
Tolerance of nonsteroidal anti-inflammatory drug-sensitive patients to the highly specific cyclooxygenase 2 inhibitors rofecoxib and valdecoxib

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Background: Selective inhibitors of cyclooxygenase 2 (COX-2) are generally tolerated by patients sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit COX-1. Valdecoxib is a new sulfonamide-containing COX-2-specific inhibitor indicated for the treatment of acute pain, osteoarthritis, and rheumatoid arthritis.

Objective: To compare the clinical tolerance to rofecoxib and valdecoxib in patients who previously developed urticaria and angioedema while taking classic NSAIDs.

Methods: Patients with challenge-proven NSAID cutaneous sensitivity were submitted to single-blinded controlled oral challenges with rofecoxib, 50 mg, and valdecoxib, 40 mg.

Results: Twenty-eight patients (19 females and 9 males; mean $\pm$ SD age, 28.6 ± 15.0 years; age range, 10–61 years) participated in this study. Twenty-two (85%) of 26 patients who underwent skin tests were atopic, as demonstrated by a clinical history of rhinitis and/or asthma plus positive immediate-type skin hypersensitivity test results. A previous exclusive cutaneous reaction pattern (urticaria and/or angioedema) had occurred in 10 patients (36%), whereas a mixed pattern of skin and respiratory symptoms had occurred in 18 patients (64%). Twenty patients (71%) were multiple reactors, and 8 patients (28%) were single reactors. In this current study, 2 patients (7%) taking rofecoxib experienced angioedema, and 1 patient (4%) taking valdecoxib experienced urticaria.

Conclusions: Rofecoxib and valdecoxib can be safely used by most NSAID-sensitive patients with cutaneous reactions. Our findings suggest that isolated cross-reactions may occur in these patients, and for this reason, controlled oral provocation may be prudent when prescribing valdecoxib or rofecoxib for patients who have previously had urticaria or angioedema triggered by NSAIDs.

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INTRODUCTION

Urticaria and angioedema triggered by nonsteroidal anti-inflammatory drugs (NSAIDs) are disorders commonly observed in clinical practice, having a prevalence of 0.1% to 0.3% in the general population.¹ Some risk factors for these conditions have been identified, including female sex, atopy,² young adulthood,³ chronic urticaria, and intermittent NSAID use for the relief of acute pain.⁴

We have previously reported that selective inhibitors of cyclooxygenase 2 (COX-2) are better tolerated by patients with cutaneous reactions to classic NSAIDs,⁵ and this observation has been recently confirmed by other investigators.^{6–9} Although rare, urticaria and angioedema have been observed in some patients who reacted to the old NSAIDs when they were exposed to inhibitors of COX-2, and in our experience this occurred more often with celecoxib than with rofecoxib.⁵

The reasons for such discrepancy are unknown, and we have speculated the following possible explanations: (1) an immunologic reaction directed to the sulfonamide residue, present in celecoxib but not in rofecoxib; (2) celecoxib has the potential for inhibition of COX-1 *in vivo*¹⁰; and (3) another currently unknown mechanism.

Valdecoxib, (4–5-methyl-3-phenyl-4-isoxazolil) benzene sulfonamide, is a new selective COX-2 inhibitor that has been approved for the treatment of acute pain, dysmenorrhea, osteoarthritis, and rheumatoid arthritis.¹¹ Since this drug also contains a sulfonamide group, we decided to study the safety of valdecoxib compared with another highly specific COX-2 inhibitor, rofecoxib, in NSAID-sensitive patients with prior cutaneous reactions to classic NSAIDs to increase our understanding of the mechanisms involved in the pathogenesis of cutaneous reactions to NSAIDs.

MATERIALS AND METHODS

Patients

Patients with a history of urticaria or angioedema after taking NSAIDs and a positive oral challenge when provoked with aspirin (500 mg) or ibuprofen (400 mg), of any age or sex, were included in this study after giving written informed

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consent. Patients with dermatographism, aspirin-exacerbated respiratory disease, previous or current chronic urticaria, or pregnancy were excluded. The medical history for atopic diseases, previous drug reactions, incriminated NSAIDs, and symptoms of adverse reactions to NSAIDs were recorded for classification in clinical patterns (cutaneous, mixed, or anaphylactoid).^{4,12} The protocol was approved by the ethics committees of the participating institutions.

