
Safety of etoricoxib, a specific cyclooxygenase-2 inhibitor, in asthmatic patients with aspirin-exacerbated respiratory disease

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Background: Treatment of rheumatic conditions is limited in patients with asthma owing to concerns of nonsteroidal anti-inflammatory drugs potentially provoking asthma. Cross-sensitivity to all anti-inflammatory drugs that inhibit cyclooxygenase enzymes occurs in these individuals.

Objectives: To study the safety of etoricoxib, a specific cyclooxygenase-2 inhibitor, and to determine whether it cross-reacts with asthma in patients with aspirin-exacerbated respiratory disease (AERD).

Methods: This study included 77 patients who had experienced asthma induced by aspirin and at least 1 other nonsteroidal anti-inflammatory drug. Baseline evaluation included blood pressure measurement, nasal examination, spirometry, and peak expiratory flow rate measurement. Patients were given placebo the first day and then were challenged with once-daily etoricoxib in 3 different doses: 60 mg on day 2, 90 mg on day 3, and 120 mg on day 4. If no evidence of intolerance was seen, each patient was rechallenged with 60 or 90 mg of etoricoxib once daily (according to the rheumatic condition) 7 days later. Reassessment of the baseline measurements was performed daily from day 1 to day 4 after the initial challenge, on day 7 after rechallenge, and after 1 month of drug intake. If the patient developed any mucosal or skin reaction, hypotension, upper or lower airway obstruction, conjunctival reaction, or laryngeal edema during the challenge test, it was considered a positive response.

Results: Etoricoxib was well tolerated, without any signs of immediate or delayed hypersensitivity in aspirin- and nonsteroidal anti-inflammatory drug-induced asthmatic patients. None of 77 study patients experienced any symptoms or developed dyspnea, change in nasal examination, significant variation in peak expiratory flow rate greater than 20%, or decline in forced expiratory volume in 1 second greater than 15% during etoricoxib challenge. The exact 1-sided confidence interval for the probability of etoricoxib inducing cross-reactions in patients with AERD was 0% to 2%.

Conclusions: These results confirm the lack of cross-reactivity between specific cyclooxygenase-2 inhibitors and aspirin in AERD. Etoricoxib was safe for treating inflammation in patients with AERD.

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INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD), formerly known as aspirin-sensitive asthma or aspirin-induced asthma, is a complex inflammatory process that affects a subset of patients with asthma. Patients with AERD present with the classic triad of asthma, rhinitis with nasal polyps, and aspirin sensitivity. However, this description has become more complicated across the years and, more recently, has been expanded to include chronic sinusitis.¹ Aspirin-exacerbated respiratory disease is seen almost exclusively in adulthood. Giraldo et al² noted that 5% of hospitalized adult asthmatic patients reported a history of aspirin-induced respiratory reactions. In 1972, the Scripps Clinic and Research Foundation found that 9% of challenged adult asthmatic patients were aspirin sensitive. The prevalence of aspirin sensitivity in

asthmatic patients with associated rhinitis or nasal polyps increased this number significantly to 30% to 40%.³ Patients with AERD are intolerant of aspirin and most NSAIDs and experience an acute asthma attack within a few minutes to 3 hours after ingestion of the offending agent.^{4,5}

The mechanism behind AERD, although not fully understood, has become clearer in recent years.^{4–7} The predominant theory is related to inhibition of the cyclooxygenase (COX) enzyme, which exists in 2 isoforms, COX-1 and COX-2. Cyclooxygenase-1 is the constitutive form found in most tissues, with an increased amount found in the stomach, kidneys, and platelets; COX-2 is the inducible form that is formed during inflammation. The physiologic effects of COX-1 include the production of prostaglandin E₂ (PGE₂), which functions as a bronchodilator; it reduces the formation of leukotrienes (LTs) through inhibition of the 5-lipoxygenase enzyme and inhibits the release of histamine. Leukotrienes are inflammatory mediators that are present in elevated amounts in the lungs of asthmatic patients. Cysteinyl LTs LTC₄ and LTE₄ cause bronchoconstriction, inflammation, and mucus production. Decreased formation of LTC₄, LTD₄, and LTE₄ by PGE₂ inhibition of 5-lipoxygenase prevents LT-induced bronchoconstriction. The respiratory and cutane-

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ous reactions seen in AERD are a result of inhibition of COX-1, which causes decreased PGE₂ formation. Decreased PGE₂ formation leads to increased LT production and increased histamine release. In addition, when both COX enzymes are inhibited, metabolism of arachidonic acid is shunted toward the lipoxygenase pathway, resulting in increased production of inflammatory LTs.

