

Tolerability to nabumetone and meloxicam in patients with nonsteroidal anti-inflammatory drug intolerance

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Background: Because nonsteroidal anti-inflammatory drug (NSAID) intolerance depends on COX-1 inhibition, preferential or selective COX-2 inhibitors have been thought to be well tolerated by these patients.

Objective: The aim of this study is to evaluate tolerability to nabumetone and meloxicam in patients with NSAID intolerance.

Methods: Seventy patients intolerant to NSAIDs were selected. Thirty subjects were patients with asthma with respiratory (rhinitis-asthma) intolerance to NSAIDs (group A); 40 patients (group B) had cutaneous-mucous (urticaria-angioedema) NSAID intolerance. Diagnosis was based on clinical histories in all patients, and it was confirmed by positive single-blind placebo-controlled oral challenge test in 36 patients. After written informed consent, a single-blind placebo-controlled oral challenge test with nabumetone in all patients (2 g except for 11 patients who reached 1 g) and meloxicam (15 mg) in 51 patients was performed.

Results: Ninety-four, 3%, tolerated 1 g nabumetone. In those who reached the 2-g dose, the tolerability was 83.6%. With respect to meloxicam, 96.1% of patients, tolerated 15 mg.

No significant difference in nabumetone and meloxicam tolerability was observed between groups A and B. **Conclusion:** The results of this study confirm a high percentage of tolerability to the maximum therapeutic dosage of nabumetone and meloxicam in patients with NSAID intolerance, both in those with cutaneous/mucous manifestations and in those with respiratory disease.

Clinical implications: Nabumetone and meloxicam are safe alternatives in NSAID-intolerant patients. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Nonsteroidal anti-inflammatory drug intolerance, nabumetone, meloxicam

Abbreviations used

NSAID: Nonsteroidal anti-inflammatory drug

PEF: Peak expiratory flow

SBPCOCT: Single-blind placebo-controlled oral challenge test

Patients with nonsteroidal anti-inflammatory drug (NSAID) intolerance experience either cutaneous-mucous (urticaria/angioedema) or respiratory (rhinitis/asthma) symptoms after taking these drugs. This reaction is provoked through the inhibition of the enzyme COX and thereby of prostaglandin and thromboxane synthesis. At least 2 isoforms of this enzyme exist: COX-1 is constitutively expressed in many cells, whereas COX-2 is not present in healthy tissues, and its expression is induced by inflammatory processes. NSAID intolerance is thought to be mediated through COX-1 inhibition.¹⁻³

Nonsteroidal anti-inflammatory drugs that poorly inhibit COX-1 such as acetaminophen or salsalate are frequently well tolerated by many patients.⁴ Unfortunately, these drugs have a relatively poor analgesic and anti-inflammatory potential. Other preferential or selective COX-2 inhibitors such as nimesulide or rofecoxib with anti-inflammatory efficacy and a good profile of tolerance in these patients have been withdrawn from the market because of relevant hepatic or cardiovascular adverse effects. Therefore, at this time, patients with NSAID intolerance continue to have poor alternatives to treat pain or inflammatory diseases.

Nabumetone and meloxicam are NSAIDs that preferentially inhibit COX-2. The aim of this study is to evaluate tolerability to nabumetone and meloxicam in patients with NSAID intolerance.

METHODS

Seventy patients intolerant to NSAIDs consecutively attended in our drug allergy department were included in this study: 37 females and 33 males, age 19 to 75 years (mean age, 43.4 years). The diagnosis was based on clinical histories in all patients (clear symptoms after taking 2 or more NSAIDs of different groups and on different occasions), and it was confirmed by positive single-blind

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TABLE I. Data from the 30 patients (group A) with asthma and NSAID hypersensitivity and the nabumetone and meloxicam tolerated doses

