

ORIGINAL ARTICLE

Safety of meloxicam in patients with aspirin/ non-steroidal anti-inflammatory drug-induced urticaria and angioedema

Özlem GÖKSEL, Ömür AYDIN, Zeynep MISIRLIGİL, Yavuz S. DEMIREL,
Sevim BAVBEK

Department of Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey

ABSTRACT

It has been proposed that aspirin (ASA) and other non-steroidal anti-inflammatory drug (NSAID)-induced urticaria (UR)/angioedema (AE) are mediated through inhibition of cyclooxygenase-1 (COX-1) enzymes. Therefore, drugs with COX-2 selectivity may be well tolerated in such patients. We investigated the safety of preferential COX-2 inhibitor meloxicam in subjects with UR or AE type intolerance reaction to classical ASA/NSAIDs. Subjects with reliable or documented history of UR/AE due to classical ASA/NSAIDs underwent a single-blinded, placebo-controlled oral challenge with a cumulative dose of 7.5 mg meloxicam on 2 separate days. One-quarter and three-quarter divided doses of placebo and the active drug were given at 1-h intervals. A total of 116 patients (86 women and 30 men, mean age 39.6 ± 12.7 years) were enrolled to the study. The rate of atopy was 25.9%. Mean duration of drug reaction was 87.4 ± 110.8 (1–720) months. Almost half of the patients were multi-reactors. The most comorbid disease was asthma and the two most frequent NSAIDs inducing UR/AE were paracetamol (19.6%) and ASA (19%). No reaction to placebo was observed. Ten out of 116 patients (8.6%) developed mild UR/AE, or only erythema and pruritus at a one-quarter or cumulative dose of 7.5 mg of meloxicam. The remaining subjects (91.4%) tolerated perfectly meloxicam challenge. This study indicates that 7.5 mg meloxicam is a safe alternative for ASA/NSAID-intolerant UR/AE patients. Intolerance reactions to meloxicam are much milder forms of the patients' historical ASA/NSAID-induced cutaneous reactions.

Key words: angioedema, aspirin intolerance, drug allergy, meloxicam, non-steroidal anti-inflammatory drug tolerance, urticaria.

INTRODUCTION

Patients with aspirin (ASA)-sensitive respiratory and cutaneous reaction experience cross-reactions to all classical non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit cyclooxygenase (COX-1 and COX-2) enzyme. Cross-reactivity among NSAIDs has been attributed to their inhibitory effect on COX-1 enzyme.¹ The main clinical problem deriving from cross-reactivity from NSAIDs is to find a potentially non-cross-reactive one and to assess this cross-reactivity by diagnostic tests. Because of limited

sensitivity of *in vitro* testing in drug allergy diagnosis, the most approved way of establishing the tolerability of NSAIDs is a placebo-controlled, graded oral provocation test (OPT).^{1,2}

Considering the role of COX-1 enzyme in ASA/NSAID-induced intolerance reactions, selective and preferential COX-2 inhibitors have been developed and marketed.^{1,3} In keeping with that, in the last few years, selective COX-2 inhibitors such as rofecoxib, celecoxib and valdecoxib were reported as reliable alternative drugs for ASA/NSAID-intolerant patients.^{4–8} However, after their worldwide

Correspondence: Sevim Bavbek, M.D., Angora Evleri, Buluşmalar cad. C1-2A, Beysukent, Ankara, Turkey. Email: bavbek@medicine.ankara.edu.tr
Received 29 December 2009; accepted 7 March 2010.

withdrawal from the market due to significant cardiovascular side-effects, it has been a common problem in clinical practice to find another alternative drug.

Meloxicam is an enolic-acid derivate NSAID belongs to the oxicam group developed for the treatment of rheumatoid arthritis and osteoarthritis. The drug is recommended at a dose of 7.5–15 mg once daily, has a similar anti-inflammatory effect to classical NSAIDs, a low incidence of gastro-erosive side-effects and is commercially available at reasonable cost throughout the world.^{3,9} It is a preferential COX-2 enzyme inhibitor, which gives the drug an opportunity to be a safe alternative for ASA/NSAID-intolerant patients.

