

Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma

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Background: Patients with aspirin-sensitive respiratory disease experience cross-reactions to all nonsteroidal anti-inflammatory drugs, which inhibit cyclooxygenase enzymes. With the introduction of antiarthritis drugs, which selectively inhibit cyclooxygenase-2, questions are raised as to whether cross-reactivity occurs between aspirin and these new cyclooxygenase-2 inhibitors.

Objective: The goal of this study was to determine whether rofecoxib cross-reacts in aspirin-sensitive patients with asthma.

Methods: Sixty patients with asthma underwent double-blinded, placebo-controlled oral challenges with rofecoxib (12.5 mg, 25 mg, and 2 placebos) over 48 hours in our General Clinical Research Center. The next day, aspirin sensitivity was proven in each of the 60 patients through use of single-blinded oral aspirin challenges.

Results: None of the 60 patients experienced any symptoms, changes in nasal examination findings, or declines in FEV₁ values during their challenges with rofecoxib. All 60 patients experienced typical naso-ocular and asthmatic reactions to aspirin with a mean provoking dose of 61 mg. The exact 1-sided CI for the probability of rofecoxib inducing cross-reactions in aspirin-sensitive patients with asthma is calculated to be between 0% and 0.05%.

Conclusion: Given that none of the 60 patients reacted to rofecoxib and given the statistical power of this large sample size, we conclude that cross-reactivity between aspirin and rofecoxib does not occur in patients with aspirin-sensitive respiratory disease. This does not exclude rofecoxib from participating in other types of reactions, including immune recognition after prior treatment with the drug. From the standpoint of the mechanisms involved in aspirin-induced respiratory reactions, this study strongly supports inhibition of cyclooxygenase-1 as the essential initiator of these types of reactions. (*J Allergy Clin Immunol* 2001;108:47-51.)

Key words: Asthma, aspirin-sensitive asthma, cyclooxygenase enzymes-1 and 2, cyclooxygenase inhibitors, rofecoxib

A distinct subgroup of patients with asthma who have aspirin (ASA)-sensitive respiratory disease (ASRD) experience respiratory reactions after ingesting ASA or any of the nonsteroidal anti-inflammatory drugs

Abbreviations used

ASA:	Aspirin
ASRD:	Aspirin-sensitive respiratory disease
COX-1:	Cyclooxygenase-1 enzyme
COX-2:	Cyclooxygenase-2 enzyme
GCRC:	General Clinical Research Center
LT:	Leukotriene
NSAID:	Nonsteroidal anti-inflammatory drug
PGE ₂ :	Prostaglandin E ₂

(NSAIDs) that inhibit cyclooxygenase-1 enzyme (COX-1) and cyclooxygenase-2 enzyme (COX-2).¹ By contrast, sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, and dextropropoxyphene do not inhibit COX enzymes and do not induce respiratory reactions in patients with ASRD.² Unfortunately, these drugs are relatively poor analgesics and have fewer anti-inflammatory effects than do the cross-reacting NSAIDs. Acetaminophen (paracetamol) and salsalate (Disalcid) inhibit COX-1 poorly, but with high doses of these drugs, cross-reactions occur with ASA in a minority of patients with ASRD.^{3,4} Meloxicam and nimesulide predominantly inhibit COX-2 but also inhibit COX-1 when patients take higher doses of these drugs.^{5,6} These latter anti-inflammatory agents have a low prevalence of cross-reactivity in ASRD and only with high doses of the drugs.

COX enzymes constitute the central core of a coenzyme called *prostaglandin H₂ synthase*, which also contains a peroxidase.⁷ Prostaglandin H₂ synthase is located next to the endoplasmic reticulum and the inner surface of cell walls, where arachidonic acid is readily available after cleavage by phospholipases from lipid membranes. The COX enzymes exist in at least 2 isoforms, COX-1 and COX-2, which are encoded by distinct genes. COX-1, the constitutive form, is found in most mammalian cells, including respiratory epithelial and endothelial cells. Because of the sheer number of cells synthesizing prostaglandins, COX-1 is the main source of prostaglandin E₂ (PGE₂) in all organ systems.⁸ COX-2 is induced during inflammation and synthesizes inflammatory prostanoids, which participate in some inflammatory diseases, including arthritis. High doses of ASA and NSAIDs inhibit both COX-1 and COX-2.

In the spring of 1999, 2 new antiarthritis drugs, celecoxib and rofecoxib, were introduced into the US market. Both drugs selectively inhibit COX-2.⁷ The original package inserts for both drugs stated that prescribing them to patients with ASRD was absolutely contraindicated.

