

Assessing potential determinants of positive provocation tests in subjects with NSAID hypersensitivity

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Summary

Background Provocation tests (PTs) with the suspected compounds are considered the 'gold standard' for establishing or excluding a diagnosis of hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs). However, only a few studies have evaluated the potential determinants of positive responses to PTs.

Objective The aims of this study are to assess the reliability of clinical histories as indicators of NSAID hypersensitivity, as well as the risk factors for a positive PT.

Methods Two hundred and seventy-five subjects with an unequivocal history of NSAID hypersensitivity reactions underwent PTs with the suspected drugs. To establish the potential determinants of positive PTs, we examined the following variables: gender, age at the time of reaction (<40 or ≥40 years), family and personal histories of atopy, patients who had reacted to one or more NSAIDs, time interval between drug intake and symptom onset (immediate or non-immediate reactions), time interval between the last drug reaction and the allergologic examination (≤12 or >12 months), and inclusion in a category of the Stevenson et al. classification.

Results Two hundred and fourteen (77.8%) subjects tolerated the suspected drugs and 61 (22.2%) reacted. Age <40 years, male gender, immediate reactions, and time interval ≤12 months were significant risk factors for a positive PT.

Conclusions and Clinical Relevance Our study confirms that clinical histories are not reliable tools for diagnosing NSAID hypersensitivity. Therefore, we recommend that suspected cases should undergo drug PTs. However, further studies on large samples of NSAID-sensitive patients are necessary to establish the risk factors that allow the number of candidates for PTs to be reduced.

Keywords clinical history, COX-inhibition, NSAID hypersensitivity, potential determinants, provocation test

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Introduction

After antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) – such as acetylsalicylic acid (ASA) and pyrazolone derivatives – are the most frequent cause of drug hypersensitivity [1]; in effect, they have been reported to be responsible for 21–25% of all adverse reactions. Specifically, ASA hypersensitivity prevalence ranges from 0.6% to 2.5% in the general population, whereas it occurs in 21–30% and 2–23% of patients with chronic idiopathic urticaria (CIU) and asthma, respectively [2].

Stevenson et al. [3] classified hypersensitivity reactions to NSAIDs in six categories: (1) NSAID-induced rhinitis

and asthma in patients with underlying asthma, nasal polyps, and sinusitis; (2) NSAID-induced urticaria and angioedema in patients with underlying CIU; (3) single drug-induced urticaria/angioedema; (4) multiple drug-induced urticaria/angioedema; (5) single drug-induced anaphylaxis; and (6) single NSAID-induced mixed reaction. Some of these reactions are immunologically mediated, as demonstrated by *in vivo* (skin tests) and *in vitro* (serum-specific IgE assays and basophil activation tests) tests for pyrazolone drugs [4, 5] and other drugs [6, 7], such as ketorolac [8], diclofenac [9], and paracetamol [10]. In the vast majority of cases, however, adverse reactions to NSAIDs are mediated by a pharmacological

mechanism. NSAIDs – such as ASA, pirazolones, indomethacin, ketoprofen, ibuprofen, piroxicam, etc. – inhibit the constitutive isoform of cyclooxygenase (COX)-1, and thus reduce protective prostaglandin (PG)E₂, as well as increase the unrestrained synthesis of cysteinyl leukotrienes and the release of mediators such as PGD₂ from mast cells. This mechanism, which is well-established in ASA-induced asthma [11], has also been supported by biochemical observations in ASA-induced urticaria [12].

Although much research has been performed to improve diagnostic methods, there are no reliable cutaneous or *in vitro* tests that allow NSAID hypersensitivity to be diagnosed. Therefore, a provocation test (PT) with the suspected compound is considered the 'gold standard' for establishing or excluding a diagnosis of NSAID hypersensitivity [13–16]. If positive, this test reproduces both allergic and non-allergic hypersensitivity symptoms, and if negative, it allows NSAID hypersensitivity to be ruled out. Several studies used such diagnostic approach in samples of more than 50 subjects with histories of hypersensitivity reactions to NSAIDs [14, 17–23], showing a rate of positive responses to PTs ranging from 13.4% [19] to 85.7% [23]. This variability can be explained by the size and characteristics of the populations evaluated.

