

# Aspirin and paracetamol tolerance in patients with nimesulide-induced urticaria

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**Background:** The administration of aspirin and other nonsteroidal anti-inflammatory drugs in patients sensitive to nimesulide might be hazardous.

**Objective:** To assess the tolerance to both acetaminophen (paracetamol) and aspirin in patients with a history of urticaria induced by nimesulide.

**Methods:** Nine patients with a history of nimesulide intolerance were submitted to single-blind, placebo-controlled peroral challenges with increasing doses of acetaminophen and aspirin.

**Results:** Acetaminophen was tolerated by all patients, whereas two experienced immediate systemic urticaria after the administration of 125 mg of aspirin.

**Conclusion:** Acetaminophen and aspirin are well tolerated by most nimesulide-sensitive patients. Since a minority of patients show aspirin sensitivity, tolerance of this agent should always be ascertained by properly performed peroral challenges.

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## INTRODUCTION

In most patients with pseudo-allergic reactions induced by aspirin or related nonsteroidal anti-inflammatory drugs, nimesulide (4-nitro-2-phenoxyethanesulfanilide), along with acetaminophen (paracetamol), represents a well-tolerated alternative drug.<sup>1-3</sup> This fact is probably associated with its weak inhibitory effect on cyclooxygenase,<sup>4</sup> an enzyme generally considered of crucial importance in the pathogenesis of adverse reactions induced by anti-inflammatory drugs. Nimesulide's anti-inflammatory effects are most probably related to its oxygen radical-scavenging activity and to the inhibition of superoxide anion production.<sup>2,5</sup> Nimesulide intolerance is rare<sup>3</sup>; nonetheless, some patients experience their first episode of drug-induced urticaria after the ingestion of this agent. In these subjects, the administration of full dose aspirin or other nonsteroidal anti-inflammatory drugs might be hazardous since nimesulide intolerance might represent the first sign of a more gen-

eral intolerance to anti-inflammatory drugs. It is generally accepted that with most drugs, the only way to rule out intolerance is to administer a test dose, followed by increments up to the scheduled therapeutic dose, by the route used in treatment.<sup>3,6</sup> In this study, tolerance to both acetaminophen and aspirin was assessed in nimesulide-sensitive subjects.

## PATIENTS AND METHODS

Nine patients (two men and seven women; mean age 39 years, range 22 to 65 years) seen at this allergy center between January 1993 and December 1997 were studied. All had an unequivocal clinical history of recent episodes of systemic urticaria/angioedema following nimesulide administration. One of them had experienced two episodes of urticaria. In two other patients nimesulide-induced urticarial rash was associated with Stevens-Johnson syndrome and with laryngeal edema, respectively. Three patients suffered from respiratory allergies and two had a history of intolerance to drugs other than nimesulide (sulfamethoxazole-trimethoprim and penicillins, respectively). Tolerance to both acetaminophen and aspirin was assessed by single-blind, placebo-con-

trolled peroral challenges. Doses given were (1) paracetamol: day 1 = 125 mg, 250 mg, 500 mg; and (2) aspirin: day 1 = 50 mg, 125 mg; day 2 = 250 mg, and 500 mg. Placebo capsules were given at the beginning of each session. Doses were given one hour apart and patients were controlled for at least one hour after the last provocative dose. Patients were also seen on day 2 (paracetamol) or 3 (aspirin) in order to detect possible late reactions. The two study drugs were challenged at least 1 week apart. All patients gave an informed written consent before each challenge session.

## RESULTS

All patients tolerated paracetamol. Two of nine (22%) patients had urticaria 45 to 60 minutes after the administration of 125 mg of aspirin; rash was easily controlled by conventional therapy. These subjects did not suffer from respiratory allergy; one had a history of drug intolerance (penicillins). Clinical findings and challenge tests results are summarized in Table 1.

## DISCUSSION

This study aimed to assess acetaminophen and aspirin tolerance in patients who experienced the first episode of urticaria induced by anti-inflammatory drugs after the ingestion of nimesulide. The results of peroral challenges clearly show that seldomly does nimesulide sensitivity represent the first clinical sign of a more generalized intolerance to nonsteroidal anti-inflammatory drugs. Most patients with nimesulide intolerance seem to have a true allergic (IgE-mediated ?) sensitivity. By contrast, in a minority of nimesulide intolerant patients, cyclooxygenase inhibition seems to represent the relevant pathogenetic mechanism.

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Table 1. Clinical Features and Challenge Tests Results

| Patient* | Sex | Age | Respiratory Allergy | Other Drug Intolerance | Challenge Tests |     |
|----------|-----|-----|---------------------|------------------------|-----------------|-----|
|          |     |     |                     |                        | ASA             | PAR |
| A.E.     | M   | 22  | +                   | —                      | —               | —   |
| C.L.     | F   | 50  | —                   | —                      | —               | —   |
| D.P.     | M   | 26  | —                   | S†                     | —               | —   |
| F.M.     | F   | 53  | —                   | —                      | +               | —   |
| G.C.     | F   | 30  | +                   | —                      | —               | —   |
| M.T.     | F   | 35  | —                   | P‡                     | +               | —   |
| O.L.     | F   | 28  | +                   | —                      | —               | —   |
| P.A.     | F   | 46  | —                   | —                      | —               | —   |
| P.M.     | F   | 65  | —                   | —                      | —               | —   |

\* All patients had a history of urticaria/angioedema after ingestion of nimesulide. In patients G.C. and P.A. the drug also induced laryngeal edema and Steven-Johnson syndrome, respectively.

† S = sulfamethoxazole.

‡ P = penicillins.

Due to the presence of this last subgroup, peroral challenges with alternative anti-inflammatory drugs always should be performed in nimesulide-sensitive patients. Such procedures are potentially hazardous and should be carried out by trained personnel and in an adequately equipped setting.

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