

Parecoxib tolerability in patients with hypersensitivity to nonsteroidal anti-inflammatory drugs

To the Editor:

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid (ASA) and pyrazolone derivatives, are among the most frequent causes of adverse drug reactions, particularly among patients with chronic urticaria or asthma.¹ Many subjects report cutaneous (urticaria and/or angioedema), respiratory (rhinitis and/or asthma), or anaphylactic symptoms after the intake of 1 or more drugs of this class. In some patients, NSAIDs, particularly pyrazolones, can elicit allergic hypersensitivity reactions,^{2,3} but in the vast majority of cases NSAID hypersensitivity is mediated by the inhibition of COX-1 (the constitutive isoform), which, through depletion of the protective prostaglandin E₂, promotes the unrestrained synthesis of cysteinyl leukotrienes and release of mediators such as prostaglandin D₂ from mast cells.⁴ For this reason, selective NSAIDs, which inhibit mainly the induced isoform of COX (COX-2) without affecting the arachidonic acid metabolism, can be considered good alternatives for patients with hypersensitivity to nonselective NSAIDs (which inhibit both COX-1 and COX-2).⁴⁻⁷ However,

in these patients—in particular those with cutaneous reactions—highly selective COX-2 inhibitors, such as rofecoxib, celecoxib, valdecoxib, and etoricoxib, also provoke hypersensitivity reactions with a frequency of 1.6%, 11.1%, 3.5%, and 7.1%, respectively,⁸ although not all the studies on which these percentages are based were well controlled.

Parecoxib sodium is a new selective COX-2 inhibitor, the only one that can be used for parenteral administration. It produces effective analgesia for surgery, as well as for dysmenorrhea and osteoarthritis.

We assessed the clinical tolerability of this drug in a group of patients with well-established NSAID hypersensitivity.

Twenty-seven adults (19 women and 8 men) ranging in age from 23 to 71 years (mean age, 43.7 ± 16.3) and reporting 1 or more adverse reactions to NSAIDs—manifested as cutaneous, respiratory, or anaphylactic symptoms—were evaluated between June 2004 and April 2005 in the Allergy Unit of the Complejo Integrato Columbus. Sixteen of them (patients 1-16 of Table I) reported reactions to a single NSAID (single reactors [SRs]) and 11 (patients 17-27 of Table I) to more than 1 NSAID (multiple reactors [MRs]);⁹ the most frequently involved drug was ASA. Cutaneous reactions were reported by 59.3% of the subjects (33.3% of the SRs and 26.0% of the MRs),

TABLE I. Clinical data and results of allergologic tests with culprit NSAIDs

Patient n/sex/age (y)	Culprit drug	Type of reaction	Skin test/ patch test	Oral challenge test	
				Drug	Reaction
1/F/25	keto	UA/D (nI)	keto–	keto+	U
2/F/69	ASA	A/D (I)		ASA+	UA/D
3/F/33	ASA	A/D (I)		ASA+	U
4/M/53	nor	UA/D (I)	nor–	nor+	U
5/F/60	nor	An (I)	nor+		
6/F/71	ASA	UA (nI)		ASA+	U
7/F/26	ASA	U (I)		ASA+	U
8/F/35	ASA	U (nI)		ASA+	U
9/F/34	ket	U (nI)	ket+		
10/F/23	nim	An (I)		nim+	An
11/M/68	ASA	UA (I)		ASA+	UA
12/F/23	ASA	UA (I)		ASA+	U
13/M/42	ASA	UA (nI)		ASA+	An
14/F/58	ASA	UA (I)		ASA+	U
15/F/65	ASA	U (I)		ASA+	U
16/F/60	nor	An (I)	nor+		
17/F/33	ASA/nor	R (I)	nor–	ASA–/nor+	R
18/M/58	ASA/nor	UA (I)	nor–	ASA+/nor+	UA/D
19/F/45	ASA/nor	R/D (I)	nor–	ASA+/nor+	R/D
20/M/29	ASA/nor	U (I)	nor–	ASA+/nor+	U
21/M/34	ace/ASA	UA (nI)		ace–/ASA+	U
22/M/31	ace/prop	An (I)	prop–	ace–/prop+	An
23/M/39	ace/ASA	UA (I)		ace–/ASA+	U
24/F/26	keto/ASA	An (I)	keto–	keto+/ASA+	An
25/F/38	ket/ASA	UA (nI)	ket–	ket+/ASA+	UA
26/F/68	ket/ASA	A (nI)	ket–	ket–/ASA+	A
27/F/34	nim/ASA	U (nI)		nim–/ASA+	U

A, Angioedema; ace, acetaminophen; An, anaphylaxis; ASA, acetylsalicylic acid; D, dyspnea; I, immediate; ket, ketoprofen; keto, ketorolac; nI, nonimmediate; nim, nimesulide; nor, noramidopyrine; prop, propyphenazone; R, rhinitis; U, urticaria; UA, urticaria/angioedema.

