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Single NSAID hypersensitivity is associated with atopic status

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Key words

Drug allergy; NSAID hypersensitivity; oral provocation testing; urticaria

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Summary

Background: *The relationship between hypersensitivity to NSAID and atopic status is still incompletely defined. Previous studies found a high prevalence of atopic diseases in multiple NSAID reactors. The present study aimed to investigate whether this is the case also in Italian adults hypersensitive to NSAIDs.* ***Methods:*** *Skin tests with a large panel of seasonal and perennial airborne allergens were carried out in 252 patients with a clear-cut history of acute urticaria induced by nonsteroidal anti-inflammatory drugs. Patients were classified as single or multiple NSAID reactors based on clinical history, presence/absence of chronic urticaria, re-challenge with the reported offending drug in case of doubt history, and oral challenges with aspirin or propionic acid derivatives.* ***Results:*** *Single NSAID reactors showed a much higher prevalence of atopic diseases than multiple NSAID reactors either with or without chronic urticaria (61% vs 19% and 19%, respectively; $p < 0.001$).* ***Conclusion:*** *As a difference from previous reports, in Italian patients hypersensitive to NSAID atopy is much more prevalent among single reactors, a finding that indirectly supports the possible IgE-mediated origin of this type of adverse drug reaction.*

Introduction

Non-steroidal anti-inflammatory drugs (NSAID) are the most frequent causes of hypersensitivity adverse drug reactions (1). Hypersensitivity reactions to NSAID have undergone several classifications over the years; the most recent of these (2) identifies five categories: a. NSAID-exacerbated rhinitis/asthma (also called NERD; NSAIDs exacerbated respiratory disease [3]); b. NSAID-exacerbated chronic urticaria (NECD; NSAIDs exacerbated cutaneous disease); c. Multiple NSAID-induced urticaria (NIUA; NSAIDs-induced urticaria-angioedema); d. Urticaria/angioedema or anaphylaxis induced by one single NSAID class (SNIUAA; single NSAID induced urticaria-angioedema or anaphylaxis); and e. Selective delayed-type hypersensitivity reaction (SNIRD; single NSAID-induced delayed hypersensitivity reaction). The first three phenotypes of adverse reactions are considered as non-immunologically-mediated, and are characterized by cross-reactivity between chemically unrelated NSAIDs. It is generally believed that in these adverse reactions the pathogenesis involves COX-1, as suggested by the fact that cross-reactions occur among COX-1 inhibiting drugs and by the reported protective effect exerted by leukotriene receptor antagonists. In fact, previous studies showed the existence of common eicosanoid alterations in aspirin reactors with underlying urticaria and asthma (4).

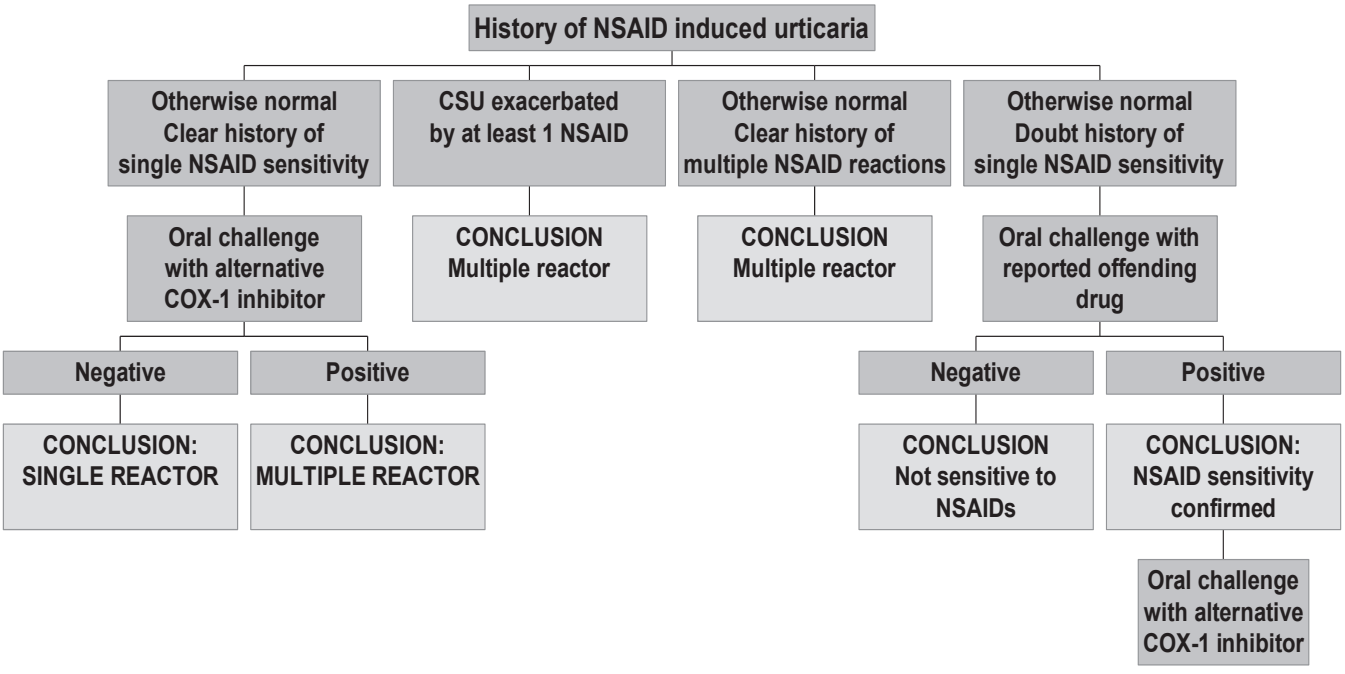
The relationships between atopic status and NSAID hypersensitivity are still incompletely defined. There have been several reports of an association between these two conditions in the past (5-7). Some studies found an association with hypersensitivity to specific airborne allergens, such as house dust mites, particularly in patients with multiple NSAID hypersensitivity without underlying chronic urticaria (1,8), but the association has been reported for other types of NSAID-induced hypersensitivity reactions as well (9). One study found that atopy represents a risk