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Supported by a Medical Schools Grant from Merck & Co and the General Clinical Research Center, NIH Grant M01RR00833.

Received for publication February 8, 2001; revised March 29, 2001; accepted for publication March 30, 2001.

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0091-6749/2001 \$35.00 + 0 1/81/116290

doi:10.1067/mai.2001.116290

cated and urged caution with regard to giving them to any patients with asthma. This warning did not make any sense, because both rofecoxib and celecoxib would be incapable of depleting PGE₂, an essential protective prostanoid, generated through constitutive COX-1. Since then, preliminary information developed from small numbers of patients, published in the form of an abstract⁹ and 2 recent letters to the editor regarding celecoxib,^{10,11} suggests that selective COX-2 inhibitors can safely be ingested by patients with ASRD. In addition, a recent article by Szczeklik et al¹² challenged 12 patients with ASA-induced asthma with rofecoxib in a double-blinded, placebo-controlled study over 5 days. During the rofecoxib challenges, none of the patients experienced any symptoms or changes in FEV₁ values, and concomitant measurements of urine leukotriene (LT) E₄ and 9 α 11 β prostaglandin F₂ remained unchanged.

The purpose of the present study was to determine whether a large, statistically significant sample of patients with ASRD could tolerate rofecoxib without adverse effects.

METHODS

Selection of patients

The Human Subject Committee and the General Clinical Research Center (GCRC) Advisory Committee approved this study. Patients with asthma who had histories of asthma attacks after ingesting ASA and/or NSAIDs were admitted to the GCRC of the Scripps Green Hospital. Every attempt was made to admit patients during remissions of their asthma. For the most part, patients continued taking the medications that had been controlling their asthma and rhinitis as outpatients. Nasal, bronchial, and systemic corticosteroids were continued, but antihistamines, cromolyn sodium, nedocromil sodium, salmeterol, albuterol, and ipratropium bromide were discontinued on admission. In a few patients with mild asthma, LT modifiers were discontinued. Pregnant women were excluded, and before beginning any challenges, women with childbearing potential underwent urine pregnancy testing to prove that they were not pregnant. None of the patients had taken rofecoxib previously.

Rofecoxib challenges

During the first day in the GCRC, a single-blinded oral placebo challenge was conducted. Nasal examinations were carried out, and bronchial airway stability was documented. A wedge spirometer with integrated flow/volume output (Koko Spirometry; Pulmonary Data Services Instrumentation, Inc, Louisville, Colo) was used for monitoring pulmonary functions. FEV₁ determinations were recorded every hour.

After the first day of placebo challenges, a decision was made on the basis of previously established inclusion criteria to begin double-blinded rofecoxib challenges. For a patient to enter this study, his or her baseline FEV₁ values had to be more than 70% of the predicted values and hourly FEV₁ values had to vary by less than 10% during the placebo challenges on day 1.

Rofecoxib, supplied by Merck & Co, was placed in green gelatin capsules by the nurse coordinator. Placebo capsules, also green, were filled with sucrose. A charge nurse prepared 4 envelopes, each holding a single green capsule; 1 capsule contained rofecoxib 12.5 mg, 1 capsule contained rofecoxib 25 mg, and 2 capsules contained sucrose. At 7:00 AM and noon on the first challenge day, the blinded nurse gave 1 capsule and watched the patient ingest it; capsules 3 and 4 were given at 7 AM and noon on the second challenge day.

The 12.5-mg dose of rofecoxib was always given before the 25-mg dose. Nasal, ocular, cutaneous, and chest examinations were conducted hourly. Any complaint from the patient was recorded. A flow/volume recording was conducted hourly. The code for the contents of the capsules was broken at the end of the third day on completion of the 2-day, double-blinded challenges with rofecoxib.

ASA challenges

At 7:00 AM on the morning of the fourth day, single-blinded oral ASA challenges were begun. Identical green capsules containing varying doses of ASA were used. The first ASA dose was 30 mg; 3 hours later, if no reaction had occurred, the dose was increased to 45 or 60 mg of ASA (the choice being made by the physician on the basis of the severity of historical reactions to ASA or NSAIDs). If there was no reaction to the 45 or 60 mg of ASA after 3 hours, the next highest dose of 60 or 100 mg was given. Escalating doses of ASA (100, 150, 325, and 650 mg) were given every 3 hours during the day until a reaction occurred or the patient reached a dose of 650 mg without reaction. Reactions to ASA were observed and documented, as previously described.¹³ ASA respiratory sensitivity was defined as a decline of 15% or more in FEV₁ values and/or nasocular reactions within 3 hours of incremental oral ASA challenges.

