

Etoricoxib Tolerability in Patients with Hypersensitivity to Nonsteroidal Anti-Inflammatory Drugs

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Key Words

Etoricoxib • Hypersensitivity • Nonsteroidal anti-inflammatory drugs • Pyrazolones • Skin test • Oral challenge test

Abstract

Background: Adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly observed, particularly among patients with chronic urticaria or asthma. The identification of a safe and reliable alternative is a frequent problem in clinical practice. Our aim was to investigate the clinical tolerability of etoricoxib, a new selective cyclooxygenase-2 inhibitor, in a group of patients with well-established NSAID hypersensitivity. **Methods:** We assessed 31 adults (21 women and 10 men) who reported one or more adverse reactions to NSAIDs, manifested as cutaneous, respiratory or anaphylactic symptoms. Sixteen of them reported reactions to a single NSAID (single reactors) and 15 to more than one NSAID (multiple reactors); the most frequently involved drug was acetylsalicylic acid. First, each patient underwent allergologic tests (skin and/or oral challenge tests) with culprit NSAIDs and then tolerability tests with increasing doses of etoricoxib up to 120 mg. All challenges were performed under single-blind, placebo-controlled conditions. **Results:** NSAID hypersensitivity was diagnosed in all 31 patients: 3 displayed

positive results to pyrazolone skin tests and the other 28 to challenges with culprit NSAIDs. None reacted to either placebos or etoricoxib. **Conclusions:** Etoricoxib seems to be a safe alternative for patients with well-demonstrated NSAID hypersensitivity.

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Introduction

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 one or more drugs of this class. Some of these reactions are immunologically mediated, as demonstrated by in vivo (skin tests) and in vitro (serum-specific IgE assays) tests for pyrazolone drugs [2–4]. In the vast majority of cases, adverse reactions to NSAIDs are mediated by a pharmacological mechanism. NSAIDs such as ASA, pyrazolones, indomethacin, diclofenac, ketoprofen, ibuprofen and piroxicam inhibit the constitutive isoform of cyclooxygenase (COX)-1, and thus, reduce protective prostaglan-

din E₂ and increase unrestrained synthesis of cysteinyl leukotrienes and release from mast cells of mediators such as prostaglandin D₂. This mechanism, which is well established in ASA-induced asthma [5], has also been recently supported by biochemical observation in ASA-induced urticaria [1, 6]. Nimesulide and meloxicam, preferential inhibitors of COX-2 (the induced isoform), can often be safely administered to NSAID-sensitive patients [7, 8]. The newer NSAIDs, such as rofecoxib, celecoxib, valdecoxib, parecoxib and etoricoxib, which selectively inhibit COX-2 without affecting the arachidonic acid metabolism [5], showed no clinical crossreactivity and can be considered good alternatives for patients with hypersensitivity to nonselective NSAIDs [5, 9–13]. However, selective NSAIDs may provoke hypersensitivity reactions in a minority of patients, particularly in those with cutaneous reactions, with a frequency ranging from 1.6% for rofecoxib to 11.1% for celecoxib [14].

Etoricoxib is a new selective COX-2 inhibitor approved in Europe and Latin 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 shows the highest in vitro selectivity for COX-2. In effect, it is more than 100-fold more selective for COX-2 than COX-1 in whole-blood assays [15]. In addition, etoricoxib displays improved gastrointestinal safety compared with nonselective NSAIDs and has a favorable overall safety and tolerability profile.

Previously, etoricoxib tolerability has been evaluated in 56 subjects with cutaneous hypersensitivity reactions to NSAIDs [14] and in 141 patients with a history of cutaneous reactions to NSAIDs [16], with reaction rates of 7.1 and 1.4%, respectively.

In the present study, we assessed the clinical tolerability of etoricoxib in a group of patients with well-established NSAID hypersensitivity.

Materials and Methods

Thirty-one adults (21 women and 10 men) ranging in age from 23 to 71 years (mean age 42.9 ± 16.4) and reporting one or more adverse reactions to NSAIDs – manifested as cutaneous, respiratory or anaphylactic symptoms – were evaluated between June 2004 and February 2006 in the allergy units of the Complesso Integrato Columbus and Oasi Maria Santissima.

