

Long-term tolerability of nimesulide and acetaminophen in nonsteroidal anti-inflammatory drug-intolerant patients

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Background: Oral challenges are used to identify alternative nonsteroidal anti-inflammatory drugs (NSAIDs) for patients who react adversely to drugs of this class, but challenge conditions often differ from those in which the drug will actually be used.

Objective: To determine whether the results of oral challenges with nimesulide or acetaminophen, using cumulative administration of a single therapeutic dose while the patient is in good health, can predict the response to multiple doses of the drug during future illness.

Methods: Follow-up interviews were conducted with 248 NSAID-intolerant subjects who had tolerated oral challenges with nimesulide and/or acetaminophen 1 to 3 years earlier. We analyzed the adverse reaction rate in light of the febrile/non-febrile nature of the condition treated and the number of doses consumed.

Results: Nimesulide was tolerated by 115/122 (94.2%) of the patients who had tried it; acetaminophen by 71/75 (94.6%). A total of 8/159 (5%) patients had experienced reactions (seven urticarial and one asthmatic) to one or both drugs. Intolerance was unrelated to the nature of the condition treated or the number of doses administered, but all four patients who failed to tolerate acetaminophen and 3/7 of those who reacted to nimesulide had histories of chronic urticaria.

Conclusions: Oral challenges can reliably predict long-term NSAID tolerability in patients with previous adverse reactions to other drugs of this class, except for patients with chronic urticaria.

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INTRODUCTION

The frequency of adverse reactions such as asthma, rhinitis, urticaria/angioedema and anaphylaxis associated with nonsteroidal antiinflammatory drugs (NSAIDs) is higher than that of most other commonly used drugs.¹⁻³ These events are particularly common in patients with chronic asthma or urticaria.^{4,5} Although the first case of an adverse reaction to aspirin was reported almost a century ago (Hirsch-

berg, 1902),⁶ the mechanism(s) underlying NSAID intolerance has yet to be defined. One of the hypotheses that is widely accepted is that, in susceptible individuals, aspirin and other NSAIDs trigger a nonspecific activation of basophils and mast cells that would explain the urticarial/angioedematous and anaphylactoid reactions associated with these drugs.^{7,8} A fundamental role appears to be played by the blockade of cyclo-oxygenase produced by these drugs,^{9,10} which results in an overproduction of leukotrienes from arachidonic acid.^{5,11} This hypothesis is supported by clinical observations of cross-reactivity to various NSAIDs with significant inhibitory effects on cyclo-oxygenase activity.^{4,11,12-16}

Many physicians feel, therefore, that patients who have displayed intoler-

ance to one or more NSAIDs should avoid all members of this drug class. Skin testing and in vitro assays such as the RAST are of little help in these cases, since most of these reactions are pseudoallergic,¹⁷ ie, not mediated by the immune system. The only currently available alternative to a complete ban is to identify an alternative NSAID that is well tolerated by administration of oral challenges.¹⁸ In a number of studies, nimesulide and acetaminophen challenges have proved to be better tolerated by patients who have reacted to other NSAIDs.^{5,14,19-22} Since these challenges involve the administration of a single therapeutic dose when the patient is in good health, the lack of reaction might be a poor indicator of the drug's tolerability during illness and/or the administration of multiple doses. The present study furnishes follow-up data on 248 patients with histories of adverse reactions to one or more NSAIDs, all of whom appeared to tolerate nimesulide and/or acetaminophen based on oral challenges performed between January 1992 and December 1994. Follow-up interviews were conducted to determine the long-term tolerability of these alternative drugs in these subjects under actual clinical conditions.

PATIENTS AND METHODS

The original study population consisted in 248 subjects (78 males and 170 females) ranging in age from 4 to 85 years (mean: 37 years) who had experienced two or more episodes of intolerance to NSAIDs 6 to 24 months prior to our workup. In 132 cases, reactions had been provoked by a single drug or by more than one drug of the

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same class (single intolerance group = SIs). The remaining 116 had experienced reactions to two or more NSAIDs of different classes (multiple intolerance group = MIs). The adverse manifestations described by the patients included urticaria/angioedema in 212 cases, rhinitis/asthma in 14, and anaphylactoid reactions in 5. As shown in Table 1, the drugs most frequently implicated in the reactions were the pyrazolones, aspirin, and acetaminophen.

