

Tolerability to Etoricoxib in Patients With Aspirin-Exacerbated Respiratory Disease

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■ Abstract

Background: The use of selective cyclooxygenase (COX) 2 inhibitors as an alternative to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been suggested for patients with aspirin-exacerbated respiratory disease (AERD).

Objective: To evaluate tolerability to etoricoxib, a second-generation COX-2 inhibitor with high in vitro selectivity for COX-2 in patients with AERD.

Methods: We conducted a retrospective review of patients with suspected aspirin intolerance seen between October 2007 and April 2012. Single-blind, placebo-controlled oral challenges with increasing doses of aspirin and etoricoxib were performed on 3 different days.

Results: Of 262 patients with suspected aspirin intolerance, 248 underwent challenge testing with aspirin and 122 (49.2%) showed positive test results. In 104 of these aspirin-sensitive patients, etoricoxib was tested as an alternative drug and was tolerated in all but 3 (2.9%), who developed a positive asthmatic reaction.

Conclusions: The highly selective COX-2 inhibitor etoricoxib was tolerated in most but not all patients tested. An oral provocation test is therefore recommended before prescribing etoricoxib for patients with AERD.

Key words: Aspirin-exacerbated respiratory disease. Asthma. COX-II inhibitor. Etoricoxib. Hypersensitivity

■ Resumen

Introducción: El uso de inhibidores selectivos de la ciclooxigenasa-2 (COX-2) como alternativa a la aspirina y otros analgésicos antiinflamatorios no-esteroides (AINEs) puede ser una alternativa terapéutica para pacientes con enfermedad respiratoria exacerbada por aspirina (EREA).

Objetivo: Evaluar la tolerancia a etoricoxib, un inhibidor de segunda generación de la COX-2 con alta selectividad in vitro para COX-2, en pacientes con EREA. Para ello se realizó una revisión retrospectiva de pacientes con sospecha de intolerancia a aspirina vistos entre 10/2007 y 04/2012. Se realizaron pruebas de provocación oral controladas con dosis crecientes de aspirina y etoricoxib en tres días diferentes.

Resultados: De los 262 pacientes con sospecha de intolerancia a aspirina, 248 fueron sometidos a prueba de provocación con aspirina y 122 (49,2%) mostraron un resultado positivo. En 104 de estos, el etoricoxib se testó como un medicamento alternativo y fue tolerado en todos, excepto en 3 pacientes (2,9%) que desarrollaron una reacción asmática.

Conclusión: El etoricoxib se toleró en la mayoría de los pacientes estudiados. Es recomendable una prueba de provocación antes de indicar este medicamento en el tratamiento de pacientes con EREA.

Palabras clave: Enfermedad respiratoria exacerbada por aspirina. Asma. Inhibidor de COX II. Etoricoxib. Hipersensibilidad.

Introduction

Hypersensitivity reactions to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been attributed to the inhibition of cyclooxygenase (COX) 1, an enzyme that metabolizes arachidonic acid to prostaglandins, thromboxanes, and prostacyclin [1]. Aspirin hypersensitivity can present clinically as aspirin-induced bronchial asthma/rhinosinusitis (AIA/R) or aspirin-induced urticaria/angioedema (AIU) [2]. Aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome that affects patients with asthma, chronic hypertrophic eosinophilic sinusitis/nasal polyps, and hypersensitivity to aspirin and other NSAIDs [3]. The diagnosis of AERD can be established definitively only through aspirin provocation tests [4]. Aspirin desensitization and ongoing daily treatment with aspirin can significantly improve overall symptoms and quality of life, decrease formation of nasal polyps and sinus infection, reduce the need for oral corticosteroids and sinus surgery, and improve nasal and asthma scores in patients with AERD [5]. The use of selective COX-2 inhibitors as an alternative to aspirin and other NSAIDs has been suggested for patients with AERD [6,7]. Etoricoxib is a second-generation COX-2 inhibitor with the highest in vitro selectivity for COX-2 [8]. Only a few cases of cutaneous hypersensitivity reactions to etoricoxib have been documented in patients with AIU [9-11], and apart from 1 case report from our study group [12], no respiratory hypersensitivity reactions have been reported in patients with AERD [13,14]. The aim of this study was, therefore, to evaluate tolerability to etoricoxib in patients with AERD.