Naso-ocular reactions

Signs and symptoms of reactions in the upper airways were simultaneously recorded through use of a standard scoring system.¹⁴ A positive response consisted of rhinorrhea accompanied by any of the following: ocular chemosis, injection, and periorbital swelling; swelling and congestion of the turbinates; and paranasal sinus pain. The scores were recorded as follows:

- 0, absence of any reaction
- 1, rhinorrhea and nasal congestion
- 2, rhinorrhea, nasal congestion with conjunctival injection
- 3, complete nasal obstruction with conjunctival injection and paranasal headache
- 4, severe reactions with periorbital edema in addition to manifestations of all naso-ocular signs and symptoms.

All patients continued challenges with ASA to complete ASA desensitization.

Statistical analysis

Means, SEMs, and Wilcoxon signed rank test results for challenge data at baseline were compared with challenge results by means of StatView 4.01 for Macintosh (Abacus Concepts Inc, Berkeley, Calif).

The method of calculation of exact 1-sided CIs for binomial probabilities was based on the following parameters: in the situation of no successes in the number (N) of independent trials with underlying probability (p) of successes at each trial, the calculation of the 1-sided (1 - α)% CI for P is (O,P), where P satisfies the equation (1 - P)ⁿ = α .¹⁵

RESULTS

Demographic data

Seventy-two patients with asthma who believed they were ASA/NSAID-sensitive volunteered to enter this study. Seven patients were excluded from the study because their asthma was unstable on the first day of placebo challenges or their FEV₁ values were below 70% of the predicted values. Five other patients completed the 2-day, double-blinded, placebo-controlled oral chal-

lenges with rofecoxib without adverse effects but then failed to react to ASA on day 4 or day 5. Although they might have had ASRD, we were unable to prove ASA sensitivity; this excluded them from the study. It is interesting that 1 of these 5 patients received 40 mg of prednisone per day and 3 of the 5 took daily montelukast for control of asthma. There were no exclusions because of pregnancy. Sixty patients with asthma who met all criteria for entry completed the 2-day rofecoxib challenges (days 2 and 3) and then experienced respiratory reactions to ASA on day 4 or day 5.

Table I presents clinically relevant information about the 60 patients who completed the study. Their average age was 47 years, and 39 of them were female. All but 1 of the 60 patients had experienced asthma attacks after ingesting full therapeutic doses of ASA, another NSAID, or both. Most of them had required emergency room or hospital treatment for these asthma attacks. All patients had nasal polyposis and sinusitis, and most had anosmia.

The numbers of patients who were taking significant controller medications (systemic corticosteroids and LT modifiers) during this inpatient study are shown in Table II. Both systemic corticosteroids and LT modifiers interfere with ASA-induced bronchospasm in some ASRD patients^{14,16,17} but generally do not block naso-ocular reactions in patients with ASRD. These drugs are frequently essential in maintaining stable bronchial airways, particularly in the asthma population participating in this study. Antihistamines, which can block the naso-ocular reaction induced by ASA,¹⁸ were discontinued at the time of admission.

Challenge study results

Table III shows the results of the double-blinded challenges with 2 placebos and rofecoxib 12.5 and 25 mg. Statistically significant differences between the mean naso-ocular scores or changes in FEV₁ values when placebo was compared with either dose of rofecoxib did not occur. Other symptoms recorded during challenges with rofecoxib were as follows: epigastric pain in 1 patient; improved arthritis pain in 2 patients; heavy chest (without change in FEV₁ values), which spontaneously resolved, in 1 patient; and 1+ nasal congestion in 2 patients. During the 2 placebo challenges, 1+ nasal congestion occurred in 5 patients, including the 2 patients for whom this was recorded during their rofecoxib challenges. Rashes did not occur in any patients during rofecoxib/placebo challenges.

Table III also presents data collected during the single-blinded oral ASA challenges. The mean provoking dose of ASA was only 61 mg; this compared with full therapeutic doses of rofecoxib. Of the 60 patients, 32 experienced both naso-ocular and bronchospastic reactions (FEV₁ values declined by >15%). The largest drop in FEV₁ values was 52% after 100 mg of ASA. Of the 28 patients whose FEV₁ values did not decline by >15%, all had naso-ocular reactions with scores of 2 or higher. Ten of these 28 patients experienced hives, flush, or gastrointestinal cramping pain in addition to their naso-ocular

