

Original study

## Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs: does age matter?

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### Abstract

**Background:** Nonsteroidal anti-inflammatory drugs (NSAIDs) are reported to be the leading cause of drug hypersensitivity reactions. The aim of this study was to characterize a cohort of patients with NSAID hypersensitivity and establish if there are any differences between two groups of adult patients, under 55 years old and over 55 years old, and identify safe alternative options. **Methods:** Patients with NSAID hypersensitivity who were referred to a single tertiary Allergy center from January 2019 to December 2021 were included. Clinical information was obtained from a review of medical records. **Results:** A total of 135 patients with a history of NSAID-induced hypersensitivity reactions were included, 80 patients under 55 years old and 55 patients older than 55. Most of the patients enrolled were female (80.74%) and the mean age was 50.21 years, ranging from 18 to 78 years old. The time interval between the first reaction and the allergy work-up was longer in the older group (average timeframe 6.87 years) than in the younger group (average timeframe 3.77 years). The main culprit was metamizole in both groups. An oral provocation test to paracetamol was performed in most of the patients who tolerated the intake of 1000 mg, except for 2 patients who developed angioedema. **Conclusion:** Angioedema was the most encountered symptom in our population. Age does not influence the allergy work-up of patients with a history of NSAID-induced hypersensitivity reactions. The drug provocation challenge remains the gold standard for finding a suitable alternative in patients with NSAID-induced hypersensitivity.

**Keywords:** NSAID hypersensitivity; drug allergy; oral provocation test; metamizole hypersensitivity

### Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used, having analgesic, antipyretic, and anti-inflammatory properties.

They are reported to be the leading cause of drug hypersensitivity reactions (DHRs), due to their increasing usage over time. There are few analgesic and antipyretic therapeutic choices once hypersensitivity is suspected [1]. NSAIDs cause a wide range of hypersensitivity reactions in susceptible individuals, with differing timing, organ manifestations, and severity, involving either immunological (allergic) or nonimmunological mechanisms [2]. The main mechanism of action of NSAIDs is the inhibition of cyclooxygenase (COX-1 and COX-2), which results in a reduction of

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prostaglandins and an increase in leukotrienes [3]. The dysregulation of this balance may induce symptoms and signs of hypersensitivity reactions. COX-1 inhibition seems to be the

cause of adverse events. NSAIDs have been classified based on their mode of action and chemical structure, as depicted in Table I [2,4].

**Table I.** Classification of NSAIDs available in Romania (Kowalsky et al. [2] and Sanchez-Borges et al. [4]).

Selectivity	Chemical group	Drug
COX-1 and COX-2 inhibitor	Salicylic acid derivates	Aspirin (acetylsalicylic acid) Sulfasalazine
	Propionic acid derivates	Ibuprofen Naproxen Flurbiprofen Ketoprofen Dexketoprofen
	Acetic acid derivatives	Diclofenac Ketorolac Indomethacin
	Enolic acid derivatives	Metamizole Phenylbutazone Aminophenazone
	Oxicams	Piroxicam Tenoxicam Lornoxicam
Weak COX-1 inhibitors	Para-aminophenol	Acetaminophen (paracetamol)
Preferential COX-2 inhibitor	Sulfonanilide	Nimesulide
	Oxicams	Meloxicam
	Phenylacetic acid derivative	Aceclofenac
Selective COX-2 inhibitor	Coxibs	Celecoxib
		Etoricoxib
		Parecoxib

NSAID-induced DHRs are classified as immediate if they occur within 6 hours of drug administration, and delayed if they occur more than 6 hours after drug intake. The latter are single-NSAID induced. In immediate reactions, a single NSAID may elicit hypersensitivity reactions or there may be cross-reactivity between different NSAIDs. Single NSAID-induced urticaria, angioedema, or anaphylaxis is IgE-mediated and hypersensitivity is restricted to one representative or to a chemically related group. Cross-reactivity occurs in NSAID-exacerbated respiratory disease, NSAID-exacerbated chronic urticaria, and in the case of NSAID-induced urticaria/angioedema, although blended reactions have been described [2]. Until now,

there are few diagnostic tools and if NSAID hypersensitivity is diagnosed, finding an alternative analgesic and antipyretic drug is of utmost importance. The oral provocation test (OPT) remains the gold standard for the diagnosis and also for finding safe alternatives.

