this study was to evaluate the characteristics of self-reported NSAID hypersensitivity and identify patients at high risk of NSAID hypersensitivity. ***Methods:*** Patients who presented at a single tertiary care hospital between January–December 2017 with reported NSAID hypersensitivity were evaluated. Clinical information obtained from a review of medical records was further supplemented with data gained from a telephone-administered questionnaire. ***Results:*** From a total of 535 patients with reported NSAID hypersensitivity, 301 were included in the study. The mean age of onset of NSAID hypersensitivity reaction was 30.3 ± 14.9 years old. A total of 84 patients (27.9%) were hypersensitive to 2 or more chemically unrelated NSAIDs. The leading NSAID hypersensitivity was to propionic acid derivatives (73%) followed by acetic acid derivatives (28.9%). Immediate reaction (≤1 h) was identified in 171 patients (57.8%), and angioedema was the most frequently reported symptom (179 patients, 59.5%), followed by urticaria and anaphylaxis in 85 (28.2%) and 62 (20.6%) patients, respectively. A drug provocation test was performed on 53 patients, and NSAID hypersensitivity was confirmed in 38 patients (71.6%). The independent factors identified, which could predict NSAID hypersensitivity, were personal history of allergic rhinitis/chronic rhinosinusitis (AR/CRS), onset of NSAID hypersensitivity over 15 years old, and immediate reaction. ***Conclusion:*** Angioedema was the most typical symptom, and propionic acid derivatives were the most frequently reported culprit drugs. The significant risk factors predicting NSAID hypersensitivity were personal history of AR/CRS, onset of NSAID hypersensitivity reaction over 15 years old, and immediate reaction.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs used as analgesics, antipyretics, and anti-inflammatory drugs. NSAID use has increased over time.

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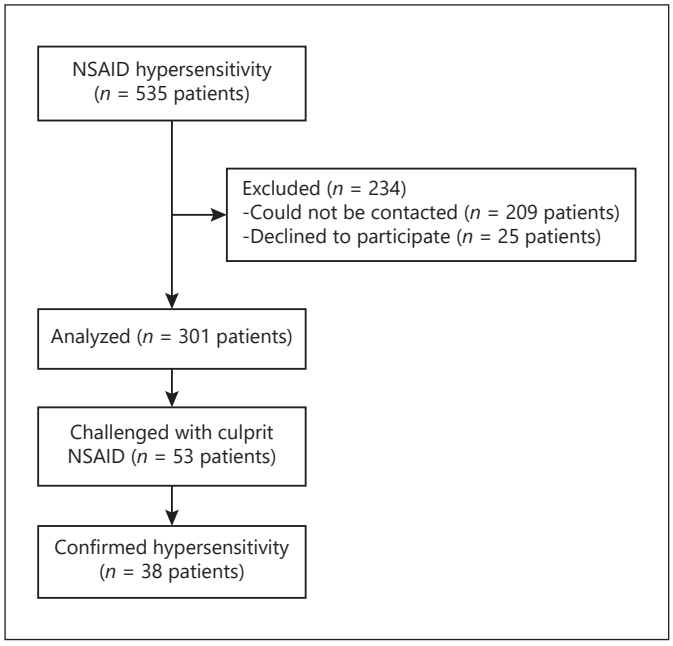

Fig. 1. Flowchart of study participants. The diagram includes detailed information on the excluded participants. NSAID, nonsteroidal anti-inflammatory drug.

Currently, hypersensitivity to NSAIDs is reported to be the most common, adverse drug reaction [1]. The true incidence is not known, but recent studies have reported prevalence of self-reported NSAID hypersensitivity of 19.4–27.5% [2–4].

NSAID hypersensitivity has been classified by the EAACI/GA2LEN experts based on the timing of the reaction, the clinical manifestations, the type of reaction, the presence of an underlying disease, and the putative mechanism [5]. Similar hypersensitivity reactions to more than 1 chemically unrelated NSAID has been defined as cross-reactive NSAID hypersensitivity, which is thought to be non-immunologic. Hypersensitivity reactions to more than 1 NSAID belonging to the same chemical group are considered to be immunologically mediated and are defined as allergic hypersensitivity reactions. Kowalski et al. [6], further classified NSAID hypersensitivity as an NSAID-exacerbated respiratory disease, NSAID-exacerbated cutaneous disease, NSAID-induced urticaria/angioedema, single NSAID-induced urticaria/angioedema and/or anaphylaxis, and single NSAID-induced delayed reaction in 2013.

