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Prevention of nonsteroidal inflammatory drug-induced urticaria and/or angioedema

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ABSTRACT

Background: Urticaria and/or angioedema (U/AE) are the most frequent and less severe forms of nonallergic hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Management of NSAID-induced U/AE includes (1) the avoidance of the culprit drug and of cyclooxygenase (COX) 1 inhibitors, (2) the use of weak COX-2 inhibitors, and/or (3) desensitization to aspirin. Because these possibilities may have drawbacks, we tested the possibility of preventing NSAID-induced U/AE by the administration of antihistamines and/or a combination of antihistamines and leukotriene antagonists.

Objective: To test the preventive effect of antihistamines and/or leukotriene antagonists on the development of U/AE in patients with a history of NSAID hypersensitivity confirmed by a positive challenge result.

Methods: A single, placebo-controlled, oral challenge using the culprit NSAID was applied to 65 patients with a history of NSAID-induced U/AE. In the case of recurrence of the symptoms, another oral challenge was performed under premedication with antihistamines alone or combined antihistamines and leukotriene antagonists.

Results: A total of 59 of 65 patients (90%) tolerated a normal dose of NSAID, confirming previous data on the poor reproducibility of nonallergic hypersensitivity reactions to NSAIDs on challenge. Of the 6 patients who experienced recurrence of the U/AE on NSAID challenge, antihistamines and combined antihistamines and leukotriene antagonists prevented the hypersensitivity reactions in 2 and 3 of them, respectively. Only 1 patient still developed a moderate NSAID-induced urticaria despite the double premedication.

Conclusion: Treatment with NSAIDs at normal doses is possible and well tolerated in patients who have experienced NSAID-induced U/AE, which could be prevented by the concomitant use of antihistamines and leukotriene antagonists.

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Introduction

Hypersensitivity reactions induced by nonsteroidal anti-inflammatory drugs (NSAIDs) affect approximately 1% of the general population.¹ The term *NSAID hypersensitivity* encompasses a wide spectrum of clinical symptoms that occur in the minutes after intake of aspirin or NSAIDs and affect the skin and the respiratory mucosa. The symptoms range from benign urticaria and/or angioedema (U/AE) to severe bronchospasm. NSAID hypersensitivity corresponds to nonallergic hypersensitivity mediated by

the pharmacologic properties of the drugs.² Indeed, NSAIDs inhibit cyclooxygenase (COX) 1 and 2 isoforms, thus blocking prostaglandin synthesis and increasing the production of leukotrienes and other proinflammatory molecules. This prostaglandin-leukotriene imbalance favors mediator release from mast cells and U/AE exacerbations. All NSAIDs that inhibit the COX-1 isoform could precipitate hypersensitivity reactions, whereas selective COX-2 inhibitors induced reactions with very low incidence (0.008%).³

Definite withdrawal of NSAIDs, without alternative treatment, is questionable, especially for patients who need NSAIDs, such as those with coronary ischemic diseases or rheumatologic disorders.^{4,5} According to the European Academy of Allergy and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA2LEN), the management of NSAID hypersensitivity

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expressing as U/AE relies on the avoidance of the culprit NSAID and on the ability to take another NSAID at pharmacologic doses, if necessary. Two possibilities are proposed: (1) prescription of a COX-2 inhibitor when the hypersensitivity reaction is induced by aspirin and/or COX-1 inhibitors (although COX-2 inhibitors generally do not provoke cutaneous hypersensitivity reactions, they have a number of adverse effects that may limit their long-term use, such as in chronic rheumatic diseases⁶) and (2) induction of tolerance to aspirin and NSAIDs using desensitization protocols. These protocols are effective but need a regular administration of the drug because the tolerance will disappear within 2 to 5 days after NSAID treatment interruption. Therefore, such strategy is not applicable to most patients who need only short-term NSAID treatments.⁷

In this article, we suggest a third alternative to NSAID avoidance—the use of antihistamines and/or leukotriene antagonists to prevent NSAID-induced U/AE flares. Indeed, association of antihistamines and leukotriene antagonists has been reported to be useful in preventing drug-induced urticaria in a few previous studies.^{8–10} In this study, we investigated the tolerability and safety of a normal dose of a NSAID with or without premedication in patients with a well-documented history of NSAID-induced U/AE.