NSAIDs are the most frequently used agents to treat rheumatologic disorders, particularly among the elderly, thus raising problems in this age group when DHRs occur [5].

The aim of this study was to characterize a cohort of patients with NSAID hypersensitivity and establish if there are any differences between two groups of adult patients, under



55 years old and over 55 years old, and identify safe alternative options.

## Materials and Methods

### Selection of patients

This study was conducted over a period of 3 years (from January 2019 to December 2021) and included patients who were referred to our tertiary care allergy department with a suggestive clinical history of NSAID hypersensitivity reaction.

Patients were included in the study if there was a suggestive clinical history of NSAID hypersensitivity or after a positive oral provocation test with the suspected drug. The occurrence of the reaction within 6 hours after the intake of a single drug, which was precisely recalled by the patient or noted by a doctor, or if two or more reactions to the same or different NSAIDs taken at different times were described, were considered suggestive clinical histories [6,7].

We classified the reactions as immediate if the symptoms occurred under 6 hours after the drug intake and delayed if more than 6 hours passed after the drug intake [2]. The data of the patients were recorded using the ENDA questionnaire [8]. Patients diagnosed with chronic urticaria or with aspirin-exacerbated respiratory disease were not included. All patients signed the informed consent at the admittance to the hospital. The study was approved by the local ethics committee and institutional review board.

Data collected referred to: age, sex, personal history of asthma, allergic rhinitis, and reported hypersensitivity to NSAIDs. According to the clinical history, the allergy work-up included atopy assessment, skin tests to the NSAIDs involved, and OPT with the drug or other possible safe alternatives. For immediate reactions skin prick tests and intradermal with immediate readings were performed; for delayed reactions, intradermal tests with late readings and patch tests were used. Each patient was assessed for the presence of atopy, defined by at least one positive skin prick test to a common aeroallergen, elevated total IgE (>100 Ku/l).

We evaluated the relationship between sensitization to house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*) or to pollens (*Betulaceae*, *Gramineae*, *Ambrosia elatior*, *Artemisia vulgaris*) and the occurrence of urticaria, angioedema or anaphylaxis. When only one drug was suspected and the history was compatible with an IgE-mediated reaction, skin tests for the drug involved and alternative options were performed. The drugs tested were metamizole, paracetamol, ketoprofen and meloxicam. The concentrations used were according to ENDA recommendations [9], except for metamizole where the maximum non-irritative concentrations were 400 mg/dl for prick test and 40 mg/dl for intradermal test [10]. To investigate the delayed reactions, we also performed patch tests to acetylsalicylic acid, paracetamol, diclofenac, and piroxicam using the Chemotechnique Diagnostics haptens.

To provide safe alternatives, oral provocation testing was performed. The patients were monitored closely during the OPT and 24 hours after. Escalating doses of NSAIDs were orally administered at 30 minutes intervals. The following substances were tested: paracetamol, nimesulide, meloxicam, celecoxib, and etoricoxib. The choice of drug tested depended on the history of the patients and their needs. Not every patient received all the drugs tested. Throughout the study duration, no relevant modifications were made to the allergy work-up procedure.

### Statistical analysis

The data was processed using the R statistical software, version 4.2.0 (R Core Team, 2022) for Windows. A  $p$ -value of <0.05 was considered statistically significant [11].

### Results

During the study period, a total of 135 patients with a history of NSAID-induced DHR were evaluated in our department, 80 patients under 55 years old and 55 patients older than 55. The characteristics of the patients are shown in Table II. Most of the patients enrolled were female (80.74%) and the mean age was 50.21 years, ranging from 18 to 78 years old.



One of the variables studied was the time interval between the first DHR and the allergy work-up.

