

Provocation tests with the offending nonsteroidal anti-inflammatory drugs in patients with urticaria/angioedema reactions

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ABSTRACT

The provocation test (PT) with the suspected drug represents the gold standard in the diagnosis of non-IgE hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Nevertheless, there is no consensus regarding the clinical management of suspected NSAID-sensitive patients. This study assessed if a PT with the suspected drug is a reliable and safe proceeding to confirm NSAID hypersensitivity in patients with a clinical history of urticaria/angioedema (Urt/AE). It also analyzed different patient characteristics (such as gender, age, atopy, dermatographism, time interval between the last drug reaction, and number of previous NSAID reactions) in relation to PT positivity. One hundred fifty-nine patients with Urt/AE apparently related to assumption of one or more NSAIDs underwent PT with the suspected drugs. Moreover, to distinguish single/multiple NSAID reactivity in patients who did not tolerate the offending NSAID, another strong cyclooxygenase-1 inhibitor PT was performed. PT was negative in 142/159 patients (89.31%), ruling out a diagnosis of NSAIDs hypersensitivity; 17/159 patients (10.69%) experienced a reaction of Urt/AE during the PT: 8 patients were diagnosed as single reactors to NSAIDs and 4 as multiple reactors to NSAIDs. Those with a history of multiple NSAID reactions and male patients were both more likely to have a positive PT. Our results suggest that in all patients with history of NSAID cutaneous reactions, the NSAID hypersensitivity should be confirmed by an oral PT and that the diagnostic proceeding can safely start with the offending NSAID.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are a frequent cause of cutaneous adverse drug reactions, representing 21–25% of all hypersensitivity reactions to drugs^{1,2} and occurring in 0.1–3% of patients consuming these drugs.^{3,4} Hypersensitivity to NSAIDs is classified as acute reactions, occurring within 24 hours of administration of the drug, and delayed reactions after >24 hours.⁵ Acute reactions include patients with underlying diseases such as NSAID exacerbated (aspirin-exacerbated respiratory diseases in asthma and NSAID-exacerbated cutaneous diseases in chronic idiopathic urticaria [Urt]) and patients without underlying diseases with multiple or single NSAID-triggered Urt, angioedema (AE), and anaphylaxis.⁶ The provocation test (PT) with the suspected drug represents the gold stan-

dard in the diagnosis of hypersensitivity reactions to NSAIDs. Nevertheless, at the moment, there is no consensus regarding the clinical management of suspected NSAID-sensitive patients.^{5,7} The diagnosis of NSAID hypersensitivity is often based only on clinical histories and in few studies NSAID hypersensitivity is confirmed by specific PTs.^{1,4,8–11} Some authors advise an oral challenge with a chemically unrelated NSAID,^{12–14} a weak cyclooxygenase-1 (COX-1) inhibitor and/or a highly selective cyclooxygenase-2 (COX-2) inhibitor.^{4,5,15} In clinical practice many patients with NSAID-related Urt/AE are frequently labeled as NSAID-intolerant patients only based on the clinical history even if they experienced a single episode. A recent position paper of European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network group emphasizes the need for drug PTs to confirm the diagnosis of NSAID hypersensitivity.⁵

The aim of this study was to assess whether PT with a suspected drug is a reliable and safe proceeding to confirm/exclude NSAID hypersensitivity in patients with clinical history of Urt/AE.

We further assessed if the outcome of the PT was associated with some patients' characteristics.

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MATERIALS AND METHODS

The study was conducted according to the ethical standards of our hospitals, after written informed consent was obtained for each patient, or parents for minors, and was approved by the institutional review boards.

All of the patients of the allergy centers in Novara and Domodossola Hospitals (northwest Italy), who experienced at least one episode of acute Urt/AE induced by NSAIDs, were enrolled between July 2004 and June 2010. All subjects reporting chronic Urt, NSAID-induced asthma, or systemic anaphylaxis were excluded.

Skin-prick tests with a panel of common aeroallergens (grass, birch, ragweed, *Parietaria judaica*, and olive pollen, mites, cat and dog dander, and *Alternaria*) were performed in all patients. A patient was considered atopic if one skin-prick test was positive for at least one aeroallergen. During the first visit, dermatographism was evaluated. Testing for immediate dermatographism consisted of stroking the skin of the upper part of the back with a blunt object. The stroked skin was observed for linear infiltration and surrounding flare and assessed after 10 minutes.

