Etoricoxib: a safe alternative for NSAID intolerance in Asian patients

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Summary

Background: **NSAID intolerance is not uncommon. Etoricoxib, a cox-2 inhibitor NSAID, has been shown to be a safe alternative in these patients. This study aims to determine the rate of NSAID intolerant patients who are able to tolerate etoricoxib without adverse reactions.**

Methods: **This study analyzed charts and electronic databases of all patients referred to the allergy clinics of the National University Hospital and Gleneagles Hospital in Singapore from 2006-2011 for oral provocation tests to etoricoxib (cumulative dose of 120mg), on the background of NSAID intolerance. Demographics, atopic comorbidities, history of chronic urticaria, inciting NSAID, onset and type of reaction, and provocation test outcomes were obtained.**

Results: **A total of 74 patients (mean age 37; range: 16-72 years) underwent provocation tests to etoricoxib. Of these, 59% were female. Majority were Chinese (69%), followed by Malay (12%), Caucasian (8%), Indian (5%) and various other races (6%). Forty-six percent of the study population had atopic comorbidities, and 4% had concomitant chronic urticaria. Eighty percent of patients had a history of intolerance to 1 NSAID, while the rest (20%) had intolerance to multiple NSAIDS. Forty-one percent of patients had concomitant acetaminophen intolerance. Some of the patients had multiple symptoms on presentation, the most common of which were periorbital and facial edema (90%), breathing difficulties (26%) and urticaria (25%), with the onset of reaction occurring mostly within 30 minutes to 1 hour. Etoricoxib was tolerated in 95% of the patients. Subjects who reacted to the challenge all had mild reactions which resolved with antihistamines.**

Conclusions: **Etoricoxib is a safe alternative in NSAID intolerant patients. Nevertheless, it is advised that patients should undergo provocation tests to confirm tolerance.** ***(Asian Pac J Allergy Immunol 2013;31:330-3)***

Key words: *Non-steroidal anti-inflammatory drug, drug reaction, oral provocation test*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are medications commonly used to alleviate pain and inflammation. It is estimated that over 30 million people worldwide consume it, with the trend increasing in the past 20 years.[1,2] The prevalence of NSAID intolerance ranges from 0.6-2.5% in the general population, to as high as 30% in patients with asthma, nasal polyposis, and chronic idiopathic urticaria.[2,3] In different populations, it currently ranks second or third to the beta-lactam antibiotics in producing "allergic-type" drug reactions.

NSAID-induced reactions can be classified as immunologic and non-immunologic. Immunologic reactions can be in the form of an immediate hypersensitivity reaction (IgE mediated), or a type IV allergic reaction through drug-specific cytotoxic T cells.[2] For NSAIDS, the most well described reaction is non-immunologic and involves inhibition of the 2 isoforms of the cyclooxygenase enzyme (cox-1 and cox-2), thereby decreasing the production of potent inflammatory mediators, namely prostaglandin and thromboxane.[2,4] Inhibition of prostaglandin induces mast cell degranulation. With the inhibition of the cyclooxygenase pathway, the lipooxygenase pathway is favored, producing leukotriene, which

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promotes bronchoconstriction.[5] These mechanisms are responsible for the signs and symptoms exhibited by NSAID intolerant patients.

The therapeutic effects are primarily related to their ability to inhibit the cox-2 pathway, and the most frequent adverse effects are caused by cox-1 inhibition.[4] It has been thought that specific cox-2 inhibitor NSAIDs such as etoricoxib can be a potential safe alternative for patients with adverse reactions to NSAIDs. Indeed, this has been shown in 2 previous studies where most of the NSAID intolerant patients who underwent provocation tests were able to tolerate etoricoxib.[6,7]

In Asia, the exact prevalence of NSAID intolerance is unknown. Furthermore, there are no studies or reports on the tolerability to etoricoxib among these patients. Thus, this is the first study in Asia that aims to determine the safety of using etoricoxib in NSAID-intolerant patients.

Methods

This study reviewed charts and electronic databases of all patients referred for NSAID intolerance to two allergy units in Singapore, one at the National University Hospital (NUH) and the other at Gleneagles Medical Centre (GMC), from 2006-2011. These patients underwent oral provocation tests to a cumulative dose of 120 mg of etoricoxib. In NUH, etoricoxib was given in 3 divided doses, 30 minutes apart(1st dose: 30mg, 2nd dose: 30mg, 3rd dose: 60mg) whereas in GMC, it was given in 4 divided doses (1st dose: 15mg, 2nd dose: 15mg, 3rd dose: 30mg, 4th dose: 60mg). Information such as demographic data, atopic comorbidities, history of chronic urticaria, inciting NSAID, onset and type of reaction, presence or absence of concomitant acetaminophen intolerance, and provocation test outcomes were obtained. This study was approved by the Institutional Review Board (NHG Domain Specific Review Board; Reference number 2011/01851).

