

Safety of Meloxicam in Aspirin-Hypersensitive Patients with Asthma and/or Nasal Polyps

A Challenge-Proven Study

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Key Words

Aspirin hypersensitivity • Aspirin provocation test • Asthma • Meloxicam • Nasal polyposis

Abstract

Background: The anti-inflammatory actions of acetylsalicylic acid (ASA)/non-steroidal anti-inflammatory drugs (NSAIDs) are thought to be due to inhibition of COX-2, whereas the side effects such as gastric damage and aspirin-induced asthma are mediated through inhibition of COX-1. Therefore, a new class of drugs with COX-2 selectivity may be well tolerated by patients with ASA/NSAIDs hypersensitivity.

Objective: We investigated whether subjects with asthma and/or nasal polyps (NP) and analgesic intolerance proven by oral ASA provocation test tolerated the selective COX-2 inhibitor, meloxicam. **Methods:** All subjects were first challenged with ASA using a 2-day, single-blind, placebo-controlled oral provocation test. Thereafter, the subjects showing positive response to ASA provocation underwent a single-blind, placebo-controlled challenge with a cumulative dose of 7.5 mg of meloxicam on 2 separate days. One and three fourths of the divided doses of placebo and the active drug were given at 1-hour intervals. Clinical symptoms, lung function, and blood pressure were monitored during these challenge protocols. **Results:** Twenty-one pa-

tients with asthma and/or NP (10 males and 11 females; mean age: 38.4 ± 2.9 years) who reacted to ASA challenges were enrolled in the study. Response to ASA provocation was rhinitis + bronchospasm in 13, and extrabronchial reactions in 8 (isolated rhinitis in 3) patients. Mean PD₂₀ was 163.4 ± 39.9 mg ASA among patients who reacted with bronchospasm to ASA. Only 1 patient reacted to meloxicam challenge at a cumulative dose of 7.5 mg. **Conclusion:** This study indicates that 7.5 mg of meloxicam is a safe alternative treatment for ASA-hypersensitive asthma and/or NP patients with proven hypersensitivity via oral ASA challenges.

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Introduction

Aspirin (acetylsalicylic acid, ASA) and other non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs due to their analgesic and anti-inflammatory properties, but a variety of treatment-related adverse reactions has been reported [1]. Although the mechanisms underlying the adverse reactions to ASA/NSAIDs still remain unclear, inhibition of the cyclooxygenase (COX) pathway seems to be the most accepted explanation responsible for both the efficacy and side effects of these drugs [2, 4]. There are at least two isoforms of the

COX enzyme; COX-1 is constitutively expressed in most tissues and in blood platelets and is responsible for the production of prostaglandins, whereas COX-2 is only expressed in response to proinflammatory agents in epithelial cells, fibroblasts, eosinophils, monocytes and macrophages. The anti-inflammatory actions of ASA/NSAIDs are thought to be due to the inhibition of COX-2, whereas side effects such as gastric damage and aspirin-induced asthma are mediated through the inhibition of COX-1 with subsequent release of leukotrienes [5].

The discovery of two isoforms of the COX isoenzyme led to the development of new NSAIDs, the selective COX-2 inhibitors [6]. New, very selective COX-2 inhibitors, rofecoxib, celecoxib and valdecoxib, have been marketed in many countries. Thereafter, they have been the subject of several studies in ASA-/NSAID-hypersensitive patients [7–11]. These studies demonstrated the safety of these drugs particularly in patients with ASA-/NSAID-hypersensitive asthma. However, some adverse events, including cutaneous and systemic reactions, were observed with the COX-2 inhibitors [12–14]. More importantly, placebo-controlled trials provided new evidence about the cardiovascular risks of rofecoxib, celecoxib, and valdecoxib [15, 16]. The association between rofecoxib and an increased cardiovascular risk (the risk of major cardiovascular events was doubled among patients with a history of colorectal adenomas) has been reported by the Adenomatous Polyp Prevention on Vioxx Trial Investigators. After the publication of this study, Merck withdrew the drug from the market [16]. Since then challenges with rofecoxib and celecoxib performed in our department restricted treatment to the use of two preferential COX-2 inhibitors, nimesulide and meloxicam.

