
Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs

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Background: Adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are frequent, particularly among patients with chronic urticaria or asthma. The need to identify an alternative drug that is safe and reliable is a common problem in clinical practice.

Objective: To assess the tolerability of meloxicam, a new NSAID that selectively inhibits the inducible isoform of cyclooxygenase, in a group of NSAID-sensitive patients.

Patients and Methods: We studied 177 patients who had suffered adverse reactions to one or more NSAIDs. Cutaneous reactions were reported by 83.1% of the subjects (urticaria in 55, angioedema in 52, urticaria/angioedema in 39, and maculopapular rash in 1), respiratory symptoms by 3.9%, both cutaneous and respiratory symptoms by 9%, Stevens-Johnson's syndrome by 2.3%, and anaphylactoid reactions by 1.7%. All subjects underwent a single-blind, placebo-controlled oral challenge with divided therapeutic doses of meloxicam (1.9 mg + 5.6 mg 1 hour later = cumulative dose 7.5 mg).

Results: Positive reactions were observed in only two cases (1.1%), both manifested exclusively by cutaneous symptoms (urticaria/angioedema in one case and maculopapular rash/facial edema in the second).

Conclusion: Meloxicam seems to be well tolerated by NSAID-sensitive subjects whose reactions are manifested by urticaria/angioedema. Additional study is needed for a more complete assessment of its tolerability in patients with aspirin-induced asthma and other severe manifestations of NSAID sensitivity.

Ann Allergy Asthma Immunol 2000;84:613–617.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid (ASA) and the pyrazolone derivatives, are among the most common causes of adverse drug reactions,^{1–3} and many patients report a history of reactions to several different drugs of this class. The symptoms may be respiratory (rhinitis and asthma) or cutaneous (urticaria and angioedema). Occasionally both

types of symptoms occur in the same patient, and some reactions have the characteristics of anaphylaxis.^{4–6}

The frequency of NSAID sensitivity is particularly high among patients with chronic urticaria or asthma^{4,5} but the pathogenesis is still unknown. Only a few of the case reports published thus far contain convincing evidence of the involvement of allergic mechanisms. Immune-mediated reactions have been reported following the use of pyrazolone derivatives^{5,7} and, less commonly, aspirin,^{8,9} anthranilic-acid derivatives,¹⁰ diclofenac,^{11–13} and flurbiprofen.¹⁴

In other cases, however, the reactions are thought to be related to the drugs' blockade of the cyclooxygenase (COX) pathway of arachidonic-acid

metabolism,^{15,16} which results in an overproduction of leukotrienes.^{5,17} This hypothesis is supported by clinical observations of cross-reactivity to those NSAIDs that significantly inhibit COX activity.^{4,17–22} There are at least two isoforms of COX, each encoded by a different gene²³: the constitutive isoform, COX-1, which is expressed in most tissues and clearly has physiologic functions and the COX-2 isoform, which is induced by pro-inflammatory stimuli in various cells. The therapeutic actions of the NSAIDs seem to be related to their inhibition of the latter isoform, while inhibition of COX-1 is thought to be responsible for their adverse effects.²⁴

Acetaminophen and nimesulide are generally accepted as alternative drugs in NSAIDs-sensitive patients.^{5,18,25–28} In previous studies we found that 91.1% of 101 patients with adverse reactions to NSAIDs tolerated these drugs.²⁹ This tolerability is characterized by long-term persistence³⁰; however, adverse reactions have been reported to both drugs^{22,26,28,31–38} and the search for a well tolerated NSAID thus continues.

Meloxicam is a new enolic-acid derivative developed for the treatment of rheumatoid arthritis and osteoarthritis. It has been shown to exert selective inhibition of the COX-2 isoform in both in vitro and in vivo studies^{39,40} and is reportedly characterized by anti-inflammatory effects that are similar to or greater than those of other NSAIDs and a higher therapeutic ratio.³⁹ Reports of adverse reactions to meloxicam have been registered in both Ireland and Germany.⁴¹ Most of these events have involved gastrointestinal

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Received for publication May 29, 1999.

Accepted for publication in revised form January 8, 2000.

disturbances (one of which was fatal), but there have also been skin reactions including isolated cases of Stevens-Johnson syndrome, erythema multiforme and exanthema, and cases of anaphylactoid or anaphylactic reactions. The literature on the safety of meloxicam in NSAID-sensitive subjects is currently limited to a few studies of relatively small groups of patients.^{42,43}

We recently evaluated the tolerability of this new drug in a group of 177 patients with histories of adverse reactions to NSAIDs.