Patient no.	Sex	Age (y)	NSAID intolerance	Diagnostic	Nabumetone dose reached	Meloxicam dose reached
1	F	53	R/A-AE	CH	1 g	NP
2	F	28	A-U/AE	CH	1 g	15 mg
3	F	38	A-U/AE	SBOCT	1 g	15 mg
4	F	62	A	CH	2 g	15 mg
5	F	27	R	CH	2 g	15 mg
6	F	65	R-U/AE	CH	2 g	NP
7	M	28	A-AE	SBOCT	2 g	15 mg
8	M	30	A-U	SBOCT	2 g	R/A with 3.75 mg
9	M	36	A	SBOCT	2 g	15 mg
10	F	22	A	SBOCT	1 g, A with 2 g	15 mg
11	F	70	A	CH	2 g	NP
12	F	65	A	CH	2 g	NP
13	F	53	A	CH	2 g	NP
14	F	66	A	CH	2 g	NP
15	M	40	A	CH	2 g	NP
16	F	19	R/A	SBOCT	1 g, R/A with 2 g	15 mg
17	M	38	R/A	CH	2 g	15 mg
18	M	51	A	CH	2 g	15 mg
19	M	36	R/A	CH	2 g	15 mg
20	F	51	A	CH	2 g	15 mg
21	F	30	A	CH	2 g	15 mg
22	F	58	R/A	SBOCT	750 mg, R with 1 g	15 mg
23	M	47	A-U/AE	CH	2 g	15 mg
24	F	70	A-AE	CH	2 g	15 mg
25	M	46	R/A-U/AE	SBOCT	1 g, U R/A with 2 g	15 mg
26	F	69	A	CH	2 g	15 mg
27	F	42	A	SBOCT	A with 250 mg	15 mg
28	M	22	A	CH	2 g	15 mg
29	F	74	A	CH	2 g	15 mg
30	F	56	A	CH	2 g	15 mg

A, Asthma; AE, angioedema; CH, clinical history; F, female; M, male; NP, not performed; R, rhinitis; SBOCT, single-blind oral challenge test; U, urticaria.

placebo-controlled oral challenge test (SBPCOCT) in 36 patients. They were challenged with a NSAID different from those implicated in previous adverse reactions and with potent COX-1 inhibitory properties (aspirin or ketoprofen or indomethacin). Thirty subjects were patients with asthma with respiratory (rhinitis-asthma) intolerance to NSAIDs (group A); 10 of them also manifested mucous-cutaneous symptoms with NSAIDs. The remaining 40 patients (group B) had cutaneous-mucous (urticaria-angioedema) NSAID intolerance. Patients with active chronic urticaria or angioedema were not included because this disease activity as well as the antihistamine treatment could confuse the results of challenge tests. Patients with asthma were at a stable phase at the moment of the challenge test, documented by baseline spirometry (FEV₁ values had to be more than 70% of predicted values). Pregnant women were excluded.

After written informed consent, SBPCOCT with nabumetone and meloxicam were performed. β_2 -Agonist agents, ipratropium and tiotropium bromide, cromolyn and nedocromil sodium, and antileukotrienes were discontinued at the time of the challenge test. No patient required oral corticosteroids or antihistamines at this time. Patients with asthma/rhinitis patients continued their inhaled/nasal corticosteroid treatment at the same doses that had been controlling their symptoms. Both placebo (lactose) and drugs (nabumetone and meloxicam) were placed in white gelatin capsules by the pharmacy. Nabumetone SBPCOCT was made in all 70 patients: on day 1, 2 doses of placebo were administered. On day 2, patients were given 2 doses of 250 mg and 500 mg nabumetone with a 2-hour interval. On day 3, they received a dose of 1 g nabumetone. All patients

who tolerated 1 g, except for the 11 patients evaluated first, were given an additional dose of 2 g nabumetone on day 4. Meloxicam SBPCOCT was performed in 51 patients (23 in group A and 28 in group B) 15 days after nabumetone administration, as follows: 2 doses of placebo on day 1; 2 doses of 3.75 and 7.5 mg with a 2-hour interval on day 2; 15 mg on day 3. All patients were observed for a 3-hour period after the last dose drug challenge, evaluating the onset of cutaneous-mucous or respiratory signs or symptoms (pruritus, hives, erythema, angioedema, dysphonia, nasal stuffiness, rhinorrhea, cough, wheezes, dyspnea, and so forth) Peak expiratory flow (PEF) was registered before and after challenge with a peak flow meter, and also on day 1 with placebo (PEF values had to vary by less than 10% with placebo). Decreases in PEF by more than 15% after drug challenge were considered significant responses. Patients were advised to communicate any adverse reaction occurring during the next hours at home.

