International Archives of Allergy and Immunology

Clinical Allergy – Research Article

Int Arch Allergy Immunol 2021;182:131–138
DOI: 10.1159/000510335

Received: June 29, 2020
Accepted: July 21, 2020
Published online: September 21, 2020

Descriptive Analysis of Cross-Reactive Anaphylaxis as a Different Clinical Subtype of Nonsteroidal Anti-Inflammatory Drug (NSAID) Hypersensitivity

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Keywords
Anaphylaxis · Cross-reactive · Nonsteroidal anti-inflammatory drug · Hypersensitivity · Blended reaction

Abstract
Introduction: The European Network of Drug Allergy and the European Academy of Allergy and Clinical Immunology have classified hypersensitivity reactions induced by nonsteroidal anti-inflammatory drugs (NSAIDs) into 5 phenotypes according to the pathophysiology, clinical manifestations, number of drugs involved, and the presence of underlying diseases. This classification does not include anaphylaxis as part of NSAID cross-reactivity. The objective of this study was to characterize a group of patients with anaphylactic NSAID cross-reactivity. ***Method:*** This was a retrospective, descriptive, observational study. Patients who developed anaphylaxis to one NSAID plus another acute reaction (anaphylactic or not) to at least one other NSAID of a different chemical group were included. Demographic and clinical characteristics and the diagnostic approach were studied. ***Results:*** A total of 38 patients were included, 28 (73.7%) of whom were women. The mean age was 40 ± 17.7 years. The main organs affected in the anaphylactic reaction were the skin and the respiratory system, occurring in 35 (92.1%) and 33 (86.8%) patients, respectively. Thirty-two (84.3%) patients presented with cutaneous and respiratory involvement simultaneously. The main anti-inflammatory agent involved in anaphylactic reactions was acetylsalicylic acid in 9 (23.7%) patients, followed by dipyrone in 8 (21.1%). The most frequent allergic comorbidity was rhinitis in 20 (52%) patients. Skin tests were performed in 15 (39.5%) patients, showing positivity in 12 (80%), mainly to mites. A total of 36 of 38 patients were challenged with alternative drugs, and 35 (97.2%) tolerated meloxicam and/or etoricoxib. ***Conclusion:*** In the present study, NSAID cross-anaphylaxis was more frequent in women, and acetylsalicylic acid and dipyrone were the main triggers. Rhinitis was the main allergic comorbidity, and there was a high incidence of atopy. The majority tolerated selective COX-2 NSAIDs.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to treat pain, fever, and inflammation. Their mechanism of action is the inhibition of cyclooxygenase isoenzymes (COX-1 and COX-2), decreasing the production of pro-inflammatory mediators such as prostaglan-

Edited by: H.-U. Simon, Bern.

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dins [1]. These drugs are available over the counter in most countries, which facilitates their availability and consumption. Because NSAIDs are widely used, it is possible for susceptible individuals to have hypersensitivity reactions that can be life-threatening.

Hypersensitivity to NSAIDs has a prevalence of 0.6–5.7% in the general population [2] and accounts for 42% of all drug hypersensitivity reactions [3–5]. NSAID hypersensitivity can be triggered by nonimmunological mechanisms, such as imbalance in the arachidonic acid metabolism pathway, as well as by immunological mechanisms, such as immunoglobulin E-mediated allergy (immediate reactions) or by cellular hypersensitivity (delayed reactions) [6]. The spectrum of its clinical presentation is broad, ranging from the presence of mild urticaria and/or angioedema to anaphylaxis or severe delayed skin reactions.

Anaphylaxis is a severe systemic allergic reaction with rapid onset and progression that is life-threatening, occurring soon after contact with a trigger and involving at least 2 body systems [7–10]. The pathophysiological mechanisms by which anaphylaxis occurs can be both immunological and nonimmunological [11]. Drug-induced anaphylaxis has a prevalence of 0.04–3.1%, but this can vary with the population studied. Its mortality rate is 0.065% [11]. NSAIDs are the main group of drugs that induce anaphylaxis, accounting for 48.7–57.8% of cases. These reactions are typically of immunological origin (IgE-mediated) [11], though anaphylaxis induced by cross-hypersensitivity to NSAIDs has also been described [5, 12].