There are only a few studies evaluating the safety of meloxicam in patients with a reliable history of ASA/NSAID hypersensitivity [17–19]. In fact, the history of patients is not always reliable enough for the diagnosis of analgesic intolerance (AI), and the only way to accurately diagnose intolerance is through a provocative challenge test [20]. However, a confirmatory provocation test with the culprit drug has been used in only a few studies evaluating the safety of selective COX-2 inhibitors in patients with AI [7–21]. Therefore, we performed this study to determine the tolerability of a preferential COX-2 inhibitor, meloxicam, in ASA-/NSAID-hypersensitive asthmatics and/or patients with nasal polyposis (NP) in whom ASA hypersensitivity was demonstrated by an oral ASA provocation test described by Nizankowska et al. [22].

Patients and Methods

Patient Selection

The study was conducted among patients admitted to our tertiary outpatient clinic located in Ankara, the capital of Turkey. Patients were selected among patients with a history of naso-ocular symptoms, mild-to-severe bronchospasm, and/or anaphylactoid reactions within 2 h after ingesting a prescribed ASA, NSAID, paracetamol, and/or metamizol or a positive response to oral ASA challenge without a history of ASA hypersensitivity.

Asthma was diagnosed by the presence of recurrent symptoms of wheezing, shortness of breath, cough and demonstration of objective signs of reversible airway obstruction, according to the guidelines of the American Thoracic Society [23]. The diagnosis of NP was based on the following two criteria: visualization of bilateral polyps in the nasal cavities on endoscopic examination and a CT scan of paranasal sinuses showing NP. All these evaluations were done by ear nose and throat surgeons. Patients taking systemic antihistamines, systemic corticosteroids, cromolyn, oral sympathomimetics, or β -blockers during the preceding week were not included in the study. Asthmatic patients were eligible for the study if their asthma was stable for at least 2 weeks and their forced expiratory volume in 1 s (FEV_1) was $>70\%$ of predicted. All asthmatics were free of respiratory infections for at least 6 weeks. They were allowed to continue their maintenance therapy with inhaled corticosteroids and inhaled salbutamol as needed, but the drug was not allowed 6 h before the challenge procedure. Additionally, aminophylline and long-acting β_2 -agonists were withheld for 48 h before the challenge.

After study entry, age, sex, duration of ASA hypersensitivity, implicated analgesic(s), reaction patterns, and the number of drug(s) inducing reactions were recorded. Duration of drug allergy was defined as the time period between the first reaction to ASA, NSAIDs, paracetamol, and/or metamizol, and hospital admission for an alternative analgesic.

Oral ASA and meloxicam provocation tests were approved by the Ethics Committee of the Faculty of Medicine. All patients gave written informed consent to participate in the drug challenge. An experienced allergist of the hospital performed oral challenge tests.

Aspirin Provocation

An oral provocation test with ASA was performed as a single-blind challenge using a method described previously [22]. On the 1st day, two tablets of placebo were administered every 2 h. If FEV_1 increased $>15\%$ during the placebo challenge, the patient was excluded from further oral provocation tests with ASA. On the 2nd day, oral provocation with consecutive doses of ASA was carried out according to the protocol. The starting dose, 10 mg of ASA, was followed by 17, 44, 117, and 312 mg of ASA. These doses are given at 90-min intervals. The total cumulative dose was 500 mg of ASA. The provocation test was considered positive if FEV_1 was at least 20% lower than the baseline value after saline, and/or if strong extrabronchial symptoms occurred. The provocative dose of oral ASA causing a 20% fall in FEV_1 (PD_{20}) was calculated. The PD_{20} was derived by linear interpolation from the respective base 10 logarithm cumulated dose-response curves. The most frequent extrabronchial symptoms were: hoarseness, rhinorrhea, nasal congestion, redness of the face and the upper chest, ocular infection and/or periorbital swelling, nausea, vomit-

Table 1. Demographic and clinical features of the study group

Patients	21
Gender, females/males	11/10
Age, years (range)	38.4 ± 2.9 (16–62)
Atopy	7 (33.3%)
Diagnosis	
Only NP	6
Only asthma	1
NP + asthma	7
NP + allergic rhinitis	2
NP + asthma + allergic rhinitis	5
History of ASA/NSAID hypersensitivity	18 (85.7%)
Mean duration of hypersensitivity, years (range)	7.19 ± 1.37 (0.5–22)
Reactions to oral ASA provocation	
Rhinitis	3
Rhinitis + bronchospasm	13
Cutaneous	1
Systemic	4
Mean PD ₂₀ ± SE, mg ASA (range)	163.42 ± 39.89 (27–500)

ing, stomach cramps, and hypotension. These extrabronchial symptoms were scored as follows: 0 = no symptom; 1 = small intensity; 2 = moderate intensity; 3 = strong intensity, and 4 = very strong intensity. Extrabronchial symptoms were considered strong when a patient attained at least 12 score points.

