
Safety of etoricoxib, a new cyclooxygenase 2 inhibitor, in patients with nonsteroidal anti-inflammatory drug-induced urticaria and angioedema

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Background: The use of selective inhibitors of cyclooxygenase 2 (COX-2) has been shown to be safe in patients with aspirin-induced asthma. However, a few individuals with cutaneous reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) experience urticaria or angioedema when challenged with various coxibs.

Objective: To investigate the clinical tolerance of NSAID-sensitive individuals to the selective COX-2 inhibitors etoricoxib and celecoxib.

Methods: Patients with NSAID-induced urticaria or angioedema were challenged in a double-masked, placebo-controlled design protocol with etoricoxib (120 mg) and celecoxib (200 mg). Cutaneous, respiratory, and general symptoms; vital signs; and pulmonary function were monitored hourly for 3 hours.

Results: Fifty-eight patients (46 females and 12 males) with a mean $\pm$ SD age of 31.7 ± 14.1 years (range, 13–66 years) who showed urticaria or angioedema when challenged with NSAIDs were included in this study. A cutaneous clinical pattern was observed in 34 patients (59%), and a mixed pattern (cutaneous and respiratory) was seen in 24 (41%). Celecoxib provocation of 54 patients induced urticaria in 3, urticaria and angioedema in 2, and urticaria, rhinorrhea, and conjunctival erythema in 1 (reaction rate, 11.1%). Etoricoxib challenges performed in 56 patients induced urticaria in 3 and angioedema in 1 (reaction rate, 7.1%).

Conclusions: These results confirm that most NSAID-sensitive individuals with cutaneous reactions to classic NSAIDs will tolerate specific COX-2 inhibitors, supporting the use of these drugs after careful oral provocation in such patients.

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INTRODUCTION

Coxibs, specific inhibitors of prostaglandin G/H synthase 2 (cyclooxygenase 2 [COX-2]), were developed by the pharmaceutical industry with the aim of producing analgesic and anti-inflammatory compounds devoid of the gastrointestinal adverse effects commonly observed during long-term therapy with classic nonsteroidal anti-inflammatory drugs (NSAIDs) and mediated by the inhibition of prostaglandin G/H synthase 1 (COX-1).^{1,2}

Because COX-1 inhibition has been shown to participate in the pathogenesis of nonallergic hypersensitivity to NSAIDs, such as aspirin-exacerbated respiratory disease (aspirin-induced asthma)³ and urticaria,⁴ investigators hypothesized that coxibs could be tolerated by patients sensitive to nonselective NSAIDs. For patients with aspirin-induced asthma, several studies have demonstrated that celecoxib and rofecoxib do not trigger respiratory reactions (reviewed in the study by Sánchez-Borges et al⁵). On the other hand, in patients with

cutaneous reactions to NSAIDs, there is controversy, with some researchers reporting absolute tolerance to coxibs and others observing urticarial reactions in such patients.^{6,7} Among patients who have a history of cutaneous reactions to aspirin or a conventional NSAID, some patients have specific sensitivity without cross-reactivity with other conventional NSAIDs or nonspecific COX inhibitors (apparently related to the chemical structure of the agents), whereas other patients (particularly those with a history of idiopathic urticaria) have cutaneous cross-reactions with all significant inhibitors of COX-1.

In a recent review article, our group⁷ summarized the present information on cutaneous reactions to coxibs. Of 1,101 NSAID-sensitive patients challenged with rofecoxib in 18 studies, 18 (2%) showed urticaria. Of 133 patients in 6 studies published for celecoxib, 15 had positive cutaneous reactions (11%). We reported oral challenges with valdecoxib in 28 patients, with only 1 (4%) developing urticaria.⁸ Systemic reactions of an anaphylactic or anaphylactoid nature and a group of miscellaneous cutaneous reactions, such as vasculitis, toxic epidermal necrolysis, Sweet syndrome, maculopapular rash, and erythema multiforme, induced by coxibs have also been reported, more often in relation to celecoxib administration.⁷

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Etoricoxib (5-chloro-2-[6-methylpyridine-3-yl]-3-[4-methylsulphonylphenyl] pyridine) is a new specific inhibitor of COX-2 approved in various countries in Europe and Latin America (not currently approved in North America) for the treatment of acute and chronic pain, rheumatoid arthritis, osteoarthritis, acute gouty arthritis, and primary dysmenorrhea. Of the coxibs currently in clinical use, etoricoxib exhibits the highest selectivity for COX-2 in vitro.^{9,10} Etoricoxib might also have a high selectivity for COX-2 in vivo. Because we previously proposed that the ability to inhibit COX-1 in vivo may constitute an important factor determining the potential for induction of adverse skin reactions of the urticaria or angioedema type by coxibs, this study was performed to investigate the tolerance of NSAID-sensitive patients to etoricoxib compared with tolerance to celecoxib, a drug previously shown to trigger urticaria and angioedema in this patient population.