When we reviewed studies examining safety and tolerability of meloxicam we observed that the drug has been mainly investigated in either NSAID-sensitive patients with any clinical presentation of intolerance reactions or selectively ASA-intolerant asthma patients.^{4,8,9–14} NSAID-hypersensitive patients could exhibit different allergic and pseudo-allergic clinical manifestations, which are classified as respiratory, cutaneous, mixed and systemic patterns.^{15,16} Cutaneous reactions with a percentage of up to 80% have been reported as the most frequently encountered clinical pattern among NSAID-intolerant patients.^{15,16} Also, the average relative risk of urticaria (UR)/angioedema (AE) in a large cohort of patients exposed to these agents was between 1.1% (for those who used NSAIDs chronically) and 3.6% (for those who took NSAIDs intermittently, for treatment of acute pain).¹⁷ However, there are only a few studies evaluating the safety of meloxicam in patients with ASA/NSAID-induced UR/AE.^{18–22} Therefore, in this study we aimed to assess the tolerability of meloxicam specifically in patients with NSAID-induced UR/AE.

METHODS

Patient selection

The adult patients admitted to our tertiary allergy clinic from November 2005 to June 2009 in Ankara University School of Medicine with a reliable or documented history of UR/AE triggered by one (single NSAID reactor) or more than one (multiple NSAID reactor) NSAIDs were chosen for inclusion in this study. Patients with a history of hypersensitivity reactions such as cutaneous fixed eruptions, exfoliatif

dermatitis, toxic epidermal necrolysis, Steven–Johnson syndrome, erythema multiforme and allergic contact dermatitis were all excluded from this study. Patients with ASA-intolerant asthma and patients with active UR/AE were not included to the study. Patients who were taking drugs other than the suspected NSAID at the time of the reaction were also excluded. Drugs, which interfere with the results of meloxicam challenge such as H1 receptor antagonists, were stopped 3 days before challenge. After inclusion into the study, age, sex, duration of analgesic intolerance, implicated analgesic(s) and reaction patterns were all recorded. Duration of drug allergy was defined as the time period between the first reaction to ASA/NSAIDs, paracetamol, metamizol and hospital admission for an alternative analgesic. All patients gave written informed consent to participate in the drug challenge with meloxicam. An experienced allergist in the hospital setting performed OPT where emergency equipment was available.

Meloxicam challenge

Meloxicam OPT was designed as a single-blinded, placebo-controlled oral drug challenge. The challenge protocol consisted of p.o. administration of the drug with increasing doses as described in our previous studies.⁴ On 2 consecutive days, one-quarter and three-quarter divided doses of placebo and the active drug meloxicam (Mobic 7.5 mg; Boehringer Ingelheim, Istanbul, Turkey) were given at 1-h intervals. During the challenge procedure, blood pressure and forced expiratory volume in 1 s (FEV₁) values as well as the 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 accepted as meloxicam tolerant.

An oral challenge test was accepted as positive if one 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 FEV₁; cutaneous reactions such as erythema, pruritus with erythema, UR/AE; and/or anaphylactoid reaction with at least skin and respiratory or skin and hypotension or skin or gastrointestinal and one of the above.

In order to find other safe alternatives for the patients who were intolerant to meloxicam, OPT with nimesulide (Nimes 100 mg; Sanovel, Istanbul, Turkey; total dose: 100 mg) or nabumeton (Relifex 500 mg; Glaxo Smith Kline, Istanbul, Turkey; total dose: 1000 mg) were performed with the same method and positivity criteria used during meloxicam challenge. All patients also gave written informed consent for OPT with nimesulide and nabumeton.

Evaluation of atopy

Atopy was defined as a positive skin prick test to at least one of the aeroallergens. Glycerinate extracts (Stallergenes, Cedex, France) of the following allergenic sources were used in SPT: *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 wheal reaction with a mean diameter of 3 mm greater than the negative control was considered a positive response.

Statistical analysis

The statistical analyses were performed by SPSS ver. 11.0 computer software. Descriptive statistics were expressed as mean $\pm$ standard deviation and n (%). Categorical data were tested by χ^2 -test. Univariate analyses were performed by Fisher's exact test while logistic analyses were used for multiply analysis. Each comorbid disease was also evaluated by Fisher's exact test separately. $P < 0.05$ was considered statistically significant.

