
Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions

Mario Sánchez Borges, MD*†; Arnaldo Capriles-Hulett, MD*‡; Fernan Caballero-Fonseca MD*‡; and Carlos Ramon Pérez, MD§

Background: The safety of new anti-inflammatory drugs in patients intolerant to classic cyclooxygenase (COX) inhibitors with urticaria and angioedema has not been determined.

Objectives: To investigate the clinical tolerance to COX-2 inhibitors in patients with cutaneous symptoms attributable to classic nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods: Patients with urticaria or angioedema triggered by NSAIDs were challenged with COX-2 inhibitors by the single-blinded, placebo-controlled oral method.

Results: One hundred ten NSAID-sensitive patients were submitted to 184 oral challenges with COX-2 inhibitors. Eighty-two patients (74.5%) were cross-reactors and 28 patients (25.4%) were single reactors. Reaction rates for COX-2 inhibitors were 21.3% for nimesulide, 17.3% for meloxicam, 33.3% for celecoxib, and 3.0% for rofecoxib.

Conclusions: Some COX-2 inhibitors, such as rofecoxib, are relatively safe in NSAID-sensitive patients with urticaria or angioedema. However, the tolerance profile varies with the drug, which might be related to a differential selectivity of the drug for COX-1 and COX-2. COX-1 inhibition would represent a major mechanism for cutaneous adverse reactions to NSAIDs. Controlled oral provocation with new NSAIDs is useful for the proper management of patients sensitive to classic NSAIDs requiring analgesic and anti-inflammatory treatment.

Ann Allergy Asthma Immunol 2001;87:201–204.

INTRODUCTION

Cutaneous and respiratory adverse reactions triggered by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase (COX) constitute one of the most common drug-related pseudoallergic reactions observed in both general practice and allergy subspecialty. These reactions occur more frequently in atopic subjects, with a frequency rate between 1% to 3% of the general population.^{1,2}

During the last decade the recognition

of two different prostaglandin synthase iso-enzymes, designated COX-1 and COX-2³ led to the development of new and more selective NSAIDs, which are better tolerated by the gastrointestinal and hematopoietic systems.^{4,5}

Although the package insert of some of these new COX-2-inhibiting drugs warns about its use in patients with aspirin-sensitive asthma (ASA), there is little information in the medical literature about whether or not they cross-react with ASA or NSAIDs and about their safety in ASA- or NSAID-intolerant subjects. The purpose of this investigation was to determine the clinical tolerance to COX-2 inhibitors in patients with cutaneous sensitivity to classic COX inhibitors. This information is required for the proper management of NSAID-sensitive subjects, especially those who need to receive analgesic and anti-inflammatory treatment for acute or

chronic conditions, such as arthritis and coronary heart disease.

MATERIALS AND METHODS

Patients

Individuals who have a history of urticaria or angioedema triggered by one or more NSAIDs were chosen for inclusion in this study. After an explanation of the possible risks and benefits, and the written informed consent, patients were submitted to controlled oral provocation tests with the suspected NSAID and those with positive challenge results underwent further oral challenges with COX-2 inhibitors. The time interval between challenges was at least 15 days and antihistamines were omitted for 96 hours (6 weeks for astemizol), whereas corticosteroids were stopped for at least 1 month. The study protocol was approved by the ethics committees of the participating institutions.

Patients with significant active medical conditions (pulmonary, gastrointestinal, cardiovascular, psychiatric, hepatic, neurologic, renal, or hematologic) and pregnant women were excluded from the study.

Oral Provocation Tests

Single-blinded oral challenges controlled with placebo were carried out with the suspected NSAIDs according to the protocol and the doses previously described.¹ For COX-2 inhibitors, maximal challenge doses were: nimesulide 100 mg, meloxicam 15 mg, celecoxib 200 mg, and rofecoxib 25 mg. Starting doses were a half of the final dose and they were given 1 hour apart. For the evaluation of the challenge tests, the "rule of nines" was used, and a test was considered to be positive if there was an increase of urticarial lesions of $\geq 30\%$ of the body surface. Challenges were done in hos-

* Allergy-Immunology Service, Centro Médico-Docente "La Trinidad," Caracas, Venezuela.

† Clínica "El Avila," Caracas, Venezuela.

‡ Centro Médico de Caracas, Caracas, Venezuela.

§ Immunology Service, Instituto de Oncología y Hematología, MSDS, Caracas, Venezuela.

Received for publication July 5, 2000.

Accepted for publication in revised form February 13, 2001.

pitals with appropriate access to emergency procedures.