TABLE I. Characteristics of the 60 patients enrolled in this study: observations

Observation	No. of patients reporting observation (%)
Prior asthmatic reactions to ASA	48 (80)
Two or more prior reactions to ASA	29 (48)
Prior asthmatic reactions to other NSAIDs	35 (58)
Previously reacted to both ASA and NSAIDs	23 (38)
ASA/NSAID-induced asthma was treated in emergency room	32 (55)
ASA/NSAID-induced asthma required hospitalization	19 (32)
Diagnosed at some point with nasal polyps	60 (100)
Diagnosed with sinusitis by means of computed axial tomography or radiography	60 (100)
Reported complete anosmia at the time of study	39 (65)
Reported partial anosmia at the time of study	17 (28)

TABLE II. Characteristics of the 60 patients enrolled in this study: medications

Medication type	No. of patients who consumed medication during study (%)
Topical nasal corticosteroids	48 (80)
Inhaled corticosteroids	45 (75)
Systemic corticosteroids	16 (26)
Leukotriene modifiers	28 (46)
Theophylline	5 (8)

reactions. Of these 28 patients, 16 were taking LT modifiers and 8 were taking systemic corticosteroids for control of their asthma. It is possible that ASA-induced bronchospasm was blocked by these drugs. However, of the 32 patients who experienced a >15% decline in FEV₁ values, 12 were also taking LT modifiers and another 8 received systemic corticosteroids during the study.

Naso-ocular scores and changes in FEV₁ values are recorded in Table III. ASA-induced changes were significantly different from either the placebo or rofecoxib challenges. In addition, the reactions for all 60 patients included the following: ASA-induced laryngospasm in 3 patients, generalized flush in 14 patients, urticaria in 4 patients, and gastric cramping pain or diarrhea in 6 patients. These extrapulmonary responses are typical in patients with ASRD who are undergoing ASA oral challenges, even when small, controlled provoking doses of ASA are used, and they provide additional evidence supporting the diagnosis of ASRD. These reactions occurred within 24 hours of challenges with rofecoxib 25 mg in 52 patients and within 48 hours in 8 additional patients.

In summary, there were no reactions to rofecoxib after ingestion of either the 12.5-mg dose or the 25-mg dose. The exact 1-sided CI for the probability of rofecoxib inducing respiratory cross-reactions in patients with ASRD is calculated to be between 0% and 0.05%.

TABLE III. Results of challenges with placebos, rofecoxib, and ASA in 60 patients

Substance used for oral challenges	Nasal score			Percent change in FEV ₁ value			Statistical difference*
	Mean	SEM	Range	Mean	SEM	Range	
Placebo #1	0.08	0.03	0-1	-1.78	0.85	+10 to -10	P = NS
Placebo #2	0.07	0.03	0-1	-2.86	0.63	+10 to -10	P = NS
Rofecoxib 12.5 mg	0.04	0.02	0-1	-1.60	0.70	+10 to -10	P = NS
Rofecoxib 25 mg	0.03	0.02	0-1	-1.45	0.69	+10 to -10	P = NS
ASA†	3.31	0.09	2-4	-15.0	1.39	+2 to -52	P = <0.0001

*Wilcoxon signed rank testing between placebo 1 and 2 and both doses of rofecoxib for both nasal scores and percent change in FEV₁ values did not reach statistical significance. Difference between ASA challenge result and any of the other 4 challenges, for both nasal score and changes in FEV₁ value, was <.0001 and is shown in the bottom cell.

†Mean provoking dose of ASA: 61 mg (range, 30-150 mg).

DISCUSSION

The results of this study show that rofecoxib, in standard therapeutic doses of either 12.5 or 25 mg, was safely ingested by 60 ASA-sensitive patients with asthma. Because cross-reactions between ASA and those NSAIDs that inhibit COX-1 occur in patients with ASRD 100% of the time, one would have expected a number of reactions to rofecoxib during this study if rofecoxib were a cross-reacting NSAID. This did not occur. Furthermore, in contrast with dose-response reactions to Disalcid, acetaminophen, meloxicam, and nimesulide, there were no changes in nasal examination findings or FEV₁ values as the doses of rofecoxib were increased from 12.5 mg on the first challenge day to 25 mg on the second challenge day. Finally, after a reaction to ASA/NSAIDs or during silent desensitization, a refractory period occurs for at least 48 hours and up to 7 days.¹³ In this study, rofecoxib could not have silently desensitized the study patients and then produced a refractory period, because all 60 patients reacted to ASA during the following 2 days.