Between January 1992 and December 1994, oral challenges with nimesulide (Aulin, Boehringer Mannheim, Milan, Italy) and/or acetaminophen (Tachipirina, Angelini, Ancona, Italy) were administered to all 248 subjects (unless one of these two drugs had been associated with a previous reaction). Informed consent was obtained from all subjects. In order to avoid provoking unnecessary risk and discomfort, and in light of findings indicating the reliability of patients' reports in cases of this type,^{18,21} intolerance to drugs identified by the patients was not confirmed with challenges. At the time of testing none of the patients presented clinically relevant cutaneous or respiratory tract symptoms, 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.

Challenges were administered, as described in a previous study,²³ under

single-blinded conditions after an overnight fast. Equipment and personnel for emergency resuscitation were present during all tests. Briefly, 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 in the same manner using divided doses of nimesulide (25 mg followed by 75 mg for a total therapeutic dose of 100 mg) or acetaminophen (125 mg + 375 mg = 500 mg). In the 157 subjects challenged with both drugs, the second challenge was performed at least 1 week after the first to avoid the refractory period that generally follows positive reactions.²⁴ All patients remained in the day hospital under medical supervision for six hours after each challenge and were seen in the outpatient department the next day to determine whether any reactions had occurred after discharge. Any symptoms that developed after the outpatient interview were to be reported to our staff by telephone.

From 1 to 3 years after testing, all the patients were interviewed to determine whether they had used the alternative drug suggested by our staff on the basis of responses to the above challenges (ie, nimesulide and/or acetaminophen). Those who had were then questioned about the conditions under which they had used the drug (in particular, whether or not the condition treated had been associated with fever), the number of doses taken and any reactive symptoms that might have developed. The data for each of the two drugs were then compared using the Fisher exact test.

RESULTS

Based on oral challenge results, 157/248 (63.3%) patients appeared to tolerate both nimesulide and acetaminophen, 60 (24.2%) nimesulide alone, and 31 (12.5%) acetaminophen alone.

At the time of our follow-up interview, 159 of the patients had actually used one or both of the drugs prescribed for them, and eight (5%) had experienced adverse reactions.

Thirty-eight had taken both nimesulide and acetaminophen on separate occasions. In 35 (92.1%) of these cases, both drugs had been well tolerated. In the remaining three (7.9%), each of the drugs had provoked urticarial reactions. None of these 38 patients had failed to tolerate only one of the two drugs.

Eighty-four other patients had used only nimesulide, which was tolerated by all but four (4.8%). One of the latter four patients suffered acute asthma; the remaining three had developed urticaria. Of those 37 patients who had used only acetaminophen, 36 had tolerated the drug, and one (2.7%) had experienced urticaria.

Considering each drug separately, nimesulide had been tried by a total of 122 patients and well-tolerated by 115 (94.2%), while acetaminophen was tolerated by 71 (94.6%) of the 75 who had used it.

An analysis of the eight patients who reacted to drugs that had been well-tolerated in challenge tests showed that seven had experienced urticarial reactions and the eighth had suffered acute asthma on the third day of treatment (nimesulide 100 mg tid). In the latter case, similar reactions had been provoked in the past by aspirin, pyrazolones, and diclofenac, and there was a history of chronic, nonseasonal rhinitis (with negative allergologic findings) and nasal polyps. The seven cases of urticarial reactions included four patients (one who had reacted to acetaminophen and three who had reacted to both drugs) with histories of chronic urticaria.

