

Tolerability of nimesulide in aspirin-sensitive patients

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In most patients with aspirin and nonsteroidal antiinflammatory drug (NSAID) intolerance, antiinflammatory treatment is a clinical problem. In this study we evaluated the tolerance to a new nonsteroidal antiinflammatory drug, nimesulide (Aulin, Boehringer Mannheim, Italia), in 429 patients presenting with clear histories of intolerance to NSAIDs. Nimesulide has been chosen due to its weak inhibitory action on cyclooxygenase and its peculiar mechanism of action. We carried out a single-blind challenge with cumulative doses of nimesulide administered on three different days, until the therapeutic dose of 200 mg or intolerance symptoms were reached. Nimesulide has been well tolerated in 418 subjects and only 11 patients (3.3%) showed a positive test. Our study demonstrates that nimesulide seems to be a suitable drug in aspirin hypersensitivity.

2.6 %

INTRODUCTION

Acetylsalicylic acid (ASA), pyrazolones, and all nonsteroidal antiinflammatory drugs (NSAIDs) are among the most frequently prescribed drugs in medical practice, due to progressive increase in indications for their use. Their widespread use explains the very high incidence of side effects.¹ Allergic or pseudo-allergic reactions to ASA and/or NSAIDs affect a percentage of the general population varying from 0.3 to 0.9%.^{2,3} This percentage markedly increases in adult asthmatic patients (10%) and reaches 30% to 40% of patients with the ASA-triad, characterized by ASA-intolerance, nonallergic asthma, and nasal polyps.⁴

The clinical symptoms of ASA-intolerance are bronchial asthma and/or rhinitis, urticaria/angioedema, and anaphylactoid shock.⁵

The mechanism of aspirin sensitivity is still unknown.^{6,7} Inhibition

of cyclooxygenase by aspirin and other NSAIDs has been proposed to cause shunting of arachidonic acid to the 5-lipoxygenase pathway, thereby increasing production of leukotrienes, LTC₄, LTD₄, and LTE₄, which are potent spasmogens for nonvascular smooth muscle.⁸ Analgesics that do not affect cyclooxygenase do not provoke bronchospasm.⁹ In the light of widespread use of ASA and NSAIDs, the use of alternative drugs is a clinical problem for the management of ASA-intolerant patients.

In the present study we have evaluated in "aspirin-sensitive" subjects tolerability to nimesulide, a newly available antiinflammatory drug, the safe use of which in ASA-intolerant patients has been reported anecdotally¹⁰⁻¹² and is based on its peculiar mechanism of antiinflammatory action and its weak inhibition of cyclooxygenase.¹³⁻¹⁵

MATERIALS AND METHODS

Our study was carried out in 429 subjects: 163 males (36%) and 266 females (64%) aged between 14 and 66 years (mean age 39.4; SD $\pm$ 20.1) and selected according to the following criteria:

(1) Documented intolerance to ASA, pyrazolones and/or NSAIDs, clinically manifested as urticaria/angioedema (71%), asthma (22%),

or anaphylactoid shock (7%) in the 6 months prior to the study. On the basis of the certainty of the anamnestic data we decided for ethical reasons not to effect the ASA challenge by oral route. The intolerant reactions to the different drugs were ASA = 150 subjects (35%), pyrazolones = 77 subjects (18%), ASA + pyrazolones = 159 subjects (37%), other NSAIDs = 43 subjects (10%), respectively naproxen (13), diclofenac (17), piroxicam (11), nabumetone.²

(2) Obtaining an informed consent by every patient submitted to provocation testing with nimesulide.

The provocation test was carried out in single-blind fashion by the oral route in three sessions. In order to perform the nimesulide challenge, patients with urticaria had to be symptom-free for at least 1 month prior to the challenge; asthmatic patients had to have an FEV₁ $\geq$ 70% of the predicted value before starting the provocation test.

The drugs' withdrawal period was 24 hours for cromolyn and sympathomimetics and 1 week for all antihistamines except astemizole, for which it was 60 days.

On the first day three placebo tablets were administered, one every three hours. In the following two sessions cumulative dosages of ni-

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Supported in part by Boehringer Mannheim, Italia, Milano, Italy.

