

NIMESULIDE AND MELOXICAM ARE A SAFE ALTERNATIVE DRUGS FOR PATIENTS INTOLERANT TO NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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SUMMARY :

■ **Background:** Pseudoallergic reactions to ASA and NSAIDs in general are frequent and difficult to manage. The challenge with the suspected drug is considered unethical, therefore the only possible approach is a challenge with alternative drugs. Selective COX2 inhibitors are considered the most suitable alternative drugs. We describe the comparative results and follow-up of an oral challenge with nimesulide and meloxicam, in NSAIDs intolerant patients.

■ **Methods:** 381 patients (118 male, 263 female, mean age 53.2 years) with a well documented pseudoallergic reaction to NSAIDs underwent an oral challenge with these alternative drugs. All 381 patients were given nimesulide 88 of them were also given meloxicam. All patients were re-interviewed at six-month intervals up to two years after challenge.

■ **Results:** 98.4% of the patients tolerated nimesulide and 95.4% tolerated meloxicam. The reactions occurred during challenges were mild and easily manageable. Three out of the six nimesulide-intolerant patients could tolerate meloxicam, whereas only one of the four meloxicam-intolerant patients could tolerate nimesulide. At the follow-up, 96% of patients with previous negative challenge could tolerate nimesulide and within the patients which took meloxicam after challenge no pseudoallergic reaction occurred.

■ **Conclusions:** The herein described challenge with alternative drugs, meloxicam and nimesulide, is a safe tool for the management of NSAIDs-intolerant patients. The two tested drug are safe and reliable alternatives for these patients.

Key-words: Pseudoallergic reactions - Nonsteroidal antiinflammatory drugs - Oral challenge - Nimesulide - Meloxicam.

INTRODUCTION

Aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) in general, are the most widely prescribed compounds in clinical practice, and the large use accounts for the high incidence of side effects, being gastro-intestinal damage and renal toxicity the most common ones (1). These side effects are well known, dose dependent and predictable, whereas pseudoallergic reactions (urticaria, angioedema, asthma, anaphylaxis) are not. Pseudoallergic reactions are rare in the general population (2), but quite common in patients with chronic asthma or urticaria (3). The exact mechanism of pseudoallergic reactions is still unknown, although several consistent hypotheses have been proposed. In aspirin-sensitive asthma, the blockage of cyclo-oxygenase (COX) induced by these drugs (4),

seems to play a major pathogenic role since it results in an overproduction of leukotrienes (5). COX exists in two isoforms: COX1 is constitutively expressed in most tissues, whereas COX2 activity is strongly upregulated during inflammatory processes. Predominant COX1 inhibition is thought to be responsible for the side effects of NSAIDs (6). This hypothesis is, at least in part, supported by the common clinical observations of cross-reactivity within different NSAIDs with significant inhibitory effects on COX1 activity. Based on these premises, NSAIDs which are selective inhibitors of COX2 should be considered the most suitable alternative drugs for the management of NSAIDs-intolerant patients.

As far as the diagnosis is concerned, skin testing and RAST are of little or no value in the case of pseudoallergic reactions (7, 8), since the disease is not IgE-mediated. Recently, an *in vitro* assay, measuring the production of sulfidoleukotrienes from leukocytes after NSAIDs stimulation has been proposed, but its results

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were controversial (9). Therefore, the oral challenge with aspirin is still considered the most scientific diagnostic approach (10, 11). However, this test is considered unethical by the Consensus Report of the Italian Society of Allergology and Clinical Immunology; the document states that "challenges should be used for testing only alternative drugs and not those reported as responsible for previous reactions" (12).

From a practical viewpoint, we need to provide NSAIDs-intolerant patients with safe alternative analgesic/anti-inflammatory drugs. Acetaminophen has been considered for years the most suitable drug for these subjects, but very recently more selective COX2 inhibitors (e.g. nimesulide, meloxicam) began to be regarded as optimal alternatives (13, 14). In the present study we evaluated and compared the safety of these molecules, used as alternative drugs, in patients with adverse reactions to NSAIDs. Moreover we followed-up patients for a long period, since a single challenge test in hospital setting cannot be considered always as a certain predictor of subsequent drug tolerability, during illness and/or after multiple doses.