PATIENTS AND METHODS

The study population consisted in 177 consecutive patients (47 males and 130 females) ranging in age from 13 to 83 years (mean 40.33 ± 15.67 years) who had reportedly experienced one or more adverse reactions to NSAIDs. Criteria used to judge the relationship between the suspected NSAID and the adverse event were (1) the amount of time between use of the drug and the onset of reactive symptoms (a few minutes to 12 hours) and (2) the suspected culprit drug was the only drug being taken by the patient prior to the reaction. Challenges to confirm the patient's intolerance of drugs identified as probable causes of previous reactions were deferred in order to avoid provoking unnecessary discomfort or risk. To identify an alternative drug that might be better tolerated, each of the subjects submitted to an oral challenge with a cumulative dose of 7.5 mg of meloxicam (Mobic, Boehringer Mannheim, Milan, Italy). All subjects were challenged at least 4 weeks after their most recent adverse reactions. The mean time between the most recent reported reaction and the study challenge was 7.2 ± 4.28 months (range: 1 to 18 months). None of the patients presented significant cutaneous or respiratory-tract symptoms at the time of testing, and pulmonary function tests showed stable FEV₁s that were >80% of predicted values in all cases. Antihistamines had been discontinued seven days or more before challenges (8 weeks in the case of

astemizole), and no drugs of any type were used 48 hours before testing. Informed consent was obtained from all subjects.

Challenges were administered, as described in previous studies,^{29,30} under single-blinded conditions during the morning hours after an overnight fast. Equipment and personnel for emergency resuscitation were present during all tests. On the first day, each patient received a placebo (lactose) challenge; if no reactive symptoms were noted, the placebo was re-administered after one hour. One week later, the challenge was repeated using divided doses of meloxicam: one-fourth of the therapeutic dose (ie, $\frac{1}{4}$ of 7.5 mg = 1.9 mg) was administered initially; the remaining $\frac{3}{4}$ (5.6 mg) was given 1 hour later if no symptoms had developed with the initial administration.

The patients were observed in the day hospital for 6 hours after the challenge and were seen in the outpatient department the next day to determine whether any reactions had occurred after discharge. In patients with histories of rhinitis and/or bronchial asthma unrelated to drug use and those whose past adverse reactions had included bronchospastic or rhinitic symptoms, the FEV₁ was measured with computerized spirometry (Pony Spirometer, Cosmed, Rome, Italy) before the challenge, at 30-minute intervals during the first 2 hours after administration of the drug, and every hour thereafter through the sixth post-challenge hour. The response to the challenge was considered positive if any of the following symptoms developed: erythema, pruritus accompanied by erythema, urticaria/angioedema, rhinorrhea, nasal obstruction, sneezing, dyspnea, or cough associated with a decrease of at least 20% in the FEV₁, hypotension.

RESULTS

Of the 177 adults with histories of adverse reactions to NSAIDs considered here, 52 (29.4%) had personal histories of allergies or allergy-like diseases. Thirty-two reported respiratory symptoms: allergic rhinitis in 31 cases, in-

cluding 4 who also had mild bronchial asthma, and moderate bronchial asthma associated with negative allergologic findings in one case. Fourteen suffered from chronic idiopathic urticaria/angioedema syndrome (with negative findings in routine tests used to evaluate these symptoms), and one of these had also allergic seasonal rhinitis. Six had histories of allergic contact dermatitis involving the hands. None of the patients presented nasal polyps at the time of our study, and none had histories of sinusitis.

Sixty-nine patients (39%) reported one episode of NSAID sensitivity: in 33 the reaction had apparently been provoked by ASA, in 13 by one of the pyrazolone derivatives, in 9 by a propionic acid derivative, in 5 by nimesulide, in 5 by diclofenac, in 2 by acetaminophen, and in 2 by morniflumic acid. The remaining 108 patients (61%) reported two or more reactive episodes involving different NSAIDs. The most frequent patterns were the following: ASA and pyrazolone drugs (38 cases), ASA and propionic acid derivatives (16 cases), ASA and acetaminophen (13 cases), ASA, pyrazolone drugs, and acetaminophen (8 cases), ASA, pyrazolone drugs, and propionic acid derivatives (8 cases).

The NSAID sensitivity had been manifested by cutaneous symptoms in 147 patients (83.1%): urticaria in 55 cases, angioedema in 52, urticaria/angioedema in 39, and maculopapular rash in one. Seven other patients reported respiratory symptoms: bronchial asthma in 2, dyspnea in 4, and rhinitis accompanied by dyspnea in one. An association of cutaneous and respiratory symptoms was reported by 16 patients. The NSAIDs had provoked Stevens-Johnson syndrome in four cases and anaphylactoid reactions in three.

None of the patients reacted to the placebo challenge. Positive responses to meloxicam challenge were observed in 2 of the 177 patients (1.1%). In the first case, a 30-year-old woman developed diffuse urticaria and angioedema of the eyelids 30 minutes after administration of the total dose of meloxi-

cam. All symptoms resolved within a few hours after administration of loratadine. This subject had reportedly experienced several similar episodes of urticaria/angioedema following the use of a number of other NSAIDs including ASA, pyrazolone derivatives, nimesulide, diclofenac, and naproxen. The second positive challenge was that of a 31-year-old woman, who developed facial edema and a generalized maculopapular rash 3 hours after ingestion of the second dose fraction of meloxicam (cumulative dose was 7.5 mg). She was treated with 6-methylprednisolone (80 mg intravenously) and chlorphenamine (10 mg intravenously). After 10 hours, she was completely asymptomatic. She had experienced two similar reactive episodes that she attributed to noramidopyrine and aminophenazone (both pyrazolone derivatives). Neither of the positive challenges was associated with respiratory symptoms or FEV₁ changes.