RESULTS

Patient demographics

A total of 116 patients (86 women and 30 men, mean age 39.6 ± 12.7 years) admitted to our tertiary allergy clinic with reliable or documented histories of UR/AE after NSAID intake were included in this study. The prevalence of atopy was 25.9% and this ratio was similar to the general adult population of Turkey (25.9% vs 25%, $P > 0.05$).²³ Mean duration of drug reaction was 87.4 ± 110.8 (1–720) months. Of the 116 patients, 59 (59.2%) had a history of UR/AE with one NSAID (single reactor), 57 (49.1%) had a history

of UR/AE with two or more NSAIDs (multi-reactor). Almost half of the patients had a comorbid disease in which the most common was asthma. Only seven patients (10%) among the study group suffered chronic idiopathic urticaria. The two most frequent NSAIDs inducing UR/AE in our study population were paracetamol (19.6%) and ASA (19%). ASA-induced UR/AE was confirmed with ASA OPT described in our previous trial in six patients (5%).¹² According to history, 29.6%, 33.3% and 37% of the patients had experienced UR alone, AE alone and UR plus AE, respectively, after consumption of various NSAIDs. One-quarter of the patients also had history of reaction to other drugs, which were mainly antibiotic. The demographic data of patients and clinical characteristics of their previous reactions with culprit agents are given in Tables 1 and 2 respectively.

Meloxicam provocation

No reaction was observed with placebo. Ten of 116 patients (8.6%) reacted to meloxicam provocation and the drug was well tolerated by the remaining 106 patients (91.4%). Of the 10 patients who reacted to meloxicam challenge, five had pruritus/erythema and five had localized AE along with erythema. The dose of meloxicam inducing reaction was mainly the total cumulative dose, but one-quarter dose of the drug induced erythema in three patients. No patient showed asthmatic or naso-ocular reaction during challenges. Although we did not grade previous intolerance reactions to ASA/NSAIDs, reactions to meloxicam were defined as much milder than their prior reactions by the patients. As another safe alternative, OPT was performed with nimesulide and nabumeton in six and one patient, respectively, of these 10 patients. A cutaneous type reaction was observed in one of the six patients tested with nimesulide and in one patient tested with nabumeton. All intolerance reactions were easily controlled with oral antihistamines. Results of positive OPT and clinical details of these patients are given in Table 3.

Risk factors associated with meloxicam intolerance

Univariate analysis of risk factors including age, sex, atopy, comorbid diseases, duration of drug allergy, reactions to more than one NSAID or other drugs in patients with positive response to oral meloxicam

Table 1. Demographic and clinical features of the study group

	<i>n</i> = 116	%
Age mean $\pm$ SD (min–max), years	39.6 $\pm$ 12.7 (18–81)	
Sex (F/M) (<i>n</i> , %)	86/30	74.1/25.9
Single NSAID reactors (<i>n</i> , %)	59	50.9
Multiple NSAID reactors (<i>n</i> , %)	57	49.1
Duration of drug allergy mean $\pm$ SD (min–max), month	87.4 $\pm$ 110.8 (1–720)	
Atopy (<i>n</i> = 53) (<i>n</i> , %)	30	25.9
Patients with comorbid disease (<i>n</i> , %)	52	44.8
With only one comorbid disease	39	75
With 2–3 comorbid diseases	13	25
Comorbid diseases (<i>n</i> , %)	69	–
Asthma	16	23.2
Allergic rhinitis	10	14.5
Chronic idiopathic urticaria	7	10.1
Food allergy	1	1.4
Venom allergy	2	2.9
Psychiatric disease	2	2.9
Thyroid disease	4	5.7
Malignancy	1	1.4
Hypertension	7	10.1
Atherosclerotic heart disease	4	5.7
Chronic obstructive pulmonary disease	1	1.4
Others	14	20.2
Patients with additional drug reactions (<i>n</i> , %)	31	26.7
Reaction with one group of additional drug other than NSAIDs	30	96.8
Reaction with more than one group of drugs other than NSAIDs	1	3.2
Patients with other drug reactions (<i>n</i> , %)	31	26.7
Antibiotics	24	77.4
H2 receptor antagonists	1	3.2
Chemotherapy drugs	1	3.2
Myorelaxants	1	3.2
Antifungals	1	3.2
Antibiotics + antifungals	1	3.2
Reaction with unknown drug	2	6.4

NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation.

provocation showed that only presence of one or more than comorbid diseases was a risk factor for test positivity ($P = 0.041$). However, any significant differences could not be detected by multivariate analysis. Each comorbid disease was evaluated by Fisher's exact test separately but none of them had positive significant effect on meloxicam OPT positivity.

DISCUSSION

In the present study, we found that the majority of patients (91.4%) with ASA-induced UR/AE perfectly tolerated a 7.5-mg therapeutic dose of meloxicam. The safety of meloxicam has been demonstrated in our previous studies in ASA/NSAID-intolerant patients with different clinical pattern of intolerance reaction^{4,12} but not specifically in patients with ASA-

induced UR/AO. In the current study, as consistent with other previous data, meloxicam appeared to be a very safe alternative for patients with ASA/NSAID-induced UR/AE.^{18–22}

With respect to meloxicam and ASA/NSAID-induced UR/AE, there are a few published studies. In one of them, Nettsi *et al.* reported safety of meloxicam in 148 patients with clinical history of UR/AE after ingestion of different NSAIDs. Two patients (1.35%) reacted to a total dose of 7.5 mg.¹⁸ Similarly, Domingo *et al.*¹⁹ reported that five patients (4.62%) developed reactions to meloxicam challenge among 108 patients with histories of NSAID-induced cutaneous reactions, and these reactions were defined as “slight UR” of cutaneous type. More recently, positive response manifested as UR/AE to 15 mg meloxicam oral challenge was observed in six of 29 ASA-induced UR/AO patients.²¹

Table 2. Generic names and types of intolerance reaction with the culprit NSAIDs

	Reaction type <i>n</i> (%)			Total <i>n</i> (%)
	UR	AE	UR + AE	
Acetyl salicylic acid	9	16	11	36 (19)
Dipyron	7	4	9	20 (10,6)
Paracetamol	12	11	14	37 (19,6)
Flurbiprofen	6	5	8	19 (10,5)
Diclofenac	3	3	6	12 (6,3)
Etodolac		2		2 (1)
Ketorolac			1	1 (0,5)
Naproxen	7	12	10	29 (15,3)
Methamizole	1	4	6	11 (5,8)
Tenoxicam	1			1 (0,5)
Acemetacin		2		2 (1)
Nimesulide			1	1 (0,5)
Ibuprofen	1	1	1	3 (1,6)
Piroxicam		1		1 (0,5)
Unknown	9	1	2	12 (6,3)
Dexketoprofen		1	1	2 (1)
Total numbers of reactions (<i>n</i> , %)	56 (29.6)	63 (33.3)	70 (37)	189

Some patients had more than one UR/AE type reactions to different NSAIDs. Thus; the number 189 represents the total number of reactions of 116 ASA/NSAID-intolerant patients. AE, angioedema; ASA, aspirin; NSAIDs, non-steroidal anti-inflammatory drugs; UR, urticaria.

There are only two previous challenge-proven studies with quite low numbers of patients. Meloxicam was challenged in only two patients and with a negative result among 15 patients with challenge-proven NSAID-induced UR/AE.²⁴ In another challenge-proven study with 20 patients from Japan, six patients challenged with 10 mg of meloxicam and two responded (33.3%) with UR/AE.²²

Our study is one with a large number of patients. Reactions to meloxicam were observed in only 10 patients (8.6%) in our group. The analysis of available data exhibits variable rates of intolerance to meloxicam, ranging 1.35–33.3%.^{18–22} Discrepancies between different studies may be related to methodology, selection of the patients, dose of the drug and the number of patients involved. One of our results was that in patients who reacted to meloxicam, the cutaneous reactions were much milder than their historical reactions to ASA/NSAIDs, which has also been reported previously.^{22,24}

