

Evaluating the negative predictive value of provocation tests with nonsteroidal anti-inflammatory drugs

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Abstract

Background: The nonsteroidal anti-inflammatory drugs (NSAIDs) hypersensitivity work-up is based on clinical history, skin tests, and drug provocation tests. The negative predictive value (NPV) of the latter is not established.

Method: A cohort study was conducted in the Allergy Department in Montpellier to evaluate the NPV of the provocation test with NSAIDs in patients with clinical presentation suggestive of hypersensitivity, and negatively tested. Patients were contacted at least 6 months after the work-up. Patients who took NSAID and reacted were proposed a new allergy work-up, which included a provocation test with the culprit drug.

Results: Among the 393 patients contacted, 279 (71.0%) were followed up. Two hundred and sixty (93.2%) patients had taken a NSAID at least once: 139 (53.5%) the same drug as the one tested and 215 (82.7%) an alternative (94, 33.7% taking both the tested NSAID and an alternative). Eight patients (3.1%) reported a reaction (five with the negatively tested NSAID and three with another NSAID). All the reactions occurred immediately after the first administration and were not severe. Among the five patients who reacted with the negatively tested NSAID, only three accepted a re-challenge, negative in two cases and positive in one, representing a NPV of 97.8% (95% CI: 95.4–100%). Three patients (3/215) reported a reaction when an alternative NSAID was taken, representing a NPV of 98.6% (95% CI: 97–100%).

Conclusion: The NPV of NSAIDs drug provocation test is high. This should reassure physicians who might hesitate to prescribe NSAIDs, especially in patients with negative allergic work-ups.

Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is the second most common drug hypersensitivity, after β -lactam antibiotics (1). Several subtypes of hypersensitivity to NSAIDs have been distinguished (2, 3) depending on symptomatology (respiratory, cutaneous, anaphylaxis), timing (immediate, delayed), underlying chronic disease (otherwise healthy subjects, asthmatics, chronic urticaria patients), or putative mechanism of the reaction (allergic, nonallergic mediated).

The strategy used to confirm a suspicion of drug hypersensitivity is based on clinical history (4). A definite diagnosis sometimes requires skin tests (allergic reactions) and more frequently a drug provocation test, as recommended by the European Network for Drug Allergy (ENDA) (4). There are

several limitations to the procedure of drug provocation testing. Reproducing the original symptoms, this test is potentially dangerous and must be performed under medical surveillance in specialized hospital centers (1). Often, provocations are negative, and drug hypersensitivity is ruled out (1). However, crucial co-factors such as co-medication, viral infection, and physical exercise might be absent during the test procedure. Therefore, false-negative results can occur. The risk for patients, with a suspicion of NSAID hypersensitivity and a negative provocation to react later when they take the NSAID again, is still unknown.

A cohort study, using the Drug Allergy and Hypersensitivity database (DAHD), was conducted to evaluate the negative predictive value of provocation tests with NSAIDs in

patients with clinical suspicion of hypersensitivity and a negative provocation test to at least one NSAID.

Patients and methods

Patients

This study was conducted at our Hospital, in the Allergy Department in Montpellier. It included all patients seen between January 2005 and March 2009 relating a clinical history of hypersensitivity to NSAIDs and negatively tested. It excluded patients with a previous diagnosis of chronic idiopathic urticaria. For the patients with a positive provocation test to a NSAID, a second provocation test was proposed with another NSAID and these patients were followed up as well, considering the later negatively tested NSAID. None of the patients were on angiotensin-converting enzyme inhibitors.

The initial drug allergy work-up started with the standardized ENDA questionnaire on drug allergy (5). If the suspected reaction was compatible with a potential drug hypersensitivity, an oral provocation test with the suspected drug was proposed. It consisted of ingesting increasing doses of the suspected causal drug once every 30 min until the usual daily dose or until symptoms of a drug reaction occurred, as described previously (1). Patients with a history of anaphylactic shock had intravenous catheters in place during the test. Antihistamine medications had to be stopped 1 week before, and beta-blockers (when anaphylaxis was the initial clinical history) 2 days before the provocation test.

Follow-up

For the follow-up, a questionnaire was proposed to all patients with a negative drug provocation test. It was first sent by regular mail to the patients. A reminder was sent after 2 months. Finally, if the patients did not respond, a phone call was made after 3 months. The patient was considered lost to follow-up after three attempts.

This questionnaire can be summarized as follows:

- Has the patient taken the previously suspected NSAID or another one since the negative provocation?
- If yes, what was (were) the name(s) of the drug and did a reaction occur? If so, what kind of reaction?
- If no, what were the reasons for not taking a NSAID?