All patients underwent a single-blind placebo-controlled PT with the suspected offending drug. Acetylsalicylic acid, meloxicam, diclofenac, ibuprofen, paracetamol, and nimesulide were prepared as pills in the hospital pharmacy, and ketoprofen, naproxen, piroxicam, metamizole, flurbiprofen, indomethacin, etoricoxib, celecoxib, ketorolac, and morniflumate were administered in their commercial formulation.

All oral PTs were started with a single dose of talc or normal saline as placebo, and then increasing doses of the NSAID in identical opaque capsules were given every hour (Table 1). PT was considered positive if any of the following symptoms developed: cutaneous (Urt and/or AE), respiratory (rhinorrhea, nasal obstruction, sneezing, cough, and dyspnea), or cardiovascular (*i.e.*, hypotension), eventually associated to gastrointestinal ones.^{16,17} Patients were observed for 2 hours after the last dose and they were instructed to contact the allergy center in case of delayed reaction.

In patients who tolerated the suspected offending drug, diagnosis of NSAID hypersensitivity was ruled out. Patients with positive PT (PPT) with the suspected NSAID underwent further PT with another strong COX-1 inhibitor. Acetylsalicylic acid was tested to differentiate single from multiple hypersensitivities to NSAIDs; in patients who reacted first to acetylsalicylic acid, diclofenac was given.

Patients who did not react to the strong COX-1 inhibitor were diagnosed as single reactors (SRs) whereas reacting patients were diagnosed as multiple reactors

Table 1 The consecutive and cumulative doses of NSAIDs used in oral challenge

Drug	Consecutive Dose (mg)	Cumulative Dose (mg)
Paracetamol	25, 50, 100, 250, and 250	675
Acetylsalicylic acid	10, 50, 100, 200, and 200	560
Naproxen	50, 100, 200, and 200	550
Metamizole	25, 50, 100, 150, and 175	500
Morniflumate	50, 100, and 200	350
Ibuprofen	10, 30, 60, and 100	200
Celecoxib	10, 20, 20, 50, and 100	200
Nimesulide	25, 25, 50, and 50	150
Etoricoxib	10, 20, 30, and 60	120
Flurbiprofen	25, 25, and 50	100
Ketoprofen	20, 20, and 40	80
Diclofenac	10, 10, 20, and 20	60
Indomethacin	12.5, 12.5, and 25	50
Meloxicam	2.5, 5, and 7.5	15
Piroxicam	5, 5, and 10	20
Ketorolac	1, 2, 4, 6, and 7	20

NSAIDs = nonsteroidal anti-inflammatory drugs.

(MRs). Patients with confirmed multiple NSAID hypersensitivity underwent further PT with a weak COX-1 inhibitor and/or a highly selective COX-2 inhibitor (*e.g.*, meloxicam, paracetamol, nimesulide, and/or etoricoxib; Fig. 1).

Demographic and clinical characteristics of patients with PPT (such as gender, age <40 or ≥40 years old, atopy, dermatographism, time interval between the last drug reaction and examination ≤12 or >12 months, and number of previous NSAID reactions) were analyzed and compared with patients with negative PTs (NPT).

Statistical Analysis

The χ^2 -Yates test and two-tailed Fisher's exact test at 5% significant level, odds ratio (OR) with confidence interval (CI) at 95%, were used. Statistical analysis was performed by SAS System (SAS System Version 9.1, SAS Institute Inc., Cary, NC).

RESULTS

One hundred fifty-nine patients, 100 women (62.89%) and 59 men (37.11%), were enrolled. One hundred forty-eight patients were adults, aged 15–73 years old (mean age, 38.49 years), and 11 were children (6 girls and 5 boys) from 4 to 14 years old (mean age, 9.72 years).