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

Immediate-reading prick and/or intradermal tests were performed in order to diagnose an IgE-mediated hypersensitivity in patients who had suffered immediate reactions to pyrazolones.

Skin tests were performed on volar forearm skin. The concentrations used were 5 and 50 mg/ml for noramidopyrine and 3 and 30 mg/ml for propyphenazone. These concentrations were nonirritant in a control group of 20 healthy patients. First, we performed skin prick tests and, if no positive reactions occurred, we carried out immediate-reading (20 min) intradermal tests. Prick tests with histamine at 10 mg/ml were used as positive controls, while normal saline was used as a negative control for both prick and intradermal tests.

In patients with negative skin tests for pyrazolones or previous reactions to other NSAIDs (table 1), we performed challenges with the culprit drugs under single-blind, placebo-controlled conditions.

On the first day, patients underwent a placebo challenge (talc); 1 h later, if no adverse symptoms had been observed, the placebo was readministered. Culprit drugs were administered orally 1 week after the placebo. Challenges were performed as follows, at least 4 weeks after the most recent adverse reaction.

For ASA and noramidopyrine, we administered increasing doses of each drug at 2-hour intervals. As far as ASA is concerned, we administered 50 + 100 mg on the first day and 250 + 500 mg on the following one, while patients were given 25 + 50 mg, 125 + 250 mg, and 500 mg, respectively, of noramidopyrine on 3 consecutive days (table 2).

For propyphenazone, nimesulide, paracetamol, ketoprofen and ketorolac, we initially administered one hundredth of the therapeutic dose, then a tenth, and finally the full dose. The time interval between doses was either 1 h in case of a previous immediate reaction (i.e. occurring less than 1 h after drug administration) or 3–7 days (depending on the time interval between drug intake and adverse reaction) in case of previous nonimmediate reactions (i.e. occurring more than 1 h after the last drug administration).

We increased the dose only in case of negative results after the previous dosage.

In the second stage, we performed tolerability tests with 120 mg etoricoxib (Tauxib; Sigma Tau, Rome, Italy), administering 12 mg orally (one tenth of the therapeutic dose) and, if no symptoms developed, the remaining 108 mg 1 h later (table 2). In case of anaphylaxis after NSAID intake, we started the etoricoxib challenge by administering 1.2 mg (one hundredth of the therapeutic dose).

At the time of testing, no subject displayed significant cutaneous or respiratory tract symptoms or concomitant illnesses (i.e. underlying cardiac, hepatic, neurologic, psychiatric, renal, hematologic or other diseases). Subjects on β -blocker treatment, as well as pregnant or lactating women, were excluded from the study. Before allergologic evaluations, H₁ antihistamines had been withheld for at least 7 days, leukotriene receptor antagonists and cromones for 2 days, long-acting β -agonists for 3 days, and short-acting β -agonists for 6 h. For a few days before and after challenges, patients were asked to avoid food with artificial flavoring or preservatives. The study was conducted according to the ethical standards of our hospital, which require the informed consent of each patient, and its protocol was approved by the institutional review board.

Physicians and nursing staff monitored both symptoms and cutaneous signs throughout the test and observed the patients for

Table 1. Clinical data and results of allergologic tests with culprit NSAIDs

Patient No./sex/age	Allergy/allergy-like disease	Culprit drug	Type of reaction	Skin test	Oral challenge test	
					drug	reaction
1/F/25		keto	UA/D (nI)		keto+	U
2/F/69		ASA	A/D (I)		ASA+	UA/D
3/F/33		ASA	A/D (I)		ASA+	U
4/M/53	De	nor	UA/D (I)	nor–	nor+	U
5/F/60	As	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		nor	U (nI)	nor+		
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	R, cU	ASA	UA (nI)		ASA+	An
14/F/58	R, De	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	De	ASA/nor	R/D (I)	nor–	ASA+/nor+	R/D
20/M/29		ASA/nor	U (I)	nor–	ASA+/nor+	U
21/M/34	cU, latex h	par/ASA	UA (nI)		par–/ASA+	U
22/M/31		par/prop	An (I)	prop–	par–/prop+	An
23/M/39		par/ASA	UA (I)		par–/ASA+	U
24/F/26		keto/ASA	An (I)		keto+/ASA+	An
25/F/38		ket/ASA	UA (nI)		ket+/ASA+	UA
26/F/68	antibiotic h	ket/ASA	A (nI)		ket–/ASA+	A
27/F/34		nim/ASA	U (nI)		nim–/ASA+	U
28/M/24		nim/ASA	U (nI)		nim–/ASA+	U
29/F/35	R	ASA/par	UA (nI)		par–/ASA+	U
30/M/64		ASA/nim/par	U (I)		par–/nim–/ASA+	U
31/F/27	De	ASA/nim/par	UA (nI)		par–/nim–/ASA+	U