The European Network of Drug Allergy and the European Academy of Allergy and Clinical Immunology (EAACI) have classified NSAID-induced hypersensitivity reactions into 5 phenotypes according to the pathophysiology, clinical manifestations, number of drugs involved, and presence of underlying diseases: (1) NSAID-exacerbated respiratory disease (NERD), (2) NSAID-exacerbated cutaneous disease (NECD), (3) NSAID-induced urticaria/angioedema (NIUA), (4) single NIUA or anaphylaxis, and (5) single NSAID-induced delayed hypersensitivity reaction [13, 14]. The first 3 phenotypes correspond to cross-reactions, that is, caused by 2 or more NSAIDs of different chemical groups; the last 2 phenotypes are caused by a selective reaction, that is, caused by 1 or more NSAIDs of the same chemical group.

Although this classification is the most used and accepted, it leaves out other types of reactions, described as "blended reactions." In these reactions, more than 1 organ is affected, usually the skin and respiratory system, after the consumption of 2 or more NSAIDs of different chemical groups. According to diagnostic criteria of anaphylaxis, these reactions could be considered like this and could be explained by a physiopathological mechanism similar to that of NSAID-induced cross-hypersensitivity [15]. Their exclusion from the European Network of Drug Allergy/EAACI classification can generate confusion when performing a diagnosis and choosing a therapeutic approach. The main objective of this study was to describe the demographic, clinical, and pharmacological characteristics of a group of patients who presented with at least 1 episode of anaphylaxis as part of NSAID-induced cross-reaction.

Materials and Methods

This was a retrospective, descriptive, observational study. A search was conducted for pediatric and adult patients who underwent oral drug provocation testing in the Allergology Service of Fundación Valle del Lili in Cali, Colombia, between 2011 and 2018. Their medical histories were reviewed, and those who developed anaphylaxis, defined as the presence of clinical symptoms involving 2 or more different organs, after the consumption of at least 1 of 2 or more NSAIDs of different chemical groups, including acetaminophen, were included in the study. The inclusion criteria were as follows: (1) patients with a clinical history of anaphylaxis to 2 or more NSAIDs or of anaphylaxis to 1 NSAID and an acute non-anaphylactic reaction (presentation <24 h, usually between 1 and 6 h) from another NSAID (1 or more) who were challenged with alternative NSAIDs (etoricoxib or meloxicam) and (2) patients with a history of anaphylaxis to at least 1 NSAID and a positive provocation test to 1 or more different NSAIDs. Patients with the following were excluded: (1) history of anaphylaxis to only 1 NSAID and a negative provocation test to that drug, to another conventional NSAID, or to an alternative NSAID; and (2) patients with a history of non-anaphylactic reactions to 2 or more NSAIDs of different chemical groups (NERD, NECD, and NIUA). Once the clinical histories were determined, the ANAINES database in BdClinic was filled out, and variables that described demographic, clinical, and pharmacological characteristics were included.

A descriptive statistical analysis of the demographic, clinical, and pharmacological variables was performed. The numerical variables are expressed as means with standard deviations; the categorical variables are described as proportions and percentages. The statistical software Stata 14.0 was used for data analysis.

Results

2011–2018, 298 patients with NSAID hypersensitivity diagnosed were screened, and 38 (12.7%) patients were included. Their mean age was 40 ± 17.7 years. Twenty-eight (73.7%) were women. Twenty (52.6%) had an allergic comorbidity, rhinitis 18 (47.4%) being the most com-

Table 1. Demographic characteristics

N	38
Age	40±17.7
Sex, *n* (%)	
Female	28 (73.7)
Male	10 (26.3)
Antecedents, *n* (%)	
Rhinitis	18 (47.4)
Asthma	8 (21.1)
Atopic dermatitis	1 (2.6)
Food allergy	4 (10.5)
Chronic urticaria	1 (2.6)
Nasal polyps	0 (0)
Allergy to other drugs	4 (10.5)
Family history of atopy	3 (7.9)

Table 2. Specific clinical characterization[a]