Received for publication December 31, 1992.

Accepted for publication in revised form July 2, 1993.

mesulide (Aulin, Boehringer Mannheim, Italia) were administered: 75 mg in the second session and 200 mg, a dosage equal to that normally used in therapy, in the third session (Table 1). Between the second and the third session an interval of at least 48 hours elapsed to exclude possible delayed reactions. Before each administration of the drug and at the end of the provocation test the patient also performed pulmonary function testing to exclude the possibility of a bronchospastic reaction provoked by the nimesulide.

At the end of the provocation test the patient was asked to return after 24 hours to exclude a delayed reaction. A positive reaction was defined as (1) appearance of urticaria/angioedema, (2) a $\geq 20\%$ decrease of FEV₁ from baseline, and (3) occurrence of nasal or ocular symptoms.

RESULTS

Of the 429 patients submitted to the provocation test, 11 patients (2.6%) showed a positive test. In ten patients the appearance of widespread urticaria was noticed at the cumulative dosage of 100 mg in seven subjects and of 200 mg in three others. These side effects have been successfully treated with antihistamines (cetirizine, 10 mg per day for three days). One patient complained of urticaria and laryngeal edema at the cumulative dosage of 75 mg and was successfully treated with epinephrine (0.5 mg SC), betamethasone (4 mg IV), and cetirizine (10 mg PO). The remaining 418 subjects tolerated the 200 mg dosage well without signs of immediate or delayed reactions. No bronchospastic reactions were recorded. Mild gastrointestinal symptoms occurred in 22 (5%) subjects.

Table 1. Challenge Test with Nimesulide

	Day 1	Day 2	Day 3*
Baseline	placebo	25 mg	100 mg
3 h	placebo	25 mg	100 mg
3 h	placebo	25 mg	
Cumulative dose		75 mg	200 mg

* 48 hours later.

An ASA challenge was performed in the 11 patients with positive responses to nimesulide challenge. All patients had urticaria at various doses of aspirin. Details about these 11 positive patients are shown in Table 2.

DISCUSSION

On the basis of our study nimesulide seems to be a safe drug in ASA- and/or NSAID-intolerant patients. In fact also taking into account the possibility that 15% of all patients studied have false positive reactions to aspirin, the incidence of cross-reactivity between aspirin/NSAIDs and nimesulide in our study of 3.1% is lower than the cross-reactivity of acetaminophen, considered a safe drug in patients with ASA intolerance.⁵ The weak inhibition of cyclooxygenase is a common feature of nimesulide and acetaminophen,¹⁴⁻¹⁶ a drug well tolerated by patients with ASA sensitivity even though cross-reactivity occurs in 4% to 6% of patients, mostly at high doses (>1000 mg).¹⁷⁻¹⁹ Acetaminophen, however, has less antiinflammatory activity than nimesulide.²⁰

An aspirin challenge could have avoided false positive cases; however, an informed consent about aspirin challenge would have been difficult to obtain in these patients. Further, the very low percentage of side effects, which were very mild, and the large number of patients

enrolled lead to the conclusion that nimesulide is a safe drug in ASA intolerance.

The reasons for this good tolerability of nimesulide in ASA intolerance are not clear but the following explanations can be suggested.

Nimesulide is a methane-sulfonamide compound (Fig 1), with marked antiinflammatory, antipyretic, and analgesic properties.¹⁵⁻¹⁶ The rationale for the development of nimesulide originated from the observation that the use of other nonsteroidal antiinflammatory drugs, acting mainly through prostaglandin (PG) synthesis inhibition, is associated with serious drawbacks, ASA/NSAID-intolerance included. Indeed the reduction of PG levels is thought to be responsible not only for their thera-

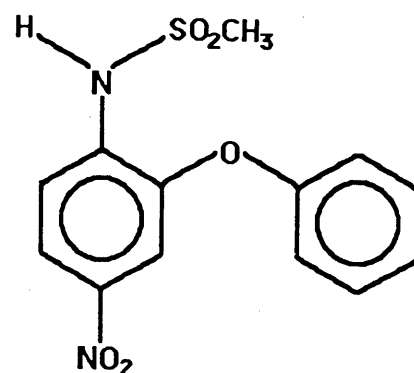


Figure 1. Chemical structure of nimesulide.