Two recent studies [23, 24] – regarding exclusively subjects with ASA-exacerbated respiratory disease – identified an age younger than 40 years, a severe respiratory disease and severe or multiple asthmatic reactions to ASA and other NSAIDs as the main potential determinants of a positive PT. In a study of 164 children with NSAID-induced hypersensitivity reactions, Hassani et al. [22] found that anaphylaxis, immediate and accelerated reac-

tions, personal atopy, and older age were risk factors for a positive PT. Other studies – regarding patients with either NSAID-induced respiratory symptoms [25, 26] or mainly cutaneous reactions [27], in either case confirmed by PTs – showed that female gender [25, 26] and a personal history of atopy [27] were risk factors for a positive PT.

We conducted this prospective study in order to evaluate the usefulness of PTs in diagnosing NSAID hypersensitivity in a large group of patients with histories suggestive of such hypersensitivity, as well as to assess the potential determinants of positive responses to PTs in these patients.

Methods

Patients were recruited prospectively from a large outpatient population with histories of hypersensitivity reactions to one (single reactors, SRs) or more (multiple reactors, MRs) NSAIDs. This sample was evaluated between January 2004 and December 2008 in the allergy units of the Complesso Integrato Columbus, Rome, Italy and Oasi Maria Santissima, Troina, Italy. The inclusion criterion required an unequivocal history of NSAID hypersensitivity reactions manifested as objective symptoms. We did not include subjects with: (a) subjective symptoms, such as isolated generalized itching, faintness, and headache, or isolated gastrointestinal symptoms (abdominal pain, vomiting); (b) symptoms disappearing without cessation of the suspected drug; (c) unknown responsible compounds; and (d) symptoms elicited by NSAIDs in association with other drugs.

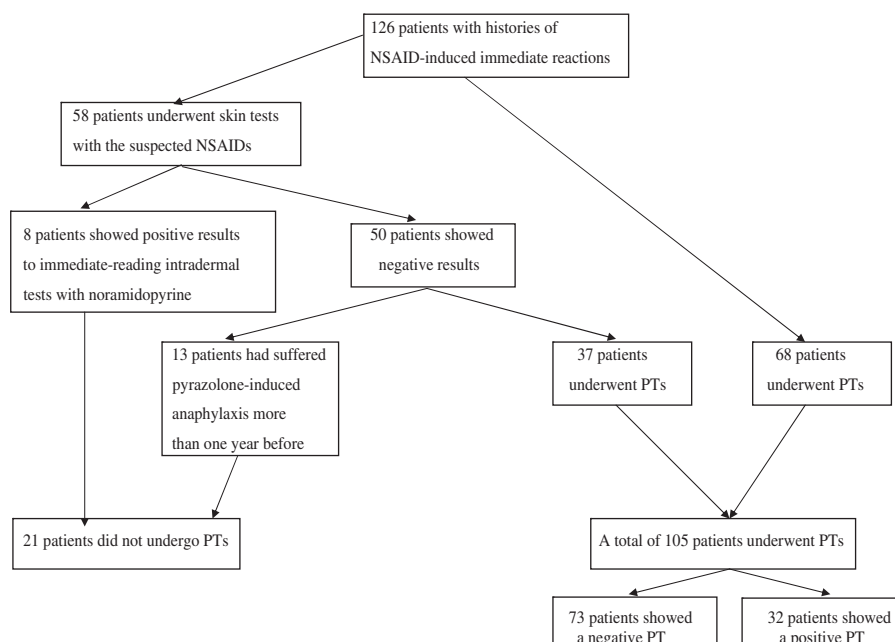
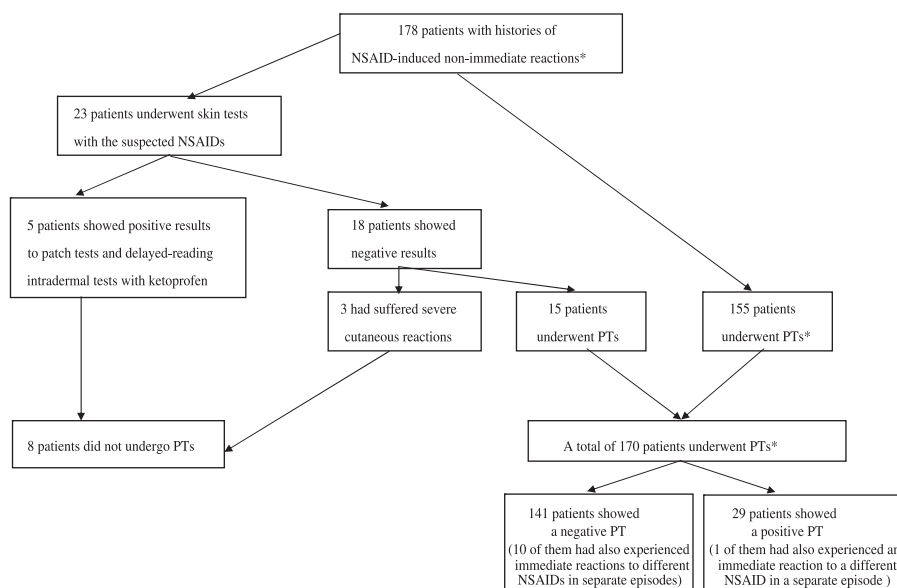