Patients and Methods

Patients

We retrospectively reviewed the medical records of all patients with suspected hypersensitivity to aspirin or other NSAIDs seen between October 1, 2007 and April 30, 2012 at the Fachkrankenhaus Coswig, Center for Respiratory Medicine and Allergy in Coswig, Germany. Data about history of aspirin (NSAID) hypersensitivity, asthma, and chronic rhinosinusitis/nasal polyps were analyzed. Aspirin (NSAID) hypersensitivity was categorized according to reported nasal (rhinorrhea, nasal congestion), respiratory (dyspnea, wheezing, chest tightness), systemic/anaphylactoid (nausea, stomach cramps, unconsciousness), and cutaneous (erythema, wheals, angioedema) symptoms. The diagnosis of asthma had to be physician-based and patients had to have stable, controlled asthma with a forced expiratory volume in the first second (FEV₁) greater than 70%. The diagnosis of chronic rhinosinusitis/nasal polyps had to be established by an ear-nose-throat specialist. Patients with a history of chronic rhinosinusitis/nasal polyps were divided in 2 groups depending on whether or not they had undergone sinonasal surgery.

The ethics committee of the University of Dresden approved the study.

Challenge Tests

Oral, single-blind, placebo-controlled aspirin challenge tests were performed according to the EAACI/GA2LEN guidelines [4]. Saccharin lactate in gelatin capsules with an identical appearance to those containing aspirin or etoricoxib was administered as placebo.

Increasing doses of aspirin (25, 45, 115, 315, 500 mg) were administered every 1.5 hours until a cumulative dose of 1000 mg was reached. In the same way, increasing doses of etoricoxib (15, 30, 60 mg) were administered until a cumulative dose of 105 mg was reached.

The schedule consisted of a placebo challenge on day 1, an etoricoxib challenge on day 2, and an aspirin challenge on day 3. In patients who experienced an adverse event of any kind after etoricoxib challenge, the aspirin challenge was started after at least 5 days.

FEV₁ and blood pressure were measured before each consecutive dose and subsequently after 30 minutes. Patients were also observed for bronchial (dyspnea, wheezing, chest tightness), nasal (rhinorrhea, nasal congestion), ocular (ocular injection), cutaneous (erythema, wheals, angioedema), and systemic (nausea, stomach cramps) symptoms. The challenge tests were evaluated as positive if a decrease in FEV₁ of 20% or more from baseline was reached or if severe extrabronchial symptoms occurred, even without a significant drop in FEV₁ (eg, nasal congestion and profound rhinorrhea). All patients who underwent the challenge tests provided signed informed consent.

Results

The demographic and clinical data of the 262 patients evaluated over the given time period are presented in Table 1.

Table 1. Demographic Data of the Study Population^a

Patients, No.	262
Median age, y (range)	51.6 (19-79)
Male/female	108 (41.2)/154 (58.8)
History of aspirin hypersensitivity	
No	94 (35.9)
Yes	168 (64.1)
Nasal	17 (10.1)
Respiratory	113 (67.3)
Systemic/anaphylactoid	9 (5.4)
Cutaneous	29 (17.3)
History of bronchial asthma	
Yes	214 (81.7)
No	48 (18.3)
History of chronic rhinosinusitis/nasal polyps	
No	58 (22.1)
Yes	204 (77.9)
With surgery	190 (72.5)

^aData shown as number (%) of patients unless otherwise specified.

