
Long-term use and tolerability of cyclooxygenase-2 inhibitors in patients with analgesic intolerance

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Background: Cyclooxygenase-2 (COX-2) inhibitors are reported to be well tolerated in patients with analgesic intolerance (AI). However, limited data are available about the long-term tolerability of these drugs.

Objective: To determine the long-term tolerability of COX-2 inhibitors in patients with AI.

Methods: Patients with AI who previously underwent single-masked, placebo-controlled oral provocation tests and were found to tolerate nimesulide, meloxicam, rofecoxib, or celecoxib were interviewed regarding the long-term use and tolerability of these drugs.

Results: Of 87 patients, 61 (70%) had used the recommended COX-2 inhibitor(s). Of the 61 users, 54 (89%) tolerated the drug(s) well and 7 (11%) reported adverse events. Three patients reporting adverse events were rechallenged with the responsible COX-2 inhibitor, and their results were found to be negative.

Conclusions: Long-term use of COX-2 inhibitors was tolerated well by most patients with AI, and placebo-controlled oral provocation tests, as a single test, seemed to predict tolerability. Furthermore, self-reported positive reactions in the long-term should also be confirmed with rechallenge tests for definite diagnosis.

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INTRODUCTION

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used for the treatment of many diseases and clinical disorders.¹ However, adverse reactions, including pruritus, urticaria, bronchospasm, and anaphylaxis, have been reported in particular individuals with analgesic intolerance (AI).^{2,3} The mechanisms underlying aspirin and NSAID intolerance have not been clearly identified. The inhibition of cyclooxygenase-1 (COX-1) enzyme, leading to a decrease in prostaglandin E₂ (PGE₂) followed by an increase in cysteinyl leukotriene release due to the removal of the inhibitory effect of PGE₂ on cysteinyl leukotriene release, emerged as a current suggestion in the pathogenesis.^{4,5}

Because there is no skin or in vitro test to identify patients who will react to NSAIDs, placebo-controlled oral provocation tests (OPTs) have been performed to confirm the diagnosis and to find safe alternatives for patients with AI.^{6–8} Highly selective COX-2 inhibitors, such as rofecoxib and celecoxib, and NSAIDs that preferentially inhibit COX-2, such as nimesulide and meloxicam, have been tested and used as safe alternatives for patients with AI because constitutive COX-1 will continue to synthesize the protective prostanoid, PGE₂. Meloxicam and nimesulide were found to be well tolerated, whereas the tolerability of COX-2 inhibitors increased parallel to the selectivity of the drug.^{9–18}

A drug provocation test involves the administration of a single therapeutic dose, but the lack of reaction may not reflect the drug's tolerability in multiple doses.⁶ In addition, a negative test result might not prove tolerance for future use because other crucial factors, such as concomitant medication use, viral infection, physical exercise, and psychological status, might be absent during the test procedure. Because there is a paucity in the literature concerning the long-term use and tolerability of COX-2 inhibitors in patients with AI,^{19,20} we aim to determine whether a negative OPT result with a single administration of a COX-2 inhibitor might predict long-term tolerability in patients with AI.

MATERIALS AND METHODS

Patient Database

Since 1997, single-masked, placebo-controlled OPTs have been performed in the Department of Allergy, Ankara University School of Medicine, using several COX-2-inhibiting drugs, including nimesulide, meloxicam, rofecoxib, and celecoxib, to find alternative, safe NSAIDs for patients with AI.^{10,13,18} The target population for this study consisted of 235 patients with AI who underwent these tests between January 1, 1997, and June 30, 2003, and were found to tolerate COX-2 inhibitors (Fig 1). The diagnosis of AI had been based on documentation or a history of urticaria/angioedema, nasoo-ocular symptoms, bronchospasm, or anaphylactoid reaction induced by aspirin or NSAIDs on at least 2 separate occasions in these patients.

Depending on the study protocol, single or multiple NSAIDs were used, and the drug selection was performed