keto = Ketorolac; UA = urticaria/angioedema; D = dyspnea; nI = nonimmediate; U = urticaria; ASA = an-gioedema; I = immediate; De = dermatitis; nor = noramidopyrine; As = asthma; An = anaphylaxis; nim = nimesulide; R = rhinitis; cU = chronic urticaria; h = hypersensitivity; par = paracetamol; prop = propyphenazone; ket = ketoprofen.

6 h after the challenge. Patients were instructed to return to the allergy unit in case symptoms occurred after discharge. In patients with histories of rhinitis and/or bronchial asthma not related to drug use, as well as in those who reported NSAID-related bronchospastic or rhinitic symptoms, nasal endoscopy was performed to exclude the presence of polyps. In such subjects, we assessed the forced expiratory volume in 1 s (FEV₁) with computed spirometry (2120 Spirometer; Vitalograph, Buckingham, UK) before the challenge, at 30-min intervals during the first 2 h, and every hour thereafter for 6 h. Pulse and blood pressure were also monitored.

Challenges were considered positive if any of the following symptoms developed: cutaneous (erythema, urticaria/angioedema, exanthem), respiratory (rhinorrhea, nasal obstruction, sneez-

ing, cough, dyspnea associated with a decrease of at least 20% in the FEV₁) and/or other (hypotension, lipothymia).

To standardize the assessment of skin eruption severity, we used the Psoriasis Area and Severity Index as modified by Zembowicz et al. [17], who replaced desquamation with itching for the assessment of urticaria. However, we did not attribute any score to itching not accompanied by objective symptoms. Therefore, we determined the degree of itching, erythema and infiltration, as well as the percentage of involvement of the 4 main body areas: head, trunk, upper extremity and lower extremity. Each variable was assessed on a scale of 0–4, with 0 indicating no involvement and 4 severe involvement. Calculated Psoriasis Area and Severity Index scores range from 0 to 72, with those >10 being considered as indicating a severe reaction. To assess any respiratory symp-

Table 2. Drugs, doses and administration time intervals used in challenges

Drug	Dose, mg	Time interval
Talc	350, 350	1 h
ASA	50, 100 (1st day)/250, 500 (2nd day) ¹	2 h (I/nI)
Noramidopyrine	25, 50 (1st day)/125, 250 (2nd day)/500 (3rd day) ¹	2 h (I/nI)
Propyphenazone	3, 30, 300	1 h (I)
Ketoprofen	0.5, 5, 50	3–7 days (nI)
Paracetamol	5, 50, 500	1 h (I)/3–7 days (nI)
Nimesulide	1, 10, 100	1 h (I)/3–7 days (nI)
Ketorolac	0.1, 1, 10	1 h (I)/3–7 days (nI)
Etoricoxib	(1.2), 12, 108	1 h

I = Immediate; nI = nonimmediate.

¹ With regard to ASA and noramidopyrine, doses were administered on 2 and 3 consecutive days, respectively.

toms, we used the scoring system of Nizankowska et al. [18] with a five-step scale (0 = no symptoms; 1 = weak intensity; 2 = moderate intensity; 3 = strong intensity; 4 = very strong intensity).

Twenty-seven of the 31 patients of the present study had also participated in a previous study of ours [13] regarding tolerability of parecoxib in patients with well-established NSAID hypersensitivity, and all 27 subjects had tolerated this drug.