In many cases, the clinical history is uncertain and various studies have reported that NSAID hypersensitivity was confirmed only in 22–31.7% of study cases [7–11]. To confirm the diagnosis of NSAID hypersensitivity, a drug provocation test (DPT) with the culprit drug remains the gold standard to confirm the diagnosis. In vivo and in vitro tests are not currently recommended as a routine practice except for non-cross-reactive IgE-mediated reactions [6].

In general populations, previous studies on clinical manifestations of NSAID hypersensitivity found that the most reported symptom was an isolated cutaneous reaction, with acetylsalicylic acid being the drug most often involved in the reaction [12, 13]. Other studies have reported that cross-reactivity was identified in 50.3–74.3% of their cases [9, 14]. Proposed risk factors are based on the immediate reaction [12, 15]. An association between personal history of atopic diseases and NSAID hypersensitivity has been suggested by some investigators [16].

Based on clinical history alone, it is difficult to confirm drug allergy which leads to unnecessary avoidance of the presumed culprit drug and prescription of alternative NSAIDs with higher costs. The aim of this study was to evaluate the clinical features of self-reported NSAID hypersensitivity and identify patients at high risk of NSAID hypersensitivity.

Materials and Methods

Patients who presented to a single tertiary care hospital, in Thailand, between January–December 2017 with reported NSAID hypersensitivity were retrospectively identified from our database. Participants younger than 6 months or older than 60 years old were excluded.

Clinical information obtained from a review of medical records was further supplemented with data gained from a telephone-administered questionnaire. The procedures in this study were performed in accordance with the Declaration of Helsinki's ethical principles for medical research involving human participants. This study was approved by the local ethics committee and institutional review board. The following data were collected: age, sex, personal history of doctor-confirmed asthma, allergic rhinitis or chronic rhinosinusitis (AR/CRS), atopic dermatitis, food allergy and chronic urticaria, reported hypersensitivity to any drugs, characteristics of adverse reactions (NSAID-involved, time between drug intake and reaction onset, symptoms experienced), NSAID use and tolerance, family history of atopy and drug hypersensitivity, NSAID hypersensitivity that was confirmed by a DPT in the clinic, and accidental repeated intake of the culprit drug.

Statistical Analysis

The data were recorded using EpiData and analyzed using R statistical software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as means and standard deviations and were compared using independent *t* tests. Categorical data are given as numbers of cases and percentages and were compared using the χ^2 test and Fisher's exact test. A p value <0.05 was regarded as significant. Univariate and

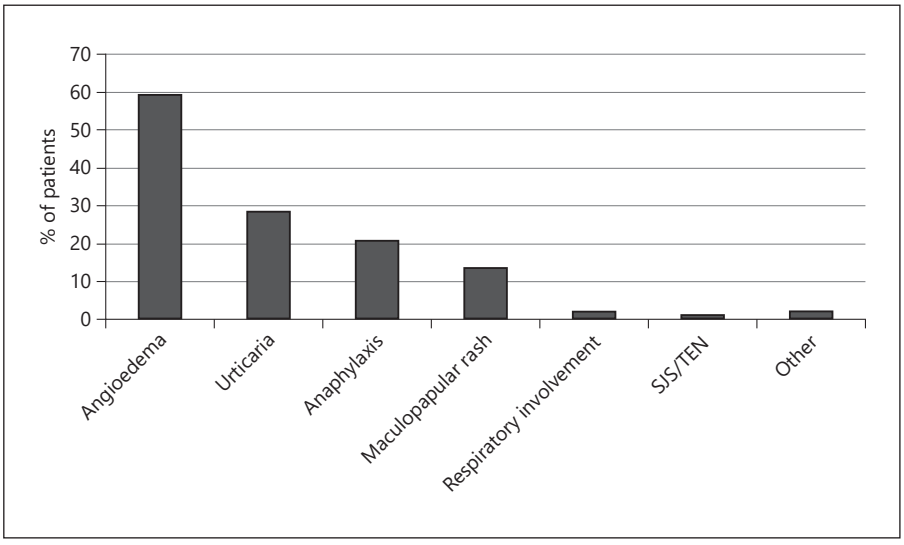

Fig. 2. Frequencies of reported symptoms of NSAID hypersensitivity reactions. NSAID, nonsteroidal anti-inflammatory drug; SJS-TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

multivariate logistic regression analyses were performed. A stepwise binary logistic regression analysis was used to test the considered predictors of NSAID hypersensitivity among patients with conclusive results. Results were adjusted for potential confounding factors as appropriate and possible.

