

Avoidance of nonsteroidal anti-inflammatory drugs after negative provocation tests in urticaria/angioedema reactions: Real-world experience

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ABSTRACT

Drug provocation tests (DPTs) are the gold standard in diagnosing nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity; however, only few data about follow-up of patients with negative DPTs are actually available. The aim of this study was to assess patients' behavior in taking NSAIDs again and to evaluate NSAID tolerability after negative allergological workup. This is a follow-up study involving patients evaluated for history of cutaneous reactions (urticaria and/or angioedema) after NSAID intake and with negative DPTs with the suspected NSAID. Patients were asked during a phone interview about the intake of NSAIDs, tolerance, or reasons of avoidance. The negative predictive value (NPV) of NSAIDs DPTs was calculated. One hundred eleven of 142 patients were successfully contacted; 46/111 (41.44%) took the same NSAID previously tested with two adverse reactions reported (4.34%). Fifty-three of 111 (47.74%) patients did not take the same NSAID, but 34 of them took at least another strong cyclooxygenase (COX) 1 inhibitor, with 1 adverse reaction (2.94%) and 19 of them took only weak COX-1 inhibitors. Twelve of 111 patients (10.8%) did not take any NSAID. Reasons for drug avoidance were mainly fear of reactions (70.8%) and no need (29.2%). NPV, overall, was 96.97% (95% confidence interval, 91–99%). Although NSAID hypersensitivity diagnosis was ruled out by oral provocation test, the majority of patients with a history of urticaria/angioedema avoided the intake of the tested NSAIDs for fear of new reactions, particularly when strong COX-1 inhibitor NSAIDs were involved. The high NPV value of DPT resulting from this study should reassure NSAID intake.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) may induce cutaneous manifestations in 0.3% of the general population,^{1,2} and the prevalence of NSAIDs hypersensitivity reaches 27–35% in patients with chronic urticaria.³ In recent studies NSAIDs are proven to be the medications most frequently involved in hypersensitivity drug reactions.⁴ The occurrence of urticaria and/or angioedema as the sole manifestation of NSAID hypersensitivity is frequently observed as an immediate reaction in subjects with no history of pre-existing chronic urticaria; cross-intolerance to cyclooxygenase (COX) 1 inhibitors of various chemical groups (multiple-NSAID induced) or selective mechanisms (single-drug induced) can be involved.^{5,6}

Drug provocation tests (DPTs) with NSAIDs (with the suspected molecule or with an alternative strong COX-1 inhibitor one) are actually the gold standard in diagnosing NSAIDs hypersensitivity, because standardized cutaneous or *in vitro* tests are available only for a limited number of NSAIDs and are indicated when selective mechanisms are suspected; DPTs are recommended by the European Network for Drug Allergy to establish a definite diagnosis.⁶ DPTs have to be performed in hospital centers and require specialized staff and are time-consuming.

After a negative oral DPT rules out the diagnosis of NSAIDs hypersensitivity, little is known about follow-up of patients and their resultant behavior about drug intake. On the other hand, missing cofactors, such as infections, comedications, and physical exercise, may lead to false negative DPT results and patients may experience a new adverse reaction after drug intake. The aims of this study were to assess patients' behavior in taking NSAIDs again after a negative allergological workup and to evaluate the subsequent NSAIDs tolerability.

MATERIALS AND METHODS

This is a follow-up study involving patients evaluated in the allergy centers in Novara and Domodossola

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Table 1 Patient interview questionnaire

1. Have you taken the drug tested in the hospital after negative challenge?
2. If yes, have you had adverse reactions? If yes, what kind of reaction?
3. If no, what were the reasons for avoidance?
4. Have you taken other types of NSAID? Which ones?*
5. If yes, have you had adverse reactions? If yes, what kind of reaction?
6. Have you adopted alternative methods to control pain/inflammation?

*To facilitate patients, a list of NSAIDs brand names was presented.

NSAIDs = nonsteroidal anti-inflammatory drugs.

Hospitals between July 2004 and June 2010, with a history of immediate cutaneous reactions (urticaria and/or angioedema) after NSAID intake. The Ethics Committee of our Hospital approved the study protocol.

Exclusion criteria were chronic urticaria, NSAID-induced respiratory symptoms, anaphylaxis, severe delayed cutaneous reactions, and clinical contraindications to DPT. All of the patients underwent single-blind placebo-controlled DPT with the suspected offending NSAID as previously described.⁷ All of the patients with a negative DPT with the suspected culprit NSAID were contacted by phone not <11 months after the provocation test and were asked to answer to the questions shown in Table 1. Patients were considered dropouts if not answering after five phone calls were made on different days. The brand names of the NSAIDs taken after the DPT were collected and categorized in "strong" and "weak" COX-1 inhibitors and "selective COX-2" inhibitors according to COX inhibition capability.