Fig. 1. Diagnostic algorithm and results of patients with non-steroidal anti-inflammatory drug (NSAID)-induced immediate reactions.



* 11 of them had also experienced immediate reactions to different NSAIDs in separate episodes

Fig. 2. Diagnostic algorithm and results of patients with non-steroidal anti-inflammatory drug (NSAID)-induced either non-immediate or both immediate and non-immediate reactions.

Each patient underwent a two-stage diagnostic procedure: skin tests (when advisable) and/or PTs with the suspected NSAIDs (Figs 1 and 2).

Immediate-reading prick and/or intradermal tests were performed in order to diagnose an IgE-mediated hypersensitivity in patients who had suffered immediate reactions (i.e., occurring < 1 h after the last drug administration) to single NSAIDs, specifically pyrazolones (e.g., noramidopyrine and propyphenazone), diclofenac, ketoprofen, paracetamol, and nimesulide, whereas patch tests and delayed-reading intradermal tests were carried out in order to detect a cell-mediated hypersensitivity in subjects who had experienced non-immediate reactions (i.e., occurring more than 1 h after the last drug administration), such as maculopapular exanthemas and contact dermatitis, to single NSAIDs, specifically pyrazolones, diclofenac, and ketoprofen.

Skin tests were performed on volar forearm skin, using the suspected NSAIDs: noramidopyrine at concentrations of 5 and 50 mg/mL, propyphenazone at 3 and 30 mg/mL, diclofenac at 0.25 and 2.5 mg/mL, ketoprofen at 0.5 and 5 mg/mL, paracetamol at 0.1 and 1 mg/mL, and nimesulide at 1 and 20 mg/mL, all diluted in normal saline. The aforementioned concentrations were non-irritant in a control group of 20 healthy patients, as we described previously [28]. First, we performed skin prick tests and, if no positive reactions occurred, we carried out intradermal tests at immediate (20 min) or delayed (48–72 h) readings, according to the type of reactions (immediate or non-immediate, respectively).

Patch tests were performed on back skin, using an undiluted solution of the suspected drugs: noramidopyr-

ine at a concentration of 500 mg/mL, propyphenazone at 300 mg/mL, diclofenac at 25 mg/mL, and ketoprofen at 50 mg/mL, all in normal saline.

For non-injectable drugs, we used powder obtained from tablets, diluted as described previously [29].

Patients displaying positive results in skin and/or patch tests did not undergo PTs with the suspected drugs, nor did we perform PTs in subjects with negative skin tests who (1) had suffered severe reactions [13, 30], such as anaphylaxis (classes III and IV on Ring and Messmer's severity scale) [31], Stevens–Johnson syndrome (SJS), Lyell's syndrome (LS), drug rash with eosinophilia and systemic symptoms (DRESS), etc. or (2) had reported pyrazolone-induced anaphylaxis more than 1 year before the allergologic examination. In effect, a skin-test negativization has been observed in patients with immediate reactions to pyrazolones in whom skin tests were repeated more than 1 year after the first allergologic exam [32, 33]. However, these patients underwent an ASA PT to exclude cross-reactivity [34].