Skin Tests

Skin prick tests with inhalant allergens (*Dermatophagoides pteronyssinus*, mixed molds, cat, dog, Bermuda grass; ALK Abelló, Madrid, Spain) and *Blomia tropicalis* (CBF Leti, Madrid, Spain) with reading after 15 minutes of extract application were performed on the forearm. Glycerosaline solution and 0.1% histamine phosphate were used as negative and positive controls, respectively. A test result was regarded as positive if a wheal greater than 3 mm compared with the negative control was present.

Oral Provocation Tests

Oral challenges with NSAIDs in doses previously reported² were performed in the hospital by means of the single-blinded, placebo-controlled method. For rofecoxib and valdecoxib, the maximal doses were 50 and 40 mg, respectively. A half drug dose was given 1 hour apart, and the patients were observed for 3 hours, whereas placebo challenges with 2 doses 1 hour apart were administered without patient knowledge on separate days with the same period of patient observation in the office. Vital signs, respiration, skin changes, and subjective manifestations were monitored every 30 minutes. If wheals or angioedema was observed, the extension of the lesions was expressed as the percentage of skin involved, giving the following values to each body area: head and neck, 30%; chest, 20%; abdomen, 20%; upper limbs, 15%; and lower limbs, 15%.¹² A test result was considered to be positive if an increase of 20% or greater from baseline was present. It must be stressed that no patients with previous or current chronic idiopathic urticaria or aspirin-intolerant asthma were included in this study, and therefore the baseline score was always 0. Although the occurrence of minimal urticaria could have been regarded as a positive reaction, a 20% increase in urticaria or angioedema was considered a more strict criteria, ensuring that the test result was clearly positive. Oral challenges with NSAIDs and COX-2 inhibitors were performed with a separation period of at least 2 weeks between them.

RESULTS

Clinical Data

Twenty-eight patients (19 females and 9 males) with a mean $\pm$ SD age of 28.6 ± 15.0 years (range, 10–61 years) were studied. Twenty-three had a history of atopic diseases (rhinitis, 18; rhinitis and asthma, 4; asthma, 1), and of the 26 who underwent skin tests, 22 (85%) had positive immediate-type hypersensitivity results to at least 1 inhalant allergen.

Fifteen patients had a history of skin reactions to aspirin, 11 to ibuprofen, 11 to pyrazolone, 7 to diclofenac, 5 to acetaminophen, 4 to nimesulide, 3 to ketoprofen, 2 to tiaprofenic acid, 1 to naproxen, 1 to ketorolac, and 1 to glapenine. According to patient histories, 20 patients were multiple reactors and 8 were single reactors. When challenged, 10 patients (36%) only developed urticaria and angioedema (cutaneous pattern), and 18 (64%) reacted with a blended clinical picture of respiratory and cutaneous manifestations (mixed pattern)¹³ (Table 1). It must be stressed that this last group did not have aspirin-exacerbated respiratory disease, also referred to as an aspirin triad.

Oral Provocation With Inhibitors of COX-2

Twenty-eight patients were submitted to controlled oral challenges with rofecoxib. A 59-year-old nonatopic woman with a history of chronic asthma and rhinitis not related to NSAIDs and blended reactions to multiple NSAIDs (aspirin, pyrazolone, ketoprofen, nimesulide, tiaprofenic acid, and acetaminophen) developed laryngeal angioedema with cough breathlessness and dysphonia approximately 60 minutes after receiving 25 mg of rofecoxib. She was treated with oral antihistamines and montelukast. A second patient, a 31-year-old atopic woman with mixed reactions triggered by aspirin and a history of allergic rhinitis, developed dyspnea and eyelid (periorbital) angioedema 30 minutes after taking rofecoxib, 50 mg. In both patients, this was their first exposure to rofecoxib, which suggests a non-IgE-mediated reaction. Neither of these 2 patients reacted to valdecoxib.

Oral challenges with valdecoxib resulted in a positive challenge test result in a 25-year-old woman with a history of atopic rhinitis and asthma, who was previously sensitive to pyrazolone and ibuprofen. She developed itchy urticarial wheals on her face and arms 2 hours after receiving 40 mg of valdecoxib but tolerated rofecoxib without any reaction.

