Safety of a Cyclooxygenase-2 Inhibitor in Patients With Aspirin-Sensitive Asthma*

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Background: In 5 to 10% of adult patients with asthma, aspirin (acetylsalicylic acid [ASA]) and most other nonsteroidal anti-inflammatory drugs (NSAIDs) precipitate acute asthmatic attacks. Therefore, choosing an alternative anti-inflammatory agent for patients with adverse reactions to an NSAID is a common problem in clinical practice. The discoveries that cyclooxygenase (COX)-2 is an inducible form of COX that is involved in inflammation and that COX-1 is the major isoform responsible for the production of prostaglandins have provided a reasonable basis for the development of specific COX-2 inhibitors as a new class of anti-inflammatory agents.

Objective: The purpose of this study was to demonstrate that rofecoxib, a specific inhibitor of COX-2, does not cause asthmatic attacks in patients with ASA and/or other NSAID-induced asthma.

Methods: We studied 40 patients, all of whom had experienced asthma induced by at least two different NSAIDs. The patients were challenged in a single-blind manner with different doses of rofecoxib on 3 different days, until either the therapeutic dose of 25 mg or intolerance was reached. Each patient was rechallenged with 25 mg of rofecoxib 7 days later if no evidence of intolerance had been observed previously.

Results: Rofecoxib, 25 mg, was proven to be well tolerated in all 40 patients with ASA-induced and NSAID-induced asthma.

Conclusion: Our study appears to demonstrate that rofecoxib is a suitable NSAID for treatment of patients with ASA and/or other NSAID-induced asthma. (CHEST 2002; 121:1812–1817)

Key words: aspirin-induced asthma; asthma; cyclooxygenase enzyme; cyclooxygenase-2 inhibitors; rofecoxib

Abbreviations: AIA = aspirin-induced asthma; ASA = acetylsalicylic acid; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; PEF = peak expiratory flow

A spirin-induced asthma (AIA) is an airway mucosa inflammatory disease that combines with the precipitation of asthma and attacks of rhinitis after the ingestion of aspirin (acetylsalicylic acid [ASA]) and most nonsteroidal anti-inflammatory drugs (NSAIDs).1,2 AIA affects about 10% of adults with asthma.1 Asthma attacks usually occur within 3 h after the ingestion of ASA or NSAIDs. These asthmatic attacks are often severe and, in many cases, may be life-threatening, requiring emergency mechanical ventilation.3,4

The mechanism of AIA still remains unclear. The cyclooxygenase (COX) theory proposes that precipitation of asthma attacks by ASA and NSAIDs is based on the shared pharmacologic actions of such drugs, namely specific inhibition in respiratory cells of intracellular COX enzymes.5,6

COX enzymes exist in at least two isoforms, COX-1 and COX-2, which are encoded by distinct genes. Both isoforms are coenzymes with a peroxidase, forming the complete enzyme prostaglandin H2 synthase. COX-1 is the constitutive form, and COX-2 is induced during inflammation and enhances the synthesis of inflammatory prostanoids. Both enzymes are expressed in the healthy human respiratory epithelium.7

The introduction into clinical practice of highly selective inhibitors of COX-2, namely, celecoxib and rofecoxib,8 theoretically should not cause airway mucosa inflammation because of the preservation of constitutive prostaglandin E2. So, selective COX-2 inhibitors should be safe for patients with AIA,
would provide an interesting tool for further determining the role of COX isoforms in patients with AIA, and would be an appropriate treatment for pain and inflammation. The purpose of this study was to determine the tolerance of rofecoxib (Vioxx; Merck; Whitehouse Station, NJ) in patients with AIA.

**Materials and Methods**

Patients

Forty patients (16 men, 24 women; age range, 31 to 78 years; mean age, 53.85 years [SD, 11.65 years]) comprised the final eligible study group. The majority of patients (70%) had experienced asthma for >5 years, and six patients (15%) had experienced asthma for >15 years. Epidemiologic data, the drugs involved in the adverse reactions, and the clinical presentation of ASA/NSAID intolerance are shown in Table 1. According to their clinical histories, all the patients showed intolerance reactions to ASA in addition to at least one other NSAID. Three patients had experienced asthmatic attacks after receiving three different NSAIDs, three patients had experienced attacks after receiving four different NSAIDs, and one patient had experienced attacks after receiving five different NSAIDs. Four patients required ICU assistance due to asthmatic attacks after the ingestion of NSAIDs. Rhinocconjunctivitis and asthma were the most common presenting symptoms, and a majority of patients (70%) had nasal polyps.