Results

During the study period, a total of 871 events, with 535 patients with reported NSAID hypersensitivity, were initially discovered, with recorded NSAID hypersensitivity. Two hundred thirty-four (43.7%) of them were excluded; either because, they could not be reached by phone, or they did not want to participate in the study (Fig. 1); leaving the records of 301 patients for analysis. The mean age of onset of NSAID hypersensitivity was 30.3 ± 14.9 years old and 65.1% were female. The characteristics of the patients are shown in Table 1.

Angioedema was the most frequently reported symptom in 179 patients (59.5%) followed by urticaria and anaphylaxis in 85 (28.2%) and 62 (20.6%) patients, respectively. Maculopapular rash was reported by 40 (13.3%) patients, and respiratory involvement and Stevens-Johnson syndrome/toxic epidermal necrolysis were described by 6 (2%) and 2 (0.7%) patients (Fig. 2).

A total of 84 patients (27.9%) described hypersensitivity to 2 or more chemically unrelated NSAIDs. The leading NSAID hypersensitivity involved propionic acid derivatives such as ibuprofen and naproxen (73%) followed by acetic acid derivatives such as diclofenac and indomethacin (28.9%) (Fig. 3). According to generic name,

Table 1. Characteristics of study patients with reported NSAID hypersensitivity

Characteristic	Total (N = 301)
Female, *n* (%)	196 (65.1)
Onset of NSAID hypersensitivity, mean ± SD, years	30.3±14.9
>15 years old, *n* (%)	250 (83.1)
Underlying disease, *n* (%)	
AR/CRS	110 (36.5)
Asthma	41 (13.6)
Atopic dermatitis	19 (6.3)
Food allergy	64 (21.3)
Chronic urticaria	8 (2.7)
Nasal polyposis	2 (0.7)
Additional drug allergy, *n* (%)	
Antibiotic	70 (23.3)
Intraoperative anaphylaxis	3 (1.0)
RCM	1 (0.3)
Hypersensitivity to 2 or more chemically unrelated NSAIDs	84 (27.9)
Family history of atopic disease, *n* (%)	
AR/CRS	39 (13)
Asthma	25 (8.3)
Food allergy	14 (4.7)
Chronic urticaria	2 (0.7)
NSAID hypersensitivity	14 (4.7)
Antibiotic hypersensitivity	10 (3.3)
RCM hypersensitivity	2 (0.7)

NSAID, nonsteroidal anti-inflammatory drug; RCM, radiocontrast media; AR/CRS, allergic rhinitis/chronic rhinosinusitis.

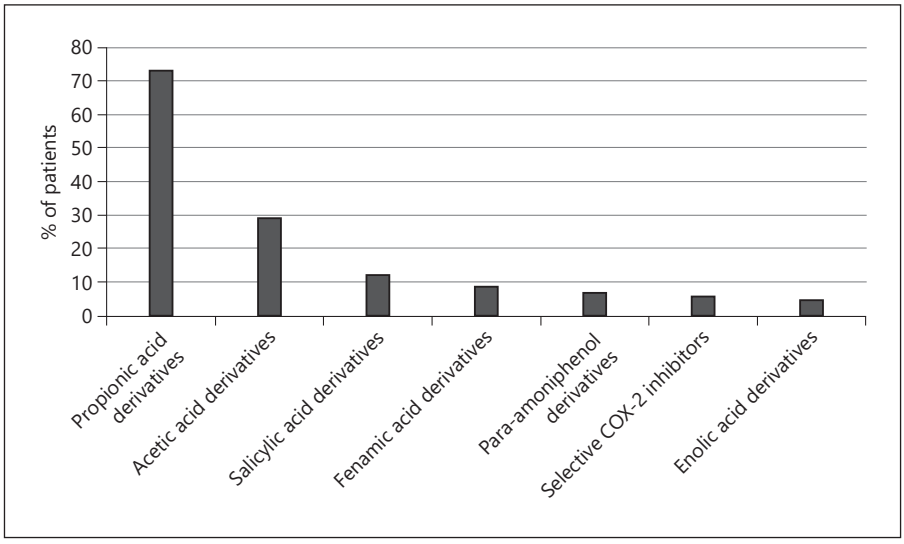

Fig. 3. Frequencies of hypersensitivity reactions to NSAIDs according to the chemical group. NSAID, nonsteroidal anti-inflammatory drug.

