
Short-term tolerability of etoricoxib in patients with cutaneous hypersensitivity reactions to nonsteroidal anti-inflammatory drugs

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Background: Etoricoxib is a novel cyclooxygenase 2 selective inhibitor. Until now, there has not been information in the literature about its tolerability in patients with a history of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).

Objective: To determine the short-term tolerability of etoricoxib in patients with a history of cutaneous adverse reactions to NSAIDs.

Methods: Single-blind challenge testing was performed on 2 different days using placebo (talc) and etoricoxib. On the first day, 2 placebo capsules were administered 1 hour apart; 7 days later, each patient received divided doses of the total therapeutic dose of 90 mg of etoricoxib: 22.5 mg initially and 67.5 mg 1 hour later if no reactive symptoms were noted.

Results: Of 141 patients who underwent challenge testing with etoricoxib, only 2 (1.4%) had positive test results; both developed wheals on the extremities. These 2 patients were treated with chlorpheniramine maleate (10 mg intravenously), and the symptoms completely resolved within 2 hours. None of the patients experienced adverse reactions to the placebo challenge.

Conclusion: The low rate of adverse reactions to etoricoxib, tested by oral challenge, suggests that patients with previous cutaneous hypersensitivity reactions to NSAIDs (primarily urticaria and angioedema) may tolerate this drug.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the drugs most frequently prescribed in medical practice owing to the progressive increase in indications for their use. The high number of prescriptions of these agents and the spread of self-medication among patients has made it necessary to point out the incidence of associated sensitivity, which ranges from 0.3% to 2.5% in the general population.¹

Several types of pseudoallergic and allergic reactions to NSAIDs have been described. The most commonly reported reactions include angioedema, urticaria, rhinitis, bronchial asthma, and anaphylactoid reactions.^{2,3} Many of these reactions depend on cyclooxygenase (COX) enzyme inhibition for their effects. In fact, it is well known that the mechanism of action of NSAIDs relies on the inhibition of the enzyme COX, which comes in 2 forms, COX-1 and COX-2. The former is constitutively expressed as a “housekeeping” enzyme in nearly all tissues, and it mediates physiologic responses (eg, cytoprotection of the stomach and platelet aggregation). In addition, this enzyme is up-regulated by inflammatory stimuli. Conversely, COX-2 is inducible in response to inflammatory or mitogenic stimuli in many tissues, and its expression has been hypothesized to be respon-

sible for the synthesis of prostaglandins, which mediate responses to pathologic processes such as pain, fever, and inflammation. The analgesic, anti-inflammatory, and antipyretic effects of all NSAIDs are believed to stem primarily from the inhibition of COX-2, whereas the reduced gastric mucosal protection associated with nonselective NSAIDs, which inhibit COX-1 and COX-2, is thought to be due to the inhibition of COX-1. However, the inhibition of these enzymes may create an imbalance between COX-1 or COX-2 and 5-lipoxygenase in the arachidonic acid cascade, resulting in lower production of the bronchodilator and anti-inflammatory prostaglandin E₂ and relatively higher production of the bronchoconstrictors and proinflammatory leukotrienes C₄ and D₄.^{4,5}

A patient with a history of adverse reactions to some NSAIDs needs to be able to take an alternative NSAID if necessary. Peroral challenge with an NSAID that is structurally different from that associated with the adverse reaction is the most common approach. Nowadays, the most common drugs tested are specific COX-2 inhibitors, including acetaminophen, nimesulide, benzydamine hydrochloride, floctafenine, and meloxicam, and, recently, selective COX-2 inhibitors, including rofecoxib, valdecoxib, and celecoxib. However, some reactions to these drugs have also been reported.^{6–12}

The present article describes the results of oral challenge with etoricoxib, a novel COX-2 selective inhibitor, in 141 patients with a history of cutaneous hypersensitivity reactions to 1 or more NSAIDs.

