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Long-term tolerability of etoricoxib in different types of NSAID-intolerant subjects

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Key words

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Summary

Background: *Non-steroidal anti-inflammatory drugs (NSAIDs) are a frequent cause of hypersensitivity reactions, therefore, in clinical practice, it's important to find safe and effective substances.* ***Objective:*** *To evaluate the tolerability of etoricoxib and its subsequent actual use and safety at home.* ***Methods:*** *Etoricoxib tolerance was assessed by single-blind-placebo-controlled oral challenges and its subsequent use was checked by a standardized telephone call. The test was performed in 139 subjects (83 single NSAID reactors and 56 multiple NSAID reactors).* ***Results:*** *The drug was not tolerated in 4 cases (2,8%) causing wheals on the face area in 3 single reactors and a severe generalised reaction occurring three hours after the intake of a therapeutic dose in a multiple reactor. The phone calls showed that 64 (52,8%) patients did not take etoricoxib, mostly due to the fear of adverse effects; in 5 cases (4,2%), the practitioner prescribed a different NSAIDs. Only 52 (43%) subjects took etoricoxib after oral challenges; all tolerated the drug but 2 single reactors, who reported a very mild labial oedema.* ***Conclusion:*** *Our study confirmed the good long-term tolerability of etoricoxib in patients with a history of hypersensitivity to other NSAIDs without differences between single and multiple reactors. Nonetheless, in NSAID-intolerant subjects this drug should be first challenged in specialised centres due to the risk of severe reactions.*

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely utilised in clinical practice for many types of diseases. The beneficial actions of NSAIDs have been linked to their ability to inhibit cyclooxigenase (COX) enzymes, namely COX-1 and COX-2, that are responsible for the production of prostaglandin (PG) H2, the first step in prostanoid biosynthesis (1).
On the basis of the target, NSAIDs can be divided in 3 groups (2).

The first one includes aspirin and other non-selective both COX-1 and COX-2 inhibiting NSAIDs; the second group includes drugs that are weak inhibitors of COX-1 and partial inhibitors of COX-2 (eg, meloxicam and nimesulide), while the third group includes selective COX-2 inhibitors (eg. etoricoxib, parecoxib). COX-2 appears to be the target of the anti-inflammatory effects of NSAIDs, while the adverse reactions to "classical" NSAIDs are probably due to the inhibition of COX-1 (1), resulting in an overproduction of pro-inflammatory molecules such as leukotrienes C4 and D4 and in con-

temporary reduction of PGE2, a substance with anti-inflammatory activity (3-5).
NSAID-induced hypersensitivity reactions are very frequent, with an incidence ranging from 0,3% to 2,5% in general population, increasing to 20-30% in patients with underlying asthma or chronic urticaria (6-8). The most frequent symptoms are urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis.
In view of the pharmacological data above, it has been hypothesized that coxibs are especially indicated for patients with a history of hypersensitivity reactions to strong non-selective or weak COX-1 inhibitors. In effect, several studies reported a good tolerance to coxibs in most cases, although severe hypersensitivity reactions have been reported (9-12).
Etoricoxib, a new selective COX-2 inhibitor approved in Latin America and Europe for the treatment of acute and chronic pain, rheumatoid arthritis, osteoarthritis, acute gouty arthritis and primary dysmenorrhea shows the highest selectivity for COX-2 and shows a very good tolerability and efficacy (13). Etoricoxib has already been evaluated in subjects with NSAID hypersensitivity. Adverse reactions observed ranged from 0% to 8% (14-18).
In this study we evaluated the safety of etoricoxib in patients with hypersensitivity reactions to 1 or more NSAIDs and assessed its subsequent and actual use in the everyday life.