Results

Sixteen subjects (patients 1–16, table 1) reported reactions to a single NSAID (single reactors, SRs) and 15 (patients 17–31, table 1) to more than one NSAID (multiple reactors, MRs) [19]; the most frequently involved drug was ASA. Cutaneous reactions were reported by 64.5% of the subjects (of whom 29% were SRs and 35.5% MRs), respiratory symptoms by 6.4% (all MRs), cutaneous and respiratory symptoms by 13% (all SRs), and anaphylaxis by 16.1% (of whom 9.7% were SRs and 6.4% MRs).

Of the 31 subjects, 9 (29%) had histories of allergies or allergy-like diseases: 4 with respiratory symptoms (rhinitis and/or asthma), 4 with allergic contact dermatitis (including 1 patient also with rhinitis), 1 with antibiotic hypersensitivity, and 2 with chronic idiopathic urticaria (1 also with rhinitis and the other also with latex hypersensitivity).

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

Of the 9 patients who underwent skin tests, 3 were positive to intradermal tests with noramidopyrine. These patients were not challenged; the other 28 reacted to chal-

lenges with at least one of the culprit NSAIDs, developing cutaneous symptoms (urticaria and/or angioedema) in 20 cases (with scores ranging from 4 to 8), respiratory symptoms (rhinitis and/or dyspnea associated with a decrease of at least 20% in FEV₁) in 2 cases (score: 2 in both), cutaneous and respiratory symptoms in 2 cases (respective scores: 7 and 2 in one case, 6 and 1 in the other), and anaphylaxis in 4 cases (table 1). Such patients were treated with 10 mg of clorphenamine and 40 mg of methylprednisolone intravenously – and, in case of anaphylaxis, also with 1 mg of epinephrine intramuscularly – with a complete resolution of symptoms in 1–2 h.

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

Discussion

A common problem in clinical practice is the need to identify an alternative treatment for pain and inflammation that can safely be administered in patients with hypersensitivity to the classic NSAIDs. The introduction of selective COX-2 inhibitors has created new expectations for such patients. Several studies have demonstrated that rofecoxib and celecoxib do not trigger respiratory reactions in subjects with ASA-induced asthma. On the other hand, coxib use in patients who have experienced cutaneous reactions after taking COX-1 inhibitors is controversial: some researchers have observed absolute tolerance and others have reported cutaneous reactions with a frequency of 1.6, 11.1 and 3.5% for rofecoxib, celecoxib and valdecoxib, respectively [14].

Among the coxibs currently in clinical use, etoricoxib shows the highest selectivity for COX-2 *in vitro*; thus, we assessed its tolerability in a group of patients with hypersensitivity to NSAIDs established on the basis of positive responses to either pyrazolone skin tests or oral challenges with culprit drugs. In effect, according to the recent position paper of the European Network for Drug Allergy, the drug provocation test is the 'gold standard' to establish or exclude the diagnosis of hypersensitivity to a certain substance, as it can reproduce hypersensitivity symptoms irrespectively of the pathogenic mechanism [20].

With regard to our study population, 27 of the 31 patients whom we evaluated had also participated in a previous study of ours regarding tolerability of parecoxib, published as a letter [13]. We studied them because they constituted an available sample of subjects with well-demonstrated NSAID hypersensitivity. On the other hand, although both etoricoxib and parecoxib are selective COX-2 inhibitors, there are significant differences regarding both their uses and their administration routes. In effect, the former is administered orally, whereas parecoxib is the only selective COX-2 inhibitor that can be administered parenterally.

