
Tolerability of rofecoxib in patients with cutaneous adverse reactions to nonsteroidal anti-inflammatory drugs

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Background: Adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are very common problems in clinical practice. Rofecoxib is a novel NSAID which selectively inhibits prostaglandin endoperoxide H synthase-2 and has no effect on prostaglandin endoperoxide H synthase-1.

Objective: To evaluate the tolerability of rofecoxib in NSAID-sensitive patients with cutaneous adverse reactions.

Patients and Methods: One hundred thirty-nine patients with NSAID-induced adverse reactions [60 urticaria alone (43.1%), 34 angioedema (24.5%), 34 angioedema plus urticaria (24.5%), 5 urticaria plus difficulty in breathing (3.6%), 4 maculopapular rash (2.9%), and 2 Stevens-Johnson syndrome (1.4%)] were submitted to a single-blind, placebo-controlled peroral challenge with increasing doses of rofecoxib.

Results: One hundred thirty-eight of 139 (99.3%) patients tolerated rofecoxib without adverse reactions; only one (0.7%) experienced weak urticaria localized at arms.

Conclusions: Rofecoxib is a well tolerated drug in patients with NSAID cutaneous adverse reactions and it may represent a valid alternative drug in NSAID-sensitive patients.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs), along with antimicrobials, are the drug categories with the highest number of allergic or pseudoallergic cutaneous adverse reactions.¹ Within allergic or pseudoallergic adverse reactions, the most frequent is urticaria/angioedema, but anaphylactic shock and edema of glottis are the most dangerous because they are life-threatening. To date, little is known on the pathogenic mechanisms of pseudoallergic adverse reactions.

The main mechanism of action of NSAIDs consists in the inhibition of prostaglandin endoperoxide H syn-

thases (PGHS),²⁻⁴ the enzymes that in the arachidonic acid cascade lead to the formation of prostaglandins (PGs) and thromboxanes, which exist in two isoforms 1 and 2, respectively. PGHS-1 is the constitutive form and is involved in the basic mechanisms to maintain the homeostasis of the organism, whereas PGHS-2 is inducible and seems to play an important role in the inflammatory processes, as well as in other important pathologic and non-pathologic conditions.⁵ The inhibition of PGHS enzymes has been proposed to explain the pathogenic mechanism of NSAID-induced bronchial asthma. The inhibition of these enzymes may create an imbalance between PGHS (1 and/or 2) and 5-lipoxygenase (5-LO) in the arachidonic acid cascade with a consequent lower production of the bronchodilator prostaglandin (PG) E₂,⁶⁻⁸ and with a relatively higher production of the bronchoconstrictors leukotrienes (LT) C₄ and D₄.

It is known that many adverse reactions to NSAIDs (such as gastrointestinal damage, renal failure, and bronchial asthma) are related to the inhibition of PGHS-1, whereas the anti-inflammatory effects are related to the inhibition of PGHS-2.⁹⁻¹⁰ For this reason, pharmacologic research in past years has been specifically oriented toward finding a selective PGHS-2 antagonist with no activity to PGHS-1.

Rofecoxib¹¹⁻¹² is the first NSAID which specifically inhibits PGHS-2 and has no effect on PGHS-1. It was approved by the US Food and Drug Administration in 1999. In theory, it represents a step forward in the treatment of pain and inflammation. In particular, it has been approved for the treatment of primary dysmenorrhea, relief of the signs and symptoms of osteoarthritis, and the management of acute pain in adults. Studies on the safety of rofecoxib will be necessary to evaluate the toxicity to the gastrointestinal tract and to the kidneys.

As for all NSAIDs, rofecoxib is also contraindicated in patients with aspirin triad and in patients with NSAID-adverse reactions and should be used with caution in patients with preexisting asthma.

The objective of this study was to evaluate the tolerability of rofecoxib in patients with NSAID-induced cutaneous allergic and/or pseudoallergic reactions.

MATERIALS AND METHODS

Patients

Over a period of 9 months (July 5, 2000-April 5, 2001), all patients referred to our clinic as having a recent (within the last 12 months), unequivocal

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cal history of cutaneous adverse reactions to NSAIDs were enrolled in the study.

Patients not providing a documented medical report were excluded. Inclusion criteria used to establish if the ingestion of NSAIDs induced the adverse reactions were 1) if a reaction occurred within 12 hours, and 2) no other drugs have been ingested by the patient apart from NSAID before the reaction. The study population consisted of 139 subjects [42 (30.2%) male and 97 (69.8%) female; mean age ($\pm$ SD) 35.8 years (15.52); range 14 to 75 years]. All had experienced adverse manifestations after the use of NSAIDs: sixty subjects experienced urticaria alone (42.1%), 34 angioedema (24.5%), 34 angioedema plus urticaria (24.5%), 5 urticaria plus difficulty in breathing (3.6%), 4 maculopapular rash (2.9%), and 2 Stevens-Johnson syndrome (1.4%).