METHODS

STUDY DESIGN

Outpatients with well-documented pseudoallergic reactions were carefully selected based on definite criteria (see below). All patients underwent blindly an oral incremental-dose challenge with nimesulide and a subgroup of 88 subjects also with meloxicam, under controlled conditions. If the drug(s) were tolerated the patients were allowed to use them when needed. All the challenged patients were re-interviewed at 6-month intervals up to 2 years in order to assess whether the tested drugs had been taken without adverse events.

PATIENTS

During the period 1995-2000, 381 outpatients were studied. Out of them, 118 were male (31%) and 263 female (69%), aged between 16 and 72 years (mean age 53.2 yr.). They had previous pseudoallergic reaction due to a single (42%) or multiple (58%) NSAIDs. As shown in table 1, aspirin, pyrazolones and acetaminophen were most frequently responsible for pseudoallergic reactions. Clinical manifestations of NSAIDs intolerance in these patients were: urticaria/angioedema in 308 subjects (80.9 %), rhinitis/asthma in 61 (16%), anaphylactoid reactions in 12 (3.1 %).

The patients were selected according to the following criteria:

- > history of at least one pseudoallergic reaction during the past 12 months;
- > a documented relationship between the intake of the drug and the onset of symptoms (no more than 12 hours);
- > a single NSAID drug was taken before each episode
- > no previous adverse reaction to nimesulide or meloxicam
- > informed consent to undergo the challenge.

Drug	Cases
Aspirin	1222
Pyrazolone derivatives	123
Diclofenac	41
Acetaminophen	33
Piroxicam	23
Arilpropyones	31
Other	9

Table 1: Nonsteroidal anti-inflammatory drugs reported as causes of adverse reactions.

ORAL CHALLENGE PROCEDURE

All 381 subjects were challenged with nimesulide (Aulin[®], Roche, Milan, Italy), whereas only 88 of them were challenged with meloxicam (Mobic[®], Boehringer Ingelheim, Firenze, Italy), being this drug commercially available in Italy only since October 1998. The challenge test was performed in single-blind fashion, in three steps (table 2). A placebo was blindly administered at the beginning of each challenge.

Conditions required for starting the challenge with active drug were:

- > absence of cutaneous or respiratory symptoms;
- > FEV1 > 80% of the predicted value.
- > No drug intake during 48 hours preceding the test. Antihistamines, if any used, had to be withdrawn at least one week before challenge.
- > No reaction following placebo administration.

Drug	Day 1	Day 2	Day 4
Nimesulide	placebo	50 mg	100 mg
Meloxicam	placebo	7.5 mg	15 mg

Table 2: Schedule of challenge tests.

The challenges were performed in day-hospital regimen. Equipment and trained personnel for emergency resuscitation were available during the whole procedure. Respiratory function (FEV1), blood pressure and pulse rate were recorded before and 30 minutes after

placebo or active drug administration. All patients were seen again 24 hrs after the end of the challenge in order to exclude a delayed reaction. Pregnant women were also excluded.

The response to challenge was considered positive if one or more of the following symptoms appeared: erythema, urticaria/angioedema, rhinorrhea, nasal obstruction, sneezing, dyspnea or cough associated with a fall of FEV1 > 20% of the baseline, hypotension.

FOLLOW-UP

All patients were re-interviewed every 6 months up to 2 years after the challenge in order to determine whether they took the tested drugs, nimesulide or meloxicam. Patients were also questioned about the disease leading to use the drug and the possible onset of intolerance symptoms. If the patients reported not to have used the drugs, they were asked why: absence of illness or fear to take them.