METHODS

Patients

After providing written informed consent, patients with a history of urticaria or angioedema presumably triggered by NSAIDs were submitted to oral challenges with aspirin given in incremental doses from 25 to 500 mg. For single-drug reactor patients, challenge was performed using the NSAID suspected to induce the reaction as deduced from patient questioning. Patients with positive challenge results (urticaria or angioedema involving $\geq 20\%$ from baseline of body surface area) were included in the investigation. Patients with dermatographism, other physical urticarias, aspirin-induced asthma, previous or current chronic urticaria, or pregnancy were excluded. The medical history registered previous atopic diseases, responsible NSAIDs, and clinical manifestations of adverse reactions to NSAIDs. This information permitted patient classification into 2 clinical patterns: cutaneous and mixed.¹¹ The protocol was approved by the institutional review boards of the participating institutions.

Oral Provocation Tests

Oral challenges with aspirin and other NSAIDs were performed by means of a double-masked protocol. The drugs or placebo, given on different days, were concealed in identical opaque capsules, and half doses were administered 1 hour apart, with 3 hours of observation in the hospital and a telephone recall 24 hours later. Aspirin and NSAID doses have been reported previously.¹² Maximal doses for etoricoxib and celecoxib were 120 and 200 mg, respectively. Vital signs and pulmonary function (forced expiratory volume in 1 second [FEV₁], forced vital capacity, forced expiratory flow between 25% and 75%, and peak expiratory flow) were monitored at baseline and hourly for 3 hours, and the skin, nose, eyes, and thorax were examined at the same intervals. The presence of breathlessness, cough, wheezing, dysphonia, nasal or ocular itching, sneezing, rhinorrhea, nasal obstruction, and conjunctival erythema was specifically investigated at every hourly physical examination. For urticaria and an-

gioedema, the percentage of skin involved was calculated as follows: head and neck, 30%; chest, 20%; abdomen, 20%; upper limbs, 15%; and lower limbs, 15%. The test result was regarded as positive for urticaria or angioedema if involvement of 20% or more of the body surface area was present¹³ and for respiratory reactions if symptoms or signs appeared or a decrease in FEV₁ greater than 20% of the basal condition was detected. Oral provocation tests with coxibs were performed at least 2 weeks apart from aspirin and NSAID challenges. Patients were enrolled during a period of 18 months at 3 large medical centers, with 1 principal investigator involved in each institution, using exactly the same challenge protocol. Patients were challenged during remission of the urticaria or angioedema and with antihistamines withheld for at least 96 hours before testing.

RESULTS

Demographic and Clinical Data

The clinical features of the studied patients are given in Table 1. Fifty-eight patients (46 females and 12 males) with a mean $\pm$ SD age of 31.7 ± 14.1 years (range, 13–66 years) were studied. Forty-nine patients (84%) had a history of atopic diseases (36 had rhinitis, 8 had rhinitis and asthma, 3 had asthma, and 2 had rhinitis, asthma, and atopic dermatitis), and 12 (21%) had a family history of NSAID hypersensitivity. Positive immediate-type hypersensitivity skin test reactions to at least 1 inhalant allergen were present in 49 (98%) of 50 tested patients. According to medical history, reactions were triggered by aspirin in 42 patients, ibuprofen in 31, dipyrone in 26, acetaminophen in 15, diclofenac in 12, ketoprofen in 8, rofecoxib in 2, mefenamic acid in 2, naproxen in 1, ketorolac in 1, nimesulide in 1, and valdecoxib in 1. Fifty patients (86%) were cross-reactors by history, and 8 (14%) had reactions to a single NSAID. During aspirin or NSAID oral challenges, a cutaneous clinical pattern (urticaria or angioedema) was observed in 34 patients (59%), and a mixed pattern (cutaneous and upper respiratory tract or ocular manifestations) was seen in 24 (41%). All 24 patients showed objective signs of an upper respiratory tract or ocular reaction, and only 7 had a significant decrease in FEV₁.