There was a statistical difference between the two age groups regarding this variable. The time interval between the first DHR and the allergy work-up was longer in the older group (average timeframe 6.87 years) than in

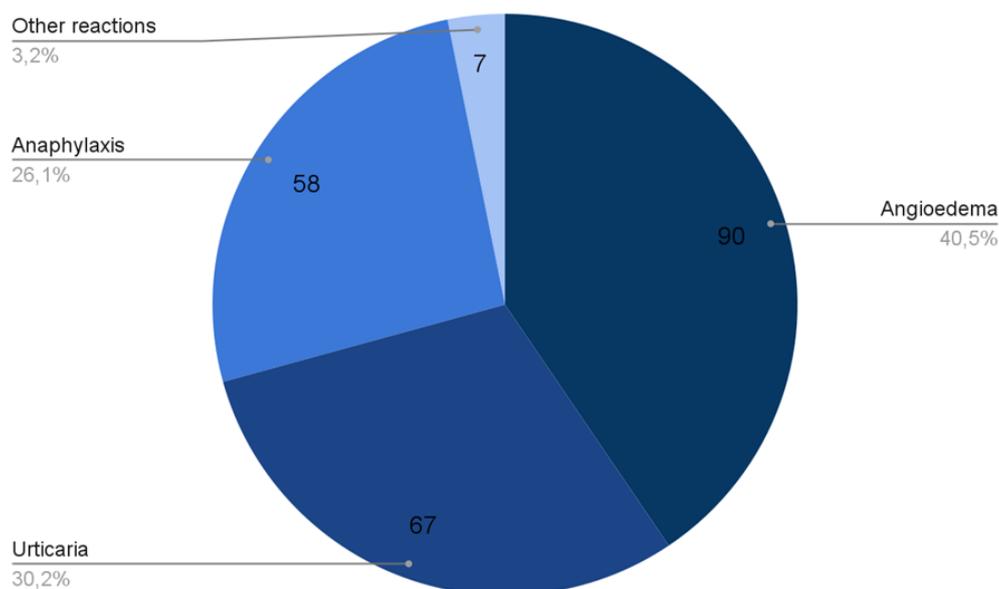
the younger group (average timeframe 3.77 years), ( $p=0.0429$ ). We did not find any significant differences regarding the number of adverse events, most of the patients reported one episode of DHR, although 4 patients in the first group and 6 in the second one reported 4 or more DHRs.

**Table II.** Characteristics of the studied patients diagnosed with NSAID hypersensitivity.

Characteristic	Total (N=135)	< 55 years old (N=80)	≥55 years old (N=55)
Female	109 (80.74%)	66 (82.5%)	43 (81.13%)
Co-morbidities:			
- Allergic rhinitis	25 (18.51%)	16 (20%)	9 (16.36%)
- Asthma	10 (7.4%)	3 (3.75%)	7 (12.72%)
- Cardio-vascular disease	41 (30.37%)	10 (7.4%)	31 (58.49%)
- Rheumatologic disease	29 (21.48%)	12 (15%)	17 (30.9%)
Atopy			
- Sensitization to house dust mites	23 (17.03%)	14 (17.5%)	9 (16.36%)
- Sensitization to pollens	22 (16.29%)	14 (17.5%)	8 (14.54%)
- Total IgE > 100 KU/l	9 (6.66%)	4 (5%)	5 (9.09%)
Time from first reaction to allergy work-up (years)	5 (0.1-31)	3.77 (0.1 - 25)	6.87 (0.1-31)
Hypersensitivity to 2 or more chemically unrelated NSAIDs	59 (43.7%)	37 (46.25%)	22 (40%)

According to the time of onset, most of the DHRs reported by the patients were immediate (94 patients, 69.63%), while 17 patients (12.59%) reported delayed reactions. 24 patients (17.78%) could not recall the time passed between the drug intake and the occurrence of the symptoms. Angioedema was the most reported symptom, followed by

urticaria and anaphylaxis. Maculopapular exanthema was reported by 5 patients, fixed drug eruption was diagnosed in 1 patient and there was a case of Stevens-Johnson syndrome. The incidence of the most frequent symptoms or types of reactions is depicted in Figure 1.