Table 2. Frequencies of hypersensitivity reactions to NSAIDs according to generic name

Culprit drugs	*N* (%)
Ibuprofen	193 (64.1)
Diclofenac	82 (27.2)
Aspirin	36 (12.0)
Naproxen	27 (9.0)
Mefenamic acid	25 (9.0)
Paracetamol	20 (6.6)
Celecoxib	15 (5.0)
Meloxicam	9 (3.0)
Indomethacin	5 (1.7)
Piroxicam	5 (1.7)
Etoricoxib	1 (0.3)

NSAID, nonsteroidal anti-inflammatory drug.

ibuprofen was the most reported NSAID hypersensitivity followed by diclofenac and aspirin (Table 2). Time between drug intake and reaction onset was 4.2 ± 8.2 h, and immediate reaction (≤1 h) was identified in 171 patients (57.8%).

Of 53 (17.6%) patients who were challenged with the culprit NSAIDs, NSAID hypersensitivity was diagnosed in 38 (71.7%) patients. The clinical characteristics of patients with NSAID hypersensitivity or tolerance are shown in Table 3. Significant differences between NSAID hypersensitivity and tolerant patients were onset of NSAID hypersensitivity after the age of 15 ($p < 0.001$), personal history of AR/CRS ($p = 0.021$), immediate reaction ($p = 0.01$), and type of reaction (angioedema $p = 0.028$, maculopapular rash $p < 0.001$). There were no significant differences between the groups with and without confirmed NSAID hypersensitivity in terms of sex, hypersensitivity to 2 or more chemically unrelated NSAIDs, family history of atopy, and the presence of NSAID or antibiotic drug hypersensitivity in the family.

When statistically significant parameters were analyzed in a multivariate logistic regression model, a personal history of AR/CRS (OR 11 [95% CI, 1.33–90.83]; $p = 0.01$), onset of NSAID hypersensitivity over 15 years old (OR 22.62 [95% CI, 3.03–168.84]; $p = <0.001$), and immediate reaction (OR 10.66 [95% CI, 1.55–73.59]; $p = 0.016$) were found as the independent factors to predict NSAID hypersensitivity (Table 4).

Discussion/Conclusion

In this study, we evaluated 301 patients with reported NSAID hypersensitivity reactions in a single center. Only 17.6% who were then assessed for a suspected hypersensitivity reaction were formally diagnosed with such a reaction. Over half of the patients were female and one-third had allergic rhinitis, association also noted in other studies [14, 15, 17, 18].

Cutaneous reactions (urticaria and angioedema) were the most common manifestation. This is again similar to other studies, for example, the study published by Nissen et al. [9], who evaluated 129 patients with a clinical history of NSAID hypersensitivity referred to the Allergy center and found urticarial/angioedema was the most frequently reported symptoms (51.0%). We also noted the

Table 3. Comparison of characteristics between the patients with confirmed NSAID hypersensitivity and NSAID tolerance

Characteristic	NSAID hypersensitivity (n = 38)	NSAID tolerance (n = 15)	p value
Onset of NSAID hypersensitivity, years	24.6±12	9.7±11.4	<0.001
>15 years old, n (%)	29 (76.3)	3 (20)	<0.001
Sex, n (%)			
Male	13 (34.2)	7 (46.7)	0.597
Female	25 (65.8)	8 (53.3)	
Underlying disease, n (%)			
Asthma	4 (10.5)	4 (26.7)	0.202
AR/CRS	20 (52.6)	2 (13.3)	0.021
Atopic dermatitis	2 (5.3)	1 (6.7)	1.000
Chronic urticaria	2 (5.3)	2 (13.3)	0.568
Food allergy	17 (44.7)	5 (33.3)	0.653
Family history of atopic disease, n (%)			
AR/CRS	9 (23.7)	2 (13.3)	0.482
Asthma	1 (2.6)	2 (13.3)	0.190
Food allergy	2 (5.3)	1 (6.7)	1.000
Chronic urticaria	0 (0.0)	1 (6.7)	0.283
NSAID hypersensitivity	2 (5.3)	0 (0.0)	1.000
Antibiotic hypersensitivity	2 (5.3)	1 (6.7)	1.000
Hypersensitivity to 2 or more NSAIDs, n (%)	16 (42.1)	2 (13.3)	0.095
Immediate reaction, n (%)	30 (78.9)	6 (40.0)	0.010
Type of reaction, n (%)			
Angioedema	29 (76.3)	6 (40.0)	0.028
Urticaria	12 (31.6)	8 (53.3)	0.247
Anaphylaxis	12 (31.6)	1 (6.7)	0.080
Maculopapular rash	0 (0.0)	6 (40.0)	<0.001

NSAID, nonsteroidal anti-inflammatory drug; AR/CRS, allergic rhinitis/chronic rhinosinusitis.