Personal history data of allergic diseases were obtained by the investigators: self-reported allergy history, including rhinitis, rhinoconjunctivitis, asthma, atopic dermatitis, allergic contact dermatitis, chronic urticaria, and food allergy; and self-reported medical history including any current or previous medication allergies apart from NSAID sensitivity. All subjects underwent a skin-prick test with common inhalant allergens (Bayropharm DHS, Milan, Italy): *Dermatophagoides pteronyssinus* and *D. farinae*, Parietaria pollen, grass pollen, olive pollen, cypress pollen, *Artemisia vulgaris*, *Alternaria tenuis*, *Aspergillus*, and dog and cat dander.

Skin prick tests were performed using histamine (10 mg/mL) and normal saline as positive and negative controls, respectively. Wheals of 3 mm or more were regarded as positive in the absence of a reaction to normal saline.

Oral Challenge Test

These subjects agreed to undergo single-blind, placebo-controlled peroral challenge with rofecoxib to identify a valid alternative drug.

All the patients were in good health and free of symptoms and signed an informed consent before challenge. They presented a forced expiratory

volume in 1 second (FEV₁) >80% of predictive and normal blood pressure.

Antihistamines were stopped 2 weeks before challenges (6 weeks for astemizole); cromolyn, corticosteroids, LT receptor antagonists, and inhaled sympathicomimetic agents were discontinued 48 hours before the provocation test. Oral challenge was conducted in our department with all resuscitation facilities at hand. It was performed in 2 days with placebo (talco) and rofecoxib (Vioxx, Merck Sharp & Dome, Rome, Italy) with inert capsules as a vehicle. On the first day, two placebo capsules were administered, one every hour; after 7 days each patient received divided doses of rofecoxib: one-quarter of the therapeutic dose (6.1 mg) initially and three-quarters (18.9 mg) 1 hour later if no reactive symptoms were noted. Thus, the total therapeutic dose was 25 mg. During execution of the test, arterial pressure and FEV₁ were monitored (30 minutes and every hour after administering each drug or placebo dose or at any time when other symptoms occurred). Each patient was kept under medical control in hospital for at least 6 hours after challenges and was then asked to return after 24 and 48 hours to exclude delayed reactions. Patients with a history of chronic urticaria were challenged during a period of clinical remission of disease.

The test was considered positive if 1) cutaneous and mucosal manifestations (erythema and/or wheals and/or angioedema) appeared; or 2) respiratory symptoms or a decrease of at least 20% in the FEV₁ or hypotension developed.

RESULTS

History of Allergic Diseases

Data concerning a personal history of atopic and allergic diseases in the subjects included in the study are shown in Table 1. Of the 139 patients considered, 36 (25.9%) had a personal history of an atopic disease: allergic rhinitis or rhinoconjunctivitis in 20 cases (14.4%), bronchial asthma associated to rhinitis in 7 cases (5%), bronchial asthma in 5 cases (3.6%), and atopic dermatitis in 4 cases

Table 1. History of Allergic Diseases apart from Adverse Reactions to NSAIDs and Skin Prick Tests

Clinical condition	Patients (%)	
Allergic rhinitis	16	11.5
Allergic rhinitis + asthma	7	5
Allergic asthma	5	3.6
Allergic rhinoconjunctivitis	4	2.9
Atopic dermatitis	4	2.9
None	103	74.1
Atopic diseases	36	25.9
Chronic urticaria	13	9.3
Allergic contact dermatitis	7	5
Food allergy	6	4.3
Allergy to other drugs	32	23
Skin test positivity	25	18

(2.9%). Thirteen subjects (9.3%) suffered from chronic urticaria and 7 (5%) from allergic contact dermatitis. Six individuals (4.3%) had a food allergy history [fish 2 (1.4%), egg 1 (0.7%), nuts 1 (0.7%), soy 1 (0.7%), and celery 1 (0.7%)]. Further, in the study group, 32 (23%) had a positive history of urticaria/angioedema after ingestion of drugs not included in NSAIDs: 24 (17.3%) antimicrobials [β -lactams 20 (14.4%), macrolides 2 (1.4%), cotrimoxazole 1 (0.7%), tetracyclines 1 (0.7%)], 3 (2.1%) gastrointestinal agents, 3 (2.1%) cardiovascular agents, 2 (1.4%) local anesthetics, and 1 (0.7%) bronchopulmonary agent.

Skin Prick Test Results

Twenty-five subjects of the 139 total who were prick tested had a positive response to one or more of the aeroallergens tested (18%) (Table 1). Fifteen patients (10.8%) reacted to *D. and D. farinae*, 7 (5%) to Parietaria pollen, 7 (5%) to grass pollen, 3 (2.1%) to cypress pollen, 4 (2.9%) olive pollen, 1 (0.7%) dog dander, 1 (0.7%) cat dander, 1 (0.7%) *A. tenuis*, respectively. No patient reacted to *A. vulgaris* or *Aspergillus*.

Adverse Reactions to NSAIDs

The study population consisted of 139 NSAID-sensitive subjects. NSAIDs responsible for cutaneous reactions are reported in Table 2. The prevalent drugs were acetylsalicylic acid (36%) and nimesulide (17.3%). One hundred five patients (73%) were sensitive to one drug, 30 (22%) to two drugs, and 7 (5%) to three drugs.