**Fig. 1.** The frequencies of the reported NSAID-induced hypersensitivity reactions. Other reactions include: maculopapular exanthema (5 patients), fixed drug eruption (1 patient), and Stevens-Johnson syndrome (1 patient).

We evaluated the relationship between atopy and the occurrence of urticaria, angioedema, or anaphylaxis. There was no statistically significant dependence between the sensitization to house dust mites ( $p = 0.6193$ ) or pollens ( $p=0.8453$ ) and urticaria, nor between angioedema and sensitization to house dust mites ( $p = 0.571$ ) or pollens ( $p=0.9343$ ).

The drugs most frequently involved in the whole group and in the younger group were metamizole, ibuprofen, and paracetamol.

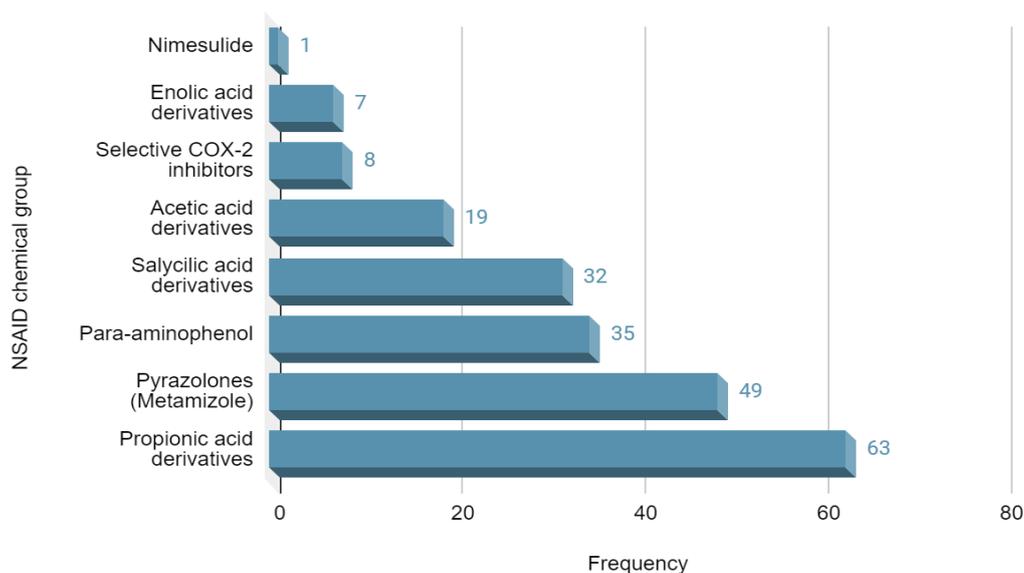
Metamizole, acetylsalicylic acid, and diclofenac were more frequently held responsible by patients over the age of 55.

Diclofenac was the third most common culprit for the elderly group ( $p=0.001189$ ) and ibuprofen was the second most frequent offender for the younger group ( $p=0.03801$ ), with a statistically significant difference between the two groups for both drugs. The frequency of each elicitor is shown in Table III. Figure 2 depicts the incidence of each chemical NSAID group involved in the DHR.

**Table III.** Frequencies of each NSAID as reported by the patients.

Culprit drug	N (%)	< 55 years old	≥ 55 years old	Chi-squared test (p-value)
Metamizole	49 (36.3%)	26 (29.36%)	23 (17.04%)	0.2686
Ibuprofen	43 (31.85%)	31 (22.96%)	12 (8.89%)	0.03801
Paracetamol	35 (25.93%)	25 (18.52%)	10 (7.4%)	0.08867
Acetylsalicylic acid	31 (23%)	17 (12.6%)	14 (10.37%)	0.5682
Ketoprofen	17 (12.6%)	11 (8.15%)	6 (4.44%)	0.6249
				<b>Chi-squared test with Yates' continuity correction (p-value)</b>
Diclofenac	16 (11.85%)	3 (2.22%)	13 (9.63%)	0.001189
Naproxen	6 (4.4%)	5 (3.7%)	1 (0.74%)	0.4221
Etoricoxib	5 (3.7%)	3 (2.22%)	2 (1.48%)	1.000