Table 4. Multivariate logistic regression analysis of factors related to confirmed NSAID hypersensitivity

Variable	Adjusted OR* (95% CI)	p value
Personal history of AR/CRS	11 (1.33–90.83)	0.01
Onset of NSAID hypersensitivity over 15 years old	22.62 (3.03–168.84)	<0.001
Immediate reaction	10.66 (1.55–73.59)	0.016

NSAID, nonsteroidal anti-inflammatory drug; AR/CRS, allergic rhinitis/chronic rhinosinusitis. * Adjusted odds ratio by sex.

study by Chaundry et al. [19] that investigated NSAID-induced urticaria, angioedema, or anaphylaxis in 68 patients and found 64% were purely cutaneous manifestations. In our study, we found angioedema was the most frequent clinical reaction.

Most studies have reported that 38.76–40.3% of NSAID hypersensitivity reactions involved aspirin [9, 13, 17], although 1 recent study evaluated 370 patients with a history of hypersensitivity reactions to NSAIDs and found aspirin (30.2%) was the second leading cause of hypersensitivity reactions, following metamizole [14]. In our study, the most common culprit was propionic acid derivatives (73%), and ibuprofen (64.1%) was the leading cause of hypersensitivity reactions. This may be explained by the current common use of ibuprofen in our country and is similar to the results reported by Luanghirun et al. [20] who investigated the prevalence of NSAIDs use in a rural community in Thailand and reported that ibuprofen

(58.3%) was the most identified NSAIDs used in this community in Thailand.

In this study, 71.6% of the patients who were challenged with the culprit NSAID were confirmed as having NSAID hypersensitivity. This is a significantly higher rate than described by other authors, that is, Caimmi et al. (12.5%) [17], Viola et al. (22.2%) [15], Gomes et al. (21%) [18], and Quiralte et al. (35.2%) [13], which may arise from deletion of many NSAID-tolerant patients from the database, thus the remaining patients are more likely to have NSAID hypersensitivity.

Potential risk factors for NSAID hypersensitivity have been defined in various reports and include age <40 years, immediate reaction, hypersensitivity to 2 or more non-chemically related NSAIDs, and time interval ≤12 months [15, 21]. A recent study reported that the risk factors for NSAID hypersensitivity confirmation depended on the number of previous reactions (≥2) and the immediate type of reaction [18]. In our study, personal AR/CRS, onset of NSAID hypersensitivity over 15 years of age, and immediate reaction were found as the independent risk factors related to confirmed NSAID hypersensitivity.

This study had a number of limitations. First, our study did not include patients older than 60 years. Our study was a retrospective study, in that we collected data from our practice. Patients older than 60 years were excluded from our study because we limit the DPT in fragile patients in our practice and use other drugs instead to avoid complications from the DPT. Second, our trial started with a high number of patients but had only 53 patients undergoing a DPT because, in our practice, we performed a DPT only in patients who had an uncertain history of NSAIDs allergy. If patients had a clear history of NSAID allergy, such as repeated self-accidental challenge that correlated with an allergic reaction, or inpatient NSAID allergic which had allergic evaluation and was documented, these patients would not undergo a DPT. Although there were limitations, we believe that our investigation gives valuable information, proposing further study in this subject.

Conclusion

Angioedema is the most typical symptom, and propionic acid derivatives are the most frequently reported culprit drug in Thailand. Only 17.6% of our patients were challenged with the culprit drug, confirmed NSAID hypersensitivity in 71.6% of them. The significant risk factors predicting NSAID hypersensitivity in our study were personal history of AR/CRS, onset of NSAID hypersensitivity over 15 years old, and immediate reaction.

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Statement of Ethics

This study was approved by the Ethics Committee and Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (EC 60-272-01-3).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A. Yuenyongviwat: study design, data collection, statistical analysis, and writing the paper. N. Chantaravisarut: data collection, statistical analysis, and writing the paper. W. Phattarapongdilok: data collection. V. Koosakulchai: data collection. Wipa Jessadapakorn: data collection. Pasuree Sangsupawanich: study design and statistical analysis.

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