Meloxicam Challenge

Meloxicam challenge was designed as a single-blind, placebo-controlled, oral drug challenge. The challenge protocol consisted of oral administration of the drug with increasing doses, as described in our previous studies [11, 18]. On 2 consecutive days, one and three fourths of divided doses of placebo and the active drug meloxicam (7.5 mg Mobic; Boehringer Ingelheim, Istanbul, Turkey) were given at 1-hour intervals. During the challenge procedure, blood pressure and FEV₁ values as well as skin, ocular, nasal, and bronchial reactions were monitored every hour after each placebo or active drug dose was given. Patients were followed up to 24 h to detect a delayed reaction. In case of no reaction at the end of 24 h, patients were regarded as meloxicam tolerant.

The oral challenge test was regarded as positive if one of the following symptoms occurred: conjunctival reaction; upper and lower respiratory tract reactions such as sneezing, rhinorrhea, nasal blockage, dyspnea, wheezing, and cough with a 20% decrease in FEV₁; cutaneous reactions such as erythema, pruritus with erythema, urticaria/angioedema, and/or anaphylactoid reactions of the skin or combined with respiratory symptoms, hypotension or gastrointestinal symptoms.

Evaluation of Atopy

Atopy was defined as a positive skin prick test to at least one of the aeroallergens. Glycerinated extracts (Stallergènes, Antony, France) of the following allergenic sources were used in skin prick tests: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, grass, tree, weed pollens, cat, dog, *Alternaria* and *Cladosporium* antigens. Positive (histamine) and negative (saline solution) controls were included. The puncture method with a 1-mm-tip disposable lancet was used, and a mean wheal diameter

of 3 mm or greater than control solution was considered positive.

Statistical Analysis

Numeric results were expressed as means ± SE. Nominal variables were expressed as percent of the patients. A p value < 0.05 was considered significant. The Statistical Package for Social Sciences (SPSS) for Windows version 10.0 (Chicago, Ill., USA) was used to analyze the data.

Results

Demographic and Clinical Data of the Patients

Demographic and clinical data of the study group are given in table 1. A total of 21 subjects (11 females, 10 males; mean age ± SE: 38.4 ± 2.9 years, range: 16–62 years) were included in the study. All patients but 1 had NP, and among them 6 patients had only NP, 12 patients had associated asthma, 2 patients had associated allergic rhinitis and 1 patient had only asthma. Mean baseline FEV₁ was 3.05 ± 0.18 liters (1.65–4.44 liters) in the whole group. The prevalence of atopy was 33.3%, and this ratio was similar to that in the general adult population of Turkey [24] (33.3 vs. 25%, p > 0.05).

According to history, reactions had been triggered by ASA in 14, NSAID in 11, metamizol in 8 and paracetamol in 2 patients. Based on history, 2 patients had reacted to ASA only, and 2 to NSAIDs only. The remainder of the patients had histories of AI to the combination of ASA/NSAIDs and paracetamol or metamizol. None of them had reacted to paracetamol or metamizol only. Mean du-