RESULTS

Three hundred and seventy five out of 381 (98.4%) patients had no adverse reactions during nimesulide challenge and 84/88 (95.4%) tolerated meloxicam. Five out of the six nimesulide reactors had generalized urticaria (three at 50 mg and two at 100 mg); they were successfully treated with 10 mg clorpheniramine parenterally. One patient had an asthma attack (34% fall of FEV1), promptly resolved by 200 mcg inhaled albuterol. All these non-tolerant subjects had a history of multiple reactions to NSAIDs. Two had a history of urticaria also after acetaminophen administration. The four patients positive to meloxicam challenge had a generalized urticaria (one with 7.5 mg and three with 15 mg). Three out of the six nimesulide-intolerant patients could tolerate meloxicam, whereas, the remaining three did not. Only one of the patients intolerant to meloxicam could tolerate nimesulide.

During the follow-up 214/381 (56.1%) of challenged subjects took nimesulide at home. Among them, 90 (42%) took the drug once, and 124 (58%) used the drug twice or more. Most of these subjects used the drug for headache or for musculoskeletal pain (82%); only 18% used it during illnesses. Among these interviewed subjects 206 (96%) tolerated the drug, whilst five complained of urticaria and three discontinued nimesulide due to heartburn. Three of the non-tolerant patients suffered from urticaria on the first home-administration of nimesulide after challenge, whilst the other presented the symptoms at the third administra-

tion. Only one non-tolerant patient took the drug during a common cold. Most of subjects (167 patients) who did not take nimesulide again after challenge did not suffer of any pathological condition (95.2%), but few patients (4.8%) did not take the drug as suggested by their GP. Among meloxicam-tested subjects 31/88 (35.2%) took the drug again, mostly just once (91%). None of them reported pseudoallergic reactions, but two subjects stopped this treatment because of gastrointestinal side effects.

DISCUSSION

The management of patients with pseudoallergic reactions to NSAIDs is a complex problem in the clinical practice, because the mechanisms are unclear and because reliable diagnostic tests lack. Many physicians believe that patients who have displayed intolerance to one or more NSAIDs, simply have to be forbidden to take all members of this drug class. This approach is rarely considered satisfactory by the patients, which usually require to be told what drugs they can take in the case of need. Until now acetaminophen has been considered one of the most suitable alternative drugs, due to its long-term tolerability (15); nevertheless, a significant positive association between acetaminophen and asthma has been evidenced (16), a certain degree of cross-reactivity with ASA (17) and episodes of anaphylaxis due to its use have been reported (18).

The recent observations about the role of COX1 and its inhibition in the pathogenesis of aspirin-induced asthma and pseudoallergic reactions have suggested that the use of selective COX2 inhibitors would be an optimal choice; this hypothesis has been confirmed in previous clinical studies with nimesulide and meloxicam (13-15, 19-21). Some investigators have concluded that meloxicam is the preferential COX2 inhibitor with the most favorable ratio of COX2/COX1 inhibition (22), although other data suggest that the drug may exert a dose-dependent COX1 inhibition *in vitro* (23).

Our results, confirm the safety of nimesulide and meloxicam in NSAIDs intolerant patients and show that the rate of adverse reactions is very low and superimposable for the two drugs. Nimesulide-intolerant patients can sometimes tolerate meloxicam, whereas it is unlikely the opposite. The safety of the challenge with these alternative drugs is apparent as well: the occurrence of adverse events during challenge was low and the reactions were easily manageable. The follow-up results confirmed the clinical usefulness of the procedure, since a large percentage of patients could use the tested drugs. Due to ethical reasons (12), we could not

confirm the NSAIDs-intolerance by means of a specific challenge, therefore it is possible that false positive cases were included in our population. However, it has to be considered that a good reliability of clinical histories in NSAIDs-intolerant patients (24,25) has been demonstrated. Moreover we tried to limit the possible confounding factors by selecting subjects taking only one NSAID at the time of reaction, in order to exclude any interference of other drugs.

In conclusions the recent insight in NSAIDs intolerance show the crucial role of COX2- selective drugs for tolerability, thus the pharmacological properties of every NSAID may represent a reliable parameter in choosing alternative molecules. We propose that an oral challenge be routinely employed. It is easy to perform and provides a strong basis for the allergist in recommending a suitable compound to general practitioner and the patient.

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