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MATERIALS AND METHODS

Patients

This study was performed between January 1, 2004, and September 30, 2004, in 141 consecutive patients (86 females and 55 males; mean $\pm$ SD age, 37 ± 17 years; age range, 14–74 years) referred to the Allergy Clinics of Bari University Hospital for cutaneous hypersensitivity reactions to 1 or more NSAIDs. Only patients who produced well-documented data from medical reports were enrolled, and patients who were taking drugs other than the suspected NSAID at the time of the reaction were excluded. Challenges to confirm the patient's intolerance to drugs identified as probable causes of previous reactions were deferred to avoid provoking unnecessary discomfort or risk.

A careful clinical history was taken for each patient that included listing every drug, antibiotics and others, involved in adverse episodes apart from the NSAID-related episodes, and data were collected about any personal history of allergic diseases, including asthma, rhinitis, conjunctivitis, atopic dermatitis, and food hypersensitivity. We also asked about history of chronic urticaria. All the patients underwent a peroral challenge test with etoricoxib, 90 mg. Written informed consent was obtained from all the participants.

Challenge Tests

Peroral challenges were performed with 90 mg of etoricoxib; it was the first exposure to this drug in all the patients. None of the patients had significant cutaneous or respiratory tract symptoms at the time of testing, and the pulmonary function tests showed stable forced expiratory volume in 1 second (FEV₁) values greater than 80% of predicted in all the patients.

Antihistamine treatment was discontinued 2 weeks before the challenge (6 weeks for astemizole); cromolyn sodium, corticosteroids, leukotriene receptor antagonists, and inhaled

sympathicomimetic agents were discontinued 48 hours before the challenge. The test was performed on 2 different days using placebo (talc) and etoricoxib (Arcoxia; Merck Sharp & Dome, Rome, Italy), with inert capsules as a vehicle. On the first day, 2 placebo capsules were administered 1 hour apart; 7 days later, each patient received divided doses of the total therapeutic dose of 90 mg of etoricoxib: 22.5 mg initially and 67.5 mg 1 hour later if no reactive symptoms were noted. During execution of the test, arterial pressure and FEV₁ were monitored (30 minutes and every hour after administering each drug or placebo dose or as soon as any symptoms occurred). Each patient was observed in the hospital for at least 6 hours after the challenges. Additional visits after 24 and 48 hours were requested to exclude delayed reactions. Patients with a history of chronic urticaria underwent the challenge during a period of clinical remission. The test result was considered positive if cutaneous and mucosal manifestations (erythema, wheals, or angioedema) appeared or if respiratory symptoms or a decrease of at least 20% in the FEV₁ or hypotension developed. Resuscitation equipment was available at all times during the tests.

RESULTS

Patient Demographics

Of the 141 patients with a history of hypersensitivity reactions to NSAIDs, 125 (88.7%) had experienced a reaction to 1 or more NSAIDs of the same class, 14 (9.9%) to NSAIDs of 2 different classes, and 2 (1.4%) to NSAIDs of 3 classes. Fifty-one patients (36.2%) reacted to salicylates, 32 (22.7%) to arylpropionics, 27 (19.1%) to pyrazolones, 17 (12.0%) to arylacetic acid, 11 (7.8%) to oxycam, 10 (7.1%) to sulfonanilides, 8 (5.7%) to fenetidines, 5 (3.5%) to fenamates, and 3 (2.1%) to indolics (Table 1). The overall adverse manifestations included urticaria alone in 60 patients (6 additional

Table 1. Nonsteroidal Anti-inflammatory Drugs Presumed to Be Responsible for Hypersensitivity Reactions and Clinical Reactions in 141 Patients

Drug class	Clinical reactions, No.							Total
	Urticaria	Angioedema	Urticaria and angioedema	Stevens-Johnson syndrome	Fixed erythema	Erythema multiforme	Exanthematous eruptions	
Salicylates	13*	14	24	0	0	0	0	51
Arylpropionics	15*	5	10	0	0	0	2	32
Pyrazolones	14†	1	5	1	2	0	4	27
Arylacetic acid	6	2	6	0	0	1	2	17
Oxycam	5	2	4	0	0	0	0	11
Sulfonanilides	6†	1	2	0	0	0	1	10
Fenetidines	4	1	2	0	0	0	1	8
Fenamates	3	1	1	0	0	0	0	5
Indolics	0	0	3	0	0	0	0	3
Total	66	27	57	1	2	1	10	164

* Urticaria was associated with difficulty in breathing in 2 patients.