Table 2. Data Concerning Patients with Nimesulide Positive Challenges

Pts	Age, yr	Sex	Clinical Features of Nimesulide Intolerance	Provocative Dose	Clinical Features of ASA Intolerance	Provocative Dose of ASA
1	31	F	U*	100 mg	U	10 mg
2	43	F	U	100 mg	U	10 mg
3	51	M	U	200 mg	U/A	10 mg
4	29	F	U	100 mg	U	50 mg
5	38	F	U	100 mg	U/A	10 mg
6	46	M	U/LE	75 mg	U/A	10 mg
7	39	F	U	100 mg	U	50 mg
8	32	F	U	100 mg	U/A	10 mg
9	56	M	U	200 mg	U	10 mg
10	61	F	U	200 mg	U	10 mg
11	60	M	U	100 mg	U	10 mg

* U = urticaria, A = angioedema, LE = laryngeal edema.

peutic efficacy but also for well-known adverse effects, especially gastrointestinal disorders.¹⁵ To overcome these limitations, antiinflammatory compounds displaying alternative modes of action were investigated, leading to the characterization of the methane sulfonanilides, a new class of compound with a weak effect on the cyclooxygenase pathway.^{14,22} The presence in nimesulide of a functional sulfanilidic group instead of the more conventional carboxylic (indomethacin, naproxen, ibuprofen), enolic (phenylbutazone, piroxicam), or hydroxylic groups is considered to be an important determinant of the potential efficacy and safety of these compounds in the control of the inflammatory response. The mechanism by which nimesulide seems to affect the inflammatory process involves other inflammatory mediators in addition to PGs, such as toxic oxygen derivatives and histamine.¹⁵ Nimesulide affects the production of superoxide anions by activated polymorphonuclear leukocytes without any modification of the chemotactic properties of these cells.^{23,24} So the good tolerability of nimesulide in patients with respiratory intolerance to NSAIDs can be attributed, at least in part, to its capacity to reduce the generation of reactive oxygen species from bronchial inflammatory cells, which may contribute to the development of the bronchial obstructive reactions to NSAIDs.^{25,26} Further, an interesting property of nimesulide not shared by other NSAIDs such as indomethacin is the reduction of histamine release in vitro²⁷ and in vivo.²⁸⁻²⁹ These findings indicate that nimesulide appears to have a good potential among the NSAIDs for use as an antiinflammatory in asthmatic patients, particularly in aspirin-intolerant subjects.

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PULMONARY TOXICITY OF GAS DUE TO OVERHEATING IN A MICROWAVE OVEN

A few minutes after a woman removed cooking potatoes from her microwave oven because of the appearance of smoke, the two parakeets that were in the kitchen dropped dead. Half an hour later the woman became dyspneic and began to cough. Physical examination disclosed tachypnea, tachycardia, harsh vesicular breath sounds, and crepitant rales. There was leukocytosis. Arterial oxygen saturation was 89%. Chest radiographs disclosed a diffuse, fine reticular pattern at the lung bases. Pulmonary function testing disclosed a restrictive defect with decreased diffusion capacity. Improvement followed treatment with supplemental oxygen and intravenous prednisolone.

Examination of the dead parakeets revealed pulmonary atelectasis and hyperemia with alveolar and bronchial hemorrhage consistent with toxic damage due to a poisonous gas. Inspection of the oven disclosed a Teflon block used as an axle for a rotating platform had partially melted and was the probable source of the toxic gas. Investigators were unable to identify a cause for the overheating.

Fluoropolymers, including Teflon (polytetrafluoroethylene) are fire resistant, but in nonflaming conditions their thermal degradation products can be highly toxic. Overheating of nonstick, Teflon-coated frying pans can produce toxic fumes.

The authors indicate inhalation of an aerosol of 1% calcium chloride is a specific antidote.

—RMS

Zanen AL, Rietveld AP. Inhalation trauma due to overheating in a microwave oven. *Thorax* 1993;48:300-2.