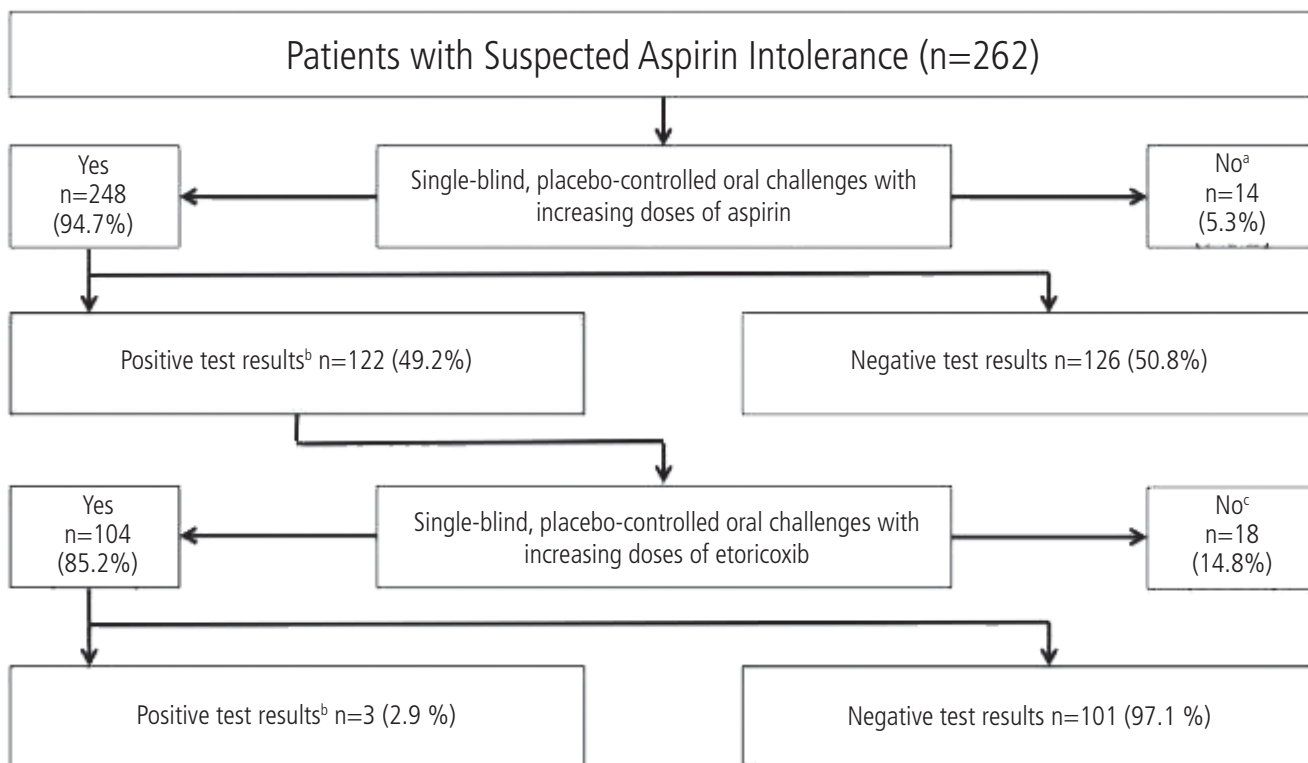


Figure. Flow chart documenting the procedure for patients with suspected aspirin hypersensitivity.

^aNo oral challenge in patients with a definite history of aspirin-induced urticaria/angioedema.

^bAll patients reacted with nasal and/or bronchial symptoms.

^cNo oral challenge in patients with a definite history of tolerability to etoricoxib or without informed consent.

Table 2. Characteristics of the 3 Patients With Asthmatic Reaction to Etoricoxib After Oral Challenge Test and 1 Patient With a Definite History of Asthmatic reaction Due to Etoricoxib

Case#/Age, y/Sex	History of Aspirin Hypersensitivity	History of Bronchial Asthma	History of Nasal Polyps	Cumulative Dose of Etoricoxib, mg	Symptoms of Intolerance Reaction
1 ^a /64/female	Asthma attack, anaphylactic	Partly controlled, allergic	One operation	90	Watery rhinorrhea, asthma attack
2/41/male	Asthma attack	Partly controlled, nonallergic	Three operations	45	Asthma attack, tachycardia
3/53/female	Asthma attack, urticaria	Uncontrolled, allergic	No	105	Nasal congestion, asthma attack, urticaria
4 ^b /43/male	Asthma attack	Controlled, nonallergic	Three operations	90	Asthma attack

^aCase 1 has already been published as a case report [12].

^bCase 4 had a definite history of asthmatic reaction to etoricoxib but rejected a challenge test.

In 94 patients (35.9%) there was no definite history of aspirin hypersensitivity, because they either reported no adverse reactions after the use of aspirin or NSAIDs or they could not remember having ever taken these drugs.

A flow chart documenting the procedure for patients with suspected aspirin hypersensitivity is presented in the Figure. In 248 patients (94.7%), an oral, single-blind, placebo-controlled aspirin challenge test was performed. Of the 122 patients with

a positive nasal and/or bronchial test result (49.2%), an oral, single-blind, placebo-controlled challenge test with etoricoxib was performed in 104 patients (85.2%).

Of those, a positive test result with respiratory symptoms and a decrease in FEV₁ ($\geq 20\%$ from baseline) was documented in 2 patients (2.9%). An additional patient with a history of asthma, nasal polyps with nasal surgery, and definite asthma attacks due to etoricoxib had a positive oral challenge with aspirin, but he rejected an oral challenge with etoricoxib to confirm his reported intolerance reaction (Table 2).

Discussion

In this study we have demonstrated that etoricoxib, a second-generation COX-2 inhibitor with the highest in vitro selectivity for this enzyme, was tolerated in most but not all patients with AERD.

In patients with AERD, other NSAIDs, which are strong COX-1 inhibitors, provoke adverse symptoms [1]. The development of selective COX-2 inhibitors raised strong hopes of establishing a group of alternative analgesic drugs that would be tolerated by patients with AERD [15].