Skin, *n* (%)	35 (92.1)
Angioedema	30 (78.9)
Urticaria	16 (42.1)
Pruritus	3 (7.9)
Respiratory system, *n* (%)	33 (86.8)
Sensation of laryngeal obstruction	11 (28.9)
Dysphonia	2 (5.3)
Cough	5 (13.2)
Rhinorrhea/nasal congestion	6 (15.8)
Wheezing	6 (15.8)
Respiratory distress	25 (65.8)
Chest pain	2 (5.3)
Gastrointestinal system, *n* (%)	2 (5.3)
Nausea/vomiting	2 (5.3)
Cardiovascular system, *n* (%)	1 (2.6)
Hypotension	1 (2.6)
Neurological system, *n* (%)	4 (10.5)
Lipothymia	1 (2.6)
Syncope	3 (7.9)
Other symptoms, *n* (%)	9 (23.7)

[a] Patients had >1 symptom in the same system.

mon. The demographic characteristics are described in Table 1.

Skin-prick tests were performed on 15 patients (39.5%), 12 of whom (80%) were positive. The main sensitizers were *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (12/12, 100%), *Blomia tropicalis* (11/12, 91.7%), animal epithelia (dog and cat) (7/12, 58.3%), grass pollen (6/12, 50%), and molds (2/12, 16.7%).

The main organs affected in the anaphylactic reaction were the skin and respiratory system in 35 (92.1%) and 33 (86.8%) patients, respectively. The nervous system was affected in 4 (10.5%) and the gastrointestinal system in 2 (5.3%). Only 1 (2.6%) patient presented hypotension. Nine (23.7%) patients presented other symptoms (Table 2).

Regarding the combination of systems involved in the anaphylaxis, 32 (84.3%) patients presented cutaneous and respiratory involvement simultaneously, and of these, 8 (21.1%) presented the involvement of another organ. In 3 (7.8%) patients, anaphylaxis presented as cutaneous symptoms associated with the involvement of a system other than the respiratory system. In 3 other patients (7.8%), there was no cutaneous involvement, and anaphylaxis presented as follows: 1 (2.6%) with respiratory and gastrointestinal symptoms, 1 (2.6%) with neurological and respiratory symptoms, and 1 (2.9%) with anaphylactic shock.

The main NSAID involved in anaphylactic reactions was acetylsalicylic acid (ASA) in 9 (23.7%) patients, followed by dipyrone in 8 (21.1%), diclofenac in 5 (13.2%), acetaminophen in 4 (10.5%), naproxen in 3 (7.9%), ibuprofen in 2 (5.3%), and piroxicam in 1 (2.6%) (Fig. 1). In 6 (15.8%) patients, the NSAIDs involved in the reaction were not specified.

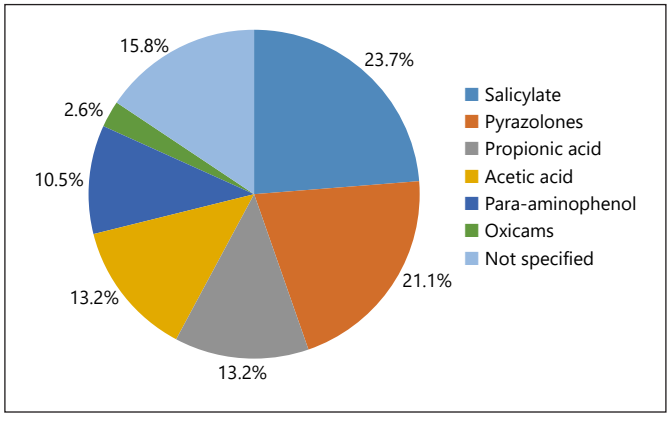

Fig. 1. Main NSAIDs involved in anaphylaxis. NSAIDs, nonsteroidal anti-inflammatory drugs.

All the anaphylactic reactions plus the acute non-anaphylactic reactions totaled 96. The analgesic most frequently involved was ASA (21/96, 21.9%), followed by ibuprofen (16/96, 16.7%), dipyrone (12/96, 12.5%), acetaminophen (11/96, 11.5%), and diclofenac (10/96, 10.4%). There were only 5 (5.2%) reactions reported with oxicams: 3 (3.1%) with meloxicam, 2 (2.1%) with piroxicam, and 3 (3.1%) with naproxen. In the clinical history of 18 (18.8%) patients, the NSAIDs involved were not specified (Fig. 2).