Aspirin and/or NSAIDs induce UR/AE in two clinical settings. First, is the development of UR/AE in patients with pre-existing chronic urticaria. The

Table 3. Characteristics of the patients with positive oral challenges with meloxicam

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age, sex	38, F	59, F	49, F	44, M	26, F	62, F	40, F	29, F	36, F	24, F
Duration of drug allergy (months)	48	3	2	204	48	96	3	170	25	24
Accompanying disease	A	HT	A	AR, ASHD	Ø	Hypothyroidism	Ulcerative colitis	AR/A	Food Allergy	Ø
Atopy	Negative	Negative	Negative	Positive	Ø	Positive	Negative	Positive	Ø	Ø
Culprit NSAIDs	ASA, Dyp, Flur, M	Dic.	Dyp.	ASA, Nap	Par, Flur	ASA, Par	Nap, Ibu.	ASA, Dyp, Nap	ASA, M, Nim	Flur.
Historical reaction to culprit NSAIDs	U + AE	U + AE	U + AE	AE	AE	PE + AE	AE	U + AE	U + AE	U + AE
Dose of meloxicam	Full dose	Full dose	1/4 tb	Full dose	Full dose	1/4 tb	Full dose	1/4 tb	Full dose	Full dose
Reaction type to meloxicam	PE + AE	PE + AE	PE	AE	AE	PE	AE	PE	Pru	Pru
OPT with Nim or Nab	Negative to Nim	Ø	Ø	Negative to Nim	Negative to Nim	Negative to Nim	Positive to Nim (AE)	Ø	Positive to Nab (Pru)	Negative to Nim

Ø: not performed. A, asthma; AR, allergic rhinitis; ASHD, atherosclerotic heart disease; NSAIDs, non-steroidal anti-inflammatory drugs; U, urticaria; AE, angioedema; Pru, pruritus; erythema; ASA, aspirin; Dic, diclofenac; M, methamizole; Ibu, ibuprofen; Nap, naproxen; Dyp, dypiron; Par, paracetamol; Flur, flurbiprofen; Nim, nimesulide; NAB, nabumeton; AB, antibiotic; OPT, oral provocation test.

prevalence of urticaria exacerbation is between 21% and 30% after NSAID intake in patients with chronic urticaria.^{25,26} In contrast to ASA-induced asthma, knowledge about the pathogenesis of ASA-induced UR is limited. However, a few recent data suggested that mechanism of ASA-induced UR in patients with chronic idiopathic urticaria is related to inhibition of COX-1 enzyme and overproduction of cystein leukotrienes.^{21,27,28} In keeping with that, the relative safety of highly selective COX-2 inhibitors, rofecoxib and celecoxib, has been well established in these patients.^{5,6,20,21,24,26} Second, is the development of acute UR in an otherwise healthy subject. These subjects can experience urticarial reactions to one NSAID (probably immunoglobulin [Ig]E mediated) or more than one NSAID (probably by COX-1 inhibition). In our study, only 10% of the patients had chronic idiopathic urticaria. Half of the study group reported UR/AE after taking a single NSAID, and the other half reported UR/AE after taking more than one NSAID. We did not perform *in vivo* or *in vitro* diagnostic tests such as prick and intradermal test or IgE measurements, which are not standardized, in the single reactor group to document IgE-mediated reactions. We also did not perform challenge test with any COX-1 inhibitor including ASA except in six patients with challenge-proven ASA sensitivity to show COX-1 cross-reactivity. None of the patients reported having taken meloxicam previously. Therefore, it seems quite difficult to define these patients as real single reactors and to exclude the role of COX-1 inhibition. Nevertheless, meloxicam-intolerant patients were mainly multiple reactors indicating the role of COX-1 inhibition.

A number of risk factors were reported for UR/AE induced by ASA/NSAID, such as atopy, female sex, intermittent NSAID use and the presence of certain comorbid conditions like asthma, rhinitis and chronic urticaria.^{15,19} Although there were patients with asthma in our study group, none of them were ASA-intolerant asthmatic and none experienced any respiratory reaction to meloxicam challenge. Similarly, almost all meloxicam-intolerant patients had a comorbid disease except chronic idiopathic urticaria, but there was no specific disease related to positive response to meloxicam challenge. This may be due to the small numbers of individuals with meloxicam intolerance.