Statistical Analysis

The frequency of adverse reactions in patients taking the drug previously tested and the reasons why patients did not assume the drug tested despite a negative DPT were recorded and statistically analyzed. Comparisons between groups were made using chi-square test or Student's *t*-test. The negative predictive value (NPV) with its 95% confidence interval (CI) was calculated. Data were analyzed with the statistical SPSS software package (Version 17; SPSS, Inc., Chicago, IL).

RESULTS

One hundred fifty-nine patients were evaluated for suspected NSAID hypersensitivity and the 142 patients who showed negative results to the DPT with the

suspected NSAID were included in the study; 111 of them (78.17%) were successfully contacted and 31 (21.8%) dropped out (10 not answering, 20 changed telephone number, and 1 deceased). Mean time between DPTs and phone contact was 29 months (SD $\pm$ 13.5 months).

Among the 111 subjects included, 39 were male and 72 female patients. One DPT was performed in 91 patients, 2 DPTs in 19 individuals, and 3 DPTs in 1 patient, with a total number of 132 DPTs performed. In Table 2, the different types of NSAIDs tested in DPTs are described according to their COX-1 inhibition capability.

Ninety-nine patients took an NSAID at least once again; 46 of them took the suspected culprit NSAID after the negative test; 34 took an alternative NSAID, similar to the drug tested for pharmacologic efficacy (a strong COX-1 inhibitor); and 19 subjects took a weaker alternative COX-1 inhibitor NSAID. The majority of these patients (88/99) took more than an NSAID on different occasions. Twelve of 111 patients did not take any NSAID, 2 only using nonconventional therapies, such as homeopathy or acupuncture.

In Table 3, characteristics of the patients in relation to NSAID use or avoidance are described. No significant differences about sex were recorded; concerning age, subjects who did not take the suspected culprit drug after the negative test were of a higher mean age than the patients who took the same NSAID (42.35 ± 16.5 years versus 33.6 ± 16.8 years; $p = 0.007$). Reasons for avoiding the suspected culprit NSAID despite a negative DPT were reported as "no need to use" in 19/65 patients (29.2%) and "fear of a new potential reaction" in 46/65 subjects (70.8%; Table 3). Patients chose a different NSAID than the one tested based on the advice of the pharmacist or the general practitioner. No patients developed further chronic urticaria.

Considering COX-1 inhibition of the NSAIDs tested (Table 2), we found that the weak COX-1 inhibitors tested were taken again in 28/46 cases; meanwhile, strong COX-1 inhibitors were taken in 28/85 cases (60.9% versus 32.9%; $p < 0.01$). In particular, paracetamol was taken in 24/35 cases (68.6%) and acetylsalicylic acid (ASA) only in 11/43 cases (25.6%; Table 2).

Among 99/111 patients taking the same drug or at least a different NSAID, 3 of them (3.03%) experienced an adverse reaction. ASA and paracetamol, tolerated in previous DPTs (cumulative dose, 560 and 675 mg, respectively), were involved in triggering urticaria in two patients at a lower than tested dose, during upper airways viral infection; a subject tolerating ASA developed urticaria after ketoprofen intake for flu. The three observed adverse reactions consisted of mild urticaria and occurred >1 hour after the first intake and controlled at home with antihistaminic therapy. None of the patients agreed to further allergological reevalua-

Table 2 Types of NSAIDs tested in DPTs

COX-1 Inhibition	NSAID	NSAIDs Used in DPTs	Took DPT (–) NSAID
Weak COX-1 inhibitors (<i>n</i> = 46)	Paracetamol	35	24 (68.6%)
Strong COX-1 inhibitors (<i>n</i> = 85)	Nimesulide	11	4 (36.4%)
	ASA	43	11 (25.6%)
	Ibuprofen	9	6 (66.7%)
	Ketoprofen	12	7 (58.3%)
	Naproxen	1	0
	Flurbiprofen	1	0
	Diclofenac	8	1 (12.5%)
	Indomethacin	1	1
	Morniflumate	1	1
	Metamizole	4	1 (25%)
	Piroxicam	1	0
Selective COX-2 inhibitors (<i>n</i> = 1)	Celecoxib	1	0

COX-1 = cyclooxygenase 1; NSAID = nonsteroidal anti-inflammatory drugs; DPTs = drug provocation tests; ASA = acetylsalicylic acid.