factor for intolerance to substances, such as acetaminophen and nimesulide, which are generally well tolerated by NSAID hypersensitive subjects (10). Recently, NSAID hypersensitivity has been suspected to act as a co-factor in patients with food allergy caused by sensitization to the pan-allergen lipid transfer protein (10,11). The present study investigated the atopic status in a group of patients with cutaneous hypersensitivity to NSAID classified according to the criteria described above.

Patients and methods

Two-hundred-fifty-two subjects with a clear-cut history of acute urticaria with or without angioedema following the ingestion of NSAID, who were addressed at the Allergy Department of the Clinica San Carlo during the last 6 years, were studied. A clinical history was considered unequivocal if acute urticaria/angioedema followed by less than 2 hours the administration of a NSAID. Most adverse reactions were seen and recorded by doctors in Emergency Services or by the family doctors at patients' homes; patients frequently showed pictures taken by themselves showing the acute phases of their adverse reactions.
The diagnostic workup followed the one recently recommended by expert panel consensus papers and research articles. Briefly, patients with a history of chronic spontaneous urticaria exacerbated by NSAID were considered as multiple NSAID reactors even in the presence of a clinical history of single NSAID reactivity (13-16). Patients without a history of underlying chronic spontaneous urticaria, were diagnosed as having multiple NSAID hypersensitivity if they experienced multiple distinct episodes of acute urticaria occurring within 2 hours after the ingestion of two or more chemically distinct NSAIDs (13,17). Otherwise normal patients with a clear-cut history of acute urticaria following the ingestion of one single NSAID, were classified as single or multiple NSAID reactors based on oral open challenges with a therapeutic dose of a different COX-1 inhibitor. Aspirin was challenged in case of hypersensitivity to any NSAID other than ASA, and Ketoprofen was challenged in case of aspirin intolerance (13,18-20). Those who reacted to the alternative drug within 2 hours after the administration, were classified as multiple reactors; those who tolerated the alternative drug were eventually classified as single NSAID reactors. Four patients with a more doubtful history of hypersensitivity to one single NSAID (aspirin in 2 cases, ketoprofen in one case, and diclofenac in one case) were re-challenged with the offending drug in order to confirm their reactivity (21) before undergoing challenges with an alternative COX-1 inhibitor. Their hypersensitivity to the reportedly offending drug was confirmed in all 4 cases.
Oral challenges were carried out giving increasing doses of the drug under investigation one hour apart as previously described (19,20). Only the occurrence of unequivocal urticaria was considered as a positive response. For ethical reasons, in view of the potential risk of extremely severe reactions, patients with a

Figure 1 *- Diagnostic workup in patients intolerant to NSAID.*



clear-cut history of hypersensitivity to one single NSAID did not undergo oral confirmative challenges with the original offending drug (17,22) but underwent directly the challenge with either ASA or ketoprofen. The whole diagnostic algorithm is depicted in **figure 1**.

Patients gave an informed written consent before the start of the oral challenge procedures. Since this study is a report of one investigator's routine clinical practice no formal Ethical Committee approval was required. The study was approved by the Local Institutional Review Board.