We preferred nimesulide and nabumeton as safe alternatives for the meloxicam-intolerant patients due

to their good anti-inflammatory and analgesic properties, proven tolerability in NSAID-intolerant patients and commercial availability in our country.^{4,9} Cutaneous reaction was observed in only one of the six patients tested with nimesulide and one patient tested with nabumeton. However, the limited number of patients prevents us from making any conclusions on that issue.

There are some limitations of our study. Diagnosis was mainly based on reliable clinical history. However, a significant correlation between history of intolerance and the result of oral challenge in ASA-intolerant patients was demonstrated previously.²⁹ Considering our experience in ASA/NSAID intolerance,^{4-6,12,30} we believe that we were very careful to select patients with a reliable history. Besides that, almost half of subjects in our study group were reacting to multiple NSAIDs suggesting the presence of cross-reactivity which may support a diagnosis of true NSAID intolerance. The other limitation was in the tested cumulative dose, which was 7.5 mg, but higher doses were not challenged. COX-2 selectivity is reduced with higher doses of COX-2 inhibitors and thus higher doses may be associated with a higher intolerance ratio.^{4,21,31}

In conclusion, 7.5 mg of meloxicam is a highly reliable alternative for patients presenting ASA/NSAID-induced UR/AE. The presence of a comorbid disease seems to be a risk factor for intolerance to meloxicam. Considering the rate of positive response to meloxicam challenge, drug tolerability should be verified by placebo-controlled OPT.

REFERENCES

- 1 Szczeklik A, Nizankowska-Mogilnicka E, Sanak M. Hypersensitivity to aspirin and non-steroidal antiinflammatory drugs. In: Adkinson NF, eds. *Middleton's Allergy. Principles and Practice*, 7th edn. Philadelphia: Elsevier Inc., 2009; 1227–1243.
- 2 Viola M, Quarantino D, Gaeta F, Rumi G, Caruso C, Romano A. Cross-reactive reactions to nonsteroidal anti-inflammatory drugs. *Curr Pharm Des* 2008; **14**: 2826–2832.
- 3 Chen Y-F, Jobanputra P, Barton P *et al.* Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2008; **12**: 1–196.

