ORIGINAL ARTICLE

Safety of Etoricoxib in Patients With Reactions to NSAIDs

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Abstract

Background: Adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are a frequently reported problem due to the fact that these molecules are often used for control of pain and inflammation. Although the use of selective inhibitors of cyclooxygenase (COX) 2 helps to prevent some of these adverse reactions, they can have cardiac side effects when taken for prolonged periods. Here we report the safety and tolerability of etoricoxib, a selective COX-2 inhibitor with fewer cardiovascular effects, in patients with adverse reactions to NSAIDs.

Patients and methods: We performed placebo-controlled oral challenge with etoricoxib in 65 patients with previous adverse reactions to NSAIDs: 13 to salicylates, 18 to arylpropionic acids, 10 to arylacetic acid, 12 to oxicam and derivates, 8 to pyrazolones, and 4 to acetaminophen (paracetamol). The reported symptoms were urticaria or angioedema in 69%, rhinitis in 3%, and 1 case of anaphylactic shock (1.5%). The challenge was done using the placebo on the first day, half dosage of etoricoxib (45 mg) on the second day, and the therapeutic dose of 90 mg on the third day. The challenge was done in the outpatient department of the hospital and the subjects were monitored for a further 4 to 6 hours after challenge.

Results: Oral challenge with etoricoxib was well tolerated in 97% of the patients. Only 2 systemic reactions were reported during the challenge test.

Conclusion: Etoricoxib can be considered a safe molecule for those patients with previous adverse reactions to NSAIDs.

Key words: Etoricoxib. NSAID intolerance. Anaphylactic reaction. Asthma. Cutaneous reaction.

Resumen

Antecedentes: Las reacciones adversas a los fármacos antiinflamatorios no esteroideos (AINE) son un problema frecuente debido a que estas moléculas se usan a menudo para controlar el dolor y la inflamación. A pesar de que el uso de inhibidores selectivos de ciclooxigenasa (COX) 2 es de gran ayuda para evitar algunas de estas reacciones adversas, pueden tener efectos secundarios cardíacos cuando se ingieren durante períodos prolongados. Hemos realizado un informe de la seguridad y tolerabilidad del etoricoxib, un inhibidor selectivo de la COX-2 con menores efectos cardiovasculares, en pacientes que han sufrido reacciones adversas a los AINE.

Pacientes y métodos: Se realizó una prueba de provocación oral controlada con placebo con etoricoxib en 65 pacientes que habían sufrido reacciones adversas previas a los AINE: 13 a los salicilatos, 18 a los ácidos arilpropiónicos, 10 al ácido arilacético, 12 al oxicano y derivados, 8 a las pirazolonas y 4 al acetaminafeno (paracetamol). Los síntomas que tuvieron fueron urticaria y angioedema en un 69 %, rinitis en un 3 % y un caso de shock anafiláctico (1,5 %). La provocación se realizó utilizando el placebo el primer día, media dosis de etoricoxib (45 mg) el segundo día y una dosis de tratamiento (90 mg) el tercer día. La provocación se llevó a cabo en la consulta externa del hospital y los sujetos se controlaron de 4 a 6 horas más después de la provocación.

Resultados: El 97 % de los pacientes toleró bien la provocación oral con etoricoxib. Sólo se produjeron 2 reacciones sistémicas durante la prueba de provocación.

Conclusión: El etoricoxib se puede considerar una molécula segura para aquellos pacientes con reacciones adversas previas a los AINE.

Palabras clave: Etoricoxib. Intolerancia a los AINE. Reacción anafiláctica. Asma. Reacción cutánea.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drugs in medical practice and we are witnessing a constant increase in the indications for their use. High prescription rates and self-administration have led to an increase in reports of side effects and adverse reactions, including dermatologic reactions in 0.1% to 0.3% of cases [1] and respiratory effects in between 0.6% and 2.5% of the exposed population [2].

Many studies have indicated that NSAIDs function as inhibitors of isoforms 1 and 2 of the cyclooxygenase enzyme (COX1 and COX2) [3,4]. COX-1, which is constitutively expressed in tissues, stimulates prostaglandin synthesis. The gastric and renal side effects of NSAIDs may thus be explained by their indirect effect on prostaglandin (PG) E2, which has cytoprotective effects in the gastroenteric system, and on PGE2 and PGI2, which are involved in regulating renal blood flow [5]. As a result, efforts have been made to develop selective COX-2 inhibitors (coxibs), such as rofecoxib and celecoxib, and recently the number of COX-2-selective inhibitors has increased with the addition of the second-generation coxibs valdecoxib, parecoxib, and etoricoxib [6].

In contrast to COX-1, COX-2 expression is inducible rather than constitutive. It is produced during inflammation, plays a role in some nervous system functions, and has protective effects in the cardiovascular system [7]. The cardiovascular effects of COX-2 are responsible for an increase in coxib side effects, notably ischemic cardiovascular events, particularly in patients subjected to high and long-lasting dosages for osteoarthritic diseases [8,9]. Recently, etoricoxib [10] has been shown to have fewer cardiovascular side effects [11-13]. Although the difficulty of evaluating the selectivity of COX-2 selective inhibitors, based on in vitro enzyme and cell-based assays, is well recognized and has been extensively discussed [14-16], etoricoxib has been reported to be more than 100-fold selective for COX-2 versus COX-1 in various cell and whole blood assays, and seems to be less active against COX-1 than other selective COX-2 inhibitors [17].