Patients underwent skin prick tests (SPT) with a large panel of commercial extracts of seasonal and perennial airborne allergens (Allergopharma, Reinbeck, Germany), including grass, mugwort, ragweed, pellitory, plantain, birch, plane, olive and cypress pollen, as well as Alternaria, house dust mite, and dog & cat dander. In case of a negative result and of an unequivocal history of food allergy, patients underwent SPT with a panel of commercial food allergens (ALK-Abellò, Madrid, Spain) as well. Skin tests were carried out following established criteria using disposable 1 mm tip lancets, and were read at 15 min. Wheals exceeding 3 mm in their mean diameter were considered positive.

Proportions were compared by chi-square test with Yates' correction. Probability values less than 5% were considered statistically significant.

Results

A total of 99 oral challenges with alternative NSAIDs were carried out in subjects presenting with a history of single NSAID hypersensitivity in order to classify study participants. Eighty-nine challenges were carried out with aspirin in subjects with a clinical history of hypersensitivity to a single NSAID other than aspirin. In subjects with a history of hypersensitivity to aspirin only, challenges were carried out with ketoprofen (n = 10). Eighty-two subjects (M/F ratio 21/61; mean age 44.9 years, range 15-80 years) were eventually classified as single NSAID reactors (SNIUAA). Fifty-four (M/F 15/39; mean age 48.9 years, range 17-80) were diagnosed as having multiple NSAID hypersensitivity without underlying chronic spontaneous urticaria (NIUA); and 116 (M/F 25/91; mean age 47.9 years, range 10-79 years) were classified as having chronic spontaneous urticaria exacerbated by NSAIDs (NECD). The clinical features of study patients are shown in **table 1**. The 3 subgroups did not differ in terms of mean age and sex distribution. A marked female prevalence was present in all three subsets. The prevalence of atopy among the three subgroups was 61% (50/82) among single NSAID reactors, 19% (10/54) among multiple NSAID reactors without spontaneous urticaria, and 19% (22/116) among chronic urticaria patients. The statistical analysis showed that the prevalence of atopy among single NSAID reactors was significantly superior to that detected in the two other subgroups ($p < 0.001$). **Table 2** shows the offending NSAIDs in single drug reactors. Pyrazolones and propionic acid derivatives were by far the most frequent drug families involved in single NSAID reactions. Aryl acetic acid derivatives as well as aspirin were also well represented. Interestingly, a significant proportion of single drug reactions was associated with two drugs that have been long been used as alternative compounds in multiple NSAID reactors with and without underlying chronic urticaria, namely paracetamol and nimesulide. With the exception of the 2 patients hypersensitive to oxicams, all subsets of SNIUAA patients showed a prevalence of atopy that was more elevated than the one found in multiple reactors either with or without chronic spontaneous urticaria. Surprisingly enough, all 7 aspirin single reactors were atopic. The pattern of sensitization to airborne allergens in single NSAID reactors is shown in **table 3**. It largely mirrored the situation observed in the general population living in this geographic area. No statistically significant association between specific allergens and specific offending drugs was found. Six patients were found to have food allergy (not shown in table); 5 were sensitized to lipid transfer protein and 1 had peanut allergy.

Table 1 *- Comparison between the 3 subgroups of NSAID hypersensitive patients.*

	SNIUAA	NIUA	NECD	p
No.	82	54	116	
Mean age (range)	44.9 (15-80)	48.9 (17-80)	47.9 (10-79)	NS
M/F	21/61	15/39	25/91	NS
No. Atopic (%)	50 (61%)	10 (19%)	22 (19%)	P < 0,001

Table 2 *- Offending NSAIDs and atopic status in 82 single NSAID reactors.*

	No.	Atopic (%)
Propionic acid derivatives (Ibuprofen, Naproxen, Flurbiprofen, Ketoprofen)	16	12 (75%)
Aryl-acetic acid derivatives (Diclofenac, Ketorolac)	9	4 (44%)
Pyrazolones (Aminopyrine, Feprazone, Aminophenazone, etc)	27	18 (67%)
Oxicams	2	0 (0%)
Nimesulide	8	4 (50%)
Paracetamol	13	5 (38%)
Aspirin	7	7 (100%)

Table 3 *- Pattern of sensitization to airborne allergens among 50 atopic single NSAID reactors.*

	Grass	Mugwort	Ragweed	Pellitory	Plantain	Birch	Olive	Cypress	Mite	Cat	Alternaria
Total	30 (60%)	5 (10%)	32 (64%)	5 (10%)	6 (12%)	13 (26%)	8 (16%)	5 (10%)	11 (22%)	9 (18%)	1 (2%)
PAD	6	1	6	0	1	5	1	0	4	3	0
AAA	3	0	2	0	1	0	0	0	1	1	0
Pyr	10	1	12	2	3	5	4	4	4	2	0
Nim	3	1	4	1	0	1	1	1	0	0	0
Paracet	3	1	4	0	1	0	0	0	2	2	0
ASA	5	1	4	2	0	2	2	0	0	1	1