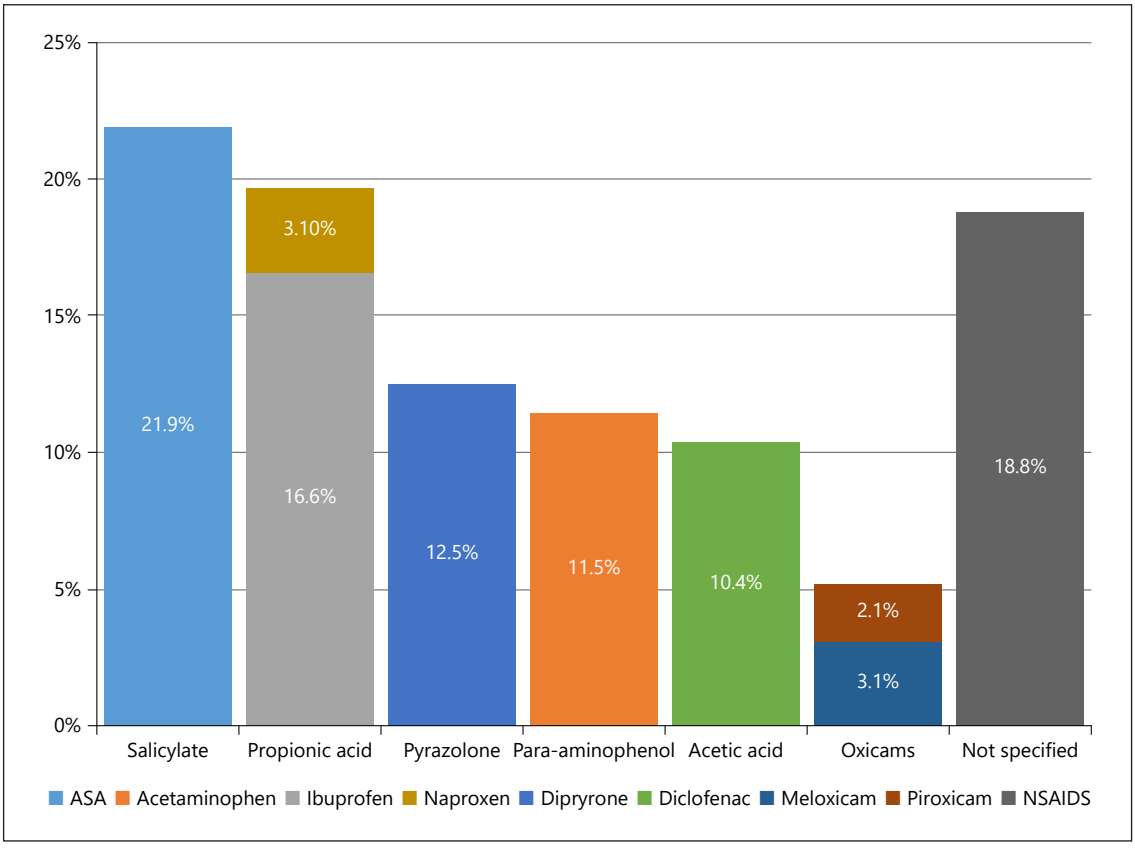

Fig. 2. Chemical groups of other implicated NSAIDs. NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 3 details the age, sex, NSAIDs involved in the anaphylaxis, organs, or systems involved in the anaphylactic reaction, and NSAIDs inducing other anaphylactic and/or acute non-anaphylactic reactions. Thirty-six (94.7%) patients underwent the oral provocation test with an alternative drug to provide treatment options for pain and/or inflammation. Of these, 35 (97.2%) tolerated selective COX-2 inhibitors. In 32 (88.9%) patients, the challenge was performed with meloxicam, and only 1 (3.1%) was positive; the rest tolerated meloxicam. Etoricoxib was administered to 3 (7.9%) patients, and all tolerated it. One patient was challenged with an opioid, which was tolerated.

Discussion/Conclusion

This study aimed to characterize patients with cross-reactions to NSAIDs who had at least 1 episode of anaphylaxis. It included 38 subjects with a mean age of 40 ± 17.7 years (range 12–74 years), indicating a predominance of adult patients; only 2 (5.3%) were children. The majority of patients were women (28 (73.7%). Allergies to medications are more frequent in women than in men, reaching a ratio of 2:1 [5, 16]. Additionally, higher consumption of NSAIDs is observed among women, as is a tendency to seek out medical care more than men [5, 15, 17].