Indomethacin	5 (3.7%)	2 (1.48%)	3 (2.22%)	0.6676
Piroxicam	4 (2.96%)	2 (1.48%)	2 (1.48%)	1.000
Celecoxib	3 (2.22%)	1 (0.74%)	2 (1.48%)	0.7413
Dexketoprofen	3 (2.22%)	2 (1.48%)	1 (0.74%)	1.000
Aminophenazone	2 (1.48%)	0	2 (1.48%)	0.3205
Sulfasalazine	2 (1.48%)	2 (1.48%)	0	0.6481
Flurbiprofen	1 (0.74%)	1 (0.74%)	0	1.000
Meloxicam	1 (0.74%)	1 (0.74%)	0	1.000
Tenoxicam	1 (0.74%)	1 (0.74%)	0	1.000
Nimesulid	1 (0.74%)	0	1 (0.74%)	0.85



**Fig. 2.** Frequencies of NSAID induced-DHRs according to the chemical group.

A total of 40 patients were skin-tested to paracetamol (both skin prick and intradermal tests). All the tests were negative. Fifty-one patients were tested to metamizole. One patient had a positive skin prick test and in 13 cases (25%) the intradermal test to metamizole was positive. Two patients had a positive intradermal test to ketoprofen, in the absence of mono-sensitization to ketoprofen.

All patch tests were negative. In one of the patients, the metamizole intradermal skin test was positive at delayed reading (24 hours). She had a history of maculopapular exanthema (symmetrical drug-related intertriginous and flexural exanthema, SDRIFE) in the context of many drugs administration in the post-operative setting. Other 5 patients with positive skin tests to

metamizole had only IgE-mediated sensitization to metamizole, being able to tolerate other NSAIDs, but the other 7 had also reacted to other NSAIDs.

To provide safe alternatives, we performed drug provocation tests. A total of 210 drug provocation tests were performed. Paracetamol was the drug most commonly tested. It was tolerated in a total dose of 1000 mg by 86 patients, 2 reacted during the drug provocation test, developing angioedema.

Patients who had a clear history of DHR induced by paracetamol or who had tolerated it since the NSAID-induced reaction were not subjected to the paracetamol challenge. The drug provocation tests performed are summarized in Table IV.

**Table IV.** Drug provocation tests performed and tolerance to alternative drugs.

Alternative drug/ total dose administered	Well-tolerated	Reaction	Not performed
Paracetamol 1000 mg	86	2	47
Nimesulid 200 mg	39	1	95
Celecoxib 200 mg	48	1	86
Etoricoxib 60 mg	16	1	118

Of the 35 patients who reported a reaction also to paracetamol, 22 surpassed the OPT to 1000 mg of the drug, and only 13 patients remained with the diagnosis of paracetamol-induced DHR.

Special consideration was made to patients with a history of hypersensitivity reactions induced by coxibs and preferential COX2-inhibitor nimesulide. Of the 5 patients who reacted to etoricoxib, one tolerated celecoxib, 4 tolerated paracetamol and 1 tolerated also meloxicam. All the 3 patients with a history of celecoxib-induced DHR tolerated paracetamol. One of them surpassed the OPT to nimesulide, and one to meloxicam and etoricoxib. The patient with a history of nimesulide-induced angioedema tolerated paracetamol.

## Discussions

In this study, we evaluated 135 patients, of which 80% were female, a percentage higher than in other studies. [12, 13]. Although in other studies [14] atopy was more frequently encountered among patients with NSAID-induced DHR, in our cohort only 1 in 7 patients had a positive skin test to house dust mites or pollens. Also, we could not find any association between atopy as defined by sensitization to either house dust mites, pollens, or high total IgE value and the occurrence of urticaria or angioedema.