DISCUSSION

The clinical management of patients who develop adverse allergic or pseudoallergic reactions to NSAIDs is a challenging issue, especially in situations where such medications are required for chronic conditions. Various groups have recently demonstrated that selective COX-2 inhibitors such as rofecoxib and celecoxib can be safely used in most patients who have had cutaneous reactions to aspirin and other classic NSAIDs.^{5–9}

The present study confirms our previous results that showed that an increased prevalence of the atopic diathesis was present in these patients.² It can also be seen that there is a preponderance of multiply reactive individuals (patients who exhibit symptoms when exposed to various chemically unrelated drugs that inhibit COX-1) over single reactors (those who will react exclusively to one chemical compound and closely related drugs, presumably through a specific immunological mechanism).

Currently, only controlled provocation testing can confirm a diagnosis of NSAID sensitivity. Immediate-type skin hy-

Table 1. Clinical Data and Results of Oral Challenges with Cyclooxygenase 2 Inhibitors

Patient No./ sex/age, y	Symptoms when challenged	Atopic disease	Prick skin test result	NSAIDs	Drug pattern	Clinical pattern	Rofecoxib	Valdecoxib
1/M/15	FA,D	R	+	Aspirin	SR	Mixed	—	—
2/F/24	AU	A	+	Ibuprofen, dipyrrone	CR	Mixed	—	—
3/F/20	AU	R	+	Dipyrrone	SR	Cut	—	—
4/M/44	FA,D	R	+	Ketoprofen, dipyrrone, Ibuprofen, diclofenac, Ketorolac	CR	Mixed	—	—
5/F/24	FA	R	+	Aspirin, dipyrrone	CR	Cut	—	—
6/F/22	FA,LE	R,A	+	Aspirin, dipyrrone	CR	Mixed	—	—
7/F/26	FA,D	R	+	Diclofenac	SR	Mixed	—	—
8/F/50	AU,HY	—	—	Glafein, nimesulide	CR	Mixed	—	—
9/F/33	FA,D	R	+	Aspirin, ibuprofen	CR	Mixed	—	—
10/F/24	FA,D	—	+	Ibuprofen	SR	Mixed	—	—
11/F/16	FA,RI	R	+	Aspirin, dipyrrone	CR	Mixed	—	—
12/F/48	AU	—	ND	Ketoprofen	SR	Mixed	—	—
13/M/61	FA,D,C	—	ND	Ibuprofen, diclofenac	CR	Mixed	—	—
14/F/10	FA	R,A	+	Ibuprofen, nimesulide	CR	Cut	—	—
15/F/59	FA,LE	R,A	—	Ketoprofen, acetaminofen, nimesulide, aspirin, dipyrrone, tiaprofenic acid	CR	Mixed	+	—
16/M/14	FA	R	—	Aspirin, Dipyrrone, naproxen, ibuprofen	CR	Cut	—	—
17/F/15	FA,D	R	+	Aspirin, acetaminofen	CR	Mixed	—	—
18/M/21	FA,D	R	+	Aspirin, acetaminofen, diclofenac	CR	Mixed	—	—
19/M/35	FA,LE	R	+	Aspirin	SR	Mixed	—	—
20/M/11	FA	R	+	Ibuprofen, acetaminofen	CR	Cut	—	—
21/F/26	FA,AU	R,A	+	Ibuprofen, dipyrrone	CR	Cut	—	+
22/F/56	FA,LE	R	+	Aspirin	SR	Cut	—	—
23/F/25	FA,D	R	+	Aspirin, ibuprofen, diclofenac	CR	Mixed	—	—
24/F/32	FA	R	+	Aspirin, tiaprofenic acid	CR	Cut	—	—
25/M/18	FA	R	+	Ibuprofen, acetaminofen, nimesulide, dipyrrone	CR	Cut	—	—
26/M/12	FA	R	+	Aspirin, diclofenac	CR	Cut	—	—
27/F/31	FA,D	R	+	Aspirin	SR	Mixed	+	—
28/F/33	FA,D	—	—	Aspirin, diclofenac	CR	Mixed	—	—