DISCUSSION

Choosing an alternative anti-inflammatory agent for a patient who has suffered an adverse reaction to a NSAID is a common problem in clinical practice. Most physicians prescribe an alternative with limited effects on COX after its tolerability has been verified with an oral challenge test. Nonsteroidal anti-inflammatory drugs vary widely in their inhibition of COX isoforms. Aspirin, indomethacin, and piroxicam, which are capable of provoking asthmatic attacks in sensitive patients even at low doses, are much more potent inhibitors of COX-1 than COX-2.⁴⁴ In contrast, nimesulide, which seems to be a preferential inhibitor of COX-2,⁴⁵ is very well tolerated by patients with aspirin-induced asthma.²⁷ Some investigators have concluded that meloxicam is the preferential COX-2 inhibitor with the most favorable ratio of COX-2/COX-1 inhibition.^{46,47} Other data, however, suggest that the drug exerts significant dose-dependent inhibition of both platelet COX-1 and monocyte COX-2.⁴⁸

In the present study, 177 patients with histories of adverse reactions to one or more NSAIDs were subjected to oral challenges to identify an alternative agent that would be better tolerated. The approach we use, which is designed for routine use in a clinical setting, has proved to be rapid, safe, and reasonably reliable.^{29,30} We do not perform challenges with the NSAID(s) suspected of having caused previous reactions. Apart from ethical considerations, this practice goes against current guidelines established in the Consensus Report of the Italian Society of Allergology and Clinical Immunology for "Diagnosis of Drug Allergy," which clearly state that challenges may be used only for testing alternative drugs and not those reported as causes of previous reactions.⁴⁹ In fact, previous studies have shown that patients' reports can generally be considered reliable in these cases.^{26,31,50} We also excluded from our study population those patients who were taking drugs other than the suspected NSAID at the time of the reaction, which at least allows us to exclude with reasonable certainty that the adverse events reported were related to other drugs. Nonetheless, we cannot determine the percentage of truly NSAID-sensitive subjects in our population, and this factor may have contributed to the low cross-reactivity rate we observed.

We feel, however, that the above weakness is offset to a certain extent by other characteristics of our study population: (1) the large number of subjects studied (177), which includes a substantial group of patients with probable cutaneous reactions to NSAIDs and (2) the relatively high percentage of patients (61%) reporting adverse reactions to multiple NSAIDs. The latter factor, in particular, suggests the presence of cross-reactivity that tends to support a diagnosis of true NSAID sensitivity. Further, patients of this type would be more likely to react to meloxicam if the new drug possessed the pharmacologic properties upon which NSAID cross-reactivity was based.

One hundred seventy-five of the patients we studied (98.9%) tolerated a therapeutic dose of meloxicam (7.5 mg). The fact that most of the past reactions to NSAIDs reported by our study population were exclusively cutaneous allows us to suggest that this new drug may well prove to be a safe alternative for this subgroup of NSAID subjects. In contrast, only five of the subjects were asthmatics, and bronchospastic reactions to NSAIDs had been reported only in two cases. For these reasons, even though the drug was tolerated by all seven of the latter patients, our results are not sufficient to allow us to draw any conclusions regarding the tolerability of meloxicam in NSAID-sensitive asthmatic patients. The same caveat applies to subjects with histories of severe reactions to NSAIDs (eg, the four patients who had developed Stevens-Johnson syndrome and three who had experienced anaphylactoid reactions in our population), although it is encouraging to note that none of the latter seven patients reacted to our challenge.

It should also be noted that the two cases of probable cross-reactivity observed among our study subjects were identified based on single-blind challenges alone. Although this finding suggests that cross-reactivity between meloxicam and other NSAIDs may occur in patients with histories of NSAID-induced cutaneous reactions, this possibility cannot be unequivocally confirmed without double-blind confirmation of our positive challenge results. Unfortunately, neither of the patients in question agreed to submit to a second challenge.

In conclusion, our findings on the tolerability of this new selective COX-2 inhibitor are encouraging. Meloxicam appears to have a very low frequency of cross-reactivity in patients with histories of urticarial/angioedema reactions to NSAIDs, even those who have reportedly reacted to multiple drugs of this type in the past. Additional studies are needed to evaluate the safety of meloxicam administration in patients with more severe reactions to NSAIDs, including those

with ASA-sensitive asthma, histories of NSAID-triggered Stevens-Johnson syndrome, or anaphylactoid reactions. Finally, although only two positive single-blind challenges were observed, these cases do suggest the possibility of cross reactivity between meloxicam and other NSAIDs in cutaneous reactors to this class of drugs; therefore, oral challenge tests must be administered before prescribing meloxicam for patients who report any type of adverse reactions to NSAIDs.

ACKNOWLEDGEMENTS

The study reported above was not in any manner funded by Boehringer-Mannheim, the producer of meloxicam, and none of the authors has any association whatsoever with this company.

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