Considering the mechanism of AERD, there has been increased attention on this topic since the advent of specific COX-2 inhibitors. The theory is that specific COX-2 inhibitors may be an alternative in aspirin- or NSAID-sensitive patients owing to minimal effects on COX-1 and PGE₂. Data have begun to emerge suggesting that COX-2 specific inhibitors can be safely ingested by patients with AERD.^{8–12} Etoricoxib is a new specific COX-2 inhibitor that has been in use since 2002. It has the highest specificity reported to date for COX-2 enzyme, and it is available in 3 different doses that are used for most of the rheumatic conditions, including acute gouty arthritis.¹³ This study was performed to evaluate the safety of etoricoxib and to determine whether it precipitates asthma attacks in patients with aspirin- or other NSAID-induced asthma in a multicenter, single-blind, placebo-controlled study.

PATIENTS AND METHODS

Study Design and Patients

The provocation test was performed in a multicenter, single-blind, placebo-controlled study. This 1-arm challenge protocol consisted of oral administration of the drug in increasing doses after a placebo trial on day 1. Seventy-seven patients aged 18 to 65 years were included. All the patients should have experienced asthma induced by aspirin and at least 1 other NSAID as documented in their medical records and verbally reported by the patient during an emergency department visit for an AERD attack. Patients were included in the study if the last episode of drug-induced asthma was within 6 months of the start of the study. Participants had to have stable asthma for at least 2 weeks, with a forced expiratory volume in 1 second (FEV₁) greater than 70%.

Patients were allowed to continue taking LT modifiers, theophylline, and corticosteroids (oral, nasal, and bronchial). No modification in the dose of these drugs was performed 2 weeks before and during the study. The use of anticholinergics, short-acting β_2 -antagonists, antihistamines, cromolyn sodium, nedocromil sodium, salmeterol, albuterol, and ipratropium bromide was discontinued. Adequate time for washout of these drugs was allowed.

All the patients presented to the rheumatology clinic with different rheumatic disorders. They were reviewed at 3 medical centers: Ain Shams University Hospitals, Cairo, Egypt; Center for Rheumatic Diseases, Heliopolis, Cairo; and Saudi German Hospital, Jeddah, Saudi Arabia. Pregnant women were not included in the study. Women of childbearing potential underwent a screening urine pregnancy test before

participating. None of the participants had previous exposure to etoricoxib.

Monitoring of Respiratory Symptoms and Adverse Events

During the study, blood pressure, pulse, and naso-ocular, pulmonary, and cutaneous symptoms were recorded. All the patients were asked to stay in the hospital under medical supervision for 5 hours. Any symptoms that developed after leaving the hospital were to be reported to our staff by telephone. A positive naso-ocular reaction was defined as the presence of rhinorrhea accompanied by any of the following: ocular chemosis, injection, and periorbital swelling; swelling and congestion of the nasal turbinates; and paranasal sinus pain. The symptoms and signs of reaction in the upper airways were recorded using a standard scoring system¹⁴: 0 indicates absence of any reaction; 1+, rhinorrhea, nasal congestion; 2+, rhinorrhea, nasal congestion with conjunctival injection; 3+, complete nasal obstruction with conjunctival injection and paranasal sinus headache; and 4+, severe reactions with periorbital edema in addition to manifestation of all oculonasal signs and symptoms. A delayed reaction was defined as symptoms occurring at least 2 hours after administration of the last dose of etoricoxib. The local protocols for the study were ethically approved, and informed consent was obtained from each participant.

Etoricoxib Challenge

Day 1. Baseline evaluation included physical and chest examination, blood pressure measurement, nasal examination, spirometry, and peak expiratory flow rate (PEFR) measurement. The patients were then given placebo tablets the first day. A placebo oral challenge was conducted to determine whether lung function was stable enough for the patient to participate in the next day's drug challenge. For a patient to participate in the study, his or her baseline FEV₁ value had to be greater than 70% of predicted, and hourly FEV₁ values and PEFRs had to vary less than 10% during the placebo challenge on day 1. Neither the patient nor the nurse knew the sequence of the placebo and active drug challenge.