Oral Provocation With COX-2 Inhibitors

Oral challenges with celecoxib induced urticaria in 3 patients (patients 6, 9, and 22 in Table 1), lip angioedema in 1 (patient 52), and eyelid wheals and angioedema in 1 (patient 43). Provocation with etoricoxib resulted in urticaria in 3 patients (patients 17, 37, and 39 in Table 1) and tongue, eyelid, and lip angioedema in 1 (patient 43). Six additional patients included in the study (patients 53–58) did not return for the second coxib masked challenge. After opening the masked codes, it was observed that 2 of these patients had been challenged with celecoxib, resulting in 1 patient who showed urticaria, rhinorrhea, and conjunctival injection (mixed pattern of reaction, patient 55), whereas no adverse reactions occurred in 4 patients who received etoricoxib. In summary, 6 of 54 patients reacted to celecoxib (reaction rate, 11.1%), and 4 of

Table 1. Clinical Data and Results of Oral Provocation Tests With COX-2 Inhibitors in 58 NSAID-Sensitive Subjects

Patient No./sex/age, y	Atopic disease	Family history of NSAID sensitivity	Aeroallergen skin tests	NSAIDs	Drug pattern	Clinical pattern*	OPT with Celecoxib	OPT with Etoricoxib
1/M/27	R, A	—	+	Asa, Ibu, Metam	CR	Mixed	—	—
2/F/19	—	—	+	Acetam, Metam	CR	Cut	—	—
3/F/34	R, A	—	+	Asa, Acetam, Metam	CR	Mixed	—	—
4/F/19	R	—	+	Asa	SR	Cut	—	—
5/F/41	—	—	ND	Ibu, Acetam, Metam	CR	Cut	—	—
6/F/66	A	—	ND	Diclof, Rofo	CR	Cut	+	—
7/F/17	R, A	—	+	Asa, Ibu, Metam	CR	Mixed	—	—
8/F/49	R	—	+	Asa, Metam	CR	Cut	—	—
9/F/35	—	—	+	Acetam, Metam, Diclof	CR	Cut	+	—
10/F/61	—	—	—	Acetam, Ibu, Diclof, Rofo	CR	Mixed	—	—
11/F/24	R, A, AD	—	+	Ibu, Metam, Diclof	CR	Mixed	—	—
12/F/21	R	—	+	Acetam	SR	Cut	—	—
13/F/49	R	—	+	Asa, Ketoprof	CR	Cut	—	—
14/F/13	R	—	+	Ibu, Diclof	CR	Cut	—	—
15/F/33	R	—	+	Asa, Ibu, Diclof, Ketopr	CR	Cut	—	—
16/F/65	R	+	+	Asa, Ibu, Acetam, Metam	CR	Mixed	—	—
17/F/56	R	—	+	Asa, Metam	CR	Cut	—	+
18/F/24	R	—	+	Asa	SR	Cut	—	—
19/F/42	R	+	+	Asa, Ibu, Diclof	CR	Mixed	—	—
20/M/25	R	—	+	Asa, Metam	CR	Cut	—	—
21/F/45	R, A	+	+	Asa, Ibu, Metam	CR	Mixed	—	—
22/F/30	R	—	+	Asa, Acetam, Metam, Ketopr	CR	Mixed	+	—
23/M/36	R	—	+	Asa, Acetam, Metam	CR	Cut	—	—
24/M/43	R	—	+	Asa, Ketopr, Ketor	CR	Cut	—	—
25/F/22	R, A	+	+	Asa, Ibu	CR	Cut	—	—
26/M/60	R	—	+	Asa, Diclof	CR	Mixed	—	—
27/F/16	R	+	+	Asa, Ibu, Metam	CR	Cut	—	—
28/F/38	R	—	+	Asa, Ketopr	CR	Cut	—	—
29/M/21	R, A, AD	—	+	Asa, Ibu, Metam	CR	Mixed	—	—
30/F/27	R	+	+	Asa, Diclof	CR	Cut	—	—
31/M/32	R	—	+	Asa, Ibu, Acetam	CR	Mixed	—	—
32/M/14	R	—	+	Diclof	SR	Mixed	—	—
33/F/51	R, A	—	+	Asa, Ibu, Metam, Diclof	CR	Mixed	—	—
34/F/41	R	+	+	Asa, Ibu, Metam	CR	Mixed	—	—
35/M/13	—	+	ND	Ibu	SR	Cut	—	—
36/F/31	A	+	+	Asa, Diclof, Ketopr	CR	Mixed	—	—
37/F/20	R	—	+	Asa, Ibu, Metam	CR	Mixed	—	+
38/F/22	—	—	ND	Asa, Ibu, Acetam	CR	Cut	—	—
39/F/28	R	—	+	Asa, Metam	CR	Mixed	—	+
40/F/29	R, A	—	+	Ibu, Metam, Mef Ac	CR	Cut	—	—
41/F/27	R	—	+	Asa, Ibu, Naprox	CR	Cut	—	—
42/F/18	R	—	+	Asa, Ibu	CR	Cut	—	—
43/F/48	R	—	+	Asa, Metam	CR	Mixed	+	+
44/F/15	R	—	+	Asa	SR	Cut	—	—
45/F/41	R	—	+	Asa, Metam, Acetam	CR	Mixed	—	—
46/F/27	R, A	—	+	Asa, Acetam	CR	Mixed	—	—
47/F/33	—	—	ND	Asa, Ibu, Acetam, Valde	CR	Cut	—	—

