

Short communication

Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal anti-inflammatory drugs

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This study evaluated the risk factors for developing allergic reactions to alternative drugs such as acetaminophen and nimesulide in 367 patients intolerant of nonsteroidal anti-inflammatory drugs (NSAID) compared to 243 healthy controls. All subjects were given test doses (TD) of acetaminophen and nimesulide, and age, sex, atopy, and history of reactions also to unrelated drugs were compared in those who reacted and those who were tolerant of the challenge. TD was positive in 49 of 367 (14%) NSAID-allergic patients and in one (0.4%) of the controls ($P < 0.001$). No difference was found in age and sex between the TD-positive and TD-negative subjects, although a significantly larger number of females were NSAID allergic ($P < 0.01$). Of the 367 patients, 208 had a history of reactions only to NSAID, and 148 to NSAID and antimicrobial drugs (AMD). TD with acetaminophen or nimesulide was positive in 6% of patients intolerant only of NSAID and in 24% of those intolerant of both NSAID and AMD, with an odds ratio of 4.82. Atopy was more frequent among patients (36%) than controls (23%) ($P = 0.004$), among TD-positive (51%) than TD-negative patients (33.5%) ($P < 0.02$), and among patients intolerant of NSAID and AMD (48%) than those intolerant only of NSAID ($P = 0.006$). The odds ratios were, respectively, 1.87, 2.57, and 3.16. This study provides evidence that atopy and history of allergic reactions to AMD increase the likelihood of intolerance of usually well-tolerated alternative drugs such as acetaminophen and nimesulide in subjects allergic to NSAID.

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Nonsteroidal anti-inflammatory drugs (NSAID), such as acetylsalicylic acid (ASA) and pyrazole derivatives, are among the drugs most frequently involved in allergic reactions (1, 2). This problem concerns a large number of outpatients, the majority of whom report a history of systemic reactions to several NSAID. Acetaminophen and nimesulide are generally accepted as alternative drugs in NSAID-allergic patients, but allergic reactions to these drugs have also been described (3, 4). It is

therefore often difficult for the general practitioner to prescribe a safe alternative drug to treat common conditions such as pain or flu, without an appropriate challenge test conducted in an allergy department. Knowledge of the factors increasing the risk of systemic reactions to NSAID could improve the management of patients allergic to these drugs.

Little is known about whether atopy facilitates allergic reactions to drugs, as atopy has been

usually related more to the severity than the frequency of the reactions (5). It is also not clear whether allergic reactions to a NSAID increase the risk of allergic reactions to drugs of other classes.

The aim of this study was to evaluate the factors increasing the risk of reaction to acetaminophen and nimesulide in a large population of patients with a history of allergy to NSAID. We did provocation tests with acetaminophen and nimesulide in 610 subjects (367 NSAID allergic and 243 non-allergic) and checked the role of factors such as atopy, age, sex, and previous reactions to different drugs in relation to the risk of reaction to challenge.

Material and methods

Study groups

Patients. All the patients referred to the allergy clinics of the University First Department of Internal Medicine and the Buzzi Hospital in Milan for allergic reactions to NSAID from January 1991 to January 1993 were enrolled in the study. A careful clinical history was collected for each patient, listing every single drug, either NSAID or antimicrobial drug (AMD), involved in allergic episodes and the symptoms arising in each allergic episode. Only patients producing well-documented data from medical reports were considered.

Controls. In the same period, a comparable number of subjects without allergic reactions to drugs was collected from the hospital nonallergic outpatient population, as a control group.

In patients and controls, the presence of atopy was assessed by a careful clinical history of seasonal or perennial rhinitis or asthma, and skin prick tests for a panel of common aeroallergens such as grass, mugwort, birch, *Parietaria officinalis*, *Dermatophagoides pteronyssinus*, cat hair and dander, and *Alternaria*. A positive skin test was defined by a wheal at least 3 mm in diameter, according to the guidelines of the European Academy of Allergology and Clinical Immunology (6).

Study protocol

All the subjects had to have been free of symptoms for at least 1 month. Patients and controls were randomly assigned to receive a test dose (TD) of either acetaminophen or nimesulide, unless they reported definite tolerance of one of them. If so, the other drug was tested.

TD with acetaminophen or nimesulide (4-nitro-2-phenoxyethanesulfonamide) was done by the protocol for oral incremental challenge (7). Non-allergic controls took the entire therapeutic dose,

administered in open conditions, and remained under medical control for at least 2 h.