The most frequent concomitant allergic disease was rhinitis, in 18 (47.4%) patients, followed by asthma in 8 (21.1%) and food allergy in 4 (10.5%). These 3 diseases have been described more frequently in patients who have cross-reactions to NSAIDs than in the general population [18]. In addition, a study found that when the entities NERD, NECD, and NIUA were compared with mixed anaphylactic reactions, there was a higher proportion of patients with rhinitis and asthma among those with anaphylactic reactions than among those with NIUA but a lower proportion than among those with NERD [19].

Table 3. NSAID-AN, systems involved in the anaphylactic reaction, other NSAIDs-AR, and results of the drug-provocation tests for each patient included

Patient	Age, years	Sex	NSAID-AN[a]	Systems involved in anaphylaxis	NSAIDs-AR[b]	Drug used for DPT	DPT result
1	58	M	Dipyrone	Cutaneous, respiratory, other	Ib	Mx	Neg
2	13	M	NS	Cutaneous, respiratory	NS	Mx	Neg
3	35	F	Acetaminophen	Cutaneous, respiratory, other	Dc	Mx	Neg
4	26	F	Diclofenac	Cutaneous, respiratory	Ib	Mx	Neg
5	58	F	Dipyrone	Neurological, other	ASA, Ib, NS	Mx	Neg
6	54	F	ASA	Cutaneous, respiratory	Dc	Mx	Neg
7	53	M	Naproxen	Cutaneous, neurological	NS	Mx	Neg
8	12	F	NS	Cutaneous, respiratory	Ib	Ac	Neg
9	56	F	Diclofenac	Cutaneous, respiratory	Dp	Mx	Neg
10	34	F	NS	Cutaneous, respiratory, other	ASA, Ib, Dc	Mx	Neg
11	23	F	Acetaminophen	Cutaneous, respiratory	ASA, Ib, Mx	Eb	Neg
12	19	F	Naproxen	Cutaneous, respiratory	ASA, Ib	Mx	Neg
13	74	F	Acetaminophen	Respiratory, gastrointestinal	ASA, NS	Mx	Neg
14	33	F	Ibuprofen	Cutaneous, respiratory	Ac, NS	Mx	Neg
15	66	F	Diclofenac	Cutaneous, cardiovascular, other	ASA	Mx	Neg
16	30	M	Dipyrone	Cutaneous, respiratory	Ac, Ib	Mx	Neg
17	38	F	ASA	Cutaneous, respiratory	NS	Mx	Neg
18	18	F	Dipyrone	Cutaneous, respiratory	Ac	Mx	Neg
19	44	F	ASA	Cutaneous, respiratory	Ac, NS	Mx	Neg
20	39	M	Naproxen	Cutaneous, respiratory	NS	Mx	Neg
21	34	F	NS	Cutaneous, respiratory	Ac	Mx	Neg
22	56	F	Dipyrone	Anaphylactic shock	Dc	Mx	Neg
23	74	F	ASA	Cutaneous, respiratory, neurological	Ac	Eb	Neg
24	21	F	Dipyrone	Cutaneous, respiratory	ASA, Ib	Mx	Pos
25	34	M	Diclofenac	Cutaneous, respiratory	ASA	Mx	Neg
26	18	F	Dipyrone	Cutaneous, respiratory	Mx, NS	Eb	Neg
27	51	F	Piroxicam	Cutaneous, respiratory, other	Dp	Mx	Neg
28	29	F	ASA	Cutaneous, respiratory	NS	Mx	Neg
29	74	M	ASA	Cutaneous, respiratory, other	Px	Mx	Neg
30	47	F	ASA	Cutaneous, respiratory	Ib, Dp	Mx	Neg
31	19	F	NS	Cutaneous, respiratory	NS	Mx	Neg
32	37	M	ASA	Cutaneous, respiratory, other	Ac, Ib, Dc	Mx	Neg
33	56	F	ASA	Cutaneous, respiratory, neurological	Dp	Mx	Neg
34	38	M	NS	Cutaneous, respiratory	ASA, Ib	Mx	Neg
35	57	M	Ibuprofen	Cutaneous, gastrointestinal	ASA	Mx	Neg
36	51	F	Diclofenac	Cutaneous, respiratory	Ib	NA	NA
37	20	F	Acetaminophen	Cutaneous, respiratory	NS	Mx	Neg
38	30	F	Dipyrone	Cutaneous, respiratory	ASA, Ac, Ib	NA	NA