† Urticaria was associated with difficulty in breathing in 1 patient.

patients had urticaria associated with difficulty in breathing), angioedema alone in 27, urticaria plus angioedema in 57, exanthematous eruptions in 10, Stevens-Johnson syndrome in 1, fixed erythema in 2, and erythema multiforme in 1 (Table 1).

Testing occurred within 3 months of the NSAID reactions in 64.5% of patients, within 4 to 6 months in 17.0%, and within 7 to 12 months in 18.5%. The adverse reactions to other NSAIDs that were reported only in 16 patients occurred 9 months to 7 years before testing. Five patients (3.5%) reported a history of chronic urticaria, defined as the appearance of hives or wheals on most days for more than 6 weeks. Three of these patients reported at least 1 episode of NSAID-related urticaria with or without angioedema; however, at the time of the reactions, no patient reported having been in the active phase of chronic urticaria. Of the 141 patients studied, 19 (13.5%) had a history of at least 1 atopic disease: allergic rhinitis or rhinoconjunctivitis in 12 patients (8.5%), food hypersensitivity in 4 (2.8%), bronchial asthma in 2 (1.4%), and atopic dermatitis in 1 (0.7%). Sixteen patients (11.3%) reported hypersensitivity reactions to antibiotics (1 patient reported 2 reactions): 11 were caused by β -lactams, 2 by sulfamethoxazole-trimethoprim, 2 by macrolides, 1 by quinolones, and 1 by teicoplanin. Five patients (3.5%) reported hypersensitivity reactions to other drugs: cardiovascular drugs in 3 patients, bronchopulmonary drugs in 1, and gastrointestinal drugs in 1.

Etoricoxib Challenge Results

Of the 141 patients who underwent challenge testing with etoricoxib, only 2 (1.4%) had a positive test result. The first patient was a 25-year-old woman with no history of atopy or chronic urticaria. She underwent challenge testing with etoricoxib because she had experienced 2 episodes of urticarial eruptions after taking the arylpropionics naproxen and ketoprofen 8 and 6 months before testing, respectively. Approximately 20 minutes after administration of a total dose of 90 mg of etoricoxib, she developed a pruritic rash. Itching was followed by the appearance of wheals on the extremities.

The second patient was a 42-year-old woman with a history of allergic rhinitis but not chronic urticaria. She underwent challenge testing with etoricoxib because she had experienced 3 episodes of urticarial eruptions after taking aspirin, arylpropionics (ibuprofen), and acetaminophen 22, 7, and 4 months before testing, respectively. In addition to the urticaria, when she took aspirin, the reaction was characterized by angioedema of the lip. Approximately 15 minutes after administration of a total dose of 90 mg of etoricoxib, a pruritic rash appeared on her hands, and wheals subsequently developed on her arms.

Neither patient experienced respiratory symptoms or FEV₁ changes. Both patients were treated with chlorpheniramine maleate (10 mg intravenously), and the symptoms completely resolved within 2 hours. The remaining 139 individuals did not report immediate or delayed reactions during or after

challenge with etoricoxib. None of the patients had adverse reactions to the placebo challenge.

DISCUSSION

In the present study, we investigated the clinical tolerability of etoricoxib in 141 patients. The drug etoricoxib (5-chloro-62-methyl-3-[4-(methylsulfonyl)-phenyl]-2,32-bipyridine) is a recent entry in the field of COX-2 selective inhibitors; it is more than 100-fold more selective for COX-2 than for COX-1 in whole-blood assays.¹³ Extensive trials have confirmed its clinical analgesic and anti-inflammatory efficacy to be at least as good as, and in some cases superior to, that of nonselective NSAIDs in a variety of diseases. In particular, etoricoxib is currently approved in several countries for the treatment of acute gouty arthritis, chronic low back pain, primary dysmenorrhea, pain associated with dental surgery, and the signs and symptoms of osteoarthritis and rheumatoid arthritis.^{14–18} In addition, etoricoxib displays improved gastrointestinal safety compared with nonselective NSAIDs and has a favorable overall safety and tolerability profile. To our knowledge, no previous studies have investigated the tolerability of etoricoxib in patients with a history of NSAID hypersensitivity.