Furthermore, it should be noted that both subject No. 17 (table 1) – who reacted to an oral challenge test with noramidopyrine, but not with ASA – and the 3 subjects who displayed positive skin tests to noramidopyrine should be classified in a different group from that of patients with nonallergic hypersensitivity to NSAIDs, as indicated by Czerniawska-Mysik and Szczeklik [2]. These authors classified patients with idiosyncratic reactions to pyrazolones in two different groups. In the first group, all patients had chronic asthma, pyrazolone skin tests were negative, and all pyrazolones, as well as several other inhibitors of COX-1, including ASA, precipitated bronchoconstriction. In the second group, some pyrazolones (such as noramidopyrine and aminophenazone) induced anaphylaxis and/or urticaria; skin tests with these drugs were highly positive, whereas other, structurally different pyrazolones (e.g., phenylbutazone and sulfinpyrazone) and ASA were tolerated, and chronic bronchial asthma was present in only one fourth of the patients. It was suggested that the pathogenic mechanisms responsible for the idiosyncratic reactions involve an inhibition of COX in the first group and an IgE-mediated hypersensitivity in the second group. This distinction is clinically important because patients of the latter group can tolerate other, structurally different pyrazolones (e.g., phenylbutazone and sulfinpyrazone), as well as ASA-like drugs. However, subject No. 17 (table 1), unlike the other 3 cases,

presented negative skin tests to noramidopyrine. In this patient, an inhibition of skin reactivity by inadvertent use of antihistamines was ruled out because of a positive response to the histamine prick test. With regard to her negative challenge with ASA, even though a tolerance induction during this test cannot be excluded, it seems to be unlikely because many other patients reacted to ASA challenges performed with the same protocol. In any case, we advised her to avoid ASA until she underwent another ASA challenge.

In the present study, none of the NSAID-sensitive patients reacted to etoricoxib administration, confirming the perfect tolerability of this drug observed by Nahar et al. [21]. However, our results differ from those of Sánchez-Borges et al. [14] and Nettis et al. [16], who observed a rate of crossreactivity to etoricoxib of 7.1 and 1.4%, respectively.

However, it is difficult to compare these data because the crossreactivity rate might vary according to the characteristics of the samples assessed and the dose of etoricoxib administered.

Nahar et al. [21] assessed etoricoxib tolerability at a 90-mg dosage in 16 subjects with mild to moderate asthma and histories of sensitivity to ASA or NSAIDs not confirmed by challenges with responsible drugs.

Sánchez-Borges et al. [14] administered the same amount of etoricoxib as we did to 56 patients with NSAID hypersensitivity diagnosed on the basis of both positive histories and positive responses to challenges performed with responsible NSAIDs. Such challenges provoked cutaneous reactions both with and without respiratory symptoms. Therefore, the difference in etoricoxib tolerability between the study by Sánchez-Borges et al. [14] and ours may be due mainly to the difference in the size of the samples assessed, and we do not know if a larger sample would have entailed adverse reactions to etoricoxib.

With regard to the study by Nettis et al. [16], patients had been selected only on the basis of clinical histories of adverse reactions, mainly cutaneous, after NSAID administration. However, large studies that performed challenges with the suspect NSAIDs in patients with histories of NSAID hypersensitivity observed a rate of positive responses ranging from about 15 to 30% [22–24]. Moreover, Nettis et al. [16] administered 90 mg of etoricoxib, while Sánchez-Borges et al. [14] and we administered 120 mg. Thus, we assessed the tolerability of etoricoxib at the highest dosage, showing that this selective COX-2 inhibitor does not lose its selectivity when the dose is increased.

In conclusion, although there are some discrepancies among the studies performed, etoricoxib seems to be a safe alternative for patients with allergic and nonallergic hypersensitivity to NSAIDs who report anaphylactic, cutaneous and/or respiratory symptoms. However, because adverse reactions to etoricoxib may occur [14, 16, 25], we

recommend that it first be administered in a specialized center. In any case, further studies in larger samples of NSAID-sensitive patients are necessary to firmly establish the tolerability of this new selective COX-2 inhibitor.