Table 2. NSAIDs Causing Adverse Reactions in 139 Patients*

Drug	Number	%
Aspirin	50	36
Nimesulide	24	17.3
Noramidopyrine	18	12.9
Ibuprofen	11	7.9
Diclofenac	9	6.5
Ketoprofen	15	10.8
Paracetamol	11	7.9
Morniflumate	6	4.3
Propyphenazone	14	10.1
Piroxicam	3	2.1
Naproxen	7	5
Flurbiprofen	3	2.1
Tiaprofenic acid	3	2.1
Ketorolac	4	2.9
Niflumic acid	2	1.4
Indomethacin	1	0.7

* One hundred two patients (73%) were sensitive to one drug, 30 (22%) to two drugs, 7 (5%) to three drugs.

Oral Challenge Test

Of the 139 patients who received a challenge test with rofecoxib, only 1 showed a positive test (0.7%). This was a 53-year-old man who developed some wheals located on the arms approximately 15 minutes after the administration of a total dose of 25 mg of rofecoxib. He did not show respiratory symptoms or FEV₁ changes. He was successfully treated with chlorphenamine (10 mg intravenously); in fact, the symptoms resolved within 1 hour after therapy. This patient had a history of allergic rhinitis and a negative family history in terms of drug reactions. He suffered from chronic idiopathic urticaria with a disease duration of approximately 2 years. He came to our attention because of an adverse reaction that occurred 20 minutes after the assumption of the third tablet of aspirin (500 mg) which was characterized by generalized urticaria and palpebral-labial edema.

Also, 11 months before the visit, he presented an adverse reaction with generalized urticaria, after the ingestion of naproxen. The remaining 138 individuals did not report immediate or delayed reactions during and after challenge with rofecoxib. None of the

patients suffered adverse reactions to the placebo challenge.

DISCUSSION

NSAIDs are the most frequently prescribed drugs worldwide. They have a wide application in clinical practice, treating arthrosis, osteoarthritis, rheumatoid arthritis, headache, fever, dental pain, inflammation, flu, dysmenorrhea, and many others. Their efficacy is very high, but they are often responsible for adverse reactions. The most frequent adverse reactions are related to the damage they provoke in the gastrointestinal tract and kidneys. These adverse reactions are related to the inhibition of PGHS-1 enzyme. The inhibition of PGHS-1 in the stomach and kidneys provoke a lower production essentially of PGE₂ and possibly other PGs that are necessary in the physiologic homeostasis of those organs. NSAIDs, along with antimicrobials, are the drug categories with the highest number of allergic and pseudoallergic adverse reactions, particularly urticaria/angioedema, anaphylactic shock, and edema of glottis. Allergic reactions are explained with the classical type I immunologic reaction with the identification of IgE mainly, but also IgG, which are able to trigger the allergic reaction. The pathogenic mechanisms of pseudoallergic reactions are still obscure. Until the year 1999, all the NSAIDs in commerce inhibited both isoenzymes PGHS-1 and -2 with a different potency. The analysis of the data on NSAID-induced pseudoallergic reactions reported in literature^{10,13-17} suggest that among NSAIDs, those who preferentially inhibit PGHS-2 are better tolerated than those that inhibit preferentially PGHS-1. On the basis of these observations, some authors have suggested that pseudoallergic reactions to NSAIDs may be related to the inhibition of PGHS-1 enzyme and thus a NSAID with no activity on PGHS-1 could be void from pseudoallergic reactions. The data reported here on the first selective PGHS-2 antagonist, rofecoxib, seem to support this hypothesis. Rofecoxib seems to be a tolerable NSAID as reported also by Sanchez Borges et al.¹⁷

Only one of 139 (0.7%) patients had a weak adverse reaction in the peroral challenge. This percentage is the lowest found to date. Further, the positive-challenge patient developed hives localized at the arms only. In any case, selective PGHS-2 antagonists represent a new class of drugs among NSAIDs, and this may partly explain the tolerability of rofecoxib. We do not have sufficient data to make any conclusions on the pathogenic mechanisms of pseudoallergic reactions.

CONCLUSION

The data reported here permit us to conclude that rofecoxib is a tolerable drug. Further, it is a tolerable NSAID in patients with NSAID-induced allergic and/or pseudoallergic cutaneous reactions, and thus represents a valid alternative to NSAID-sensitive patients. As reported by Lipsky et al,¹² although the safety of rofecoxib has not been fully studied, expert opinion recommends its use rather than cyclooxygenase nonspecific NSAID in patients who are at increased risk for serious upper gastrointestinal complications. Of course it would be interesting if these data are confirmed by other authors who have conducted similar studies on the tolerability of rofecoxib. It would also be needed to evaluate the tolerability of other PGHS-2 selective antagonists than rofecoxib. If other selective PGHS-2 antagonists confirm these results on the tolerability, it will be possible to draw conclusions on the pathogenic mechanisms of NSAID-induced pseudoallergic reactions.

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