Methods

Patients

Sixty-five patients who presented with multiple cutaneous NSAID-induced hypersensitivity reactions were studied. They were mostly treated by a general practitioner or a rheumatologist. All the patients developed several attacks of urticaria and/or facial angioedema in the minutes or hours after the drug intake, mainly prescribed for rheumatologic indication, migraine, or menstrual pain. Almost all patients developed symptoms after the use of different classes of NSAIDs. None of the patients developed systemic symptoms suggestive of anaphylaxis. We excluded from the study the patients with NSAID-induced respiratory symptoms. None of the recruited patients refused to take part to the study. The allergologic workup of these patients consisted of a careful clinical history and skin tests, including prick and intradermal tests, with one selected NSAID, which was chosen among the molecules responsible for reactions according to its indications and its potential tolerance (selective COX-2 NSAIDs were preferred). Drug solutions were prepared by the hospital pharmacy. Although NSAID hypersensitivity is not an IgE-mediated disease, these tests were performed systematically before the challenge with the NSAID for both medical responsibility concerns and to reassure the patients and their physicians. Indeed, this study was conducted in 2010 before the publication of the guidelines stating that skin testing is not recommended in the management of NSAID-induced U/AE.⁷ Since publication of the guidelines we no longer perform skin tests in patients with NSAID-induced U/AE. Skin tests and drug challenges were performed during a 2-day hospitalization. If not contraindicated, oral challenges were performed to assess the potential contribution of premedication. All individuals gave oral informed consent and the study was approved by the Multidisciplinary Review Board in Allergology—University Hospital Lyon-Sud. Furthermore, this observational study, which evaluated the current treatment of patients in our department, was considered a non-interventional study.

Oral Challenge

A single-blind, placebo-controlled, oral challenge procedure with the culprit NSAID was applied to the patients. The procedure included 3 steps: a placebo oral administration (1 mL of saline serum), then (30 minutes later) the intake of 1/100 dilution (in 1 mL of saline serum) of the total dose, followed (60 minutes later) by the total dose. The total dose corresponds to the recommended dose for

adult (eg, 1 g of aspirin and 400 mg of ibuprofen). This protocol is different from the EAACI/GA2LEN guidelines, which have been put forward for aspirin hypersensitivity with respiratory symptoms and which propose oral NSAID challenge for 2 days using increasing doses of the drug. In our patients, who had cutaneous symptoms only, the risk of severe NSAID hypersensitivity was considered nil, and we decided to give the drug as a single full-dose challenge. Patients were monitored for 24 hours after the provocation test in a hospital setting. In the case of a positive oral challenge result to the drug, the patient was discharged and another oral challenge was performed the following week during a 1-day hospitalization. The new oral challenge was performed using the same NSAID preceded by a premedication of antihistamines (desloratadine, 5 mg) with or without a leukotriene antagonist (montelukast, 10 mg) 2 hours before. The association of desloratadine and montelukast was chosen for its efficacy and tolerance in the treatment of chronic urticaria, and we applied this therapeutic alternative in case of U/AE flare induced by NSAID, despite a premedication by antihistamines alone.¹¹

Statistical Analyses

Data are expressed in percentage of patients. We performed the Pearson χ^2 test to evaluate whether the tolerance of NSAID oral challenge in patients with and without chronic urticaria was different. We used the simulated *P* value (*P* values were computed by Monte Carlo simulation)¹² because some expected counts under the null hypothesis were less than 5 (R program, version 2.14; www.cran.r-project.org). *P* < .05 was considered statistically significant.

Results

Sixty-five patients were included in this study. They presented a cutaneous hypersensitivity induced by various NSAIDs. Of note, most of the patients developed hypersensitivity reactions to several drugs (eg, both aspirin and ibuprofen), which is usual in NSAID hypersensitivity.⁷ However, for skin tests and oral challenges, we only used one drug responsible for reactions, selected for its indications and its potential tolerance. Clinical data and the NSAIDs tested are summarized in Table 1. Skin test results were negative in all patients. Figure 1 shows the protocol used for oral challenge.

All patients tolerated the placebo and intake of 1/100 dose of a NSAID. Of the 65 patients, 59 (90%) tolerated the total dose of the NSAID on the first challenge without premedication by antihistamines or leukotriene inhibitors, suggesting that they only displayed a mild hypersensitivity to the drugs. This finding confirms that NSAID hypersensitivity does not develop systematically on drug intake and needs additional cofactors to occur.