To facilitate the reminder of the patient, the international nonproprietary name of the tested NSAID and a list of brand names were presented to the patient. For alternatives, a similar list was proposed to the patient with the most common NSAIDs.

When a patient reported a reaction, a contact was established with the patient and a new allergy work-up was proposed. This included a new provocation test with the culprit drug.

Statistical analysis

Data were expressed in either frequency and percent or median and inter-quartiles. The negative predictive value was

assessed with its 95% confident interval (95% CI). The analysis was conducted under SAS (SAS Institute, Cary, NC, USA).

Results

Among the 393 contacted patients with a negative oral provocation test to NSAIDs (89.3% with the culprit NSAID and 10.7% with an alternative NSAID when the culprit NSAID was first tested and was positive, Table 1), 279 (71.0%) accepted to participate in the study. One hundred and four (26.5%) refused to participate, six (1.5%) could not be located (either by mail or phone), and four (1.0%) were deceased at the time of the follow-up.

Initial clinical manifestations

Clinical presentations were equally distributed between subjects who accepted or refused to participate (Table 1). Isolated cutaneous reactions like urticaria, angioedema, and exanthema were the most frequently reported symptoms (more than 50%). Anaphylactic reaction, diagnosed according to the clinical criteria proposed by Sampson et al. (6), was described by 25% of the patients. Immediate reactions (occurring within the first six hours) were the most common manifestations (197–50.2%). Acetyl-salicylic acid (85–21.6%) and acetaminophen (80–20.9%) were the most frequently suspected drugs followed by ibuprofen and piroxicam (68–17.3%).

Follow-up

Among the 279 patients followed for a median time of 33 months (inter-quartiles: 19.4–46.6 months), 260 (93.2%) took a NSAID at least once, 139 (53.5%) the same NSAID as the one tested, and 215 (82.7%) an as potent alternative (94–33.7% taking both the tested NSAID and an alternative). The NSAID used during re-exposition were at least as potent as the one utilized during the index-reaction and included piroxicam, tiaprofenic acid, and diclofenac. Considering the 30 patients with an initial positive provocation: acetyl-salicylic acid was implicated in eight cases, ketoprofen in seven cases, ibuprofen in six cases, piroxicam in five cases, tiaprofenic acid in two cases, diclofenac and niflumic acid in one case each.

Clinical manifestations of reacting patients

Among the 260 followed patients who had taken at least one NSAID because the negative provocation test, eight (3.1%) reported a reaction: five with the negatively tested NSAID (acetaminophen in two cases, diclofenac in one case, piroxicam in one case, and tiaprofenic acid in one case) and three with a different NSAID to the one tested (acetaminophen in one patient who was initially tested with ibuprofen, diclofenac in one patient who was initially tested with piroxicam, and meloxicam in one patient who was initially tested with ketoprofen). None of the reactions were severe (i.e., anaphylaxis or anaphylactic shock). Among the five patients who

Table 1 Patients' characteristics and clinical presentation of the previous reaction

	Whole population	Followed population	Not followed population
N (%)	393	279 (71.0)	114 (29.0)
Age (median) (years)	43 (29–59)	53 (32–60)	38 (27–56)
Sex: female (%)	260 (67.0)	188 (67.3)	72 (63.1)
Atopics (%)	201 (51.1)	142 (50.8)	59 (51.8)
Asthma (%)	52 (13.2)	34 (12.2)	18 (15.8)
Clinical presentation (%)			
Anaphylactic shock/anaphylaxis	97 (24.6)	71 (25.5)	26 (22.8)
Urticaria/angioedema	182 (46.3)	129 (46.2)	53 (46.5)
Exanthema	49 (12.5)	33 (11.8)	16 (14)
Bronchial hyperreactivity	10 (2.5)	8 (2.9)	2 (1.7)
Other reaction	27 (6.9)	19 (6.8)	8 (7)
Unknown	28 (7.1)	19 (6.8)	9 (7.9)
Reaction type (%)			
<1 h	108 (27.5)	77 (27.6)	31 (27.2)
1–6 h	89 (22.7)	66 (23.6)	23 (20.2)
6–24 h	47 (12)	35 (12.5)	12 (10.5)
>24 h	79 (20.1)	55 (7.9)	24 (21.0)
Unknown	70 (17.8)	46 (16.5)	24 (21.0)
Drug tested (%)			
Celecoxib	37 (9.4)	26	11
Acetaminophen	82 (20.9)	57	25
Acetyl-salicylic acid	85 (21.6)	60	25
Nifluric acid	11 (2.8)	7	4
Tiaprofenic acid	24 (6.1)	14	10
Diclofenac	2 (0.5)	2	0
Ibuprofen	68 (17.3)	45	23
Ketoprofen	45 (11.5)	37	8
Meloxicam	2 (0.5)	0	2
Naproxen	3 (0.8)	1	2
Nimesulide	6 (1.5)	6	0
Piroxicam	68 (17.3)	52	16
Patient with a positive provocation test to one NSAID	37 (9.4)	30 (10.7)	7 (6)