The age of the patients made a difference regarding the time interval between the onset of the first hypersensitivity reaction and the allergy work-up; patients older than 55 waited longer before seeking medical advice.

The types of the reactions were similar to other studies, with angioedema and urticaria being the most frequently reported symptoms.

Yuenyongviwat et al. [12] also reported high percentages of angioedema as a clinical symptom that arose following NSAID intake. A total of 59 (43.7%) patients reported symptoms to 2 or more chemically unrelated drugs. This is in accordance with the data delivered by Demir et al. [14], who reported a cross-reactivity of 50.3% in a cohort of patients with NSAID-induced hypersensitivity reactions, and by Angeletti et al. [13] whose group reported a 60.6% of patients who developed symptoms to more than one NSAID. In another study [12], only about a quarter of the patients reported the same reactions.

Metamizole was the most common drug reported in both groups. This might be also because of its high usage in our country, given it is available over the counter and may be administered both orally and parenterally [15]. The difference with other studies [12, 13] might be because it is no longer available in many countries in Europe and the USA. Acetylsalicylic acid was the second most frequently reported NSAID that caused hypersensitivity reactions. The difference in the two groups was made by the second and third elicitor, in the younger group ibuprofen and paracetamol were reported more frequently, while in the elderly group acetylsalicylic acid and diclofenac were more often reported.

In patients with a positive history of paracetamol-induced hypersensitivity reactions, we performed skin tests that were negative. This is in accordance with the studies published by Sipahi Cimen et al. who reported only one positive skin test to paracetamol, but the patient tolerated the OPT with paracetamol [16]. The negative skin tests to paracetamol suggest that the mechanisms that underlie acetaminophen hypersensitivity are not IgE-mediated.



The positive intradermal test with late reading to metamizole may be further evidence of the intradermal test's (with late reading) diagnostic value in the diagnosis of SDRIFE. The percentage of positive skin tests to metamizole is in accordance with other published literature [10].

The mono-sensitization to metamizole in the five patients and their tolerance to other NSAIDs support the IgE-mediated mechanism of metamizole-induced DHR. The blended nature of the NSAID-induced hypersensitivity reactions, as previously documented, may be the reason why the other 7 patients also described reactions to additional NSAIDs [17].

Currently, there is a lot of evidence supporting the tolerance of paracetamol in patients with hypersensitivity to non-selective COX inhibitors [17, 18]. Nonetheless, the guidelines recommend OPT as the gold standard for diagnosis and prove the tolerability of alternatives [2]. In our study, only 2 of the patients who were challenged with paracetamol reacted and the pattern was similar to the previously described reactions.

Regarding coxibs-sensitized patients, there is little evidence about the tolerance of other NSAIDs. Our study proved the tolerance of celecoxib in one patient with etoricoxib-induced DHR and the tolerance of paracetamol in another 4. No conclusions can be drawn due to the small number of cases. Additional research is required to determine the connection between selective COX-2 inhibitors and partially selective or non-selective NSAIDs.

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## Conclusions

Angioedema was the most encountered symptom in our population. Metamizole was the most frequently reported NSAID culprit in DHRs in Romania. The clinical manifestations of the reactions are not linked to atopy. Age does not influence the allergy work-up of patients with a history of NSAID-induced hypersensitivity reactions. The drug provocation challenge remains the gold standard for finding a suitable alternative in patients with NSAID-induced hypersensitivity.

## Author Contributions

Conceptualization, S.A. and L.S.; investigation and resources, S.A., R.B, S.L.C., I.A.P and R.U.; writing—original draft preparation, S.A., R.U., R.B. and S.L.C.; writing—review and editing, S.A., S.L.C. and L.S.; statistical analysis, I.A.P; supervision, S.A. and L.S. All authors have read and agreed to the published version of the manuscript.

## Competing interests

The authors of the present study declare that none of the authors have any conflict of interest.

## Consent for publication

A written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy and all of the authors declare that confidentiality of the patient was respected.

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