One month before undergoing the provocation test, all patients but two were receiving concomitant treatment with inhaled glucocorticosteroid agents (38 subjects) and/or oral glucocorticosteroid agents (5 subjects), however, oral glucocorticosteroids, long-acting antihistamines, and antileukotriene drugs were not used during the study period. The doses of inhaled glucocorticosteroids were kept as small as possible, were not changed for at least 2 weeks before the study began, and were maintained unchanged throughout the study.

Among asthmatic individuals, the severity of asthma was diagnosed according to the Global Initiative for Asthma guidelines.9 The majority of patients (77.5%) had moderate asthma, and five patients (12.5%) had severe asthma.

Patients were selected for the study according to the following criteria:

1. The subjects must have experienced two or more different documented episodes of asthma attacks following the ingestion of at least two different NSAIDs. None of them had ever been referred to a doctor for the presence of urticaria and/or angioedema. All patients had treated in our hospital emergency department at some time due to an AIA attack and were subsequently seen as outpatients in our department. In addition, the latest episode of AIA should have occurred within 6 months prior to the start of the study, and the first attack should have occurred within the previous 2 years. Peak flow measurements should have been made during the AIA attack in the emergency department. The majority of patients (55%) had experienced a moderate asthmatic attack following the ingestion of an NSAID with a peak expiratory flow (PEF) rate between 50% and 80% of predicted values. Fourteen patients had experienced a mild asthmatic attack (PEF, 80% of predicted), and 4 patients had experienced a severe asthmatic attack (PEF, < 50% of predicted) that required ICU assistance.
2. All patients participating in the study gave signed informed consent to the protocol approved by the ethics committee of our medical center.

3. AIA patients with asthma were included if their condition had been stable for at least 2 weeks. None of the patients had a history of either respiratory tract infection or allergen exposure for at least 4 weeks prior to the start of the study. Patients with an FEV1 value < 70% of predicted were not included in the oral challenge procedure.

4. The diagnosis of AIA sensitivity was based on a detailed clinical history and emergency department reports. For ethical reasons, the diagnosis was not reconfirmed by oral challenge with the implicated drugs.

**Study Design**

The provocation test was carried out in a single-blinded, controlled fashion. The oral challenge protocol consisted of the oral administration of the drug with increasing doses in 60-min intervals. During the challenge procedure, BP, pulse, nasoocular, pulmonary, and cutaneous symptoms were monitored. All patients remained in the hospital under medical supervision for 3 h. Any symptoms that developed when the patients were out of the hospital were to be reported to our staff by telephone.

All patients were given instructions about how to use a peak expiratory flowmeter. A PEF measurement was performed daily for 1 week before the oral challenge was carried out in order to determine the variability in patients’ measurements. Once the oral challenge was concluded, new PEF measurements were made during the following week to detect any variations in the measurements.

Patients were instructed to measure their PEF rates when they had just awakened in the morning, before they had received a bronchodilator, and at bedtime 5 to 10 min after the administration of a bronchodilator.

The variability was defined as the highest value minus the lowest one divided by the highest one. A diurnal variability of > 20% was considered to be a positive response to the oral challenge.10

**Day 1 of Challenge:** Medical histories were completed, and patients underwent physical examinations. BP, pulse, and FEV1 were measured. If the results of the measurements of these parameters were normal, patients received a placebo (lactose) challenge. They were re-examined 1 h later. If all the measurements were normal, 6.25 mg rofecoxib was administered. Afterward, the subjects remained in the hospital under medical supervision for 3 h.

**Day 2 of Challenge:** Identical clinical and laboratory supervision measures were repeated 2 days later. At that time, a new oral rofecoxib challenge was performed at the higher dose of 12.5 mg. One hour after that, if no reactions had occurred, the patients were given 25 mg rofecoxib.

**Day 3 of Challenge:** Only if no symptoms were present and the PEF rate variation was < 20%, one last 25-mg dose of rofecoxib was administered to each patient after a washout period of at least 1 week. Spirometric measurements (ie, FEV1, FVC, and FEV1/FVC ratio) were made every 60 min for 8 h after the conclusion of the bronchial provocation test to rule out any potential delayed response.