A single episode of NSAID-induced Urt/AE was described by 136/159 patients (85.53%): 122 patients (76.73%) reported the ingestion of one drug and 14 subjects (8.8%) simultaneously took two or more

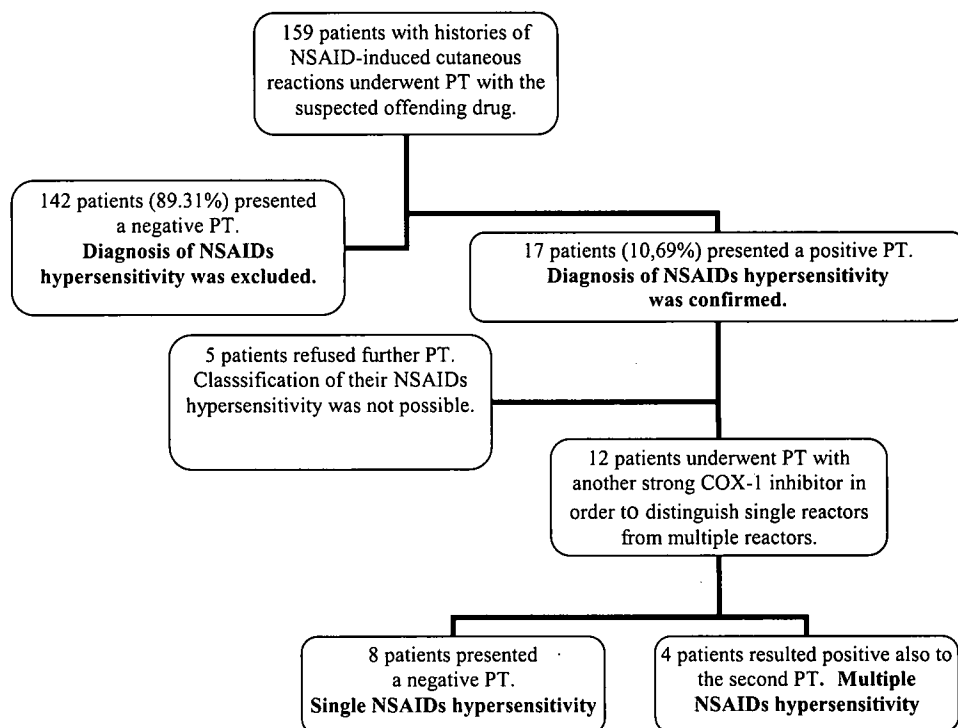


Figure 1. Graphic representation of the clinical results of provocation tests (PTs).

Table 2 Causative NSAIDs involved in reported reactions (single/multiple) *

	NSAIDs Involved							
	ASA	PAR	KET	DIC	NIM	IBU	MET	NAP
Single reaction (n = 136)								
one NSAID intake	47	30	10	9	9	7	3	1
two NSAIDs intake	5	7	5		1	3	2	1
three NSAIDs intake	1	2		1	1	1		
Multiple reactions (n = 48)	17	7	4	3	3	8	3	1

A total number of 184 NSAIDs reactions were reported: a single episode was referred by 136 patients, two distinct episodes with two different NSAIDs by 21 patients, and other three distinct cutaneous reactions with three different NSAIDs by two patients. Other NSAIDs not included in the table (piroxicam, flurbiprofen, indomethacin, etoricoxib, celecoxib, morniflumate, ketorolac, 1 unknown NSAID) were, respectively, involved only in one reaction.

ASA = acetylsalicylic acid; PAR = paracetamol; KET = ketoprofen; NIM = nimesulide; DIC = diclofenac; IBU = ibuprofen; MET = metamizole; NAP = naproxen; NSAIDs = nonsteroidal anti-inflammatory drugs.

NSAIDs (Table 2). Twenty-one of 159 patients (13.21%) described two distinct episodes of Urt/AE with two different NSAIDs, and the other 2/159 patients (1.26%) reported three distinct episodes with three different NSAIDs. A total number of 184 reactions were described: 87 erythematous rash or Urt (47.28%), 68 AEs (36.96%), and 29 both Urt and AE (15.76%). In most cases AE involved lips (n = 27) and eyelids (n = 25) and less frequently tongue (n = 11), hands, and feet (n = 5). The reaction occurred ≤1 hour (mean time, 39 minutes) after the last drug intake in 35/184 cases (19.02%). In 37/184 cases (20.1%) the time interval between drug intake and symptoms onset was >1 and ≤6 hours, in 25/184 (13.58%) >6 and ≤12 hours, in

18/184 (9.78%) >12 and ≤24 hours, and in 69/184 cases (37.5%) it was unknown.