Day 2. Participants were challenged with etoricoxib, 60-mg tablets. They were observed for 5 hours, and blood pressure, pulse, and naso-ocular, pulmonary, and cutaneous symptoms were monitored. Peak flowmetry and spirometry were regularly evaluated. A positive reaction was defined as the presence of 1 of the following: naso-ocular reactions, upper or lower respiratory tract reaction with a 15% decrease in FEV₁ or a PEFR variation greater than 20%, cutaneous reactions, hypotension, or laryngeal edema.

Days 3 and 4. Participants were challenged with 90- and 120-mg etoricoxib tablets on days 3 and 4, respectively. Each day they were monitored for blood pressure, pulse, and naso-ocular, pulmonary, and cutaneous symptoms. Both PEFR and spirometry were evaluated regularly.

Day 8 (rechallenge) and follow-up. If no evidence of intolerance was seen, each patient was rechallenged with 60 or 90 mg of etoricoxib once daily (according to his or her

rheumatic condition) 7 days later. Patients were followed up 1 month after the rechallenge of etoricoxib for evaluation of the baseline measures and response to drug therapy.

Statistical Analysis

Frequency distribution was performed for description of qualitative data. Median and interquartile range are presented in skewed distribution. Wilcoxon ranked signed test was used to elucidate any difference in pulmonary functions changes. All statistical analysis was performed using a statistical software package (SPSS version 11; SPSS Inc, Chicago, IL).

RESULTS

Demographic Data

Eighty-two patients were preliminarily evaluated for inclusion criteria. Five patients were excluded from the study because their asthma was not stable the first day after placebo challenge and their FEV₁ was less than 70% of predicted. Table 1 gives the relevant clinical data of the 77 patients who completed the study (31 men and 46 women; mean $\pm$ SD age, 55.9 $\pm$ 0.75 years). All the patients included in this study had aspirin sensitivity-induced asthma, rhinosinusitis, and nasal polyps. According to their hospital records, 58 patients (75%) had sinusitis according to computed tomography. The remaining 19 patients (25%) did not undergo computed tomography but were diagnosed at some time as having chronic sinusitis.

Rheumatic complaints included degenerative changes (31 patients), low back pain (22 patients), soft tissue rheumatism (tendonitis and capsulitis) (14 patients), and arthritis/arthralgia (10 patients). History of NSAID use included diclofenac sodium (38 patients), ibuprofen (31 patients), piroxicam (14 patients), ketoprofen (12 patients), and naproxen (10 patients). Four patients had a history of intolerance to meloxicam, 15 mg. Of the 77 patients, 71 (92%) were taking inhaled corticosteroids, 20 (26%) were taking continuous systemic corticosteroids, 39 (51%) were taking short-course systemic corticosteroids, 35 (46%) were taking montelukast, and 10 (13%) were taking zafirlukast. Eighteen patients (23%) were not taking systemic corticosteroids.

Challenge Study Results

During the etoricoxib challenge, no symptoms were reported with any of the 3 doses used. Etoricoxib, 60-, 90-, and

120-mg tablets, proved to be well tolerated, without any signs of immediate or delayed hypersensitivity in aspirin- and NSAID-induced asthmatic patients. None of the 77 study patients experienced any symptoms, including dyspnea, mucosa/skin irritation, upper or lower airway obstruction, conjunctival reaction, change in nasal examination findings, significant variation in PEFR greater than 20%, or decline in FEV₁ greater than 15% during etoricoxib challenge. None of the participants developed any significant adverse effects from etoricoxib. Mean blood pressure was 121.47/78.27 mm Hg on day 1, 120.58/77.36 mm Hg on day 4, 121.29/78.82 mm Hg on day 8, and 121.38/79.48 mm Hg on day 30. There were no significant differences among the baseline measures taken before the study, after taking placebo, and after etoricoxib challenge. There was no significant difference comparing the percentage changes in PEFR and FEV₁ with etoricoxib challenge compared with placebo challenge (Table 2). Other symptoms recorded during the challenge study with etoricoxib were epigastric pain in 2 patients, improved musculoskeletal pain scores measured using a visual analog scale ($P < .001$), and heavy chest without a change in FEV₁ or PEFR in 1 patient, which resolved spontaneously in 1 patient; rashes did not occur in any patient during etoricoxib/placebo challenge. In summary, there were no reactions after ingestion of 60-, 90-, or 120-mg doses of etoricoxib. The exact 1-sided 95% confidence interval (CI) for the underlying probability of etoricoxib inducing cross-reactions in patients with AERD was calculated to be 0 to 0.02, or 0% and 2%.