A patient was designated a *cross-reactor* if he/she had a positive challenge with more than one NSAID, generally the one suspected from the past history plus a second challenge with ibuprofen. *Single-reactors* were patients who had a positive challenge with only one NSAID, whereas a second challenge with ibuprofen was negative.

RESULTS

Demographic Data

One hundred ten patients (78 female, 32 male, with a mean age of 31.2 ± 13.1 years old, range 8 to 74 years) were included in this study. Personal history of atopic diseases was present in 87 patients (79.0%) and familial atopic history in 68 patients (61.8%). There was a family history of NSAID-sensitivity in 9 patients (8.1%) and skin prick tests with aeroallergens were positive in 83 of 96 individuals tested (86.4%; Table 1).

Clinical Data

The NSAIDs responsible for reactions in these patients, as determined by the clinical records and confirmed by means of single-blinded oral challenges, are presented in Table 2. The drugs most commonly involved were acetylsalicylic acid (aspirin), pyrazolone, ibuprofen, acetaminophen, diclofenac, and ketoprofen. All patients

Table 2. NSAIDs Responsible for Adverse Reactions in 110 Intolerant Patients

Drug	N	%
Aspirin	79	71.8
Pyrazolone	50	45.4
Ibuprofen	45	40.9
Acetaminophen	28	25.4
Diclofenac	17	15.4
Ketoprofen	9	8.1
Piroxicam	3	2.7
Glafenin	3	2.7
Mefenamic acid	1	0.9
Ketorolac	1	0.9
Flurbiprofen	1	0.9
Octafenin	1	0.9
Tiaprofenic acid	1	0.9
Sulindac	1	0.9
Naproxen	1	0.9

Single-reactors: 28 (25.4%).

Cross-reactors: 82 (74.5%).

had facial angioedema affecting the eyelids and/or lips, with or without urticaria. Thirty-eight patients (34.5%) also had respiratory symptoms consisting of rhinorrhea and difficulty in breathing because of upper respiratory tract edema and/or bronchospasm. These patients did not have any underlying aspirin respiratory disease (nasal polyps, sinusitis, and asthma). Seventy-two patients (65.4%) had exclusively cutaneous symptoms (urticaria and/or facial angioedema). Eighty-two patients (74.5%) were cross-reactors and 28 patients (25.4%) were single-reactors.

Provocation Tests with COX-2 Inhibitors

Results of 184 oral challenges with 4 different COX-2 inhibitors are shown in Figure 1. Reaction rates (RR) are expressed as a percentage of tested patients with a positive test. Sixteen patients of 75 reacted to nimesulide (RR=21.3%). For meloxicam, 8 patients of 46 had a positive test (RR=17.3%). Celecoxib induced a rate of reactions of 33.3% (10 positive of 30 provocations), whereas the reaction rate for rofecoxib was 3.0% (1 of 33 challenges). The reaction rates for single- and cross-reactors are shown in Table 3.

Twenty patients were challenged with both NSAIDs celecoxib and rofecoxib; four patients (20%) had positive tests with celecoxib. Twelve patients (60%) were negative for both drugs; in one patient (5%) the tests with both drugs were positive, and tests were positive with celecoxib and negative with rofecoxib in three (15%).

Thirteen patients were challenged with the four COX-2 inhibitors: two patients (15.3%) reacted exclusively to nimesulide, one patient (7.6%) to meloxicam, celecoxib, and rofecoxib but not to nimesulide, and 10 patients

Table 1. Demographic Data

	n	%
Sex:		
Male	32	29.0
Female	78	70.9
Personal atopic history		
Rhinitis	44	40.0
Rhinitis + asthma	28	25.4
Asthma	10	9.0
Rhinitis + conjunctivitis	3	2.7
Rhinitis + atopic dermatitis	2	1.8
Food allergy	24	21.8
Other drug allergy	19	17.2
Insect allergy	2	1.8
Familial atopic history	68	61.8
Familial NSAID-intolerance history	9	8.1
Aeroallergen prick test positivity	83/96	86.4

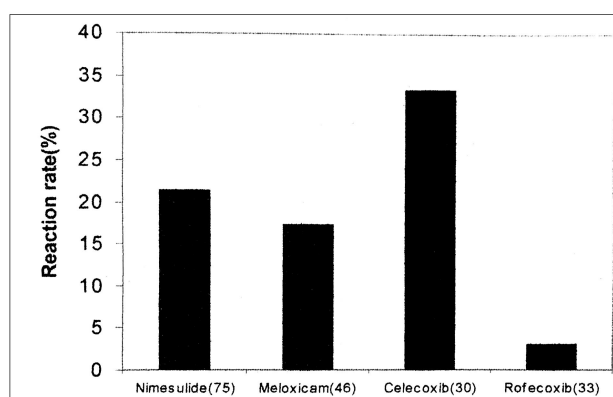


Figure 1. Reaction rates to COX-2 inhibitors in NSAID-sensitive patients. (Numbers of challenged patients are shown in parentheses).