NSAIDs, nonsteroidal anti-inflammatory drugs; NSAID-AN, NSAIDs involved in anaphylaxis; NSAID-AR, NSAIDs involved in acute reactions; ASA, acetylsalicylic acid; F, female; M, male; ASA, aspirin; Ac, acetaminophen; Dc, diclofenac; Dp, dipyrone; Eb, etoricoxib; Ib, ibuprofen; Mx, meloxicam; Px, piroxicam; DPT, drug provocartion test; Neg, negative; Pos, positive; NS, not specified. [a] NSAID-AN was the drug with which the patient initially presented anaphylaxis. [b] NSAIDs-AR were the drugs with which the patient presented another acute reaction (anaphylactic or not).

Atopy has been linked to hypersensitivity reactions to NSAIDs in several studies [12, 20, 21]. Some 60% of patients with cross-reactions have atopy [18]. The most common sensitizing allergens are dust mites, including *Blomia tropicalis*[18–20], followed by pollens [18, 19, 22]. In the present study, skin tests were performed in 15 patients (39.5%), and 80% of them showed atopy. Although dust mites were the most frequent sensitizers, which agrees with previous reports, the second-most frequent sensitizers were animal epithelia. Additionally, the ma-

Table 4. EAACI/ENDA classification [13]

Cross-reactive hypersensitivity (nonimmunological)
1. NERD
2. NECD
3. NIUA
Immunologically mediated hypersensitivity
1. Single NIUA or anaphylaxis
2. Single NSAID-induced delayed hypersensitivity reaction

NERD, NSAID-exacerbated respiratory disease; NIUA, NSAID-induced urticaria/angioedema; NECD, NSAID-exacerbated cutaneous disease; NSAIDs, nonsteroidal anti-inflammatory drugs; ENDA, European Network of Drug Allergy; EAACI, European Academy of Allergy and Clinical Immunology.

jority of atopic patients presented polysensitization (9/12, 75%), which suggests an important atopic basis in them. Patients with anaphylaxis as part of a cross-reaction to NSAIDs have a similar prevalence of atopy as patients with NIUA but higher prevalence than those with NERD.

The main clinical manifestations were cutaneous and respiratory, being simultaneous (anaphylaxis) in 32 of the patients (84.3%). In 2 previous studies, this combination was the most frequent anaphylactic reaction [15, 19]. The other patients presented other combinations of symptoms involving 2 or more organs. The frequencies of neurological, gastrointestinal, and cardiovascular symptoms were low, occurring in 4 (10.5%), 2 (5.3%), and 1 patient (2.6%), respectively. This can be explained by the pathophysiological mechanism proposed for cross-reactions, in which inhibition of the COX enzyme causes the arachidonic acid metabolic pathway to be diverted toward the lipoxygenase pathway, thus increasing the production of leukotrienes, whose properties include bronchoconstriction induction, airway inflammation, inflammatory cell recruitment, and platelet activation [6, 15]. All this generates a greater involvement of the respiratory system and the skin than of other organs. In contrast, in IgE-mediated anaphylaxis, there is release of histamine, tryptase, platelet activating factor, cytokines, etc., which produce a cascade of pro-inflammatory events and vasodilation, generating more diverse and severe cardiovascular symptoms and forms of anaphylaxis [15].

In the present study, the NSAIDs most frequently involved in anaphylactic reactions were ASA, dipyrone, naproxen, diclofenac, and acetaminophen, similar to what was found in other studies [15, 18, 19]. When evaluating the 96 acute reactions (anaphylactic and non-anaphylactic) presented by patients, ASA was again the most frequent inducer, in 21 (21.9%) patients, followed by ibuprofen in 16 (16.6%), dipyrone in 12 (12.5%), acetaminophen in 11 (11.5%), and diclofenac in 10 (10.4%). Ibuprofen's ranking of second, above dipyrone and naproxen, suggests that reactions to ibuprofen are more frequent, but those caused by dipyrone and naproxen are more severe. In turn, the presence of acetaminophen among the NSAIDs involved in anaphylaxis, even surpassing diclofenac, is curious because it is considered a weak inhibitor of the COX-1 enzyme. This finding echoes that of another case series in which a higher proportion of reactions to acetaminophen was observed in the cross-reactions that included anaphylaxis than in NERD [19].