DISCUSSION

In this study, etoricoxib, in its different therapeutic doses, was safely tolerated by the 77 asthmatic patients known to have AERD. None of the 77 patients experienced any signs of immediate or delayed reactions. Because NSAIDs that inhibit COX-1 cross-react with aspirin 100% of the time, in patients with AERD, one would have expected a significant number of reactions to occur with etoricoxib therapy in such groups of patients if etoricoxib was a cross-reacting NSAID.

The fear of this reaction has led some clinicians to avoid the use of aspirin and NSAIDs in patients with asthma.^{7,15} According to Sampson,¹⁶ the reasons for underreporting as-

Table 1. Baseline Characteristics of the 77 Study Patients

Variable	Patients, No. (%)
Previous asthmatic reaction to aspirin	77 (100)
Previous asthmatic reaction to 1 NSAID	77 (100)
Previous asthmatic reaction to 2 NSAIDs	32 (42)
Diagnosed at some time as having nasal polyps	77 (100)
Diagnosed at some time as having rhinosinusitis	77 (100)
Diagnosed by computed tomography as having sinusitis	58 (75)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Table 2. Percentage Changes in PEFR and FEV₁ With Etoricoxib Challenge Compared With Placebo Challenge

	PEFR		FEV ₁	
	Median (IQR)	P value	Median (IQR)	P value
Day 1	0.54 (−0.04 to 2.00)		1.05 (−0.09 to 2.05)	
Day 2	0.54 (−0.07 to 2.02)	.95	1.05 (−0.07 to 2.05)	.96
Day 3	0.54 (−0.09 to 2.02)	.99	1.06 (−0.08 to 1.08)	.89
Day 4	0.55 (−1.03 to 2.02)	.83	1.06 (−0.09 to 2.06)	.79
Day 8	0.08 (−0.09 to 2.02)	.88	1.05 (−0.09 to 1.32)	.80
Day 30	1.02 (−1.03 to 2.02)	.54	1.06 (−0.09 to 2.05)	.83

Abbreviations: FEV₁, forced expiratory volume in 1 second; IQR, interquartile range; PEFR, peak expiratory flow rate.

pirin sensitivity may include the deliberate avoidance of aspirin and other NSAIDs by asthmatic patients aware of the risk of adverse reactions or a lack of recognition by patients of the mild reactions due to the delayed onset of symptoms after aspirin ingestion.¹² The propensity of an NSAID to precipitate bronchoconstriction in such patients is related to its pharmacologic efficacy in inhibiting COX.¹⁷ In contrast, sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, and dextro-propoxyphene do not inhibit COX-1 enzymes and do not induce respiratory reactions in patients with AERD.¹⁵ These drugs are poor analgesics and have fewer anti-inflammatory effects than the cross-reacting NSAIDs. Drugs such as acetaminophen, which is a weak inhibitor of COX-1, are a possible alternative for analgesia in these patients.^{1,7} However, doses of acetaminophen greater than 1,000 mg are thought to induce reactions in approximately 30% of patients with AERD.¹⁸ Meloxicam and nimesulide are inflammatory tablets that have been reported to be selective for COX-2 enzyme. At therapeutic doses, both agents have this preferential inhibition of COX-2, but when given at higher doses, this selectivity is lost, causing bronchial obstruction.^{19,20} Both anti-inflammatory drugs were found to have a low prevalence of cross-reactivity in AERD; however, this might be lost with much higher doses of the drug.^{20,21} In contrast to the dose-response reactions seen with preferential COX-2 selective NSAIDs, such as nimesulide and meloxicam, no reactions to etoricoxib were seen in this study as the dose was increased from 60 to 120 mg. Because of the potential for a severe reaction, patients with asthma are usually consistently warned by treating physicians to avoid aspirin and NSAIDs. As a result, many patients are not receiving adequate anti-inflammatory therapy for a variety of rheumatic conditions. Unlike NSAIDs, etoricoxib seems to be an acceptable alternative in patients with AERD. This is important given that many patients with asthma do not know whether they are sensitive to aspirin or NSAIDs.