Table 3. Reaction Rates to COX-2 Inhibitors in Single- and Cross-Reactors

Drug	Single-reactors (%)	Cross-reactors (%)
Nimesulide	3/18 (16.6)	13/55 (23.6)*
Meloxicam	0/9 (0)	8/37 (21.6)*
Celecoxib	5/10 (50.0)	5/20 (25.0)*
Rofecoxib	0/8 (0)	1/24 (4.1)*

* χ^2 test: *P* not significant.

(76.9%) did not react to any of the COX-2 inhibitors.

DISCUSSION

There is little information available in the literature about the safety of new anti-inflammatory drugs with selective COX-2 inhibitory properties in NSAID-intolerant patients. Nimesulide has been used in many countries for approximately 10 years, and few reports exist which suggest that between 8.3 and 25% of patients with previous pseudoallergic reactions to classic NSAIDs will also react to this drug.^{1,6-10} Because meloxicam, celecoxib, and rofecoxib have been more recently introduced, we are not aware of the sensitivity rates for these drugs in a large enough series of NSAID-sensitive subjects. We feel that this information is important because NSAID intolerance occurs rather frequently in the population,¹¹ and many physicians need to be educated about the proper use of analgesic/anti-inflammatory drugs.

A better safety profile for the new compounds in ASA-sensitive individuals would be expected because unin-

hibited COX-1 would continue to synthesize prostaglandin E₂, which is thought to be protective. For the most selective COX-2 inhibitors, such as celecoxib and rofecoxib, there are no publications regarding their safety in NSAID-sensitive patients with cutaneous manifestations. Stevenson et al¹² challenged 12 aspirin-sensitive asthmatic patients with celecoxib and 3 with rofecoxib, and none of them showed significant changes in forced expiratory volume in 1 second values. Another paper¹³ described a patient whose urticaria was suspected to be caused by both rofecoxib and celecoxib.

Recently, Kosnik et al¹⁴ reported five NSAID-intolerant patients who were submitted to oral challenges with up to 11 mg of meloxicam. Four of them tolerated the drug, whereas the fifth experienced rhinorrhea and chest tightness 4 hours after provocation. It was concluded that most patients with cutaneous reactions triggered by NSAIDs can tolerate meloxicam.¹⁴ According to other studies, in therapeutic doses nimesulide and meloxicam are well tolerated by ASA-sensitive asth-

matic patients, but in higher doses they cause rhinorrhea and asthma.^{6,9,14}

In this study, we have investigated the clinical tolerance of a large number of cutaneous reactors to four different COX-2 inhibitors, and the reaction rates varied between 3.0% and 33.3% depending on the drug. These results suggest that some COX-2 inhibitors are relatively safe in this patient population, and support the hypothesis that COX-1 inhibition represents the main mechanism involved in the pathogenesis of adverse cutaneous reactions to NSAIDs. Interestingly, the degree of cross-reactivity for COX-2 inhibitors in this population of NSAID-sensitive patients is clearly related to the degree of COX-1 inhibition *in vitro* as reported by Warner et al.¹⁵ They observed that the rofecoxib inhibition of COX-1 is minimal (<5-fold), whereas etodolac, meloxicam, nimesulide, and celecoxib are in the same range of COX-1 inhibition (5- to 50-fold).

The fact that there was a tendency for celecoxib to induce a higher rate of reactions, although it did not reach statistical significance, in single-reactors than in cross-reactors would suggest that there is something different in that drug which determines adverse reactions not involving COX-1 inhibition. Further studies will be required to confirm this observation.

CONCLUSION

Because the proportion of patients reacting to different COX-2 inhibitors is variable, there would still be the need for individual oral challenges to determine the tolerance of each patient to a particular drug. Our data also suggest that COX-2 inhibitors may have different degrees of COX selectivity.

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- Requests for reprints should be addressed to:*
Mario Sánchez-Borges, MD
P.O.B.A. International #635
Miami, FL 33102-5255
E-mail: malsan@cantv.net
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