In subjects showing negative skin tests and in those whom such tests were not advisable (e.g., MRs), we performed the PT with the suspected drugs under single-blind placebo-controlled conditions [13]. In particular, in MRs we performed only drug PTs because it is common opinion that in these cases the pathogenic mechanism is due to COX-1 inhibition. In such patients, we performed the first PT with the suspected compound with the lowest capability of inhibiting COX-1, and in case of negative results, we administered the other suspected NSAIDs in order of increasing capability of inhibiting COX-1.

Specifically, we took as our reference parameter the drug concentrations that inhibit the activity of COX-1 and COX-2 (the induced isoform of COX) by 50% (IC_{50}) in assays of whole blood. According to the IC_{50} , we used the following order: nimesulide, diclofenac, meloxicam, paracetamol, naproxen, ibuprofen, propyphenazone, noramidopyrine, ASA, and ketoprofen [35].

PTs were performed as described previously [28]. On the first day, patients underwent a PT with placebo (talc or normal saline); 1 h later, if no adverse symptoms had been observed, the placebo was re-administered. Culprit drugs were administered 1 week after the placebo. We used the same administration route as when the hypersensitivity reaction had occurred. PTs were performed at least 4 weeks after the most recent adverse reaction. In patients who underwent PTs with more than one drug, the interval ranged from 1 to 3 weeks.

For ASA and noramidopyrine, we followed the protocol by Quiralte et al. [18], with modifications. We administered increasing doses of each drug at 2 h intervals. As far as ASA is concerned, on the first day we administered 50+100 mg [total maximum daily dose (TMDD) = 150 mg] and 250+500 mg (TMDD = 750 mg) on the following one, whereas patients were given 25+50 mg (TMDD = 75 mg), 125+250 mg (TMDD = 375 mg), and 500 mg (TMDD = 500 mg) of noramidopyrine, respectively, on three consecutive days [28]. In subjects with respiratory or anaphylactic symptoms, we started ASA PTs with an additional, lower dose of 5 mg.

In patients with immediate reactions to NSAIDs other than ASA and noramidopyrine – such as propyphenazone (300 mg), ketoprofen (50 mg), ibuprofen (200 mg), naproxen (275 mg), paracetamol (1000 mg), meloxicam (15 mg), diclofenac (50 mg), and nimesulide (100 mg) – we initially administered 1/100 of the therapeutic dose indicated in parentheses (which corresponds to the TMDD), then 1/10, and finally the remaining dose at 1 h intervals. In case of previous non-immediate reactions, we initially administered 1/100 of the therapeutic dose indicated in parentheses, then 1/10, and finally the full dose at 24–72 h intervals, depending on the time interval between drug intake and adverse reaction. In such patients, therefore, the TMDD was 1/100 of the therapeutic dose on the first day, 1/10 on the second, and the full dose on the third.

We increased the dose only in case of negative results after the previous one. In MRs, testing was interrupted when the first positive response to a responsible compound was observed.

Patients did not have any cutaneous or respiratory symptoms or concomitant illnesses at the time of testing and had avoided specific drugs for hours or days before [15]. The study was conducted according to the ethical standards of our hospitals, which require the informed consent of each patient, or parents for minors, and was approved by the institutional review boards.

PTs were considered positive if any of the following symptoms developed: cutaneous (erythema, urticaria/angioedema, exanthema), respiratory (rhinorrhoea, nasal obstruction, sneezing, cough, and dyspnoea with a decrease of at least 20% in the FEV_{1}), and/or hypotension, associated or not with gastrointestinal ones.

To assess the severity of cutaneous and respiratory symptoms, we used the Psoriasis Area and Severity Index (PASI) as modified by Zembowicz et al. [36] (range 0–72) and the scoring system of Nizankowska et al. [37] (range 0–4), respectively.