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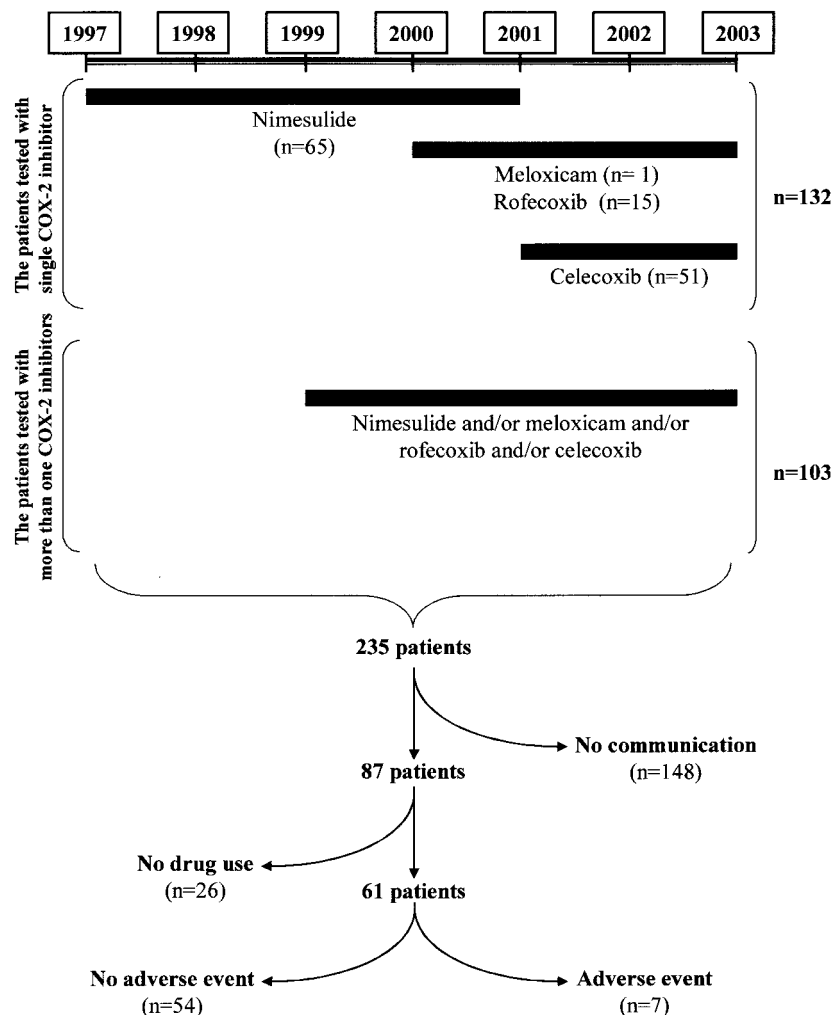


Figure 1. Flowchart of the study. COX-2 indicates cyclooxygenase-2.

according to the marketing order of COX-2 inhibitors in Turkey: 132 patients were tested for the tolerability of a single COX-2 inhibitor (nimesulide [Mesulide 100 mg; Pfizer, Istanbul, Turkey] or meloxicam [Mobic 7.5 mg; Boehringer Ingelheim, Istanbul, Turkey] or rofecoxib [Vioxx 25 mg; Merck-Sharp Domme, Istanbul, Turkey] or celecoxib [Celebrex 200 mg; Pfizer]), whereas the remaining 103 were tested with more than 1 NSAID inhibiting COX-2 (Fig 1).

OPT Protocol

After securing written informed consent, OPTs were performed in the hospital setting. The challenge protocol consisted of oral administration of the drug in increasing doses. The protocol was designed as a single-masked and placebo-controlled oral drug challenge. On 2 separate days, $\frac{1}{4}$ and $\frac{3}{4}$ divided doses of placebo (lactose) and the active drug (nimesulide, meloxicam, rofecoxib, or celecoxib) were given at 1-hour (for nimesulide and meloxicam) or 2-hour (for rofecoxib and celecoxib) intervals. For testing with more than 1

NSAID, a washout period of 3 days was given between each drug. Test results were accepted as positive if 1 of the following symptoms existed: conjunctival reaction; upper and lower respiratory tract reactions, such as sneezing, rhinorrhea, nasal blockage, dyspnea, wheezing, and cough, with a 20% decrease in forced expiratory volume in 1 second; cutaneous reactions such as erythema, pruritus with erythema, and urticaria/angioedema; or anaphylactoid reaction with urticaria or angioedema and hypotension (30-mm Hg decline in systolic blood pressure) or laryngeal edema. After a negative provocation test result, the written name(s) of the test drug(s) was given, and the patients were offered the use of only this (these) drug(s).

Long-term Use and Tolerability

Patients with AI who were previously found to be tolerant to at least 1 of the tested COX-2 inhibitors (nimesulide, meloxicam, rofecoxib, or celecoxib) were interviewed by telephone and were asked to answer the study questionnaire about the

use of the recommended COX-2 inhibitor(s). The interviews were performed by allergy specialists, and patients with 2 unanswered telephone calls were excluded from the study. In the questionnaire, patients were first asked whether they had used the tested drug(s). Those who had used the tested drug(s) were further questioned about the amount of drug consumption, the dosage of the drug, and any reaction that might have developed after drug consumption. In the case of a positive history of adverse events with the prescribed COX-2 inhibitor, patients were invited to clinical evaluation and rechallenge with the implicated drug by using the same single-masked, placebo-controlled OPT protocol. Age, sex, duration of AI, the implicated analgesic(s), reaction patterns, and the presence of comorbid disorders, such as asthma, rhinitis, chronic rhinosinusitis, and chronic urticaria, were obtained from patient records.