Certification that the 60 patients actually had ASRD is also important. As shown in Table I, before entry into the study, 59 patients experienced significant asthmatic attacks after ingesting full therapeutic doses of ASA or other NSAIDs. One patient had all of the clinical features of ASRD but had never previously ingested ASA or NSAIDs. Most of the 59 patients had to go to an emergency room or be hospitalized in an intensive care unit as a consequence of their ASA/NSAID-induced asthmatic attacks. ASA-induced respiratory reactions are dose-dependent. The purpose of single-blinded oral ASA challenges is to induce measurable respiratory reactions without producing severe asthma. Thus the mean provoking dose of ASA in these patients was 61 mg. The use of controller medications during ASA challenges also presents a difficult dilemma. In most patients with ASRD, controller medications are essential components of their asthma control. If LT modifiers or systemic steroids are discontinued during challenge studies, spontaneous bronchospasm tends to reappear. Such a situation produces false positive drops in FEV₁ values and provides a dangerous setting for conducting ASA challenges. If controller medications are continued, they can

modify or even block bronchospastic reactions.^{14,16,17} Fortunately, naso-ocular reactions are rarely inhibited by LT modifiers or systemic corticosteroids.^{14,16,17} Antihistamines, which can efficiently block the naso-ocular reactions induced by ASA,¹⁸ were withheld in this study.

Unlike NSAIDs that inhibit COX-1, rofecoxib appears to be an acceptable alternative in patients with ASRD. This is particularly important given the fact that many patients with asthma do not know whether they have ASRD, because they generally avoid these drugs. In fact, physicians, nurses, pharmacists, the Internet, package inserts, the lay literature, and interested friends all provide warnings to patients with asthma—particularly those who are known to have ASRD—to avoid ASA and NSAIDs. However, first-exposure respiratory reactions to full doses of ASA or NSAIDs occur and clearly pose a potential danger to people with undiagnosed ASRD. With the availability of rofecoxib, this medication can be safely given to any asthmatic individual without concern that first exposure to rofecoxib might induce an asthma attack.

This study addressed only the cross-reacting respiratory reactions that occur in patients with ASRD. The study participants had never ingested rofecoxib previously. Therefore, there was no possibility of immune recognition of rofecoxib followed by an IgE-mediated reaction. Misinterpretation of a reaction to rofecoxib as a COX-1 inhibited cross-reaction is a potential problem in understanding and classifying these reactions. This is an important point, not only for the integrity of this study, in which none of the patients had previously been exposed to rofecoxib, but also because other types of reactions to rofecoxib have already been recorded, both during clinical trials and in the drug reports to the manufacturer. Thus, as is true with other medications, single drug-specific reactions, including gastric intolerance, hives, angioedema, and anaphylaxis, have been reported to occur after ingestion of rofecoxib.¹⁹ Except for gastric intolerance, these reactions occurred after prior exposure to the drug, suggesting prior immunologic sensitization. Although we are not aware of any single-drug documented respiratory reactions after ingestion of rofecoxib, they might be reported in the future. At that time, it might be difficult to determine whether the reactions are immunologic (presumably IgE-mediated) or cross-

reacting. On the basis of the current study, we should remain skeptical of cross-reacting respiratory reactions involving rofecoxib and ASA/NSAIDs.

The results of our rofecoxib challenges also provided additional evidence that COX-1 inhibition, not COX-2 inhibition, is the initiating event in ASA-induced respiratory reactions. Currently, the bulk of the evidence indicates that PGE₂ is an essential prostanoid in maintaining bronchial patency.^{2,20} PGE₂ partially inhibits both 5-LO and mast cells.^{21,22} Depletion of PGE₂, which is usually generated by constitutive COX-1, appears to be the first event in the pathogenesis of ASA/NSAID-induced respiratory reactions. As levels of PGE₂ fall, their inhibitory effect on mast cells and eosinophils declines and then disappears. This allows unopposed 5-LO activity to increase and synthesis of new LTs to accelerate.²³ At the same time, discharge of preformed mediators, histamine, and tryptase from mast cells occurs. The upper respiratory reaction is predominantly caused by histamine.^{24,25}

In conclusion, it is our opinion that one can safely prescribe rofecoxib to patients who have ASRD. Because celecoxib also selectively inhibits COX-2, there is no reason to suspect that larger, peer-reviewed studies involving challenges with celecoxib in patients with ASRD will uncover instances of cross-reactivity with ASA/NSAIDs.

We are indebted to the GCRC research nurses, without whose dedicated efforts this project could not have been conducted. Special appreciation goes to Mrs Aliene Duvalian, RN, Nurse Coordinator for the GCRC Aspirin Project. We also recognize and thank James A. Koziol, PhD, Biostatistician for the GCRC, for his help in statistical analysis of our data.

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