In case of respiratory and/or cutaneous symptoms, patients were treated with two puffs of 100 µg salbutamol spray, as well as 10 mg of clorphenamine and 40 mg of metilprednisolone intravenously; in case of anaphylaxis, 0.3–0.5 mL of epinephrine was administered intramuscularly.

Statistical analysis

Data were analysed with the Stata package (Stata Statistical Software: Release 10; StataCorp. 2007, College Station, TX, USA).

The continuous variables are expressed as the median (min–max), and were compared by using a Mann–Whitney *U*-test. Categorical data are given as numbers of cases and percentages, and were compared by using a χ^2 -test. A *P*-value of 0.05 or less indicates statistical significance.

Univariate and multivariate logistic analyses were performed. Crude (for all the potential risk factors) and adjusted odds ratios (OR), as well as 95% confidence intervals (CI), are reported.

To establish the factors associated with positive PTs, we examined the following variables: gender, age at the time of reaction (<40 or $\geq$ 40 years), family history of atopy, personal history of atopy, SRs or MRs, time interval between drug intake and symptom onset (patients with either immediate or non-immediate reactions, or both), time interval between the last drug reaction and the allergologic examination ($\leq$ 12 or >12 months), and inclusion in a category of the Stevenson et al. classification. Specifically, we compared categories 1+2 (patients with underlying diseases) with the other single categories (patients without underlying diseases).

Results

We examined a total of 304 patients [209 (68.8%) women and 95 (31.2%) men] – of whom 287 adults and 17 under 14 years – with clinical histories of NSAID hypersensitivity.

We performed skin tests with the suspected NSAIDs in 81 patients. Among them, 13 had positive results (eight to immediate-reading intradermal tests with noramidopyrine and five to patch tests and delayed-reading intradermal tests with ketoprofen) and were not challenged, as well as 13 subjects with negative pyrazolone-skin tests,

Table 1. Clinical characteristics of the 275 patients who underwent NSAID provocation tests

Characteristics	N (%) of patients
Gender	
Male	91 (33.1)
Female	184 (66.9)
Age (years)	
Median [min-max]	40 [4-82]
Family history of atopy	
Yes	105 (38.5)
No	170 (61.5)
Personal history of atopy	
Yes	73 (26.5)
No	202 (73.5)
Time interval* (months)	
Median [min-max]	24 [1-600]
≤ 12	130 (47.3)
> 12	145 (52.7)
Type of reactions	
Immediate	105 (38.2)
Non-immediate	159 [†] (57.8)
Both [‡]	11 (4.0)
Stevenson et al. classification (categories)	
1	11 (4.0)
2	23 (8.4)
3	99 (36.0)
4	93 (33.8)
5	21 (7.6)
6	28 (10.2)
Reactors to one or more NSAIDs	
SRs	139 (50.5)
MRs	136 (49.5)

*Between the last drug reaction and the allergologic examination.

[†]Of whom, 80 patients with urticaria and/or angioedema, 45 with maculopapular exanthema, 17 with lip angioedema, 11 with eyelid angioedema, two with fixed exanthema, and four with contact dermatitis.

[‡]Both, patients with both immediate and non-immediate reactions.

NSAID, non-steroidal anti-inflammatory drug; SRs, single reactors; MRs, multiple reactors.

but a history of pyrazolone-induced anaphylaxis occurring more than 1 year before the allergologic exam (Figs 1 and 2). The last 13 patients underwent PTs with ASA and tolerated them.

With the exception of the aforementioned 26 subjects and three others with severe cutaneous reactions (SJS, LS, and DRESS, respectively), all patients (275) underwent a total of 318 PTs. The clinical characteristics of these subjects are shown in Table 1.

One hundred and thirty-nine patients were SRs, the most frequently involved drug being ASA (47.2%), whereas the other 136 were MRs, with the highest percentage (32.2%) reporting reactions to ASA and noramidopyrine.

Of the 73 subjects with personal histories of atopy, 52 (71.2%) reported rhinitis and/or asthma and displayed positive inhalant-allergen skin tests, whereas 11 (15.1%)

had an IgE-mediated hypersensitivity to β -lactams, two (2.7%) to hymenoptera venoms, and eight (11.0%) to foods.