Test dose

Increasing drug doses were administered to each patient at 30-min intervals in a single-blind protocol, with inert capsules as drug vehicle. Doses were 10, 50, 125, 250, 500 mg for acetaminophen and 5, 10, 25, 50, 100 mg for nimesulide. The test, conducted in hospital with all resuscitation facilities to hand, was continued until the whole therapeutic dose (a single tablet) was reached or symptoms appeared. An equal number of placebo doses was administered to the patients on a different day. The test was defined as positive for skin symptoms if persistent itching, erythema and/or wheals, or angioedema appeared; for laryngeal edema, if disturbances in swallowing and respiration, and dysphonia arose. Asthmatic symptoms were assessed by spirometric tracings and rhinitis from the appearance of sneezing, rhinorrhea, and nasal blockage. If symptoms developed during the placebo day, the patient was dropped from the study.

Statistical analysis

Age in the study and control groups and in TD-positive and TD-negative patients was compared by Student's *t*-test. Groups were matched for sex, atopy, TD positivity, and intolerance of AMD by the chi-square test. Significance was reached at $P < 0.05$. Statistical analysis was performed with the SPSS computer program (SPSS Inc., Chicago, IL, USA). Odds ratios with 95% confidence interval (CI) were used to analyze the risk of reactions to alternative drugs used as TD in subjects with previous reactions to NSAID and to NSAID and AMD, and subjects with atopy. The odds ratios were defined as the odds of the considered risk factor occurring in exposed subjects relative to the odds of its occurring in unexposed subjects (8); the higher the ratio, the higher the subject's chance of developing reactions to the alternative drugs.

Results

Patients

Exactly 610 subjects were included in the study: 367 (113 M, 254 F, mean age 36.7 years, range 4–85) NSAID-intolerant patients and 243 (97 M, 146 F, mean age 40.1 years, range 12–77) controls. No significant differences were found for age between patients and controls, but there were significantly more female NSAID-allergic patients than controls ($P < 0.01$).

In the patient group, 169 (47.5%) reported a single allergic episode to a NSAID, and 187 (52.5%) reported more than one episode to different NSAID. The NSAID most frequently reported as causing reactions were ASA (47%), pyrazolic derivatives (34%), and diclofenac (3%).

Test dose

Exactly 667 TD were conducted in the 610 patients and controls. Eleven of the 367 patients were dropped from the study because they complained of symptoms while receiving placebo. Out of the remaining 356, 148 had TD with acetaminophen and 208 with nimesulide, 53 of them receiving both drugs. TD was positive in 49 patients in the study group (13.7%), and in one of the controls (0.4%) ($P < 0.001$). No differences were found in age and sex between TD-positive and TD-negative patients or between positive TD to acetaminophen and nimesulide, which were, respectively, 15/201 (7.4%) and 34/261 (13%). Three patients were positive to TD with both drugs and underwent a third challenge with another anti-inflammatory drug (benzylamine), which gave rise to no symptoms. Table 1 sets out the provocative doses in TD-positive patients and the symptoms most frequently elicited.

AMD allergy

In the study group, 208 patients (67 M, 141 F, mean age 39.2 years) reported intolerance only of NSAID, while 148 (39 M, 109 F, mean age 38.4 years) reported reactions to both NSAID and AMD. The AMD most frequently reported as responsible for reactions were β -lactams (51%) and sulfonamides (25%). TD was positive in 13 (6%) of the patients intolerant only of NSAID and in 36 (24%) of those allergic to both NSAID and AMD ($P < 0.001$). No differences were found for age or

sex when matching patients intolerant only of NSAID and those allergic to both categories.

Atopy

Personal atopy was found in 128 patients (35.9%) and in 56 controls (23%) ($P = 0.004$). A significant difference was also observed between:

- 1) the 169 patients with an allergic reaction to NSAID (44 cases, 26%) and the 187 patients with more than one reaction (78 cases, 41.7%) ($P = 0.003$)
- 2) the 49 TD-positive (25 cases, 51%) and the 307 TD-negative patients (103 cases, 33.5%) ($P < 0.02$)
- 3) the 208 patients intolerant only of NSAID (56 cases, 27%) and the 148 who reacted to NSAID and AMD (72 cases, 48.6%) ($P = 0.006$).

Risk of reaction to TD

Tables 2 and 3 set out the odds ratio (with 95% CI) obtained by comparing the different groups for atopy and for allergy to NSAID alone or to NSAID and AMD. The highest difference in risk (odds ratio 77.8) was found between controls and patients allergic to both NSAID and AMD; however, all the comparisons gave a significant risk.