Our findings on the tolerability of this new selective COX-2 inhibitor are encouraging. It seems to have a very low frequency of cross-reactivity in patients with a history of reactions to NSAIDs, even in those who have reportedly reacted in the past to different classes of NSAIDs or different drugs (antibiotics or others). Nevertheless, the fact that confirmatory challenges of the culprit drug were not performed could introduce a bias, leading to overestimation of the actual rate of adverse reactions to NSAIDs and overestimation of the percentage of tolerability of etoricoxib.

Etoricoxib seems to be safe even in patients with severe reactions to NSAIDs, including Stevens-Johnson syndrome. The fact that the previous reactions to NSAIDs reported by our study population were exclusively cutaneous leads us to postulate that this new drug may well prove to be a safe alternative for this group. Considering the very low incidence rate of positive tolerance test results, we cannot draw any conclusions regarding the role of possible risk factors, such as atopy, history of chronic urticaria, and multiple-drug reactivity, although it is noteworthy that the 2 etoricoxib-positive patients reported adverse reactions to 2 and 3 different NSAIDs.

As noted in the "Introduction" section, the most common drugs tested are specific COX-2 inhibitors, including acetaminophen, nimesulide, benzydamine, floctafenine, and meloxicam. Recently, selective COX-2 inhibitors, such as rofecoxib, have also been tested.^{6–11} Our group⁶ previously investigated the tolerability and reliability of nimesulide and acetaminophen in a large group of patients with an exclusive well-documented history of NSAID-induced urticaria or angioedema. Of 715 patients tested with nimesulide, 8.6% had

positive test results; of 114 patients challenged with acetaminophen, 9.6% had positive test results. Next we investigated the tolerability of meloxicam and benzydamine using challenge tests in patients with an unequivocal clinical history of urticaria with or without angioedema to NSAIDs. Of 148 patients who underwent the meloxicam challenge, only 2 (1.4%) had positive test results.⁸ Of 137 patients with nimesulide-induced urticaria who underwent peroral challenge with increasing doses of benzydamine, only 2% experienced immediate reactions.¹⁰

Other researchers have evaluated the tolerability of alternative drugs in a nonhomogeneous population, that is, in patients who reported cutaneous and respiratory adverse reactions to NSAIDs. They found that floctafenine was tolerated by 91.3% of the population, whereas nimesulide was tolerated by 96.7% of patients.^{7,9} The tolerability of rofecoxib in patients with previous adverse cutaneous reactions to NSAIDs, evaluated by challenge testing, was 0% to 18%.^{11,19–21}

Although the real mechanism of adverse reaction to etoricoxib is unclear, we are more likely to consider it a nonallergic hypersensitivity reaction than an allergic one. As suggested by other researchers^{22–24} who described urticaria and angioedema to COX-2 inhibitors, the mechanism of cutaneous adverse reactions seems to be dose related (in fact, the 2 reactions in the present study appeared at a cumulative dose of 90 mg), related directly to the COX-2 action, and, considering the low rate, we could add, in a selected population (eg, a concomitant unknown factor could predispose or enhance the possibility of a reaction against the COX-2 inhibitors). In addition, we did not demonstrate whether the mechanism is IgE mediated, although we excluded it because the patients were not previously exposed so they could not be sensitized. Also, if we suppose that the sulfone group on COX-2 has anything to do with sulfonamide, so that we can image an immune response to this, the 2 subjects were absolutely not sulfonamide sensitive.

In conclusion, this study demonstrates a low rate of reactions to etoricoxib, tested by oral challenge, suggesting that patients with previous cutaneous hypersensitivity reactions to NSAIDs (primarily urticaria and angioedema) may tolerate this drug.

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