Two hundred and fourteen (77.8%) of the 275 subjects tolerated the suspected drugs and 61 (22.2%) reacted. Specifically, we observed positive responses in 32 (52.5%) of the 105 subjects with histories of immediate reactions, in 28 (45.9%) of the 159 who had suffered non-immediate ones, and one (1.6%) of the 11 who had experienced immediate and non-immediate reactions to different NSAIDs in separate episodes (Figs 1 and 2).

All the placebo PTs were negative, although eight (2.9%) patients reported subjective symptoms, such as itching, faintness, and headache.

The clinical characteristics of patients, classified on the basis of PT results, and the statistical analysis are shown in Table 2.

Patients with positive PTs displayed symptom scores ranging from 1 to 7 and from 1 to 2 for cutaneous and respiratory symptoms, respectively.

Fifty-seven (93.4%) out of 61 subjects with positive PTs displayed the same symptoms, generally less severe, and/or the same type of reaction (immediate or non-immediate) as in their history.

Two out of such 61 patients were treated with clorphenamine (10 mg) intravenously and the other 59 subjects with clorphenamine and metilprednisolone (40 mg) intravenously; in five of the latter, we also administered epinephrine intramuscularly.

Univariate logistic regressions showed that women had a 59% lower risk of a positive PT (OR, 0.41; 95% CI, 0.23-0.74; $P=0.003$); subjects aged ≥ 40 had a 50% lower risk (OR, 0.50; 95% CI, 0.27-0.91; $P=0.025$); patients evaluated more than 12 months after the last reaction had a 46% lower risk (OR, 0.54; 95% CI, 0.31-0.97; $P=0.04$); subjects in category 3 of the Stevenson et al. classification had a 68% lower risk (OR, 0.32; 95% CI, 0.13-0.80; $P=0.015$) than those in categories 1+2; and immediate reactions yielded a twofold (OR, 2.05; 95% CI, 1.15-3.67; $P=0.02$) greater risk than non-immediate ones (Table 2).

Multivariate logistic regression showed that women (OR, 0.42; 95% CI, 0.23-0.76; $P=0.004$) and subjects aged ≥ 40 (OR, 0.51; 95% CI, 0.27-0.95; $P=0.03$) had a lower probability of a positive PT result.

For all other factors, no significant ORs were found (Table 2).

Discussion

Frequently, the diagnosis of NSAID hypersensitivity is based only on clinical histories without further allergologic examinations. Patients are simply advised to avoid all NSAIDs and are prescribed second-line medications, with possible less efficacy and increased toxicity. On the other

Table 2. Clinical characteristics of the 275 patients, classified on the basis of provocation test results, and the statistical analysis

Characteristics	Patients with positive PTs, N (%) (Total no. = 61)	Patients with negative PTs, N (%) (Total no. = 214)	OR	95% CI	P-value
Gender					
Male	30 (49.2)	61 (28.5)	1		
Female	31 (50.8)	153 (71.5)	0.41	0.23–0.74	0.003
Age (years)					
<40	43 (70.5)	116 (54.2)	1		
≥40	18 (29.5)	98 (45.8)	0.50	0.27–0.91	0.025
Family history of atopy					
Yes	40 (65.6)	130 (60.8)	1		
No	21 (34.4)	84 (39.2)	0.81	0.45–1.47	0.49
Personal history of atopy					
Yes	18 (29.5)	55 (25.7)	1		
No	43 (70.5)	159 (74.3)	0.83	0.44–1.56	0.56
Time interval* (months)					
≤12	36 (59.0)	94 (43.9)	1		
>12	25 (41.0)	120 (56.1)	0.54	0.31–0.97	0.04
Type of reactions					
Immediate	32 (52.5)	73 (34.1)	1		
Non-immediate	28 (45.9)	131 (61.2)	2.05	1.15–3.67	0.02
Both [†]	1 (1.6)	10 (4.7)	0.47	0.06–3.80	0.48
Stevenson et al. classification (categories)					
1+2	11 (18.0)	23 (10.8)	1		
3	13 (21.3)	86 (40.2)	0.32	0.13–0.80	0.015
4	21 (34.4)	72 (33.6)	0.61	0.26–1.45	0.26
5	8 (13.1)	13 (6.1)	1.29	0.41–4.01	0.66
6	8 (13.1)	20 (9.3)	0.84	0.28–2.49	0.75
Reactors to one or more NSAIDs					
SRs	25 (41.0)	114 (53.3)	1		
MRs	36 (59.0)	100 (46.7)	0.61	0.34–1.08	0.09

*Between the last drug reaction and the allergologic examination.