In addition to the side effects of NSAIDs, their widespread use means that we must also take into account pseudoallergic and allergic reactions such as angioedema, urticaria, rhinitis, bronchial asthma, and even anaphylaxis [18]. Placebo-controlled oral challenge tests with alternative molecules are therefore recommended for the assessment of drug safety in patients with adverse reactions to NSAIDs [19], as skin tests and in vitro tests are not yet available.

Taking into consideration the potentially long-term use of NSAIDs, it is fundamental to introduce a drug with few adverse reactions. We report the safety and tolerability of etoricoxib, assessed by oral challenge, in patients who reported typical adverse dermatologic and respiratory reactions to NSAIDs.

Patients and Methods

Patients

We tested 65 patients—25 men (mean age, 49.5 years) and 40 women (mean age, 50.1 years)—who were referred to our allergy department for assessment after suffering dermatologic or respiratory side effects associated with the use of NSAIDs. All reactions had been documented in the patient's clinical history together with the emergency treatment performed. None of the patients had previously been treated with a coxib and furthermore all previous reactions were assumed to be secondary to the inhibitory effects of NSAIDs on COX-1. The inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
– History of adverse reactions to COX-1-selective NSAIDs with urticaria, angioedema, dermatologic and cardiovascular rections, or asthma
– Age > 18 y
Exclusion Criteria
– Stevens-Johnson syndrome and toxic epidermal necrolysis
– Pregnancy and breast feeding
– Chronic urticaria
– Uncontrolled hypertension
– Known ischemic heart disease or cerebral vascular disease
– Congestive heart failure (NYHA II-IV)
– Angioedema unrelated to NSAID use
– Treatment with H1 antihistamines or ß-blockers
– Reactions to NSAIDs in the last 3 months
– FEV_1 < 80% of predicted
– Lactose intolerance

Abbreviations: COX, cyclooxygenase; FEV_1, forced expiratory volume in 1 second; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association.

Table 2. Drugs Causing Adverse Reactions

Drug	Active Principles	Patients	Total
Salycilates		13	13
Arylpropionic acid	Ibuprofene	4	18
	Naproxene	6	
	Ketoprofene	6	
	Flubiprofene	2	
Arylacetic acid	Diclofenac	5	10
	Ketorolac	2	
	Indometacina	3	
Oxicam	Piroxicam	9	12
	Tenoxicam	1	
	Meloxicam	2	
Paracetamol		4	4
Pyrazolones	Noramidopirina	4	8
	Propifenazone	4	
			65

The reported reactions after having taken an NSAID are shown in Table 2 and symptoms are shown in Table 3. Of the 8 patients with reactions to pyrazolones, 3 also reported reactions to aspirin. Two of these patients reported asthma and 1 asthma with urticaria. Of the 5 patients who had no additional reaction to salicylates, 3 reported cutaneous symptoms, 1 asthma with urticaria, and 1 anaphylactic shock.

All patients provided signed consent to oral challenge with etoricoxib. The test was performed in the outpatient department of the hospital, with prior information received from our colleagues in the department of anesthesia and critical care, in accordance with the guidelines of the Italian Society of Allergology and Clinical Immunology [20]. Ethical committee authorization was not requested as the studies formed part of the normal standard of care.

Forced expiratory volume in 1 second (FEV_1) was assessed before and after each challenge in patients who reported asthmatic reactions in order to evaluate possible bronchoconstriction.

Table 3. Types of Reaction in Our Patients

Symptoms	Patients	%
Urticaria	23	35.4
Angioedema	8	12.3
Urticaria/angioedema	14	21.5
Rhinitis with asthma	2	3.1
Asthma	4	6.2
Respiratory and cutaneous symptoms	11	16.9
Exanthema	2	3.1
Anaphylactic shock	1	1.5

Challenge Test

All patients were subjected to placebo-controlled oral challenge with etoricoxib. During the procedure the patient was constantly monitored, and as a precaution, an emergency cart was available with all the necessary instruments in case of need.

The tests were carried out with etoricoxib and placebo (talcum) over a period of 3 days, using carefully measured fractional doses that were inserted in caps all of the same color and with the same vanilla taste in order to avoid any possible psychological influences on the patient. The challenge was done by reaching a dose of 90 mg of etoricoxib over 3 days, using the placebo on the first day with a total of 2 caps (1 dose per hour), half dose (45 mg) on the second day divided into 3 doses of 10 mg, 15 mg, and 20 mg (1 dose per hour), and the therapeutic dose (90 mg) also divided in 2 caps (1 dose per hour), on the third day.

During the test the patient's blood pressure and, where appropriate, spirometric parameters were monitored before each challenge and for 4 to 6 hours after the last dose of the drug. Subsequent reactions were reported by directly calling the hospital outpatient clinic.