Six patients had a positive oral challenge result to one NSAID (Table 2): aspirin in 5 cases and flurbiprofen in 1 case. Interestingly, no hypersensitivity reaction occurred in the 12 patients challenged with selective and highly selective COX-2 inhibitors. A second challenge with the same drug was performed 1 week later with premedication by antihistamines (desloratadine, 5 mg). Two patients tolerated the drug. For the 4 remaining patients (6%), a third challenge with a double premedication by an antihistamine and a leukotriene inhibitor (desloratadine, 5 mg, and montelukast, 10 mg) was performed 1 week later and tolerated by 3 of the 4 patients. Only a moderate urticaria occurred in 1 patient after a challenge with aspirin, despite the double premedication. The intensity of the urticaria was much less than without premedication. In summary, a total of 64 of the 65 patients (98%) tolerated a challenge with a normal dose of an NSAID without adverse reactions using the step-by-step protocol described in Figure 1.

Twenty-one patients (32%) had a history of chronic urticaria, which made them more prone to urticaria flares induced by various drugs,^{2,13} including NSAIDs.¹⁴ Oral challenges were well tolerated in

Table 1
Epidemiology and clinical data of the 65 patients studied^a

Characteristic	No. (%) of patients
Age, mean (range), y	46 (17–79)
Sex ratio, M/F	25/40
Chronic urticaria	21 (32)
Atopic diseases	15 (23)
Asthma	4 (6)
Symptoms	
Urticaria	33 (51)
Angioedema	25 (38)
Urticaria and angioedema	7 (11)
Culprit drugs that were tested	
Nonselective COX inhibitors	
Aspirin	25 (39)
Ibuprofen	11 (17)
Ketoprofen	7 (11)
Diclofenac	5 (8)
Flurbiprofen	1 (2)
Tenoxicam	1 (2)
Piroxicam	1 (2)
Naproxen	1 (2)
Sulfasalazine	1 (2)
Selective COX-2 inhibitors	
Nimesulide	10 (15)
Highly selective COX-2 inhibitors	
Celecoxib	1 (2)
Rofecoxib	1 (2)

Abbreviation: COX, cyclooxygenase.

^aData are presented as number (percentage) of patients unless otherwise indicated.

59 patients (91%) without premedication and 64 (98%) with premedication. The first oral NSAID challenge without premedication was well tolerated in 95% of these patients compared with 89% of patients without chronic urticaria. With premedication, no significant difference was found in tolerance between patients with (20 of 21 patients [95%]) and without (44 of 44 patients [100%]) chronic urticaria ($P = .65$). Collectively, these data demonstrate that NSAID cutaneous hypersensitivity and a history of chronic urticaria do not prevent the intake of normal doses of NSAIDs.

Discussion

In the present study, we found that premedication with antihistamines and leukotriene antagonists represents a practical option for NSAID treatment in patients presenting with NSAID-

induced U/AE. Indeed, 5 of 6 patients with positive drug challenge results were totally protected by the combination of antihistamines and leukotriene antagonists, whereas 2 of 6 were protected by antihistamines alone. Of note, we used a low dose of desloratadine (5 mg), and we hypothesize that a higher number of patients would have been protected by higher doses of antihistamines (10–20 mg). This strategy is easy to perform because the culprit drug (like all other NSAID) is not contraindicated and is easy to understand for both the patient and the physician because they know precisely what to do when a NSAID is needed. However, 1 of the 65 patients (2%) reacted even with double premedication, suggesting that the first dose should be given under medical supervision.

Therefore, premedication with antihistamines and leukotriene antagonists appears to be an additional tool in the management of NSAID hypersensitivity, together with those proposed by EAACI/GA2LEN (ie, avoidance of the culprit drug and chemically related drugs, use of a weak COX-2 inhibitor, or desensitization).⁷ One of the most striking findings of the study is the poor reproducibility of U/AE on drug challenge. Indeed, 90% of patients could take a normal dose of the drug that had induced cutaneous symptoms in the past. Although it is known that nonallergic hypersensitivity to drugs does not recur systematically when the culprit drug is readministered, we were puzzled by the high percentage of tolerance to NSAIDs in our patients. However, our data are in keeping with the results of the recent study by Defrance et al,¹⁵ who could induce, on challenge, clinical symptoms in only 10% of a cohort of 393 NSAID-hypersensitive patients. Several hypotheses could explain why the NSAID hypersensitivity did not recur in most of our patients. First, the diagnosis of NSAID hypersensitivity was wrong and the patients were not NSAID hypersensitive. This theory is possible for a limited number of patients whose hypersensitivity occurred several years ago or who presented with a medical certificate stating an aspirin hypersensitivity but did not remember the incident, which had occurred in infancy; however, most of the patients had developed several recent flares of U/AE using aspirin and other NSAIDs, confirming the diagnosis of drug hypersensitivity. Second, the patients included in this study only had moderate hypersensitivity to an NSAID, which was not systematically provoked by each drug intake. Along this line, we selected patients for this study who developed only skin symptoms, which may be considered as the mildest form of NSAID hypersensitivity. Third, several cofactors, necessary for the full clinical expression of NSAID hypersensitivity, were missing during the challenge