Fisher's exact test revealed no correlation between lack of tolerance and the febrile/non-febrile nature of the condition treated, the number of doses taken (single versus multiple) or the SI/MI status of the patient (based on the initial history). In contrast, the percentage of patients with histories of urticaria among those who had not tolerated the drugs we prescribed (4/8; 50%) was significantly higher than that found among the group that had not suffered reactions (27/151; 17.8%) ($P < .05$). This difference was also

Table 1. Nonsteroidal Anti-inflammatory Drugs Reported as Causes of Adverse Reactions

Drug	Cases
Pyrazolone derivatives	147
Aspirin	144
Acetaminophen	26
Diclofenac	15
Ibuprofen	12
Piroxicam	10
Nimesulide	9
Naprossene	7

evident when the two drugs were considered separately. All four of those who had experienced reactions to acetaminophen (100%), but none of the 60 who had tolerated the drug (0%), suffered from chronic urticaria ($P < .001$). Among those who had used nimesulide, histories were positive for chronic urticaria in 10/115 who had tolerated the drug (8.7%) and in 3/7 of those who experienced reactions (42.9%) ($P < .05$).

DISCUSSION

History of an adverse reaction to an NSAID is considered by some authors to be a contraindication to future use of the implicated drug,²⁰ but, in many cases, an alternative NSAID must be identified. In cases of this type, nimesulide and acetaminophen are often well tolerated, probably because their mechanism of action is related primarily to their oxygen radical-scavenging activity and their inhibition of superoxide anion production, rather than to their inhibition of cyclo-oxygenase activity, which is limited.^{5,14,19-22}

The only way to confirm the safety of these drugs in an NSAID-intolerant patient is by oral challenge.¹⁸ These tests are generally administered while the patient is in good health and conditions like asthma or underlying urticaria are in remission. In addition, the cumulative dose administered is equal to a single therapeutic dose. Nimesulide and acetaminophen are commonly found to be tolerated in challenges of this type, but there are relatively few data available on the persistence of this tolerability, particularly for nimesulide.²⁵

The present study was conducted to determine whether tolerance demonstrated in this manner would prove to be a reliable predictor of the patient's response during illness when multiple doses might be taken.

Our follow-up revealed long-term tolerance of nimesulide and acetaminophen in, respectively, 94.2% and 94.6% of the patients who had used these drugs after our challenge. The reactions that did occur appeared to be unrelated to the MI/SI status of the

patient, the febrile/non-febrile nature of the condition being treated or to the total dose administered.

Almost all of the reactions (6/7 related to nimesulide and all four of those provoked by acetaminophen) consisted of urticarial eruptions. In the remaining case, the patient experienced acute asthma on the third day of treatment with nimesulide. This reaction was similar to those provoked in the past by various other NSAIDs, and its characteristics suggest the possibility of a dose-related effect, since a single dose of the same drug had been well tolerated in the challenge. However, we cannot exclude the possibility that the patient's attack was a spontaneous occurrence unrelated to the drug.

It is also worth noting that three of the patients who reacted to nimesulide and all four of those who failed to tolerate acetaminophen had histories of chronic urticaria. Other groups have also observed that this condition appears to be a risk factor for NSAID intolerance.^{4,5,26-29} While oral challenges with a therapeutic dose of the trial drug can be useful in identifying alternative NSAIDs for most patients who have had adverse reactions to other drugs of this class, the results observed in patients with histories of chronic urticaria are much less reliable indicators of future responses. In these cases, the only solution may be premedication with antihistamines³⁰ and steroids or mast cell stabilizers.^{31,32}

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EVALUATION OF CROSS-REACTIVITY BETWEEN AMOXICILLIN AND CEPHADROXIL

To evaluate possible side-chain sensitization in patients with allergy to amoxicillin who had tolerated parenteral challenge with penicillin G the authors challenged 16 patients with cephadroxil, which has a side chain identical to that of amoxicillin. Allergy to amoxicillin was confirmed by positive skin tests in 11 (25 mg/mL) and by oral challenge in 5 (25 mg or 50 mg). Oral challenge with cephadroxil, up to 500 mg, elicited immediate allergic reactions (urticaria and generalized pruritus) in two at 250 mg and 500 mg. The other 14 tolerated cephadroxil.

These observations indicate allergy to the side chain of amoxicillin has little clinical relevance in patients with allergy to amoxicillin but not to penicillin. Others have reported patients with positive skin tests to ampicillin and negative skin tests to penicilloyl polylysine and a minor determinant mixture of penicillin, most of whom (nine of ten) tolerated oral cephalixin, which has a side chain identical to that of ampicillin. The IgE in such patients must be directed against an epitope different from the side chain and the β -lactam ring.

—RMS

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