Skin-prick tests were positive in 71/159 patients (44.65%). Allergic respiratory symptoms were described by 60/159 patients (37.74%): 3 of them presented nasal polyposis without asthma, 4 complained of only asthma, 5 were affected by rhinitis and asthma, and 48 by only rhinitis. Dermographism was present in 30 patients among 88 patients (34.09%) with clinical history of NSAID hypersensitivity studied at Novara Hospital. No patient had symptomatic dermographism requiring pharmacologic treatment.

Two hundred thirteen PTs were performed with 22 (10.33%) being positive (Table 3). The time interval

Table 3 Provocation test results

Drug	Performed Test		Positive Test	
	n	%	n	%
Acetylsalicylic acid	75	35.21	12	16
Paracetamol	50	23.47	0	0
Ketoprofen	21	9.86	0	0
Nimesulide	18	8.45	0	0
Ibuprofen	16	7.51	2	12.5
Diclofenac	13	6.10	2	15.4
Metamizole	7	3.29	2	28.57
Naproxen	3	1.41	1	33.33
Meloxicam	2	0.94	1	50
Etoricoxib	2	0.94	2	100
Celecoxib	1	0.47	0	0
Flurbiprofen	1	0.47	0	0
Indomethacin	1	0.47	0	0
Ketorolac	1	0.47	0	0
Morniflumate	1	0.47	0	0
Piroxicam	1	0.47	0	0
Total	213		22	10.33

between the last drug reaction and the allergologic examination was 1–360 months (median, 8 months). NPTs were detected in 142/159 patients (89.31%) ruling out an NSAID hypersensitivity diagnosis (Fig. 1). Seventeen of 159 patients (10.69%) experienced a reaction during the PT and underwent another PT with a strong COX-1 inhibitor (*i.e.*, acetylsalicylic acid or diclofenac in patients who reacted to acetylsalicylic acid). Five patients refused other challenges, 8/12 patients were diagnosed as SRs to NSAIDs having a good tolerance to the second tested drug (diclofenac in 6 patients and acetylsalicylic acid in 2 patients) and 4/12 patients were considered MRs resulting positively to all PTs (Fig. 1). All children tested (11/11) had NPTs.

In 14 of 22 positive challenges (63.64%) a reaction occurred within 1 hour after the last dose (mean time, 27.5 minutes) and in the other 8 (36.36%) within 12 hours after the end of the test (mean time, 6 hours). The threshold dose eliciting the reaction was $\leq 50\%$ of the lower therapeutic dose of NSAID that could be administered daily in 4/14 PPTs (28.6%) that occurred within 1 hour. Concerning acetylsalicylic acid, involved in 12/22 PPTs, the threshold dose was 160 mg in 2/12, 360 mg in 2/12, and 560 mg in 8/12. All patients tolerated paracetamol and nimesulide and we found PPTs to meloxicam (1/2) and to etoricoxib (2/2). One of the two patients sensitive to etoricoxib was MR to NSAIDs with PPTs for meloxicam and acetylsalicylic acid, and paracetamol was tolerated at a dose of 675 mg. The other

subject was an SR to etoricoxib showing a tolerance toward acetylsalicylic acid.

Reactions during PPTs, consisting in mild Urt and/or AE, were treated with prednisone at 25 mg and/or levocetirizine at 5 mg. Symptoms other than cutaneous (rhinitis, conjunctivitis, and abdominal cramps) were observed in few cases. In detail only one SR patient developed rhinoconjunctivitis 30 minutes after ibuprofen administration (100 mg) and one MR patient complained of abdominal cramps and Urt 40 minutes after etoricoxib administration (60 mg), rhinitis, and AE of eyelids 40 minutes after acetylsalicylic acid (160 mg), and rhinitis 25 minutes after meloxicam (15 mg).

No reactions to placebo were observed.

Atopy was found in 8/17 of patients with PPT (47.06%) and dermatographism in 3 of the 17 patients (17.65%). A significant association between PPT and history of multiple NSAID reactions (OR, 4.01; 95% CI, 1.31–12.25) and male gender (OR, 3.59; 95% CI, 1.25 to 10.30) was statistically observed. Otherwise PPTs were not significantly associated with other demographic or clinical patients' characteristics (age, <40 or ≥ 40 years old, atopy, dermatographism, time interval between the last drug reaction, and allergologic examination ≤ 12 or 12 months) (Table 4).