Continued

Table 1. *Continued*

Patient No./ sex/age, y	Atopic disease	Family history of NSAID sensitivity	Aeroallergen skin tests	NSAIDs	Drug pattern	Clinical pattern*	OPT with Celecoxib	OPT with Etoricoxib
48/F/39	—	—	ND	Asa, Ibu, Acetam	CR	Cut	—	—
49/M/17	R	—	+	Asa, Ibu	CR	Cut	—	—
50/F/13	R	+	+	Asa, Ibu	CR	Mixed	—	—
51/F/33	R	—	+	Asa, Ibu	CR	Cut	—	—
52/F/27	—	+	+	Ibu, Metam	CR	Cut	+	—
53/M/19	R	—	+	Ibu, Ketopr	CR	Cut	ND	—
54/M/53	A	—	ND	Metam	SR	Cut	ND	—
55/F/19	R	+	+	Asa, Ibu	CR	Mixed	+	ND
56/F/24	R	—	+	Mef Ac, Nimes	CR	Cut	—	ND
57/F/33	R	—	ND	Asa, Ibu, Metam	CR	Mixed	ND	—
58/F/16	R	—	+	Ketopr	SR	Cut	ND	—

Abbreviations: A, Asthma; Acetam, acetaminophen; AD, Atopic dermatitis; Asa, aspirin; CR, cross-reactors; Cut, cutaneous; Diclof, diclofenac; Ibu, ibuprofen; Ketopr, ketoprofen; Ketor, ketorolac; Mef Ac, Mefenamic acid; Metam, metamizol; minus sign, negative; ND, not done; Nimes, Nimesulide; NSAID, nonsteroidal anti-inflammatory drug; OPT, oral provocation tests; plus sign, positive; R, rhinitis; Rofe, rofecoxib; SR, single reactors; Valde, Valdecoxib.

* From oral challenge.

56 challenged individuals showed reactions to etoricoxib (reaction rate, 7.1%) ($P = .50$ by Fisher exact test).

DISCUSSION

The introduction of selective and specific COX-2 inhibitors for medical use was accompanied by a new treatment approach for pain and inflammation in patients with hypersensitivity to the classic NSAIDs. The expectation was that this new therapeutic class could safely be administered to these patients, and this proposal has been confirmed in many studies in patients with aspirin-exacerbated respiratory disease (aspirin-intolerant asthma).⁵

In patients who experience urticaria and angioedema with or without ophthalmic and upper respiratory tract symptoms after taking drugs that inhibit COX-1, it has been observed that most of them can tolerate rofecoxib, celecoxib, and valdecoxib. A small proportion of these patients, variable according to the coxib being investigated, experience clinical manifestations of cutaneous or mixed hypersensitivity when exposed to these drugs.⁷

Because etoricoxib is the COX-2 inhibitor currently in clinical use that shows the highest COX-2 selectivity in vitro, we studied its tolerance in NSAID-sensitive individuals. Celecoxib was used for comparison because this coxib has been previously shown to induce urticaria and angioedema in some patients who are intolerant to classic NSAIDs.^{5,7} In this study, we observed that 11.1% and 7.1% of patients did not tolerate celecoxib and etoricoxib, respectively. These results allow us to recommend the administration of these coxibs to patients previously diagnosed as being sensitive to NSAIDs only after medically supervised challenge, with the understanding that most patients will tolerate them.