The result of the challenge test was determined to be positive if one of the following symptoms existed:

1. Conjunctival reaction such as itching, tearing, burning, or photophobia;
2. Upper or lower respiratory tract reactions such as sneezing, rhinorrhea, nasal blockage, dyspnea, wheezing, cough with a 15% decrease in FEV1, and peak flow variability of > 20%; the patients were considered to have had an asthma exacerbation if physicians decided on clinical
Table 1—Patient Characteristics

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*Male; F = female; ICSb = inhaled corticosteroid, budesonide; ICSf = inhaled corticosteroid, fluticasone; OCS = oral corticosteroids; I = intermittent; MP = mild persistent; MoP = moderate persistent; SP = severe persistent; Before = before oral provocation test; After = after oral provocation test.
†There was no variation > 20%.
‡There was no decrease > 15%.
grounds to give a 1-week course of oral glucocorticosteroids or to increase the dose of oral or inhaled glucocorticosteroids for 1 week.
3. Cutaneous reactions such as erythema, urticaria, and/or anaphylactoid reaction with urticaria and/or angioedema;
4. Hypotension (ie, a 30% drop in systolic BP); and
5. Laryngeal edema (ie, excessive fluid of the loose submucosa of the lining of the elastic cone of the larynx).

Symptoms occurring 2 h following the last administered dose of rofecoxib were considered to be a delayed reaction.

Statistical Analysis

PEF measurements were expressed as diurnal variability, as stated above, while FEV₁ was expressed as a percentage of the predicted value. Numeric results were expressed as the mean ± SD. The statistical power of the study was calculated.

The Student t test for paired data was used to compare the differences for data from before and after the provocation test. A p value < 0.05 was considered to be significant. An appropriate software package (SPSS for Windows, version 10.0; SPSS; Chicago, IL) was used to analyze the data.

Results
Oral Challenges

At the end of the challenge procedure, 100% of the patients tolerated the 25-mg dosage of rofecoxib well, without any signs of immediate or delayed reactions.

The PEF variation was calculated at the end of the study. There was no variation of >20%. The mean PEF variation before the provocation test was 11.20% ± 3.28% and afterwards was 11.38% ± 3.34%. There were no significant differences between PEF variations before and after the study (p = 0.147).

Spirometric measurements were performed after the oral provocation test. There was no decrease of >15%. The mean FEV₁ before the provocation test was 90.83% ± 4.38% of predicted, and after the provocation test it was 90.68% ± 4.58% of predicted. There were no significant differences before and after the oral provocation test with rofecoxib (p = 0.183).

If the variation of values for PEF and FEV₁ before and after the provocation test were ≥15%, the power of the test for finding significant differences (α = 0.05) would reach 100%.

None of the subjects experienced reactions to the placebo challenge. No side effects, such as pyrosis or epigastric pain, were observed during the drug provocation.

Discussion

Most people tolerate ASA well. Asthmatic patients, however, are an exception. In about 10% of adults with asthma, but rarely in asthmatic children, ASA and other NSAIDs precipitate asthma attacks.1 This distinct clinical syndrome, which is called AIA, is a crucial problem since drugs for the management of common medical conditions, such as pain, fever, and inflammation, are commonly required. Therefore, patients who have adverse reactions to NSAIDs desperately need alternative drugs.

COX enzymes, which appear to be central to the mechanism of ASA sensitivity, exist in at least two isoforms, COX-1 and COX-2. Most NSAIDs inhibit both isoforms, although at different intensities. It has been suggested that the anti-inflammatory effects are due to COX-2 inhibition and that adverse effects are due to COX-1 inhibition, which explains why alternative NSAIDs that are devoid of anti-COX activity or have weak COX-1 inhibitors work safely. These NSAIDs include sodium salicylate, choline salicylate, magnesium trisalicylate, benzylamine, chloroquine, azapropazone, and dextropropoxyphene. Unfortunately, these agents are poor analgesics and have only minimal anti-inflammatory effects.1

Acetaminophen was reported to be a substitute medicine for patients with ASA/NSAID intolerance because it had a weak inhibitory action on the COX enzyme.11 However, a high cross-reactivity of acetaminophen with ASA (especially in doses of >1,000 mg), inefficient anti-inflammatory action, and some reported cases of anaphylaxis have created a need for alternative drugs.12,13 Nimesulide and meloxicam are known to inhibit COX-2 more than COX-1 and are well-tolerated by ASA-sensitive asthmatic subjects when they are given average therapeutic doses but cause rhinorrhea and mild asthma attacks when ingested in higher doses.14,15 Until now, nimesulide has been the most widely studied drug in AIA patients. Different authors have described a percentage of tolerance between 71% and 100%,16,17 but none of these studies had included patients who had experienced asthma attacks after receiving at least two different NSAIDs. The last review concerning nimesulide, which was performed on 42 asthmatic patients, reported an 81% tolerance.18 Two other well-tolerated NSAIDs, etodolac19 and nabumetone,20 may be COX-2-selective, but the evidence has not been clearly demonstrated.