Abbreviations: A, asthma; AU, acute urticaria; C, cyanosis; CR, crossed reactor; D, dyspnea; FA, facial angioedema; HY, hypotension; LE, laryngeal edema; ND, not done; NSAIDs, nonsteroidal anti-inflammatory drugs; R, rhinitis; RI, rhinorrhea; SR, single reactor; +, positive; —, negative.

persensitivity tests, in vitro methods such as specific IgE measurement or lymphocyte stimulation tests, urinary leukotriene E_4 quantification, and others have been tried unsuccessfully.¹⁴ In this investigation, we performed oral challenges with rofecoxib and valdecoxib in patients with a history of urticaria and angioedema due to NSAID sensitivity. Our results show that, with the exception of 2 patients with angioedema triggered by rofecoxib and 1 patient with urticaria caused by valdecoxib, all other individuals could tolerate these COX-2 inhibitors.

The inhibition of COX isoenzymes by NSAIDs generally conforms to 1 of 3 inhibitory mechanisms: simple reversible inhibition (eg, ibuprofen); time-dependent reversible inhibition, which includes both weaker binding inhibitors (naproxen) and tight binding inhibitors (indomethacin and meclofenamic acid); and irreversible covalent inhibition (aspirin). Selective COX-2 inhibitors bind poorly to COX-1 at high concentrations and have a weak inhibitory activity, of a

competitive and reversible nature, on COX-1. The COX-2 selective diarylheterocyclic inhibitors demonstrate distinct inhibitory mechanisms for the 2 isoforms. For example, celecoxib has been reported to be a reversible competitive inhibitor of COX-1 while demonstrating time-dependent irreversible inhibition of COX-2.¹⁴ COX inhibition involves 3 steps: reversible association of the inhibitor with COX-1, which is composed of 2 steps that may or may not appear kinetically distinct, depending on the relative magnitudes of the respective rate constants.

Selectivity for COX-2 is derived from the contribution of a third irreversible step that is exploited most effectively by those diarylheterocyclic inhibitors that contain a phenylsulfonamide or a phenylsulfone moiety. Celecoxib demonstrates inhibitory behavior that is distinct from valdecoxib in that the dissociation constant (K_i) value obtained from steady-state inhibition of COX-2 by celecoxib ($14\mu\text{M}$) is 5 times larger than the K_i obtained from time-dependent inhibition

(3.0 μ M). This difference suggests that there is an additional step subsequent to the formation of the initial binary complex followed by a second equilibrium process that is kinetically irreversible.^{15,16} Ouellet et al¹⁷ and Riendeau et al¹⁸ observed that valdecoxib, rofecoxib, and etoricoxib show much weaker abilities to inhibit COX-1 than celecoxib in different assay systems (Table 2).

In a previous study, we reported an increased frequency of cutaneous reactions when NSAID-sensitive patients were challenged with celecoxib, a sulfonamide, compared with rofecoxib, a sulfone. Therefore, it was interesting to investigate the tolerance of such patients to valdecoxib, a sulfonamide with a higher selectivity for COX-2 than celecoxib.¹⁵

Since valdecoxib, a sulfonamide, was better tolerated than celecoxib and celecoxib inhibits COX-1 better than valdecoxib and rofecoxib, we propose that cutaneous reactions to COX-2 inhibitors are not related to sulfonamide allergy but are mediated through another mechanism. For example, patient 27, a single drug reactor to aspirin, could have reacted to rofecoxib through new drug IgE sensitization. We have challenged 3 sulfonamide-sensitive patients with celecoxib, and no cutaneous reactions were observed (Sánchez-Borges et al, unpublished data, 2002). Furthermore, one of the patients included in our present study (patient 23 in Table 1), a 25-year-old woman sensitive to aspirin, ibuprofen, and diclofenac, could tolerate rofecoxib and valdecoxib but showed breathlessness, rhinorrhea, and tearing 15 minutes after receiving 100 mg of celecoxib.