Fisher exact test was used to evaluate any statistical difference in tolerance to both drugs between groups A and B.

RESULTS

Results are shown in Table I (group A) and Table II (group B). Sixty-six of 70 subjects (94.3%) tolerated 1 g nabumetone (93.3% in group A and 95% in group B). Only 1 patient with asthma reacted to the first dose (250 mg) of nabumetone (patient 27 presented cough and chest

TABLE II. Data from the 40 patients (group B) with cutaneous-mucous NSAID intolerance and the nabumetone and meloxicam tolerated doses

Patient no.	Sex	Age (y)	NSAID intolerance	Diagnostic	Nabumetone dose reached	Meloxicam dose reached
31	F	38	U/AE	CH	1 g	NP
32	F	24	U/AE	SBOCT	1 g	15 mg
33	F	20	AE	SBOCT	1 g	15 mg
34	M	21	AE	CH	1 g	NP
35	M	70	U	CH	1 g	15 mg
36	M	48	U/AE	SBOCT	1 g	15 mg
37	M	49	U/AE	SBOCT	1 g	15 mg
38	M	30	AE	SBOCT	1 g	NP
39	M	52	U	SBOCT	2 g	15 mg
40	F	47	U/AE	SBOCT	2 g	NP
41	M	52	U	SBOCT	2 g	NP
42	M	53	U	SBOCT	2 g	15 mg
43	F	19	U/AE	CH	1 g, U with 2 g	15 mg
44	M	68	U/AE	SBOCT	2 g	15 mg
45	F	31	U	SBOCT	1 g, U with 2 g	15 mg
46	M	26	U	SBOCT	1 g, U with 2 g	15 mg
47	M	46	U	SBOCT	1 g, U with 2 g	15 mg
48	F	28	U	SBOCT	2 g	15 mg
49	M	42	U	SBOCT	2 g	NP
50	F	37	U	SBOCT	2 g	NP
51	M	52	AE	SBOCT	2 g	NP
52	M	64	U	CH	2 g	NP
53	M	24	U	CH	2 g	NP
54	M	64	U/AE	CH	2 g	NP
55	F	22	AE	CH	2 g	NP
56	F	36	U/AE	CH	2 g	15 mg
57	F	75	AE	CH	2 g	15 mg
58	F	42	AE	SBOCT	1 g, AE with 2 g	15 mg
59	F	65	U/AE	CH	2 g	15 mg
60	F	57	U/AE	CH	2 g	Not tolerated by CH
61	M	43	U/AE	SBOCT	1 g, U with 2 g	15 mg
62	M	26	U	SBOCT	2 g	15 mg
63	F	26	U/AE	SBOCT	2 g	15 mg
64	M	23	U	SBOCT	2 g	15 mg
65	M	41	U/AE	CH	2 g	15 mg
66	F	20	U/AE	SBOCT	750 mg, U with 1 g	15 mg
67	M	62	U	SBOCT	2 g	15 mg
68	F	26	AE	SBOCT	2 g	15 mg
69	M	38	U/AE	SBOCT	750 mg, U/AE with 1 g	15 mg
70	M	48	U/AE	CH	2 g	15 mg

A, Asthma; AE, angioedema; CH, clinical history; F, female; M, male; NP, not performed; R, rhinitis; SBOCT, single-blind oral challenge test; U, urticaria.

tightness with a significant decrease in PEF) and 3 patients reacted to the 1-g dose (patient 22 had oculonasal pruritus, teariness and sneezing; patient 66 had facial erythema and 1 hive on her arm; patient 69 had facial urticaria, dysphonia, and dysphagia). In those who reached the 2-g dose, the tolerability was 83.6% (46/55), 88% (22/25) in group A and 80% (24/30) in group B: 6 patients presented with urticaria, 1 had palpebral angioedema, and 3 had nasal and/or bronchial symptoms, with decreases in PEF by more than 15%.