Methods

This study was approved by the ethical committee of Azienda Ospedaliera C. Poma Mantova and Azienda Ospedaliera of Verona and was performed between January and December 2008, on patients presenting with a history of hypersensitivity reactions to 1 or more NSAIDs at the Allergy Service of Major Hospital of Verona or at the Allergy Service of Asola Civil Hospital, Medicine Department. Only patients showing a well-documented hypersensitivity reactions clearly caused by NSAIDs intake were included.
Each patient underwent a careful clinical history including questions about familiar and personal history of atopy, chronic urticaria, or previous adverse reactions to other drugs.
After signing a written informed consent patients underwent an oral challenge test with etoricoxib 90 mg. At the time of testing none of the patients had significant cutaneous or respiratory tract symptoms or concomitant illnesses (i.e. cardiac, neurologic, renal, psychiatric diseases).
The pulmonary test showed stable forced expiratory volume in 1 second (FEV1) values greater than 80% of predicted in all the patients.
The test was performed in 6 consecutive days using placebo (talc) or etoricoxib in identical inert capsules.
On the first day the patients received 5 capsules of placebo at time interval of 45 minutes each other if no reactive symptom was noted.
On the second and third day, patients received only one capsule of placebo.
On the fourth day the total therapeutic dose of etoricoxib (90 mg) was administered, fractioned in 5 capsules containing respectively 1 mg, 9 mg, 20 mg, 30 mg and finally 30 mg of the drug. Increasing doses were given at 45 minutes intervals if no reaction occurred. On the fifth and sixth day, patients received one capsule containing 90 mg of etoricoxib.
During the challenge test blood pressure and FEV1 were monitored hourly and the patients were kept under control in the hospital for 6 hours after the end of challenge.
The test was considered positive if the following symptoms appeared: cutaneous or mucosal signs (erythema, exanthema, urticaria, angioedema), respiratory symptoms (rhinorrhea, nasal obstruction, sneezing, cough, dyspnoea associated with a decrease of at least 20% in the FEV1) and/or hypotension or loss of consciousness.
In a second part of the study all patients were contacted monthly by phone by nurses submitting a standardized questionnaire (Table 1).
One-hundred thirty nine patients were evaluated (M/F 37/102); median age of 44 years, range 13-78. A personal history of atopy was detected in 35 patients (25,1%): allergic rhino-conjunctivitis in 22 (15,8%), bronchial asthma in 7 (5%), food allergy in 6 (4,3%). Four subjects (2,8%) suffered from chronic urticaria. 83 (59,7%) patients had a history of

Table 1 - Questions made by phone calls to the patients

Did you utilise NSAIDs in the last month?
Did you utilise etoricoxib?
How many times did you utilise etoricoxib?
Did the intake of etoricoxib cause adverse effects?
If you didn't utilise etoricoxib, which is the reason?
Did you utilise other NSAIDs?
Which NSAID did you utilise?
Did the intake of the NSAID cause adverse effects?
Why did you utilise this NSAID instead of etoricoxib?

hypersensitivity to a single NSAID (single reactors), ASA in most cases, while 56 (40.3%) had a history of hypersensitivity to 2 or more NSAIDs (multiple reactors). The offending drugs are shown in Table 2.
26 patients (18,7%) reported hypersensitivity to antibiotics: 20 (14,3%) to beta-lactams, 2 (1,4%) to sulfamethoxazole-trimethoprim, 2 (1,4%) to ciprofloxacin, 1 (0,7%) to teicoplanin and 1 (0,7%) to clarithromycin.

Results

Symptoms and underlying diseases reported by single and multiple reactors are summarized in Tables 3 and 4, respectively.
Etoricoxib challenge scored positive in 4 subjects (2,8%) without underlying diseases, Three were single reactors with a history of NSAIDs-induced cutaneous symptoms who experienced only mild urticaria on the face 3 hours after the end of the challenge.
The other patient was a 58 years-old multiple NSAID reactor woman with a history of generalised urticaria after the intake of naproxen, piroxicam and ASA, who experienced a severe reaction, including generalised urticaria, labial oedema, bronchospasm and headache 3 hours after the intake of 90 mg of etoricoxib. The same patient underwent, one month later, a challenge test with meloxicam without any problem.
18 subjects were lost for the follow-up. Of 121 patients remaining [79 single reactors (65%) and 42 multiple reactors (35%)], 52 (43%) utilised etoricoxib that was perfectly tolerated in 50 (41%) cases, whereas 2 females, both with a history of ASA-induced cutaneous symptoms, reported very mild labial oedema appearing about 4 hours after the intake of etoricoxib and spontaneously disappearing in about 6 hours. 64 patients (52,8%) never took