COX-2 is an inducible form of COX that is involved in inflammation, and COX-1 is the major isoform responsible for the production of prostaglandins. This finding has provided a reasonable basis for the development of specific COX-2 inhibitors as a new class of anti-inflammatory agents. So, new drugs have emerged that have shown much more specificity than preferential inhibitors (eg, nimesulide or meloxicam) to such a degree that a loss of selectivity at higher doses is not likely to occur. It has been
proposed that the term COX-2 specific inhibitor should be used to describe agents that inhibit COX-2 but that have no effect on COX-1 over the whole range of doses used and concentrations achieved in clinical usage.\textsuperscript{21}

Rofecoxib, a methylsulphonylphenyl derivative, is a novel COX-2 inhibitor with a biochemical and pharmacologic profile that is clearly distinct from that of the NSAIDs currently in use.

It has been demonstrated that rofecoxib is an effective analgesic in patients with primary dysmenorrhea\textsuperscript{22} and postoperative dental pain.\textsuperscript{23} It showed antipyretic activity similar to ibuprofen in patients with upper respiratory tract infections and similar analgesic efficacy to that of naproxen sodium and ibuprofen.\textsuperscript{24} In addition, in patients with osteoarthritis, rofecoxib showed similar clinical efficacy to that observed with diclofenac (50 mg tid),\textsuperscript{25} ibuprofen (500 mg tid),\textsuperscript{26} and nabumetone (1,500 mg qd).\textsuperscript{26} Furthermore, rofecoxib (50 mg) has been well tolerated, with no effect on bleeding time and with inferior levels of gastric mucosal injury (ie, perforations, ulcers, and bleeding) compared to those of ibuprofen (2 g), ASA (2.6 g), or indomethacin (1.5 g).\textsuperscript{27}

Many reports on the anti-inflammatory activity and GI tolerance of rofecoxib have been written, but there have been none written about its safety in ASA-intolerant asthma patients. To the best of our knowledge, this is the first study to report on the tolerance of a significantly large series of AIA patients to rofecoxib.

The purpose of this study is to demonstrate that rofecoxib, a specific inhibitor of COX-2, does not cause asthmatic attacks in patients with AIA. Only patients who have had asthmatic attacks due to at least two different NSAIDs have been included in our study. In this way, we have selected attacks due to NSAID intolerance and have eliminated those due to NSAID hypersensitivity.

We would like to emphasize that three of our patients had experienced asthma induced by acetaminophen (650 mg), a drug that is usually considered to be safe. Furthermore, one patient did not tolerate nimesulide either.

The only way to confirm the safety of rofecoxib in NSAID-intolerant patients is by oral challenge.\textsuperscript{28} As we have already said, only patients with asthma whose condition had remained stable for at least 2 weeks were included in the challenge. Those with a PEF value of $<70\%$ of predicted were excluded from the challenge. However, in some patients we did not administer an oral challenge with the drug implicated in an adverse reaction based on the reliability of the patient's history and ethical limitations. Moreover, we chose only those patients with AIA whose clinical histories of intolerance had been consistently supported by oral challenge procedures.

On the basis of our study, rofecoxib seems to be a drug that is safe for use by patients with AIA, even safer than acetaminophen and nimesulide. These findings may indicate that rofecoxib should play a major role in the treatment of these patients.

These results also appear to confirm the COX theory of Szczeklik and colleagues\textsuperscript{1,5} and give new insight into the pathogenesis of asthma.

Nevertheless, further challenge procedure studies performed with rofecoxib and other new highly selective COX-2 inhibitors on larger series of AIA patients will be necessary in order to determine their actual safety for use in patients with asthma induced by ASA and other NSAIDs.

ACKNOWLEDGMENT: The authors would like to thank Dr. A. Szczeklik for his helpful review of the article.

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