TABLE II. Drugs, doses, and administration time intervals used in challenges

Drug	Dose (mg)	Time interval
Talc	350, 350	1 h
ASA	50, 100 (1st d)/250, 500 (2nd d)*	2 h
Noramidopyrine	25, 50 (1st d)/125, 250 (2nd d)/500 (3rd d)*	2 h
Propyphenazone	3, 30, 300	1 h (I)/3-7 d (nI)
Ketoprofen	0.5, 5, 50	1 h (I)/3-7 d (nI)
Acetaminophen	5, 50, 500	1 h (I)/3-7 d (nI)
Nimesulide	1, 10, 100	1 h (I)/3-7 d (nI)
Ketorolac	0.1, 1, 10	1 h (I)/3-7 d (nI)
Parecoxib	0.4, 4, 40	1 h

I, Immediate; nI, nonimmediate.

*With regard to ASA and noramidopyrine, doses were administered on 2 and 3 consecutive days, respectively.

respiratory symptoms by 7.4% (all MRs), cutaneous and respiratory symptoms by 14.8% (all SRs), and anaphylaxis by 18.5% (11.1% of the SRs and 7.4% of the MRs).

None of the patients presented nasal polyps, reported histories of sinusitis, or had previously been exposed to parecoxib.

Each patient underwent a 2-stage procedure: (1) allergologic tests (skin tests, patch tests and/or oral challenge tests) with culprit NSAIDs, and (2) tolerability tests with parecoxib.

Immediate-reading prick and/or intradermal tests were performed to investigate IgE-mediated hypersensitivity to pyrazolones^{2,3} or ketorolac,¹⁰ whereas patch tests and delayed-reading intradermal tests were performed to study cell-mediated hypersensitivity to pyrazolones, ketorolac, or ketoprofen.

Challenges were performed under single-blind, placebo-controlled conditions by a physician with full resuscitation back-up, who monitored both symptoms and cutaneous signs, regularly checked vital parameters (pulse, blood pressure, and FEV₁) throughout the test, and observed the patients for 6 hours after the challenge.

Patients with chronic asthma and urticaria did not have any symptoms at the time of the test and had avoided β -blockers and H₁-antihistamines for 1 week before.

Informed consent was required from each patient.

On the first day, patients underwent a placebo challenge (talc); 1 hour later, if no adverse symptoms had been observed, the placebo was readministered. Culprit drugs were administered orally 1 week after the placebo. Challenge protocols are described in Table II.

The dose increase and time interval between each administration varied according to the culprit drug and the type of reaction (immediate or nonimmediate) (Table II).

In the second stage, 4 weeks later, we performed tolerability tests with parecoxib (Dynastat; Pfizer, Rome, Italy), administering intravenously 1 mL normal saline as a placebo, and if no symptoms developed, 1/100 of the therapeutic dose of parecoxib (0.4 mg), 1/10 (4 mg), and finally the full dose (40 mg) at 1-hour intervals (Table II).

Of the 12 patients who underwent cutaneous or epicutaneous tests, 2 had positive results to skin tests with noramidopyrine and 1 to a patch test with ketoprofen. These patients were not challenged; the other 24 reacted to challenges with at least 1 of the culprit NSAIDs, developing cutaneous symptoms (urticaria and/or angioedema) in 16 cases, respiratory ones (rhinitis and/or dyspnea associated with a decrease of at least 20% in the FEV₁) in 2, cutaneous and respiratory symptoms in 2, and anaphylaxis in 4 (Table I). Such patients were treated with 10 mg chlorphenamine and 40 mg methylprednisolone intravenously—and, in case of anaphylaxis, also with 1 mg intramuscular epinephrine—with a complete resolution of symptoms in 1 to 2 hours.

None of the patients experienced symptoms after administration of either placebos or parecoxib.

It should be noted that the 2 subjects who displayed positive skin tests to noramidopyrine and subject number 17 of Table I, who reacted to an oral challenge test with noramidopyrine but not with ASA, should be classified in a different group from that of patients with nonallergic hypersensitivity to NSAIDs, as previously reported.²

In our pilot study, parecoxib was well tolerated by all 27 NSAID-sensitive patients. This drug thus seems to be a safe alternative for patients requiring parenteral administration; however, to have a 95% CI that reactions will not occur, about 70 parecoxib-negative challenges would have to be conducted.