Results

A total of 74 patients (mean age 37; range: 16-72 years) underwent provocation tests to etoricoxib. Of these, 59% were female. Majority were Chinese (69%), followed by Malay (12%), Caucasian (8%), Indian (5%) and various other races (6%). Forty-six percent of the study population had atopic comorbidities, and 4% had concomitant chronic urticaria. Eighty percent of patients had a history of intolerance to 1 NSAID, while the rest (20%) had intolerance to multiple NSAIDS. Some of the patients had multiple symptoms upon ingestion of the inciting NSAID. The most common symptoms on presentation were periorbital and facial edema (90%), breathing difficulties (26%) and urticaria (25%), with the onset of reaction occurring mostly within 30 minutes to 1 hour. As some patients with NSAID intolerance have concomitant acetaminophen intolerance, the history of concurrent acetaminophen intolerance was also determined. However, the definite dose that triggered the reaction was not stated, as these were only obtained from medical records, and not proven by provocation tests. It showed an incidence rate of 41%, comparable to the study done by Borges and Hulett, where 32% of patients with NSAID intolerance reacted to acetaminophen during provocation testing.[8] Table 1 describes the general characteristics if the study population.

Table 1. General characteristics of the study population

		Concomitant etoricoxib intolerance		
		YES	NO	*P*-value
		4/74 (5%)	70/74 (95%)	
Atopic comorbidities				
Positive*	**34/74 (46%)**	**3/4 (75%)**	**31/70 (44%)**	**0.328**
-Asthma		3/4 (25%)	11/70 (16%)	0.515
-Allergic rhinitis		3/4 (75%)	21/70 (30%)	0.097
-Atopic dermatitis		1/4 (25%)	4/70 (6%)	0.249
Negative	**40/74 (54%)**	**1/4 (25%)**	**39/70 (56%)**	**0.328**
Chronic urticaria	**3/74 (4%)**	**1/4 (25%)**	**2/70 (3%)**	**0.156**
Reaction				
To single NSAID	**59/74 (80%)**	2/4 (50%)	57/70 (81%)	0.181
To multiple NSAIDs	**15/74 (20%)**	2/4 (50%)	13/70 (19%)	0.181
Type of reactions to NSAIDS+				
Cutaneous signs and symptoms				
Periorbital and facial edema	**66/74 (90%)**	3/4 (75%)	63/70 (90%)	0.374
Urticaria	**18/74 (25%)**	1/4 (25%)	17/70 (24%)	1.000
Breathing difficulties	**19/74 (26%)**	0	19/70 (27%)	0.567

*Some patients have multiple comorbidities

+Some patients presented with multiple signs and symptoms

Table 2. Clinical characteristics of etoricoxib intolerant patients

Patient number/ sex/age	Atopic Disease	History of chronic urticaria	Inciting NSAID(s)	Drug pattern	Clinical reaction	Concomitant acetaminophen intolerance	OPT with etoricoxib	Cumulative dose of etoricoxib which triggere the reaction	Treatment
1/F/28	R, A	-	Multiple NSAIDs	SR	Facial urticaria	-	+	120 mg	- All patients were given antihistamines - None needed resuscitation or epinephrine administration - Reaction resolved within 4 hours
2/F/35	R	-	mefenamic acid	CR	Facial edema	+	+	30 mg	
3/M/44	-	-	ketoprofen	SR	Periorbital edema	-	+	120 mg	
4/M/49	R, AD	+	Multiple NSAIDs	CR	-Periorbital edema -Dizziness for <10 seconds -No evidence of cardio-pulmonary compromise	-	+	30 mg	

Abbreviations: A, asthma; AD, Atopic dermatitis; OPT, oral provocation test; R, rhinitis

#Drug pattern: A single-reactor (SR) is defined as a patient with clinical reaction to only one type of NSAID, while a cross-reactor (CR), to more than one type of NSAID, including acetaminophen.

Etoricoxib was tolerated by 70 (95%) of our patients. The 4 subjects who reacted to the provocation test only had mild reactions consisting of periorbital and facial edema, urticaria and transient giddiness. All these resolved with antihistamines. There were no subjects needing resuscitation or epinephrine administration. Table 2 shows the clinical characteristics of these patients.

We have shown that etoricoxib is a safe alternative in NSAID intolerant subjects. In a study done by Quercia et al. wherein 65 patients with NSAID intolerance were subjected to provocation tests to etoricoxib, 63 (97%) patients were able to tolerate it, with only 2 patients having a reaction, manifesting as urticaria and angioedema.[7] In contrast to our centre, the maximum dose administered in that study was only 90 mg. Nevertheless, the reaction rate was comparable to our centre, with no patients needing resuscitation.

In another study done by Pagani et al. wherein both the immediate and long term tolerability to etoricoxib was studied, 135 of 139 patients (97.2%) were able to tolerate 90 mg of etoricoxib. Of the 4 patients who reacted, 3 experienced mild urticaria while 1 had both cutaneous and respiratory symptoms. Furthermore, of the 121 subjects available for follow-up, 52 patients took etoricoxib subsequently, with only 2 patients having reactions, characterized as very mild lip swelling that resolved spontaneously. The tolerability rate of this study was comparable to the study done by Quercia.[6,7]

Our findings showed similar rates when compared with these 2 studies. The tolerability rate in our study may have been higher had our maximal dose been set at 90 mg. In fact, we have shown that most NSAID intolerant patients can tolerate a higher dose of 120 mg of etoricoxib.

To our knowledge, this is the first study that attempts to establish the tolerability rate to etoricoxib in NSAID intolerant patients in Asia. The limitation of the study is that NSAID intolerance was established by history alone, without any provocation tests. Nevertheless, only patients with convincing histories were included.

Conclusions

In conclusion, etoricoxib is a safe alternative in NSAID intolerant patients. However, it is advised

that patients should undergo provocation tests to confirm tolerance in a centre with trained medical personnel and good resuscitation facilities.

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Conflict of interest

The authors have no financial conflict of interest.

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