On the other hand, the latest classification of hypersensitivity reactions to NSAIDs proposes 2 groups according to the number of NSAIDs that cause the reactions, the chemical group to which they belong, and the pathophysiological mechanisms by which they occur [14] (Table 4). In the present study, patients with a clinical feature characterized by the involvement of 2 or more organs after the ingestion of NSAIDs of different chemical groups were included. This type of reaction is classified as mixed in other studies [18, 19, 22], but considering the anaphylaxis criteria, these reactions should be classified as "cross-reactive anaphylaxis to NSAIDs" [15, 23, 24]. However, this phenotype is not included in the EAACI classification, and it is not possible to include it in the others since it does not meet the criteria.

Some 60–76% of all reactions to NSAIDs are cross-reactions [2, 3, 23], while selective reactions account for 23.7% [5, 18]. Of the entities that make up the cross-reactivity group, NIUA is the most frequent (55–60% of cases). In studies that have evaluated the prevalence of anaphylactic reactions as part of cross-reactivity, this prevalence is 19–28% [3, 18, 19], being more frequent than NERD. Additionally, patients who develop anaphylactic reactions to several NSAIDs of different chemical groups share similar characteristics with patients with the other entities, such as the rate of atopy with NIUA patients and the rate of rhinitis with NERD patients [19]. It is not yet clear whether these reactions are part of a spectrum of NERD/NIUA or if they make up a different phenotype [19, 22, 25]. What is clear is that it is important to differentiate it from a selective anaphylactic reaction because the approach is different. It is also clear that cross-hypersensitivity reactions to NSAIDs can present as anaphylaxis, which has been demonstrated in several case series [15, 18, 19], including the present one.

Finally, the main limitation of the study was the nonperformance of an oral challenge with aspirin to confirm

cross-reactivity in all patients, as suggested by Perez-Alzate et al. [26]. However, most patients (20 of 38–52.6%) had presented a reaction with aspirin. In this sense, Zisa et al. [27] and Waton et al. [28], performed drug provocation tests in patients with cutaneous reactions (angioedema/urticaria and others). As has been previously mentioned, the diagnostic approach of a patient who have had non-anaphylactic reactions is an oral provocation test due to the low risk of presenting a severe reaction compared to the patients who have had an anaphylactic or severe cutaneous reaction. As the main clinical presentation of the patients in this study was anaphylaxis to 1 or more NSAIDs which generates a high risk of a new serious reaction after oral challenge with aspirin given its high inhibitory potency of COX enzymes [29], it was considered prudent not to do it. In fact, the history of anaphylactic reaction constitutes a contraindication to carry out a challenge with drugs that can potentially induce a new reaction [30, 31]. Even more, Chaudhry et al. [32] found by logistic regression that anaphylaxis history, as an index case, was a predictor of positivity for the oral challenge test.

In conclusion, the present study showed that cross-reactive anaphylaxis to NSAIDs was more frequent in women, ASA and dipyrone were the main triggers, rhinitis was the main allergic comorbidity, and there was a high incidence of atopy. The majority of patients tolerated COX-2 selective NSAIDs.

Acknowledgement

We thank the Clinical Research Center of Fundación Valle del Lili by methodological and statistical advice and translation of the manuscript.

Statement of Ethics

This study was approved by the ethics committee in biomedical research IRB/EC of Fundación Valle del Lili. Approval Number 170-2019. The participants or parents/guardians signed an informed consent.

Conflict of Interest Statement

All authors disclose no conflicts of interest.

Funding Sources

The authors did not receive any funding.

Author Contributions

Laura del Mar Vásquez collected and analyzed the data and drafted the manuscript. Carlos Daniel Serrano had the idea of the study and revised and corrected the manuscript. Diana Lucia Silva, Luis Fernando Ramirez, and Manuela Olaya contributed to the drafting and approval of the final manuscript.

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