PAD: propionic acid derivatives; AAA: aryl acetic acid derivatives; Pyr: Pyrazolones; Nim: Nimesulide; Paracet: paracetamol; ASA: Aspirin.
15 patients were monosensitized to airborne allergens. Polisensitization to pollen (i.e., sensitization to > 3 seasonal allergen sources) was detected in 8 cases, all of which showed profilin sensitization.
No statistically significant association between specific allergens and specific offending drugs was found.

Discussion

Several groups reported an association between atopy and hypersensitivity to nonsteroidal anti-inflammatory drugs. Sanchez-Borges et al. found an impressively high prevalence of atopic diseases among patients with challenge-proven NSAID hypersensitivity; in most cases, these subjects were multiple NSAID reactors (5). In their study, Quiralte and co-workers noticed that atopy was significantly more frequent among patients with NSAID-induced isolated angioedema than in patients with other sorts of NSAID-dependent hypersensitivity reactions (6), whereas Szczeklik's group found and increased prevalence of atopy in both subjects with aspirin-induced asthma and isolated pyrazolone hypersensitivity by comparison with controls without NSAID intolerance (7). More recently, in a Spanish series, the prevalence of atopy was 25% among single NSAID reactors and 52% among those with cross-intolerance, a statistically significant difference (23). The present study found a marked prevalence of sensitization to airborne (and food) allergens in single NSAID reactors. This finding contrasts with previous observations both in adults and children (4,23,24), but it is all but illogical. In fact, several cases of IgE-mediated reactions to different NSAID have been reported so far, and it is generally believed that the proportion of IgE-mediated hypersensitivity reactions detected among single NSAID reactors would increase if we had better diagnostic tests (1,25-29). Thus, it is not surprising that patients genetically predisposed to mount IgE responses to common environmental allergens may show the highest propensity to produce (possibly) IgE-mediated responses against protein/drug complexes, or against some specific parts of either parental drugs or their metabolic derivatives. The prevalence of hypersensitivity to specific drug families among single NSAID reactors in this series mirrored those reported elsewhere (3). Pyrazolones have been detected as a major cause of drug-induced hypersensitivity ever since, and the high prevalence of intolerance to propionic acid derivatives among single NSAID reactors, is possibly associated with their widespread use as an OTC medication. Interestingly, all 7 subjects showing single reactivity to aspirin were atopic ones, a finding that clearly contrasts with that in patients showing multiple NSAID hypersensitivity with or without chronic urticaria. As a difference from previous observations (8), no association between specific airborne or food allergies and specific offending drugs was found, suggesting that it is the atopic status itself, and not the sensitization to specific allergens, the risk factor for single NSAID hypersensitivity. In effect, the prevalence of sensitization to some specific airborne allergens in the general population may show an extreme variability from a geographic area to another, and evidence that NSAID hypersensitivity is rare in a certain area due to a low prevalence of allergy to a certain allergen (e.g., mite) is missing.

One potential limitation of this study might be that in most single reactors NSAID hypersensitivity was not proven beyond any doubt, because these patients tolerated the alternative challenged drug (either ASA or Ketoprofen) but were not re-challenged with the reportedly offending drug. Although the possibility that some of these patients were in effect NSAID-tolerant cannot be ruled out, it must be considered that all but 4 fulfilled the criteria for an "unequivocal" clinical history established by a recent guideline (13) (i.e., the reaction occurred < 6 hours after the intake of one single drug, the patients recalled exactly the event, and in many cases the reaction was recorded by a physician or by a member of an emergen-

cy department), that all four patients with a doubt clinical history reacted to the reported offending drug on re-exposure (3), and that several patients reported more than one episode of urticaria induced by the same drug on separate occasions. Thus, although previous studies have found that clinical history alone may be unreliable (21), it seems unlikely that many of those who were eventually classified as single reactors in this study were NSAID-tolerant (17). Finally, since this study was based on routine practice, to carry out confirmative oral challenges with probable offending drugs on a regular basis irrespective of clinical history would have posed ethical problems due to the risk of potentially severe adverse reactions (22), let alone the fact that many patients would have refused to undergo a challenge with a drug that they considered as the one responsible for their previous reaction.

In conclusion, in this geographic area single NSAID hypersensitivity is often associated with atopic status, a finding that indirectly supports the possible IgE-mediated origin of at least part of this type of adverse drug reactions.

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