Statistical Analysis

Numeric results are expressed as mean $\pm$ SEM. Nominal variables are expressed as percentage of patients. The independent samples *t* test was performed for comparison of numeric values. For comparison of ratios, the χ^2 test was performed. All *P* values were bidirectional, and *P* < .05 was

considered statistically significant. A statistical software package (SPSS for Windows version 10.0; SPSS Inc, Chicago, IL) was used to analyze the data.

RESULTS

Study Group

Of 235 patients with AI, 87 responded to the interview and constituted the eligible study population (Table 1). The demographic and disease features of the study group were comparable with those of the whole group regarding age, sex distribution, disease duration, presence of comorbid disorders, and atopy.

Long-term Use and Tolerability

Of 87 participants, 61 (70%) had used the prescribed COX-2 inhibitor(s). Of the 61 users, 54 (89%) had used the drug(s) without any adverse events in the long-term, and 7 (11%) reported adverse events (Fig 1). Age, sex distribution, duration of AI, and duration of drug use were similar in both groups (*P* > .05). Patients who underwent OPTs with nime-

Table 1. Demographic and Disease Characteristics of the 87 Study Participants

Variable	Value
Sex, F/M, No. (%)	63/24 (72/28)
Age, mean $\pm$ SEM, y	40.1 $\pm$ 1.2
Duration of analgesic intolerance, mean $\pm$ SEM, mo	92.6 $\pm$ 10.8
Drug allergy other than aspirin/NSAIDs, No. (%)	14 (16)
Atopy, No. (%)	21 (24)
Comorbid disorders, No. (%)	
Asthma	30 (34)
Allergic rhinitis	3 (3)
Chronic sinusitis	4 (5)
Chronic urticaria	4 (5)
None	46 (53)
Reaction types, No. (%)	
Respiratory	21 (24)
Cutaneous	43 (49)
Respiratory + cutaneous	12 (14)
Laryngeal edema	1 (1)
Anaphylaxis	10 (12)
Drug responsible for intolerance reactions, No. (%)	
Aspirin	15 (17)
NSAIDs	22 (25)
Acetaminophen	6 (7)
Aspirin + NSAIDs	23 (26)
Aspirin + acetaminophen	6 (7)
NSAIDs + acetaminophen	3 (3)
Aspirin + NSAIDs + acetaminophen	12 (14)
COX-2 inhibitors tested, No. (%)	
Single COX-2 inhibitor	
Nimesulide	14 (16)
Rofecoxib	13 (15)
Celecoxib	15 (17)
≥ 2 COX-2 inhibitors	
Nimesulide, meloxicam, rofecoxib, and celecoxib	45 (52)

Abbreviations: COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Demographic and Disease Characteristics According to the Development of Adverse Events

	No adverse events (n = 54)	Adverse events (n = 7)
Age, mean $\pm$ SEM, y	40.5 $\pm$ 1.6	38.8 $\pm$ 3.8
Sex, F/M, No. (%)	39/15 (72/28)	5/2 (71/29)
Duration of AI, mean $\pm$ SEM, mo	82.3 $\pm$ 11.4	124.7 $\pm$ 62.4
Comorbid disorders, No. (%)		
Asthma	23 (43)	3 (43)
Rhinitis and chronic sinusitis	4 (7)	1 (14)
Chronic urticaria	1 (2)	1 (14)
None	26 (48)	2 (29)
Drug allergy other than NSAIDs, No. (%)	10 (19)	0
Atopy, No. (%)	15 (28)	1 (14)
Drug responsible for intolerance reactions, No. (%)		
Aspirin	8 (15)	2 (29)
NSAIDs	13 (24)	0
Acetaminophen	3 (6)	0
Aspirin + NSAIDs	15 (28)	3 (43)
Aspirin + acetaminophen	5 (9)	1 (14)
NSAIDs + acetaminophen	3 (6)	0
Aspirin + NSAIDs + acetaminophen	7 (13)	1 (14)
COX-2 inhibitor use, No. (%)		
Single COX-2 inhibitor		
Nimesulide	14 (26)	3 (43)
Meloxicam	4 (7)	2 (29)
Rofecoxib	16 (30)	2 (29)
Celecoxib	17 (31)	0
≥ 2 COX-2 inhibitors	3 (6)	0
Drug use duration, mean $\pm$ SEM, mo	28.5 $\pm$ 3.2	28.8 $\pm$ 9.1
Total No. of drugs used, mean $\pm$ SEM	52.0 $\pm$ 9.9	45.5 $\pm$ 42.5
Drug use per month, mean $\pm$ SEM	2.1 $\pm$ 0.4	1.0 $\pm$ 0.9

Abbreviations: AI, analgesic intolerance; COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

sulide and meloxicam developed more adverse events ($P = .03$ and $P = .001$, respectively) (Table 2).