Table 2. Details of the patients challenged with oral ASA and meloxicam

	Age	Sex	Co-morbidity	Severity of asthma	Prick test	Duration of AI, years	Implicated drug	Oral ASA provocation test	PD ₂₀ oral ASA mg	Meloxicam challenge
1	29	M	NP	–	–	3	NSAID	rhinorrhea, nasal congestion	–	–
2	42	M	NP, A	MP	–	6	NSAID	rhinorrhea, nasal congestion, bronchospasm	140	–
3	58	M	NP	–	–	0	–	rhinorrhea, nasal congestion	–	–
4	62	F	NP, A	MoP	–	7	ASA, NSAID, M	rhinorrhea, nasal congestion, bronchospasm	27	–
5	56	M	NP	–	–	7	ASA	rhinorrhea, nasal congestion, hoarseness, nausea, vomiting (score: 12)	–	–
6	33	F	NP, A	MoP	–	10	ASA, NSAID, M	rhinorrhea, nasal congestion, hoarseness, tongue edema (score: 13)	–	–
7	43	F	NP, AR, A	MP	pollen	0.5	NSAID, P	rhinorrhea, nasal congestion, bronchospasm	43	–
8	33	M	NP	–	–	0	–	rhinorrhea, nasal congestion, bronchospasm	185	–
9	16	M	NP	–	–	0	–	rhinorrhea, nasal congestion,	–	–
10	45	F	NP, A	MoP	–	7	ASA, NSAID	rhinorrhea, nasal congestion, bronchospasm	180	–
11	30	M	NP, AR	–	mite, pollen	2	ASA	rhinorrhea, nasal congestion, ocular congestion, nausea, vomiting, abdominal cramps, hypotension (score: 16)	–	–
12	16	F	NP, AR, A	MoP	mite, pollen	1	NSAID, M	rhinorrhea, nasal congestion, bronchospasm	180	–
13	26	F	NP, A	MoP	–	2	ASA, M	rhinorrhea, nasal congestion, bronchospasm	130	anaphylactoid rx
14	31	M	NP, A	MP	–	15	ASA, M	rhinorrhea, nasal congestion, bronchospasm	500	–
15	45	F	A	MP	–	10	ASA, NSAID, M	rhinorrhea, nasal congestion, bronchospasm	450	–
16	47	M	NP, AR	–	pollen	13	ASA, M	periorbital swelling	–	–
17	35	F	NP, AR, A	MoP	pollen	13	ASA, P, M	rhinorrhea, nasal congestion, bronchospasm	44	–
18	32	F	NP, AR, A	MP	pollen	7	ASA, NSAID	rhinorrhea, nasal congestion, bronchospasm	244	–
19	25	M	NP	–	–	1	ASA, NSAID	rhinorrhea, nasal congestion, ocular congestion, cough, chest tightness, nausea, vomiting (score: 14)	–	–
20	50	F	NP, AR, A	SP	mite, cat, dog, food	5	ASA, NSAID	rhinorrhea, nasal congestion, bronchospasm	27	–
21	52	F	NP, A	SP	–	22	ASA, NSAID, M	rhinorrhea, nasal congestion, bronchospasm	94	–

A = Asthma; AR = allergic rhinitis; MP = mild persistent; MoP = moderate persistent; SP = severe persistent; M = metamizol; P = paracetamol.

ration of AI was 7.19 ± 1.37 (0.5–22) years. Three patients with NP had no history of analgesic drug intolerance.

Aspirin Provocation

Details of ASA provocation are shown in table 2. Oral challenge with ASA induced only upper airway symptoms such as rhinorrhea and nasal congestion in 3 (patients 1, 3 and 9), both upper and lower airway symptoms in 13 (patients 2, 4, 7, 8, 10, 12–15, 17, 18, 20, and 21). Mean PD₂₀ dose of ASA was 163.4 ± 39.9 mg, ranging from 27 to 500 mg. Extrabronchial reactions such as ocular congestion, hoarseness, tongue swelling, nausea, vomiting, abdominal cramps, and hypotension were observed in 4 (patients 5, 6, 11, and 19) patients. The scores for extrabronchial symptoms changed from 12 to 16 for these patients. Only 1 patient (patient 16) experienced periorbital swelling after ASA provocation. Among 3 patients with-

out a history of ASA/NSAID hypersensitivity, 2 patients experienced rhinitis symptoms and 1 patient showed both rhinitis and bronchial obstruction to oral ASA challenge with PD₂₀ with a 185-mg dose of ASA. Five patients with a history of ASA/NSAID hypersensitivity and NP showed other extrabronchial symptoms in addition to rhinitis. None of the patients required adrenaline or hospitalization after ASA provocation. All were treated with systemic steroids, antihistamines, and inhaled salbutamol according to the type of response to ASA.

Meloxicam Provocation

No reaction was observed with placebo, and only 1 patient (4.8%) reacted to meloxicam provocation (patient 13). This patient presented severe bronchial obstruction and generalized erythema during the 20 min following the challenge with a cumulative dose of 7.5 mg of meloxicam. Her FEV₁ decreased 33%, and she was treated with

inhaled salbutamol, antihistamines and systemic steroids. She had a 7-year history of asthma and NP, and had two asthma attacks following ASA and metamizol ingestion. She had reacted to oral ASA provocation with nasal and bronchial responses (PD₂₀ with 130 mg of ASA). However, she had tolerated the 25-mg cumulative dose of rofecoxib challenge previously.