References

- Mastalerz L, Setkowicz M, Sanak M, Szczeklik A: Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol* 2004;113:771–775.
- Czerniawska-Mysik G, Szczeklik A: Idiosyncrasy to pyrazolone drugs. *Allergy* 1981;36:381–384.
- Kowalski ML, Woszczek G, Bienkiewicz B, Mis M: Association of pyrazolone drug hypersensitivity with HLA-DQ and DR antigens. *Clin Exp Allergy* 1998;28:1153–1158.
- Himly M, Jahn-Schmid B, Pittertschatscher K, Bohle B, Grubmayr K, Ferreira F, et al: IgE-mediated immediate-type hypersensitivity to the pyrazolone drug propyphenazone. *J Allergy Clin Immunol* 2003;111:882–888.
- Szczeklik A, Stevenson DD: Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003;111:913–921.
- Szczeklik A, Sanak M, Nizankowska-Mogilnicka E, Kielbasa B: Aspirin intolerance and the cyclooxygenase-leukotriene pathways. *Curr Opin Pulm Med* 2004;10:51–56.
- Quaratino D, Romano A, Papa G, Di Fonso M, Giuffreda F, Purello D'Ambrosio F, Venuti A: Long-term tolerability of nimesulide and acetaminophen in nonsteroidal anti-inflammatory drug-intolerant patients. *Ann Allergy Asthma Immunol* 1997;79:47–50.
- Quaratino D, Romano A, Di Fonso M, Papa G, Perrone MR, Purello D'Ambrosio F, Venuti A: Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2000;84:613–617.
- Szczeklik A, Nizankowska E, Bochenek G, Nagraba K, Mejza F, Swierczynska M: Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2001;31:219–225.
- Stevenson DD, Simon RA: Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 2001;108:47–51.
- Perrone MR, Artesani MC, Viola M, Gaeta F, Caringi M, Quaratino D, Romano A: Tolerability of rofecoxib in patients with adverse reactions to nonsteroidal anti-inflammatory drugs: a study of 216 patients and literature review. *Int Arch Allergy Immunol* 2003;132:82–86.
- Viola M, Quaratino D, Gaeta F, Caringi M, Valluzzi R, Caruso C, et al: Celecoxib tolerability in patients with hypersensitivity (mainly cutaneous reactions) to nonsteroidal anti-inflammatory drugs. *Int Arch Allergy Immunol* 2005;137:145–150.
- Viola M, Quaratino D, Volpetti S, Gaeta F, Romano A: Parecoxib tolerability in patients with hypersensitivity to nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol* 2006;117:1189–1191.
- Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A: Safety of etoricoxib, a new cyclooxygenase 2 inhibitor, in patients with nonsteroidal anti-inflammatory drug-induced urticaria and angioedema. *Ann Allergy Asthma Immunol* 2005;95:154–158.
- Riendeau D, Percival MD, Brideau C, Charle-son S, Dube D, Ethier D, Falgout JP, Friesen RW, Gordon R, Greig G, Guay J, Mancini J, Ouellet M, Wong E, Xu L, Boyce S, Visco D, Girard Y, Prasit P, Zamboni R, Rodger IW, Gresser M, Ford-Hutchinson AW, Young RN, Chan CC: Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Ther* 2001;296:558–566.
- Nettis E, Colanardi MC, Ferrannini A, Vacca A, Tursi A: Short-term tolerability of etoricoxib in patients with cutaneous hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2005;95:438–442.
- Zembowicz A, Mastalerz L, Setkowicz M, Radziszewski W, Szczeklik A: Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. *Arch Dermatol* 2003;139:1577–1582.
- Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A: Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. *Eur Respir J* 2000;15:863–869.
- Stevenson DD, Sánchez-Borges M, Szczeklik A: Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001;87:177–180.
- Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P: European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity: Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58:854–863.
- Nahar IK, Muqim AT, Al-Qhouti BI, Al-Herz AA, Shehab DK, Uppal SS, Khadadah ME: The use of etoricoxib in patients with bronchial asthma associated with aspirin sensitivity. *Saudi Med J* 2006;27:119–120.
- Messaad D, Sahlia H, Benahmed S, Godard P, Bousquet J, Demoly P: Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;140:1001–1006.
- Lammintausta K, Kortekangas-Savolainen O: Oral challenge in patients with suspected cutaneous adverse drug reactions: findings in 784 patients during a 25-year-period. *Acta Derm Venereol* 2005;85:491–496.
- Schubert B, Grosse Perdekamp MT, Pfeuffer P, Raith P, Brocker EB, Trautmann A: Nonsteroidal anti-inflammatory drug hypersensitivity: table or reality? *Eur J Dermatol* 2005;15:164–167.
- Morais-Almeida M, Marinho S, Rosa S, Gaspar A, Rosado-Pinto JE: Multiple drug intolerance including etoricoxib. *Allergy* 2006;61:144–145.