reacted to the negatively tested NSAID, clinical manifestations were urticaria (three patients), angioedema (one patient), and undefined cutaneous reaction (one patient). Reactions occurred immediately after the first drug administration. Only three of these five patients accepted a re-evaluation, including the repeated provocation test with the culprit NSAID (diclofenac in one subject, piroxicam in one and acetaminophen in one). Two were negative. One patient presented urticaria immediately after taking diclofenac. This patient had a medical history of chronic idiopathic urticaria, but we considered that clinical manifestations observed were compatible with drug hypersensitivity. Among the three patients who reacted with a different NSAID, clinical manifestations were angioedema (two patients) and urticaria (one patient). None of them accepted a re-evaluation.

Negative predictive value

Among the 260 patients who took the tested drug or another NSAID, 8 (3.1%) reported a reaction, representing a global negative predictive value of 96.9% (95% CI: 94.8–99%).

When excluding the two patients who were negatively re-tested, the negative predictive value reached 97.7% (95% CI: 95.9–99.5%).

Restricting the analysis to those who took the same NSAID as the one previously negatively tested (139 patients), five reported a reaction, representing a negative predictive value of 96.4% (95% CI: 93.3–99.5%). Only three of them could be considered as hypersensitive, including both the patients who refused re-evaluations and the patient who presented a reaction to the repeated provocation. Thus, the negative predictive value of provocation tests was 97.8% (95% CI: 95.4–100%).

Three patients (3/215) reported a reaction when an alternative NSAID was taken, representing a negative predictive value of 98.6% (95% CI: 97.0–100%).

Reasons for avoiding the use of the negatively tested NSAID

Several questions were put forward to the patients to find out why they did not take the negatively tested NSAID or another NSAID (Table 2). It turned out that, in many cases,

Table 2 Description of the followed population according to the type of NSAID (negatively tested culprit or alternative NSAID) and the use (taken, not taken) of NSAID

	Tested not taken Alternative not taken	Tested taken Alternative not taken	Tested not taken Alternative taken	Tested taken Alternative taken
<i>N</i>	19	45	121	94
Age (median) (years)	44 (31–63)	50 (32–61)	46 (32–61)	41 (27–55)
Sex: female (%)	12 (63.0)	26 (57.8)	86 (71.0)	64 (68.1)
Atopy (%)	7 (36.8)	22 (48.9)	64 (52.9)	49 (52.1)
Asthma (%)	1 (5.3)	7 (15.5)	18 (14.9)	8 (8.5)
Clinical presentation (%)				
Anaphylactic shock/anaphylaxis	4 (21.0)	18 (40)	33 (27.3)	16 (17)
Urticaria/angioedema	8 (42.0)	13 (28.9)	60 (49.5)	48 (51)
Exanthema	3 (15.8)	6 (13.3)	12 (9.9)	12 (12.8)
Bronchial hyperreactivity	0	1 (2.2)	3 (2.5)	4 (4.2)
Other reaction	2 (10.5)	3 (6.7)	5 (4.1)	9 (9.6)
Unknown	2 (10.5)	4 (8.9)	8 (6.6)	5 (5.3)
Reaction type (%)				
<1 h	5 (26.3)	11 (24.4)	41 (33.9)	20 (21.3)
1–6 h	5 (26.3)	14 (31.1)	26 (21.5)	21 (22.3)
6–24 h	2 (10.5)	4 (8.9)	15 (12.4)	14 (14.9)
>24 h	6 (31.6)	10 (22.2)	17 (14.0)	22 (23.4)
Unknown	1 (5.2)	6 (13.3)	22 (18.2)	17 (18.1)
NSAID tested				
Celecoxib	2	8	10	6
Acetaminophen	2	22	4	29
Acetyl-salicylic acid	5	7	28	20
Nifluric acid	1	1	4	1
Tiaprofenic acid	1	1	9	3
Diclofenac	0	1	1	0
Ibuprofen	1	9	19	16
Ketoprofen	7	3	18	9
Meloxicam	0	0	0	0
Naproxen	0	0	1	0
Nimesulide	0	2	4	0
Piroxicam	1	3	29	19
Patient with a positive provocation test to one NSAID	3	4	16*	7
Reasons (%)				
No need	10 (52.6)	NA	NA	NA
Use to take another one	NA	NA	35 (28.9)	NA
Afraid of a potential reaction	6 (31.6)	NA	42 (34.7)	NA
The GP refused to prescribe	2 (10.5)	NA	19 (15.7)	NA
The GP prescribed an alternative NSAID	NA	NA	18 (14.9)	NA