Discussion

In this single-blind, placebo-controlled study, all but 1 ASA-hypersensitive NP and/or asthma patient with ASA challenge-proven ASA/NSAID hypersensitivity perfectly tolerated the 7.5-mg meloxicam challenge. Meloxicam is a new enolic acid derivative developed for the treatment of rheumatoid arthritis and osteoarthritis. Its selective inhibition of the COX-2 enzyme has been demonstrated in the microsomal assay [25]. The data regarding the safety of meloxicam as an alternative treatment in patients with ASA hypersensitivity are currently limited [17–19, 26–28]. Quaratino et al. [19] reported tolerability of meloxicam in 177 ASA-/NSAID-hypersensitive patients with a high percentage of cutaneous reactions (83.1%) to one or more NSAIDs. Positive reactions were observed in only 1.1% of the subjects to a cumulative dose of 7.5 mg of meloxicam. Similarly, in a report on five ASA-/NSAID-hypersensitive patients by Kosnik et al. [28], only 1 patient with ASA-induced asthma reacted to meloxicam, but the drug was tolerated by 4 patients with cutaneous reactions only to ASA. Contrary, in a recent study by Senna et al. [26], all patients with previous respiratory reactions to NSAIDs tolerated meloxicam. In our first trial, 61 patients were challenged with meloxicam, and 5 (8.1%) developed an adverse reaction to the drug. Among them, an asthmatic reaction was observed in 2 asthmatic patients who had histories of asthmatic response to ASA, and urticaria-angioedema was observed in 3 otherwise healthy patients who had histories of urticaria-angioedema and anaphylaxis to ASA [18]. Although 1 of our patients (4.8%) reacted to meloxicam challenge, this patient had asthma and NP giving a 12% risk of reactions in this high-risk group.

Presenting a safe alternative is a challenging procedure to physicians who are dealing with drug allergy. The common approach is to prescribe a drug whose molecular structure is different from that of the drug inducing the intolerance reaction without performing drug provocation with the drug causing intolerance reaction. AI is an underdiagnosed phenomenon. A recent study demon-

strated that 15% of asthmatic patients were unaware of AI before aspirin challenge [29]. Based on the patients' history, the incidence of aspirin sensitivity has been found to be 3–5% in patients with asthma, but this percentage doubles or triples with aspirin challenge [30]. Therefore, controlled oral, bronchial, or nasal provocation challenges are the only way to confirm ASA/NSAID hypersensitivity [20]. In keeping with that, we performed confirmatory oral challenges with ASA in the current study. In fact, none of the studies assessing tolerability of meloxicam in ASA-hypersensitive patients, including our first trial, used ASA provocation to confirm AI. To the best of our knowledge, our current trial is the first challenge-proved study which evaluated meloxicam as an alternative drug in ASA-hypersensitive asthma and/or NP patients.

The relevance of atopy as a risk factor or as a protective factor for ASA/NSAID hypersensitivity has been much debated in the past. Contrary to the common belief that atopy is not a risk factor [31], recent studies demonstrated an increased prevalence of atopy in patients with ASA/NSAID intolerance [32, 33]. Although in this trial the atopy rate of the whole group was not different from that of the general adult population in Turkey, our previous study showed that skin prick test reactivity was significantly higher in patients with AI than that reported in the healthy adult population of our country [24]. Besides the presence of atopy, a study provided evidence that a history of allergic reactions to antimicrobial drugs increases the likelihood of intolerance to alternative drugs such as nimesulide and acetaminophen in patients with NSAID hypersensitivity [34]. In the present study, the only patient reacting to meloxicam had a history of asthmatic and nasal responses to ASA and metamizol, and she was nonatopic. However, the small number of patients studied prevent us to draw a final conclusion on this issue.

In summary, meloxicam can be used as a safe alternative for ASA-/NSAID-hypersensitive patients with asthma and/or NP. Although only 1 intolerance reaction at the dose of 7.5 mg of meloxicam was observed, considering its potential for adverse reactions in high-risk groups, we suggest that the drug should be prescribed following oral challenge by an experienced allergist.

Acknowledgments

We would like to thank Tuncer Değim who provided placebo and ASA tablets for this study and Prof. Szczeklik for his valuable comments on the manuscript.

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