Table 2 - NSAIDs responsible for hypersensitivity reactions

Drug class	Total of reactions	Single reactor	Multiple reactors
Salicylates	52	24	28
Sulfonanilides	42	21	21
Paracetamol	33	6	27
Aryilpropionics	31	14	17
Arylacetic acid	20	10	10
Oxicam	8	4	4
Pyrazolones	5	2	3
Coxibs	3	2	1

Table 3 - NSAIDs-induced reactions in single reactors (n° 83)

Description of reaction	Number of patients	Underlying disease
Rhinitis and asthma	8 (10%)	2 rhinitis, 2 asthma
Urticaria/angioedema	66 (79,5%)	1 chronic urticaria
Anaphylaxis	9 (10,5%)	none

Table 4 - NSAIDs-induced reactions in multiple reactors (n° 56)

Description of reaction	Number of patients	Underlying disease
Rhinitis and asthma	3 (6%)	1 rhinitis
Urticaria/angioedema	45 (80%)	3 chronic urticaria
Anaphylaxis	8 (14%)	none

the drug, in the most of cases for the fear of adverse reactions. In 5 cases (4,1%) the practitioner advised a NSAID other than etoricoxib.

Discussion

NSAIDs are frequently used in the clinical practice and hypersensitivity is a relevant problem (6-8).
The recent introduction of selective COX-2 inhibitors (coxibs) induced many allergists to evaluate the safety of these drugs in subjects hypersensitive to "classical" NSAIDs.
During the last years, tolerance to rofecoxib, valdecoxib, celecoxib, parecoxib and etoricoxib was investigated. Some authors observed a complete tolerance to these drugs while, in other studies, coxibs induced cutaneous reactions in 0 to 8% of patients (14-19).
The aim of our study was to confirm the safety of etoricoxib in patients hypersensitive to non-selective NSAIDs and, in three cases, with adverse reactions to celecoxib.
The results are consistent with the data observed by the majority of the authors. Adverse reactions were mostly caused by selective COX-1 inhibitors (58% of cases), followed by weak COX-1 inhibitors and selective COX-2 inhibitors (42%). On oral challenge, etoricoxib caused adverse reactions in 3.8% of patients, without significant differences between single ad multiple reactors. This percentage is slightly higher than the one observed by Nettis et al (17), while Muratore et al and Sanchez-Borges et al observed a reaction rate of 8% and 7.1% respectively (14, 15). In keeping with previous studies, our patients were recruited based on clinical history alone, without performing confirmative oral challenges with the culprit drug, which represents a potential bias. Therefore, we selected only patients with a clear-cut strong cause-effect correlation, excluding those with doubtful allergic histories or those taking also drugs other than NSAIDs.
Etoricoxib was tolerated even by patients with a history of celecoxib-induced cutaneous reactions. This might be explained by the higher selectivity for COX-2 of etoricoxib. Further, etoricoxib was tolerated by patients who had experienced severe reactions to other NSAIDs, namely anaphylaxis and in the subjects with chronic urticaria, confirming the observations of Asero (18).
On the other hand, we have to stress that in one case etoricoxib caused a serious adverse reactions involving skin and respiratory system in a multiple reactor. This reaction confirms other reports of adverse effects observed during challenge test with etoricoxib (11, 12) and underlines that this drug has to be challenged first only in specialised centers, where clinical monitoring of patient and ready access to the emergency room are possible.
Regarding the second part of the study, it must be stressed that the patients who took etoricoxib at home did not have any problem, except for two cases of very mild labial angioedema that were self-reported but not directly seen by a doctor. However, and rather surprisingly, most patients (52,8%) did not take the drug during the follow-up period, mostly due to the fear of adverse effects. Notably, in 4,2% of cases, the Gps replaced etoricoxib with another NSAID who had not been tested before. Hence, a total of 57% of patients evaluated didn't take the drug advised by the allergist, with similar results in the 2 hospitals in which the study was performed. These data confirm previous results about the use of rofecoxib and etoricoxib by patients who performed a negative challenge test with these drugs (19, 20).
In conclusion, etoricoxib was well tolerated by NSAID-hypersensitive subjects, without significant differences between single and multiple reactors. However, tolerance to this drug should be tested in a specialized centre for the risk of severe reactions. On the other hand, the unsatisfactory adherence to the treatment requires an improve of relationship with this kind of subjects by healthcare givers.

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