Tested: the patient took at least one time the NSAID negatively tested during the drug allergy work-up; Alternative: the patient took at least one time another NSAID than the one negatively tested during the allergy work-up.

GP, General practitioner; NA, not applicable, NSAID, nonsteroidal anti-inflammatory drug.

*These patients had a positive provocation to the culprit NSAID, a negative provocation to one alternative and took another NSAID (not the culprit, not the negatively tested one) during the follow-up period.

patients were afraid of a potential reaction. In some cases, physicians refused to prescribe the tested NSAID and preferred an alternative.

Discussion

The present study included 393 patients with a suspicion of hypersensitivity reactions to NSAIDs and negative results in oral provocation tests. Two hundred and seventy nine

patients (71%) were contacted during 6 months after the initial allergy tests. Among the 260 patients (93%) who took the previously suspected drug or another NSAID, only eight reported a reaction (five with the negatively tested NSAID and three with another NSAID). Among the five patients who described clinical manifestations with the negatively tested NSAID, two displayed negative results to repeated challenges including oral provocation tests. Therefore, the negative predictive value after allergy re-evaluations was

97.8%. A few cases of positive reactions were observed, but they were not too severe (urticaria and angioedema) and occurred immediately after the first drug administration. Systemic reaction (anaphylaxis or anaphylactic shock) was never reported. Therefore, patients with a negative oral provocation test to NSAIDs could, if necessary, repeat this treatment at home without worrying. Patients were re-exposed either to the same NSAID (53.5%) or to a NSAID at least as potent as the one involved in the index-reaction. Therefore, it cannot be assumed that a substantial proportion of patients were tested and re-exposed only with weak cyclooxygenase inhibitors.

Two of the five patients who reacted to the negatively tested NSAID refused a repeated oral provocation test. With regard to these patients, reacting subjects were probably overestimated and the negative predictive value of oral provocation tests was lowered. Besides, only one patient who accepted a re-evaluation work-up presented a reaction.

A potential selection bias was restricted in the present study. First, the follow-up rate was high (71%). Secondly, clinical presentation and involved NSAIDs were well balanced between participant and nonparticipant groups. Thirdly, by experience, the patients who expressed a reaction were more likely to participate in such a study. Finally, when a reaction occurred, the usual contact was the initial drug allergy center. Consequently, even if a selection bias did occur, it should be equally distributed between groups or in disfavor of the group of patients who did not react and therefore increased the negative predictive value.

The number of patients who took the previously suspected NSAID or another NSAID is significant (260 of the 279 who answered the questionnaire – 93.2%) and higher than in other studies evaluating the negative predictive value of drug provocation tests (7). Indeed, in the latter study (7), only

118/365 (32.3%) patients with a negative provocation test to a β -lactam were re-exposed. Among them, 9 (7.6%) reported a nonsevere nonimmediate reaction (five urticaria, three exanthema, and one undefined cutaneous reaction). Only four accepted a re-challenge, negative in two cases and positive in the two others, giving a negative predictive value of 94.1% (95% CI: 89.8–98.3%). Similar data have recently been published by another team (8). Ideally, it would be necessary to have data on pre and postodds for each class of NSAIDs and only multicentre studies could bring the number of patients needed for such a study. Analgesic treatment is essential in daily life, is also usually used in anesthesia, and represents an alternative to corticotherapy in the case of chronic pain. However, in some cases, patients and physicians were afraid of a new reaction and preferred to avoid the tested NSAID.

In conclusion, the negative predictive value of drug provocation tests with NSAIDs is high (over 96%) whatever the NSAID (the one negatively tested or an alternative), and none of the false-negative patients described a life-threatening reaction. This should reassure physicians who might hesitate to prescribe NSAIDs, even in patients with negative allergic work-ups.

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Conflict of interest

None of the authors had any conflict of interest. None of the authors received fees for the study.

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