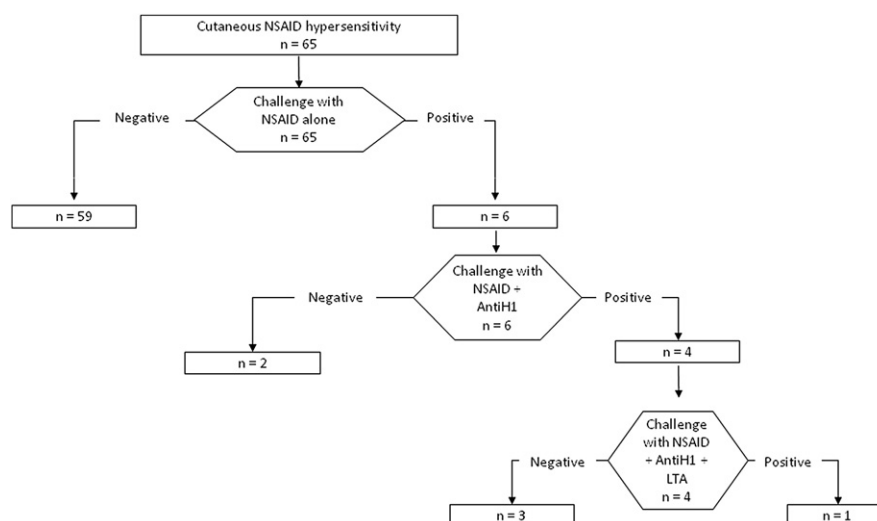


Figure 1. Results of oral challenges with nonsteroidal anti-inflammatory drugs (NSAIDs), using a step-by-step protocol. AntiH1 indicates antihistamines; LTA, leukotriene antagonists.

Table 2

Characteristics of the patients who reacted to NSAIDs without premedication

Sex/age, y	Underlying diseases	Culprit NSAID	Time to onset of the reaction, min	Type of final premedication	Tolerance of final NSAID challenge
F/35	Atopy/CU	Aspirin	30	AntiH1 and LTA	Yes
F/41	Atopy	Aspirin	60	AntiH1 and LTA	Yes
M/44	0	Aspirin	30	AntiH1	Yes
F/21	0	Aspirin	240	AntiH1 and LTA	No
F/42	0	Flurbiprofen	120	AntiH1 and LTA	Yes
M/28	0	Aspirin	30	AntiH1	Yes

Abbreviations: antiH1, antihistamine; LTA, leukotriene antagonist; CU, chronic urticaria; NSAID, nonsteroidal anti-inflammatory drug.

procedure performed in this study. Indeed, NSAID hypersensitivity usually develops during the treatment of an infectious or an inflammatory disease associated with the production of inflammatory mediators that may be contributing factors to U/AE flares. Therefore, all patients presented with NSAID hypersensitivity reactions, some of which recurred after drug challenge and others not, in an unpredictable manner. Interestingly, the current outcomes of reintroducing drugs after cutaneous drug adverse reaction revealed that most patients do not retake the drug. Recently, Waton et al¹⁶ reported that after an extensive allergological workup, including skin tests and drug rechallenge under hospital surveillance, drugs are not taken again because 25% of the patients evaluated refused to take the drug again or because their general practitioner was afraid and did not want to prescribe these products. Thus, the oral NSAID challenge under antihistamines and/or antileukotriene antagonists in a hospital setting could help to control the symptoms of a possible recurrence of the NSAID hypersensitivity, to reassure the patient and physician when a NSAID treatment is necessary, and to bring an educational value by helping the patient implement this procedure in real conditions.

In conclusion, a history of NSAID-induced U/AE often makes patients and/or physicians reluctant to prescribe NSAIDs (the culprit one or an alternative). The addition of a premedication combining antihistamines and/or leukotriene antagonists is a valuable alternative in the management of NSAID-induced U/AE. Thus, a premedication could be proposed in cases needing NSAID

intake, especially when nonselective COX inhibitors are required, reassuring the patient and the physician.

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