Studies of rofecoxib, the first highly specific COX-2 inhibitor, introduced in 1999, showed good tolerability in patients with AIA [6,16-19] and AIU [20-22], but in 1 study Nettis et al [23] reported an adverse event with urticaria. A further case report was published describing an anaphylactoid reaction due to rofecoxib in a patient with hypersensitivity to COX-1 inhibitors [24]. The tolerability of celecoxib, another highly specific COX-2 inhibitor, in patients with AIA was also demonstrated in placebo-controlled studies [7,25,26]. Good tolerability was also reported for patients with AIU [22,27,28], but again a few case reports described severe celecoxib-induced life-threatening anaphylaxis [29] and severe asthmatic reactions [30,31]. Similar experiences were documented for valdecoxib and parecoxib, 2 other highly specific COX-2 inhibitors. Valdecoxib was tolerated in all but 1 patient with AIU [32] and parecoxib, the first COX-2 selective drug for parenteral administration, was tolerated in 10 patients with AERD [33], but again, parecoxib-induced bronchospasm was described [34].

Etoricoxib, which is among the COX-2 inhibitors still approved for use, shows the highest in vitro selectivity for COX-2 [8,35]. In patients with AIU, it has demonstrated good tolerability [36,37], but cutaneous side effects have been reported in up to 8% of challenged patients [9-11]. Interestingly, a recently published study demonstrated that intolerance to etoricoxib in patients with AIU may depend on intolerance to paracetamol. Twenty-five per cent of patients with AIU and intolerance to paracetamol, compared with only 6% of patients with AIU and tolerance to paracetamol, had a positive etoricoxib challenge result [38]. Only 2 studies have analyzed tolerability to etoricoxib in patients with AERD. In the study by El Miedany et al [13], 77 patients with AERD were challenged with once-daily etoricoxib in 3 different doses (60, 90, 120 mg). No signs of immediate or delayed hypersensitivity reactions, particularly dyspnea or nasal symptoms, were detected [13].

In a smaller study, Nahar et al [14] challenged 16 patients with AERD with 90 mg etoricoxib, and again no complaints of pulmonary or nasal symptoms were reported. Etoricoxib therefore appeared to have excellent tolerability in patients with AERD.

A few years ago, however, we presented the first case report of an asthmatic reaction due to etoricoxib in a patient with severe AERD [12]. At 1-hour intervals after placebo-controlled administration of 30 and 60 mg of etoricoxib, the patient complained of moderate dyspnea and severe rhinorrhea, with a drop in FEV₁ of 24% from baseline. After this event we established placebo-controlled oral etoricoxib challenges in all patients with suspected hypersensitivity to aspirin or other NSAIDs.

In the present study, we now report on 3 patients with AERD (including the patient described above) who developed an asthmatic reaction after challenge with etoricoxib, meaning that nearly 3% of patients with aspirin hypersensitivity had cross-reactivity to etoricoxib. If we add the patient with a definite history of asthmatic reaction to etoricoxib but who rejected a challenge test, the percentage would be closer to 4%. This result differs from those of El Miedany et al [13] and Nahar et al [14], who observed no cross-reactivity to etoricoxib in patients with AERD.

Three of the 4 patients with asthmatic reactions to etoricoxib had a history of partly controlled or uncontrolled bronchial asthma, with an allergic or nonallergic phenotype. The adverse reactions occurred at both a low (45 mg) and high dose (105 mg) of etoricoxib, and we can therefore assume that there is no dose-dependent mechanism.

There are some limitations to our study. Its retrospective nature means that some patient data are missing. In 18 patients with positive aspirin challenge results (14.8%), challenge with etoricoxib was not performed. Most of these patients rejected this test because of a history of definite tolerability to etoricoxib or, in 1 case, a definite asthmatic reaction to this drug. Some patients already used paracetamol as an alternative analgesic drug and did not wish to test a further potential alternative drug.

The highest approved dose of etoricoxib is 120 mg, but we performed the etoricoxib challenge only until a cumulative dose of 105 mg was reached. Nahar et al [14] tested patients with 90 mg etoricoxib once daily and in the study of El Miedany et al [13], participants were challenged with 60, 90 and 120 mg on 3 different days and rechallenged 7 days later with 60 or 90 mg of etoricoxib if no evidence of intolerance was observed. Although these 2 studies had different challenge protocols and notably different doses of etoricoxib, this has had no influence on the interpretation of the results in the present study. We can only presume that with higher dosages of etoricoxib we may have found even more intolerance reactions to etoricoxib.

In conclusion, to the best of our knowledge, we have demonstrated for the first time that etoricoxib, a highly-selective COX-2 inhibitor, is tolerated in most but not all patients with AERD. Therefore, before prescribing this drug to patients with aspirin hypersensitivity, an oral provocation test in a specialized center is recommended because adverse reactions may occur.

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