The mechanisms that are triggered by COX-2 inhibitors continue to be elusive. First, because of the differences of the molecular structures of the sulfone side chain and sulfonamides, we are not persuaded that prior sensitization to sulfa antibiotics and antibody or T-cell cross-recognition of celecoxib and valdecoxib are responsible for these reactions. A recent study¹⁹ investigated the risk of allergic reactions within 30 days after the receipt of a sulfonamide nonantibiotic or penicillin in patients with or without evidence of prior hypersensitivity after the receipt of a sulfonamide antibiotic. In this article, 10% of patients with an allergic reaction after a sulfonamide antibiotic vs 2% of patients who had no allergic reaction after a sulfonamide antibiotic had an allergic reaction

after subsequently receiving a sulfonamide nonantibiotic (adjusted odds ratio, 2.8; 95% confidence interval, 2.1–3.7). However, the risk of allergic reactions was greater after the receipt of a penicillin among patients with a prior hypersensitivity reaction to a sulfonamide antibiotic compared with patients with no such history. The risk of an allergic reaction after the subsequent receipt of a sulfonamide nonantibiotic was lower than the risk of an allergic reaction after the subsequent receipt of a penicillin in those with a prior hypersensitivity reaction after the receipt of a sulfonamide antibiotic. Additionally, the risk of an allergic reaction after the receipt of a sulfonamide nonantibiotic was lower among patients with a history of hypersensitivity to sulfonamide antibiotics than among patients with a history of hypersensitivity to penicillins. Authors concluded that there is an association between hypersensitivity after the receipt of sulfonamide antibiotics and a subsequent allergic reaction after the receipt of a sulfonamide nonantibiotic, but this association appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs.

Second, the doses of all 3 COX-2 inhibitors are small compared with the high concentrations of drugs in vitro that show minimal inhibition of COX-1. Patients who react to COX-2 inhibitors might have an abnormality that makes their COX-1 enzyme more sensitive to small doses of these COX-2 selective drugs, which are not equivalent in regard to COX-1 inhibition when evaluated by different methods (Table 2).

Third, since all 3 COX-2 inhibitors are active molecular structures that can bind to tissue and serum proteins, each can act as a hapten and induce sensitivity, followed by IgE-mediated cutaneous and/or blended reactions. This hypothesis suggests inadvertent exposure to a specific COX-2 inhibitor. Nevertheless, the rare reactions to rofecoxib and valdecoxib observed in this study occurred during first exposure, which constitutes an argument against IgE mediation of these reactions. Finally, a currently unrecognized reaction mechanism may exist in these unusual patients.

In conclusion, we have demonstrated that rofecoxib and valdecoxib are tolerated by most NSAID-sensitive patients with cutaneous reactions. Since reactions occur in some rare cases, controlled oral provocation is recommended before

Table 2. Differences in Inhibitor Potencies for Cyclooxygenase 1 (COX-1) Inhibition among Ibuprofen and COX-2 Inhibitors*

Drugs	Irreversible inactivation of COX-1 by aspirin EC ₅₀ , μ M	COX-1 inhibition IC ₅₀ , μ M	Inhibition of ionophore stimulated production of thromboxane B ₂ in platelets IC ₅₀ , mean $\pm$ SD, μ M	Blocking of inactivation of platelet COX-1 by 10 μ M of aspirin EC ₅₀ , mean $\pm$ SD, μ M
Ibuprofen	~0.2	~70	1.4 $\pm$ 0.4	0.048 $\pm$ 0.005
Celecoxib	1.0	~70	2.2 $\pm$ 0.3	0.21 $\pm$ 0.01
Valdecoxib	13	>100	28 $\pm$ 9	0.7 $\pm$ 0.2
Rofecoxib	100	>100	>100	5.0 $\pm$ 0.8
Etoricoxib	>100	>100	>100	19 $\pm$ 4
Aspirin	-	-	1.3 $\pm$ 0.5	-

Abbreviations: EC₅₀, median effective concentration; IC₅₀, inhibitory concentration that results in a 50% reduction in proliferation.

* Modified from Ouellet et al.¹⁷

using these agents in patients previously intolerant to classic NSAIDs. On the other hand, our results should be taken cautiously with regard to the experimental design (single-blinded) and the relatively small size of the studied population, which emphasizes the need for additional investigations about COX-2 inhibitor tolerability in NSAID-sensitive patients.

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