DISCUSSION

In our study a PPT with the offending drug (one or more) was observed in 17 of the 159 patients enrolled (10.69%); this percentage is significantly lower with respect to other studies that showed a rate of positive responses to PTs ranging from 13.4 to 36%.^{1,9,18,19} This result could be explained by selection of patients with Urt/AE reactions alone and by different NSAID doses and time intervals used in PTs.^{1,4,9,10,13,16–18} Many of the patients (17/23) who described multiple NSAID reactions had NPTs, even though the statistical analysis suggested that in these patients there was a higher risk of reaction during PTs. We found also that male gender could be another potential determinant of a PPT, accordingly, with the results of Viola *et al.*¹ Our data failed to show statistical evidence of association between atopic status and NSAID hypersensitivity cutaneous reactions, according to other authors.^{4,5,9,20,21} It is interesting to note that in our population there was a high incidence of dermatographism (34%), not correlated with PPT; it could be a sign of latent Urt, in agreement with the observation that a history of a NSAID-induced Urt could precede chronic Urt.²² No child tested was found positive to PT but in larger studies NSAID-induced cutaneous reactions range from 0.55 to 4% of children.²³

Reactions occurring in PPTs consisted mainly of mild cutaneous reactions; 5/17 patients experienced facial

Table 4 Associations between patients, characteristics and PPT

	PPTs <i>n</i> (%) [*]	NPTs <i>n</i> (%) [*]	OR	95% LL	95% UL	χ^2	df	<i>p</i> Value	Exact Test
Gender									
Male	11 (18.6%)	48 (81.4%)	3.59	1.25	10.30	4.959	1	0.026	0.017
Female	6 (6.0%)	94 (94.0%)							
Age									
<40 yr	8 (9.3%)	78 (90.7%)	0.73	0.27	2.0	0.128	1	0.720	0.611
≥40 yr	9 (12.3%)	64 (87.7%)							
Atopy									
Yes	8 (11.3%)	63 (88.7%)	1.11	0.41	3.06	0.000	1	1.000	1.000
No	9 (10.2%)	79 (89.8%)							
Dermographism									
Yes	3 (10.0%)	27 (90.0%)	0.60	0.151	2.43	0.150	1	0.699	0.744
No	9 (15.5%)	49 (84.5%)							
Time interval									
≤12 mo	9 (10.8%)	74 (89.2%)	1.03	0.38	2.83	0.000	1	1.000	1.000
>12 mo	8 (10.5%)	68 (89.5%)							
Reactors									
Multiple reactors	6 (26.1%)	17 (73.9%)	4.01	1.31	12.25	4.922	1	0.027	0.020
Single reactors	11 (8.1%)	125 (91.9%)							

^{*}Row percent.

PPTs = positive provocation tests; NPTs = negative provocation tests; LL = lower limit of 95% confidence interval; UL = upper limit of 95%; CI = confidence interval; df = degree of freedom.

AE, which represents a frequent manifestation of cutaneous NSAID hypersensitivity.^{3,9,10} Some authors suggest monitoring lung function parameters, such as FEV1, in patients challenged for aspirin-induced cutaneous reactions even in absence of a history of asthma.^{8,17} In the present study none of the subjects developed anaphylaxis or asthmatic symptoms during PTs; in two patients the reaction was characterized by nasal and ocular involvement, according to results of other authors.⁹

Our results suggest that NSAID hypersensitivity diagnosis should be confirmed by oral PT in all patients with history of NSAID cutaneous reactions, as reported by other authors,^{1,8} because a single episode of acute Urt/AE can be falsely attributed to NSAIDs. A correct diagnosis has a fundamental importance to prevent improper restrictions in subsequent physician's prescriptions, sometimes depriving patients of appropriate clinical treatment (*i.e.*, acetylsalicylic acid as anti-aggregating therapy). A possible limitation of this study is the small sample size that might not completely represent all of the patients with a history of Urt/AE induced by NSAIDs, and that does not allow us to perform a stratified analysis to control potential confounders.

The results of our study suggest that in subjects with a history of Urt/AE induced by one or more NSAIDs, the diagnostic proceeding could safely start with the offending NSAID, to confirm the previous reactions.

Moreover, the PT with a weak COX-1 inhibitor and/or a highly selective COX-2 inhibitor should not be the first choice in the absence of a firm diagnosis of NSAID hypersensitivity.

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