Table 3 General characteristics and answers to questionnaire in subjects who used the suspected culprit NSAID after a negative DPT and subjects who did not take the DPT (–) NSAID

	Took DPT (–) NSAID (<i>n</i> = 46)	Did not take DPT (–) NSAID (<i>n</i> = 65)	Total (<i>n</i> = 111)
Gender M/F	17/29	22/43	39/72
Mean age ± SD (yr)	33.6 ± 16.8*	42.3 ± 16.5	38.8 ± 16.9
Another strong COX-1 inhibitor intake, <i>n</i> (%)	26 (56.5)	34 (52.3)	60 (54)
Another weak COX-1 inhibitor intake, <i>n</i> (%)	16 (34.8)	35 (53.4)	51 (45.9)
Patients who took strong and weak COX-1 inhibitor NSAIDs, <i>n</i> (%)	9 (19.5)	14 (21.5)	23 (20.7)
NSAIDs avoidance, <i>n</i> (%)		12 (18.4)	12 (10.8)
Reactions, <i>n</i> (%)	2 (4.3)	1 (1.5)	3 (2.7)
Reasons for avoiding the same NSAIDs, <i>n</i> (%):			
No need		19 (29.3)	
Fear of a potential reaction		46 (70.7)	

**p* < 0.05.

COX-1 = cyclooxygenase 1; NSAID = nonsteroidal anti-inflammatory drugs; DPTs = drug provocation tests.

tion. No significant differences in frequency of reactions were observed between patients taking the NSAID previously tested and those subjects who took another NSAID (2/46 versus 1/53; *p* = 0.59).

Considering the three reactions in patients who took at least an NSAID again (99), an overall NPV of 96.97% (95% CI, 91–99%) was calculated. If we limit our analysis to those patients who took the same NSAID or another as strong COX-1 inhibitor (80) an NPV of 96.25% (95% CI, 89.55–99.52%) was calculated; considering only the two reactions occurred in those patients who took the same drug as the one previously negatively tested (46), the NPV was 96.65% (95% CI, 93.99–99.3%).

DISCUSSION

Our study involved 111 patients who experienced an urticaria and/or angioedema reaction after NSAIDs intake and resulted in a negative DPT with the suspected culprit NSAID, and 53 used at least another NSAID; the total number of adverse reactions was 3/99, with an NPV of 96.97%.

A negative DPT performed in hospital settings should reassure patients, ruling out a diagnosis of drug hypersensitivity. However it is well known that a patient who experienced a suspected drug reaction could be anxious about taking again the same drug again, structurally correlated molecules, or even drugs of dif-

ferent categories. Sometimes this behavior may lead to complete avoidance of specific pharmacologic therapies. In real life, prospective studies show that a consistent number of subjects with a negative DPT report avoiding the same tested drug (50–57%) and the main reasons are no need, a different prescription by the general practitioner, and fear of a potential reaction.^{8,9} In our study 99 patients took at least an NSAID again (89%); this result is significantly different from some data already available in literature (percentages closer to 50%)^{8,10} but is consistent with another follow-up study about NSAIDs,⁹ probably because of the type of drug tested, because NSAIDs are commonly used also for common cold, fever, and as pain relievers. However, 58.56% of patients did not take the tested tolerated NSAID, and 10.8% of them did not take any NSAIDs, two only using nonconventional therapies, such as homeopathy or acupuncture. There was no significant difference between male and female patients taking the same NSAID and subjects avoiding the tolerated drug. Moreover, no significant correlation between age and patients' behavior was found, even though a statistical difference was observed.

It is interesting to notice that a negative DPT with paracetamol is cited by a higher intake of the drug (68.6% in our study and 73% in a study by Waton *et al.*) in comparison with other NSAIDs. In our study, many patients were afraid to use strong NSAIDs again, such as ASA, despite a negative DPT. We suppose that Italian general practitioners and pharmacists (for drugs without prescription) could recommend this behavior, because paracetamol is seen as low-risk molecule and it is widely used.

We did not find a statistically significant difference in the number of reactions between patients who have taken the same NSAID and those who have taken a different NSAID. Although none of these patients agreed to undergo a further oral DPT after the described reactions, we think that the reason for these adverse reactions was the presence of a concomitant viral infection.

Previous studies have focused on the high NPV of NSAIDs DPTs (89–97.8%).^{8,9,11} Waton *et al.* found an NPV of 89% in patients who experienced cutaneous drug reactions with NSAIDs.⁸

In a cohort study, Defrance *et al.* observed a high NPV (97.8%) in 139/279 patients who took the same NSAIDs tested before. Their study design was different, because it was testing patients with clinical manifestation of respiratory symptoms and anaphylactic shock/anaphylaxis as well as cutaneous symptoms.⁹

Limitations of this study are likely a selection bias, even if characteristics of the contacted persons were comparable from the population first tested through DPTs and the small size sample considered.

In conclusion, we observed a poor compliance to the indications provided to the patients themselves that continued to avoid the NSAID tested intake, mainly for fear of new adverse reactions, particularly when strong COX-1 inhibitor NSAIDs were involved. On the other hand, we observed a small percentage of reactions both in patients who took the same NSAID and in those who took a different NSAID. Hence, it is important to have effective communication between patients and physicians in explaining the meaning of the results of allergological tests (including its limits), to reassure the patients and their general practitioner and to avoid unjustified therapies limitation.

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