In the present investigation, single-drug reactors were challenged only with the NSAID suspected to induce the reaction, and patients with chronic urticaria were not included. These

details in protocol design might imply that we could be underestimating the risk of reactions to etoricoxib or celecoxib in cross-reactors. Our study population also contained a high proportion of patients with mixed cutaneous and respiratory reactions (41%), higher than generally found in other series of NSAID sensitivity, including previous studies by our group^{12,13} that reported prevalences of 24% and 34.5% for mixed reactors. Accordingly, the rate of cross-reactivity in the present study might differ from that of other populations with different proportions of pure respiratory, cutaneous, and mixed reactors.

In various studies, patients with aspirin-exacerbated respiratory disease have been challenged with rofecoxib and celecoxib (but not with valdecoxib or etoricoxib) without experiencing respiratory adverse reactions, and this observation suggested that coxibs did not inhibit COX-1 in vivo. Therefore, investigators have been puzzled by the observation of cutaneous reactions triggered by coxibs in COX-1 inhibitor-intolerant patients. In a recent review article, our group⁷ concluded that the reaction rates in patients with NSAID-induced cutaneous reactions for rofecoxib, celecoxib, and valdecoxib, as reported in published investigations presently available, were 1.6%, 11.2%, and 3.5%, respectively.

The pathogenesis of urticaria and angioedema due to NSAIDs in cross-reactor patients is currently explained by the inhibition of COX-1 with arachidonic acid metabolism shunting toward the lipoxygenase pathway and excessive production of cysteinyl leukotrienes, the cyclooxygenase theory.^{3,4} It has been proposed that some cutaneous reactions, including urticaria, may be produced more frequently by using sulfonamide-containing coxibs, such as celecoxib and valdecoxib.^{14,15} Shapiro et al¹⁶ looked at whether patients allergic to sulfonamide antibiotics were more likely to react to celecoxib. They concluded that because allergy to sulfonamide antibiotics usually depends on the presence of

arylamine structural subunits (that can be metabolized to immunogenic hydroxylamine determinants), there was no immunologic cross-reactivity with celecoxib (a nonantibiotic sulfonamide) because it does not contain an arylamine subunit.¹⁶

Despite the apparent absence of immunologic cross-reactivity, Strom et al¹⁷ reported that sulfonamide antibiotic and penicillin allergies are risks for nonantibiotic sulfonamide (eg, celecoxib) allergy. They concluded that the association might be explainable by a general predisposition to allergic reactions among certain patients rather than by a specific cross-reactivity with drugs that contain the sulfa moiety.¹⁷ Currently, it is not known whether this reasoning is applicable to the reactions to celecoxib observed in this study.

An IgE-mediated allergic reaction seems unlikely because most of these patients have not been exposed previously to coxibs and because most reactions are present in NSAID cross-reactor patients. The degree of COX-1 inhibition in vitro differs for the various coxibs. It is possible that some NSAID-sensitive patients with cutaneous reactions have a genetic or metabolic disturbance of arachidonic acid metabolism different from that in aspirin-intolerant asthma that makes them particularly susceptible to COX-1 inhibition by coxibs. Supporting this view, we observed a statistically significant correlation between the in vitro selectivity of coxibs for COX-2 as evaluated by various techniques and their cutaneous reaction rates (data not shown). Additional studies are required to confirm this hypothesis.

Coxib hypersensitivity also resembles classic NSAID hypersensitivity regarding the possibility of tolerance induction, as shown recently by Nucera et al,¹⁸ who desensitized a patient with Bartter syndrome and multiple-drug intolerance by using increasing doses of rofecoxib, from 2.5 to 50 mg, in an oral 8-day protocol. This patient had previously experienced generalized erythema and itching after taking rofecoxib.

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