Rechallenge Tests

Three patients were rechallenged, and their test results were negative. One of these patients had aspirin-induced asthma and had been tested previously with 3 NSAIDs—nimesulide, meloxicam, and rofecoxib. She preferred to use rofecoxib. Rechallenge with rofecoxib yielded negative results. The second patient had rhinitis, and her reaction had occurred after nimesulide intake. The third patient underwent OPT with meloxicam and had no comorbid disorders, and she developed no reaction after rechallenge testing. All rechallenged patients have been followed up, and no subsequent intolerance was reported with the implicated drugs after negative challenge results.

The provocation tests were not applicable in 4 patients. The first patient had chronic urticaria and experienced urticarial plaques 1 hour after the administration of 1 meloxicam tablet. Because he had active urticarial lesions and was taking antihistamines regularly, provocation testing with meloxicam was not performed. In the second patient, who described a reaction to nimesulide, rechallenge could not be performed because she was living in another city. The remaining 2 patients did not undergo the provocation tests.

DISCUSSION

We have been conducting single-masked, placebo-controlled OPTs with nimesulide, meloxicam, rofecoxib, and celecoxib in patients with AI since 1997.^{10,13,18} In these provocation tests, the tolerability rates of a single administration of nimesulide and meloxicam were 85.7% and 91.9%, respectively.¹³ Tolerability increased with rofecoxib and celecoxib to 98% and 100%, respectively, in accordance with previous data.^{13–18} There are limited data about the long-term tolerability of NSAIDs inhibiting COX-2 in patients with AI.^{19,20} In 1 study,¹⁹ nimesulide and acetaminophen were found to be well tolerated in 94.2% and 94.6% of participants, respectively, who had consumed the prescribed drug in long-term follow-up. According to our results, the long-term tolerability rate of COX-2 inhibitors was 88.6%.

In the long term, 11% of patients ($n = 7$) described reactions after use of the prescribed COX-2 inhibitor. Rechallenge by placebo-controlled OPTs using the same COX-2 inhibitor was performed in 3 patients, all of whom had negative test results. For a possible explanation of false-negative adverse events, even healthy individuals have been reported to experience symptoms such as sedation, urticaria, and fever with placebo use.²¹ Another explanation could be the tendency of this particular group of patients with AI to

attribute minor coincidental symptoms to drug intake. Nevertheless, when the negative rechallenge test results are included, the long-term tolerability of COX-2 inhibitors seemed to be approximately 93% in this trial.

To overcome the limitations of data collection by telephone, the interviews were performed by allergy specialists in this study. Probably owing to the characteristics of the study population, including only patients who participated in previous trials and who underwent intensive instruction about self-recognition and self-reporting of adverse events, no communication failure or suspicious or irrelevant information was noted by the interviewers during data collection.

Despite the single-dose and long-term tolerability of COX-2 inhibitors in patients with AI, the increased cardiovascular toxic effects associated particularly with rofecoxib is a current topic of interest. After the withdrawal of rofecoxib from the market in September 2004, rofecoxib challenge was also stopped in our clinic. Because our study ended on June 30, 2003, the part of the data related to the retrospective documentation of rofecoxib challenge or consumption presented herein strictly includes only the period before withdrawal of rofecoxib from the market.

Most patients who did not use the tested drug despite a negative placebo-controlled OPT result described "fear" as the main reason for not using the prescribed drug. Although it was beyond the scope of the present study, analysis of the effect of psychological factors on drug preference and consumption characteristics in patients with drug allergies deserves further investigation.

In conclusion, in the long term, COX-2 inhibitors have been well tolerated in most patients with AI, and the placebo-controlled OPT, as a single test, seemed to be as reliable in predicting long-term tolerability. The history of positive reactions reported by patients in the long-term use of COX-2 inhibitors also seemed to necessitate further verification by rechallenge tests. Nevertheless, before recommending these drugs as effective alternatives for patients with AI, one should await the full spectrum of the safety profile of COX-2 inhibitors identified in further trials.

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