The results of this study agree with earlier data suggesting that the use of specific COX-2 inhibitors is safe in patients with AERD. Szczeklik et al¹² performed a double-blind, placebo-controlled study to evaluate the safety of rofecoxib in 12 patients with AERD. All 12 patients tolerated rofecoxib, 25 mg; no patient experienced difficulty breathing or a greater than 20% decrease in FEV₁.¹² Martin-Garcia et al²² conducted a single-blind study to determine the tolerability of rofecoxib in 40 patients who experienced asthma induced by aspirin and at least 1 other NSAID. The authors concluded that rofecoxib seems to be safe to use in patients with AERD. In another study, Woessner et al²³ performed a double-blind, placebo-controlled oral challenge with celecoxib to determine whether celecoxib cross-reacts in patients with AERD. None of the 60 patients who were included in that study had a reaction to celecoxib. The authors calculated a 1-sided 95% CI of 0% to 5% for the probability of celecoxib causing a reaction in patients with AERD. To determine whether patients with AERD could tolerate rofecoxib without adverse

events, a double-blind, placebo-controlled study¹¹ challenged 65 patients with rofecoxib, 12.5 and 25 mg. The authors calculated a 1-sided CI of 0% to 5% for the probability of rofecoxib causing a reaction in patients with AERD. It was concluded also that rofecoxib can be safely given to patients with asthma.

A confounding factor in designing a challenge protocol for individuals with AERD is the issue of controller medication use. In most patients with AERD, controller medications are critical components of their asthma control. If the use of systemic corticosteroids or LT modifiers was discontinued during challenge studies, spontaneous bronchospasm tends to reappear, confounding the results. Such a situation will produce declines in FEV₁ values, which may be wrongly attributed to the challenge substance. Furthermore, discontinuing controller medicine may place the patient with AERD at risk of a serious reaction to aspirin. On the other hand, if controller medications are continued, they can modify or even block bronchospastic reactions. There is evidence that corticosteroids and LT modifiers may block the bronchospastic reactions in AERD; however, the naso-ocular reactions will still occur.^{14,24,25} Naso-ocular reactions include rhinorrhea, ocular swelling, nasal congestion and sinus pain. Therefore, continuing to take corticosteroids and LT modifiers does not prevent diagnosis of AERD. Antihistamine, which can block the naso-ocular symptoms of AERD, should not be continued with corticosteroids and LT modifiers because all symptoms of a reaction could be blocked and the patient would be misdiagnosed. Hence, patients included in this study were allowed to continue corticosteroid and LT therapy.

None of the participants had previously ingested etoricoxib. Therefore, there was no possibility of type I or IgE-mediated reactions or hypersensitivity immune reactions with ingestion of etoricoxib in this study. In contrast to IgE-mediated reactions that require previous drug exposure, aspirin- and NSAID-induced respiratory reactions can occur on first exposure in sensitive individuals.²³

A critical component of this study was confirming sensitivity in all the participants. In patients with AERD, life-threatening asthma exacerbation can occur with therapeutic doses of aspirin and NSAIDs. According to the inclusion criteria of this study, patients were included if the last episode of drug-induced asthma was within 6 months of the start of the study. Diagnosis of AERD was based on history of an emergency department visit due to an AERD attack.

The original package inserts for COX-2 specific drugs (celecoxib, rofecoxib, and etoricoxib) stated that prescribing them to patients with AERD was absolutely contraindicated and urged caution regarding giving them to patients with asthma. In view of the results of all the studies testing specific COX-2 inhibitors for patients with AERD, this should change. There is sufficient evidence to indicate that aspirin precipitates asthmatic attacks in sensitive patients not through an allergic mechanism but by a pharmacologic action, namely, by inhibition of COX enzyme. Previous studies^{8-12,15} and this study showed that patients with AERD can safely

ingest specific COX-2 inhibitors. Furthermore, research studies proved that such medications are incapable of depleting PGE₂, an essential protective prostanoid generated through constitutive COX-1.

In conclusion, the results of this study further support the notion that COX-2 specific inhibitors are likely to be safe for use in patients with AERD. Etoricoxib was found to be safe for treating inflammation in patients with AERD. These results confirm the lack of cross-reactivity between specific selective COX-2 inhibitors and aspirin in AERD.

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