- 4 Bavbek S, Celik G, Ozer F, Mungan D, Misirligil Z. Safety of selective COX-2 inhibitors in aspirin/nonsteroidal anti-inflammatory drug-intolerant patients: comparison of Nimesulide, Meloxicam, and Rofecoxib. *J Asthma* 2004; **41**: 67–75.
- 5 Bavbek S, Celik G, Pasaoglu G, Misirligil Z. Rofecoxib, as a safe alternative for acetyl salicylic acid/nonsteroidal anti-inflammatory drug-intolerant patients. *J Invest Allergol Clin Immunol* 2006; **16**: 57–62.
- 6 Celik G, Pasaoglu G, Bavbek S *et al*. Tolerability of selective cyclooxygenase inhibitor, celecoxib, in patients with analgesic intolerance. *J Asthma* 2005; **42**: 127–131.
- 7 Szczeklik A, Nizankowska E, Bochenec G, Nargaba K, Mejza F, Swierczynska M. Safety of specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2001; **31**: 219–225.
- 8 Senna G, Biló MB, Antonicelli L *et al*. Tolerability of three selective cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib and rofecoxib in NSAID-sensitive patients. *Allergol Immunol (Paris)* 2004; **36**: 215–218.
- 9 Prieto A, De Barrio M, Martin E *et al*. Tolerability to nabumetone and meloxicam in patients with nonsteroidal anti-inflammatory drug intolerance. *J Allergy Clin Immunol* 2007; **119**: 960–964.
- 10 Quarantino D, Ramono A, Di Fonso M *et al*. Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2000; **84**: 613–617.
- 11 Kosnik M, Music E, Matjaz F, Suskovic S. Relative safety to meloxicam in NSAID-intolerant patients. *Allergy* 1998; **53**: 1231–1233.
- 12 Bavbek S, Dursun AB, Dursun E, Eryilmaz A, Misirligil Z. Safety of meloxicam in Aspirin-intolerant patients with asthma and/or nasal polyps: a challenge-proved study. *Int Arch Allergy Immunol* 2007; **142**: 64–69.
- 13 Senna G, Passalacqua G, Dama A *et al*. Nimesulide and meloxicam are safe alternative drugs for patients intolerant to nonsteroidal anti-inflammatory drugs. *Allergol Immunol (Paris)* 2003; **35**: 393–396.
- 14 Karakaya G, Fuat K. Safety of nimesulide, meloxicam and rofecoxib as alternative analgesics. *Allergol Immunopathol* 2000; **28**: 319–321.
- 15 Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. The multipl faces of nonsteroidal anti-inflammatory drug hypersensitivity. *J Invest Allergol Clin Immunol* 2004; **14**: 329–334.
- 16 Stevenson DD, Sánchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001; **87**: 177–180.
- 17 Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. NSAID-Induced Urticaria and Angioedema. A reappraisal of its clinical management. *Am J Clin Dermatol* 2002; **3**: 599–607.
- 18 Nettis E, Di Paola R, Ferrannini A, Tursi A. Meloxicam in hypersensitivity to NSAID. *Allergy* 2001; **56**: 803–804.
- 19 Domingo MV, Marchuet MJC, Culla MTD, Joanpere RS, Guanado EM. Meloxicam tolerance in hypersensitivity to nonsteroidal anti-inflammatory drugs. *J Invest Allergol Clin Immunol* 2006; **16**: 364–366.
- 20 Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F, Ramon Pérez C. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001; **87**: 201–204.
- 21 Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. Cutaneous Hypersensitivity reactions to inhibitors of Cyclooxygenase-2. Results from 307 oral provocation tests and review of the literature. *Allergy Clin Immunol Int-J World Org* 2007; **19**: 44–49.
- 22 Inomata N, Osuna H, Yamaguchi J *et al*. Safety of selective cyclooxygenase-2 inhibitors and a basic non-steroidal anti-inflammatory drug (NSAID) in Japanese patients with NSAID induced urticaria and/or angioedema: comparison of meloxicam, etodolac and tiaramide. *J Dermatol* 2007; **34**: 172–177.
- 23 Çelik G, Mungan D, Bavbek S, Sin B, Demirel YS, Misirligil Z. The prevalence of allergic diseases and atopy in Ankara, Turkey: a two-step population-based epidemiological study. *J Asthma* 1999; **36**: 281–290.
- 24 Quirarte J, San Pedro BS, Florido JF. Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. *Ann Allergy Asthma Immunol* 2002; **89**: 63–66.
- 25 Namazy JA, Simon RA. Sensitivity to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2002; **89**: 542–550.
- 26 Simon RA, Stevenson DD. Cross-reactivity of cyclooxygenase 2 inhibitors in patients with a history of cutaneous reactions to cyclooxygenase 1 inhibitors. *Ann Allergy Asthma Immunol* 2005; **95**: 8–11.
- 27 Mastalerz L, Setkowicz M, Sanak M, Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol* 2004; **113**: 771–775.
- 28 Mastalerz L, Setkowicz M, Szczeklik A. Mechanism of chronic urticaria exacerbation by aspirin. *Curr Allergy Asthma Rep* 2005; **5**: 227–283.
- 29 Ispano M, Fontana A, Scibilia J, Ortolani C. Oral challenge with alternative nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol in patients intolerant to these agents. *Drug* 1993; **46**(Suppl 1): 253–256.
- 30 Bavbek S, Erkeköl FO, Dursun B, Misirligil Z. Meloxicam-associated anaphylactic reaction. *J Invest Allergol Clin Immunol* 2006; **16**: 317–320.
- 31 Bavbek S. Use of safe alternatives in ASA/NSAID-intolerant patients. In: Charles LM, eds. *New Research on Aspirin and Health*. New York: Nova Science Publishers, Inc, 2007; Chapter IX, 213–230.