The test was considered positive if the patient presented cutaneous symptoms (rash, itching, urticaria, angioedema), respiratory symptoms (dyspnea with a reduction in $FEV_1 \geq 20\%$ of baseline), dysphonia, or cardiovascular symptoms (hypotension or shock).

Results

Out of the 65 patients subjected to etoricoxib challenge, only 2 (3%) had positive reactions to the test and did not tolerate the drug at the 90 mg dose. The first patient was a nonatopic, nonasthmatic 28-year-old man with a previous reaction to salicylates involving urticaria and angioedema. An hour after taking the maximum dose (90 mg), he presented a generalized cutaneous reaction involving a pruritic, exanthematous rash. The patient experienced a relapse even after the challenge was interrupted. These symptoms regressed only after 2 to 3 days of treatment with H1 antihistamines and corticosteroids. The second patient was a nonatopic, nonasthmatic 67-year-old man with a history of angioedema to indomethacin and naproxen. He developed a Quincke giant edema 5 hours after having taken the total dose of 45 mg of etoricoxib during the second day of challenge test. The symptoms were successfully resolved with oral corticosteroid treatment.

The remaining 63 patients (97%) did not suffer from any systemic reactions once the challenge was over and none of them presented any reactions to placebo. Variables such as blood pressure, heart rate, and FEV_1 remained stable. In particular, no adverse reactions were recorded in those 4 patients with secondary reactions to paracetamol.

Discussion

In 1971, the Nobel Prize winner John Vane [21] proved that the anti-inflammatory and analgesic effect of NSAIDs was due to an imbalance in the enzymatic pathways involving lipoxygenase and COX leading to a reduction in PGE levels caused by COX inhibition and production of cysteinyl-leukotriene (Cis-LTC4-D4-E4), which is produced by mast cells, eosinophils, basophils, and macrophages and is probably higher in individuals who are intolerant to those drugs [22]. Later on it was further demonstrated that there were 2 isoforms of COX: COX-1 and COX-2. COX-1 is constitutively expressed in nearly all tissues and mediates physiologic responses (cytoprotection of the stomach and platelet aggregation). Moreover, this enzyme is upregulated by inflammatory or mitogenic stimuli [23,24] Conversely, COX-2 is almost absent in physiologic conditions but is inducible in response to inflammatory or mitogenic stimuli in many tissues, and its expression has been hypothesized to be responsible for the synthesis of prostaglandin, which mediates responses to pathologic processes such as pain, fever, and inflammation [24]. It is also responsible for some cardioprotective effects such as inhibition of cell proliferation, regulation of cytokines and endothelin-1 release, and expression of intercellular adhesion molecule-1 [7].

The data obtained from a limited number of cases shows that coxibs are definitely well tolerated in challenge tests [25-28] and represent a valid alternative in those patients who have experienced even serious systemic adverse reactions to

NSAIDs. However, it must be kept in mind that recently a few anaphylactic reactions to celecoxib [29,30] and rofecoxib [31] have been reported. Although to date no cases of anaphylaxis to etoricoxib have been reported, we considered it essential to select the patients tested (Table 1).

The low incidence of adverse reactions in the patients reported here supports the hypothesis that this molecule is safe in relation to both dermatologic and respiratory reactions. In our 14 patients with respiratory reactions to salicylates, arylpropionic acids, and arylacetic acids, we did not witness any reduction in FEV_1 after the challenge with etoricoxib.

Our results are very similar to those obtained with rofecoxib by Szczeklik et al [32] in 12 patients and with celecoxib by Martin-Garcia et al [33] in 33 patients. This finding provides indirect confirmation that the COX-2 expressed in asthmatic individuals is not responsible for bronchospasm with urinary leukotriene E4 release or PGD2 and F2, which are probably more sensitive to the COX-1 effect.

Previous studies involving patients with urticaria, angioedema, and respiratory symptoms following use of NSAIDs revealed adverse reactions in tolerance tests with first-generation coxibs (relatively selective COX2 inhibitors) in between 0% and 18% of patients [27,34], and in a study of highly selective COX2 inhibitors in 23 patients who had already presented urticaria to NSAIDs the percentage increased to 28.7% [35].

Etoricoxib has been reported to exhibit a better safety profile than first-generation coxibs [4], although further studies involving more cases are still necessary. It is important to highlight that in our study etoricoxib was found to be harmless even in those 4 patients who had reactions to paracetamol, the most widely used drug as a result of its low COX-1 effect. It will therefore be of particular interest to address the use of this drug in at-risk subjects who have presented secondary adverse reactions to paracetamol and nimesulide.

We believe that etoricoxib can be considered safe for use in patients with systemic allergic reactions to or intolerance of NSAIDs. Our study confirms the findings of other authors such as Nettis et al [36] and El Mediany et al [37], in which systemic adverse reactions to etoricoxib occurred in less than 3% of cases. We would like to emphasize that although the tolerability of the drug is clear, the albeit negligible possibility of side effects makes it essential to perform the tests in a fully equipped hospital to guarantee immediate action in case of systemic reactions.

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