In any case, considering a recent report on 2 cases of severe bronchospasm after administration of parecoxib in subjects with asthma without previous histories of sensitivity to ASA or other NSAIDs,¹¹ further studies in larger samples of NSAID-sensitive patients are necessary to confirm the tolerability of this parenteral COX-2 inhibitor.

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The leukotriene C4 synthase (A-444C) promoter polymorphism is associated with the severity of exercise-induced asthma in Korean children

To the Editor:

Exercise-induced bronchoconstriction (EIB) is a common problem of childhood asthma. Although the exact mechanism of bronchoconstriction after exercise is not completely understood, studies have shown that inflammatory mediators including the leukotrienes (LTs) may play important roles.¹ However, no previous study has examined the association of LTC4 synthase (LTC4S) with exercise-induced asthma in children.

The gene encoding LTC4S is located on chromosome 5q35. Previous studies have reported weak associations between LTC4S promoter polymorphism with the asthma phenotype,² bronchial responsiveness to methacholine,³ and the severity of asthma regardless of aspirin sensitivity.⁴ The LTC4S polymorphism has also been strongly associated with a specific subgroup of patients with aspirin-intolerant asthma.⁵

Although LTs are important mediators of allergic inflammation, the association between the LTC4S

polymorphism and the presence or severity of asthma has been controversial.²⁻⁸ Here, we examined whether the LTC4S (A-444C) polymorphism is associated with the phenotype of asthma, especially with the exercise-induced asthma, and the severity of asthma.

Children with asthma (N = 445) and nonatopic healthy children (N = 146) were enrolled. An exercise challenge test was performed in 270 children with asthma, and we measured bronchial responsiveness to methacholine and exercise, and lung function. EIB was defined as a 15% or greater reduction in FEV₁ after exercise compared with FEV₁ at baseline. The LTC4S (A-444C) gene polymorphism was determined by genotyping using PCR-RFLP assays.

Our results revealed that there was no difference between children with asthma and healthy control Korean children in terms of the frequency of the LTC4S (-444) C allele (34.17% vs 33.48%; data not shown). These findings collectively suggest that the C allele of the LTC4S (A-444C) promoter polymorphism may not be associated with asthma per se.

However, we investigated whether there was an association between this polymorphism and the severity of EIB. The combined frequency of the AC and CC genotypes in children with asthma and severe EIB (+) showing more than 30% fall of FEV₁ (%) after exercise challenge was significantly lower than that in children with asthma and EIB (-) showing less than a 15% fall of FEV₁ (%; adjusted odds ratio [aOR], 0.47; 95% CI, 0.25-0.88; Table I), further indicating that the C allele of the LTC4S (A-444C) polymorphism may be associated with protection from severe exercise-induced asthma in Korean children.

When we evaluated the association between the LTC4S polymorphism and clinical parameters (eg, pulmonary function and bronchial responsiveness), we found that the maximum percent fall of FEV₁ (%) after exercise challenge was significantly lower in children harboring 1 or 2 C alleles compared with children with the AA genotype in the asthmatic, atopic asthmatic, and asthmatic with EIB groups (Table II). Furthermore, atopic children with asthma harboring the C allele (CC or AC) showed lower bronchial responsiveness to methacholine (PC₂₀) than those with the AA genotype. These results suggest that the C allele of the LTC4S (A-444C) polymorphism may be related to lower bronchial responsiveness in children with asthma.

TABLE I. Allele frequencies of the LTC4S (A-444C) polymorphism related to the severity of bronchoconstriction after exercise challenge in children with asthma*

Genotype	Maximum % fall of FEV ₁ (%)				
	<15%	15% to 30%		>30%	
	N = 79 (%)	N = 91 (%)	aOR (95% CI)	N = 100 (%)	aOR (95% CI)
AA	45 (56.96)	54 (59.34)	1.00	74 (74.00)	1.00
AC	32 (40.51)	33 (36.26)	0.86 (0.46-1.61)	23 (23.00)	0.44 (0.23-0.84)
CC	2 (2.53)	4 (4.40)	1.67 (0.29-9.54)	3 (3.00)	0.91 (0.15-5.66)
AC+CC	34 (43.04)	37 (40.66)	0.91 (0.49-1.68)	26 (26.00)	0.47 (0.25-0.88)
Frequency (A)	0.77	0.77		0.86	

*aOR by age and sex. Logistic regression analysis was performed.