[†]Both, patients with both immediate and non-immediate reactions. P-value in bold type is statistically significant.

NSAID, non-steroidal anti-inflammatory drug; SRs, single reactors; MRs, multiple reactors; OR, odds ratio; 95% CI, 95% confidence interval.

hand, in the presence of a positive PT result, culprit drug avoidance is optimized and therapeutic options can be found, such as the administration of alternative drugs – weak COX-1 inhibitors and/or preferential or highly selective COX-2 inhibitors – or desensitization to the culprit NSAIDs.

However, literature data indicate that the clinical history is not a reliable indicator of true NSAID hypersensitivity, and, in addition, *in vitro* and cutaneous tests (except for some immediate reactions to pyrazolones) are not considered fully validated diagnostic tools [15]. Therefore, PTs with the suspected compound are considered the 'gold standard' for establishing or excluding a diagnosis of NSAID hypersensitivity. With regard to ASA, the EAACI/GA²LEN guidelines [15] report that oral PTs have a sensitivity and specificity of 89% and 93%, respectively.

Our study confirms that the clinical history is not a valid tool for diagnosing NSAID hypersensitivity. PTs were negative in 77.8% of the patients who underwent such tests. On the other hand, our rate of positive responses to PTs (22.2%, 61 out of 275 patients) falls

within the range of 13.4 [19]–36.0% [18] found in the aforementioned studies [18–22], which evaluated patients with NSAID-induced symptoms, mainly cutaneous, by performing PTs with the suspected drugs. Specifically, this rate is similar to that (20.1%) found in a study by Schubert et al. [21].

Only a few studies assessed the potential determinants of a positive PT [18, 19, 22–24]. In the present study, we found that age younger than 40 years and male gender are risk factors. With regard to age, our study confirms the results of the studies by Dursun et al. [23] and Hope et al. [24], while with regard to gender it conflicts with literature data [25, 26], which indicate female gender as a risk factor.

Such difference is probably due to the fact that other studies evaluated only samples with NSAID-induced respiratory reactions [25, 26], whereas in the present study most subjects had experienced cutaneous or mixed reactions.

Comparing categories 1+2 of the Stevenson et al. classification with the other single categories, we found

that patients in category 3 have a lower risk of a positive PT.

In addition, subjects evaluated <12 months since the last reaction and those reporting immediate reactions have a higher risk of a positive PT. To our knowledge, the former variable has not been investigated previously.

In any case, PTs allowed us to diagnose an NSAID hypersensitivity in 61 subjects (22.2%), who were advised to avoid both the culprit drug and others with a similar or higher capability of COX-1 inhibition. In these patients, weak COX-1 inhibitors and/or preferential or highly selective COX-2 inhibitors, which have a capability of COX-1 inhibition lower than that of the culprit drug, were prescribed on the basis of negative responses to controlled administrations [28]. On the other hand, NSAID hypersensitivity was ruled out in 214 (77.8%) of the 275 subjects who had undergone PTs. Therefore, these patients did not suffer from the negative consequences of an inappropriate exclusion of the suspected NSAIDs. This could be impor-

tant, especially for the 137 (64%) subjects in whom ASA was the suspected compound, considering its peculiar therapeutic characteristics [38].

In summary, the results of controlled PTs reveal that the medical community overestimates NSAID hypersensitivity. For this reason, we recommend that suspected cases of NSAID hypersensitivity undergo PTs in accordance with the position paper and guidelines concerned [13, 15, 16]. However, the decision to subject patients to PTs should not be based on the potential determinants of positive results found in the present study. Further studies on larger samples of NSAID-sensitive patients are necessary to identify subjects with strongly specific risk factors and thus reduce the use of potentially dangerous PTs.

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Conflicts of interest: The authors do not declare any competing interests.

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