With respect to meloxicam, 96.1% (49/51) of patients tolerated 15 mg, 95.6% (22/23) in group A and 96.4% (27/28) in group B (patient 8 in group A, showed rhinitis and bronchospasm with 3.5 mg; patient 60 in group B related an episode of urticaria/angioedema with meloxicam

in the previous clinical history, so meloxicam was not administered in this patient).

All adverse reactions were easily controlled with parenteral antihistamines and corticosteroids and inhaled β_2 -agonists. No significant difference in nabumetone and meloxicam tolerability was observed between patients with cutaneous-mucous or respiratory intolerance.

DISCUSSION

Because NSAID intolerance depends on COX-1 inhibition, preferential or selective COX-2 inhibitors have been thought to be well tolerated by these patients. Nimesulide, a preferential inhibitor of COX-2 with good anti-inflammatory

properties, has been proven to be tolerated by many of these patients,^{5,6} but it was withdrawn from the market in Spain because of renal and hepatic impairment (although it is available in other countries in Europe, Asia, and South America). In 1999, a new class of anti-inflammatory drugs, selective inhibitors of COX-2 such as celecoxib and rofecoxib, were introduced in the market.⁷ Several studies have shown a very good profile of tolerance to these drugs in this kind of patient.^{6,8-10} They are also well tolerated without gastroerosive side effects and have potent anti-inflammatory properties. Nevertheless, because of cardiovascular side effects, rofecoxib was withdrawn from the market.^{11,12} There are other selective COX-2 inhibitors commercially available, but their long-term use is limited because of these side effects, mainly in patients with cardiovascular disease. They are also expensive drugs, and the cost of the drug treatment for chronic osteomuscular inflammatory processes is high. Nabumetone and meloxicam are preferential COX-2 inhibitors. Both have shown anti-inflammatory efficacy similar to other NSAIDs, as well as a low incidence of gastroerosive side effects.¹³⁻¹⁸ Nabumetone is a prodrug of the 2,6-disubstituted naphthyl alkanone class. It is metabolized in the liver to its active metabolite, 6-methoxy-2-naphthylacetic acid. The optimum oral dosage is 1 g once daily, but an additional 0.5 to 1 g can be administered for patients with persistent symptoms. Its nonacidic chemical properties as well as its COX-1/COX-2 inhibitor profile are responsible for the low incidence of gastrointestinal ulcerations, perforations, and bleeding.¹⁵ Nabumetone is commercially available in the United States, Europe, Asia, Canada, South America, and South Africa. Meloxicam belongs to the oxycam group and is recommended at a dosage of 7.5 to 15 mg once daily. Meloxicam is available throughout the world, including the United States.

To our knowledge, there is only 1 report evaluating safety of nabumetone in patients intolerant to NSAID.¹⁹ In this report, Confino-Cohen and Goldberg¹⁹ studied 24 patients with clinical histories of intolerance reactions to at least 2 different NSAIDs on 2 different occasions. None of them had asthma. They received a single dose of 1 g nabumetone. Twenty-three patients tolerated nabumetone. One patient developed a single urticarial lesion on his eyelid. Tolerability to nabumetone had never been evaluated before in such a large group of patients and never in patients with asthma and NSAID hypersensitivity and reaching a dosage of 2 g.

There are some previous reports that demonstrate a good profile of tolerance to meloxicam in NSAID-intolerant patients.^{6,20-27} Most of them reached a 7.5 mg dose, but Gala and Fernández²⁸ reported a 100% tolerance to meloxicam in 20 NSAID-intolerant patients, reaching a dosage of 22.5 mg. Only 2 of these patients had asthma, and 8 of them were diagnosed with rhinitis. Therefore, our study confirms a high tolerability to higher doses of meloxicam (15 mg) in a large group of patients, including cutaneous/mucous and respiratory NSAID-intolerant subjects.

In conclusion, the results of this study confirm a high percentage of tolerability to maximum therapeutic dosage

of nabumetone and meloxicam, similar for both drugs, in patients with NSAID intolerance, both in those with cutaneous/mucous manifestations and in those with respiratory disease. Although tolerability to nabumetone and meloxicam is very high, it should always be previously verified by an allergologist before prescribing the drug to NSAID-intolerant patients, especially in patients with asthma, because severe adverse reactions could exceptionally occur.

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