Discussion

This study confirms that acetaminophen and nimesulide are quite well tolerated by patients allergic to ASA and other NSAID. In fact, 49 of 356 patients (14%) and one of the controls reacted to challenges with these drugs. Out of 201 challenged patients, 15 (7.4%) reacted to acetaminophen, and 34 of 261 (13%) reacted to nimesulide, this difference not being significant. Acetaminophen is usually considered safe in ASA-sensitive

Table 1. Provocative doses and symptoms elicited for each drug administered with test dose

Drug	Overall no. of challenged patients	Provocative dose (mg)	No. of positive patients	Symptoms	
Nimesulide (4-nitro-2-phenoxy-methansulfonamide)	261	100	22	Urticaria	13
		50	8	Urticaria/angioedema	6
		25	3	Dermatitis	11
		10	1	Itching/erythema	3
				Asthma	1
			Total	34	
Acetaminophen	201	500	8	Urticaria	7
		250	5	Urticaria/angioedema	2
		125	2	Dermatitis	5
				Asthma	1
			Total	15	

Table 2. Atopy and risk of drug allergy

Case groups	Atopics	Nonatopics	Odds ratio (95% CI)
Drug-allergic patients (356)	128	228	1.87 (1.30–2.71)
Control subjects (243)	56	187	
NSAID-allergic patients (208)	56	152	2.57 (1.65–4.01)
NSAID- and AMD-allergic patients (148)	72	76	
Control subjects (243)	56	187	3.16 (2.04–4.91)
NSAID- and AMD-allergic patients (148)	72	76	

patients, although Settignano et al. recently reported that 24% of ASA-sensitive asthmatic patients, increasing to 32% if a maximum dose of 1500 mg was administered, reacted to acetaminophen (9). This study cannot be compared with ours, for the following reasons:

- 1) in our population, only 4% had had an asthmatic reaction to the culprit drug, most of them having had skin reactions, and the different clinical picture may be the hallmark of distinct, differently reactive populations
- 2) in our study, ASA sensitivity was not diagnosed by challenge, as in Settignano et al.'s study, but on the basis of a well-documented history; therefore, a proportion of patients might have outgrown their intolerance
- 3) we administered doses lower than Settignano et al.'s, the aim being to assess the tolerance of common therapeutic doses of alternative drugs, and not cross-reactivity between ASA and alternative drugs.

The present results suggest that, in patients with systemic reactions to NSAID, acetaminophen and nimesulide are both well tolerated at current dosages, although the risk of reaction is far higher than in the control population (odds ratio 38.6) and justifies a test dose in these patients rather than simply suggesting the use of the alternative drugs at home.

Another interesting observation was that the risk of reactivity to acetaminophen and nimesulide was about five times higher (odds ratio 4.82) in patients with reactions only to NSAID than in those with reactions to NSAID and AMD. This implies that patients with allergic reactions to several classes of

drugs have a greater likelihood of developing intolerance of other drugs not similar in chemical structure or mechanism of action.

The observation that history of allergic reactions to AMD increases the risk of developing intolerance of acetaminophen and nimesulide in patients allergic to NSAID is difficult to explain on a pathogenetic basis. Allergy to AMD, at least penicillin, is IgE-mediated, while allergy to NSAID seems to be related to a shift to leukotriene production due to inhibition of the cyclooxygenase pathway (10). However, Sullivan et al. (11) noted that patients with a history of penicillin allergy present a frequency of reactions to other AMD, not chemically related and with no clear demonstration of IgE-mediated mechanism, 10 times higher than the general population, and proposed the definition of a "multiple drug allergy" to describe this reactivity to several classes of drugs. A subsequent study confirmed this finding, reporting that 14% of patients with previous AMD allergy, compared with 1.3% of patients not allergic, suffered from allergic reactions to alternative AMD (12).

These results, taken together, suggest that history of allergic reactions to drugs may predispose to reactions to unrelated pharmacologic compounds, and highlights the possibility of patient-related factors more than drug-related factors.

In this respect, we looked into the role of atopy, and our results suggest that personal atopy does play a part in drug allergy. The prevalence of atopy in nonallergic controls was comparable to that of the general population (13), but it was about two times higher (odds ratio 1.87) in patients with a history of drug allergy. This may reflect the fact that atopic patients consult an allergist more often

Table 3. Risk of reactions to alternative drugs in patients allergic to NSAID and to NSAID and AMD, and in control subjects

Case groups	Positive	Negative	Odds ratio (95% CI)
Drug-allergic patients (356)	49	307	38.6 (5.30–282)
Control subjects (243)	1	242	
NSAID-allergic patients (208)	13	195	4.82 (2.45–9.47)
NSAID- and AMD-allergic patients (148)	36	112	
Control subjects (243)	1	242	77.8 (10.5–575)
NSAID- and AMD-allergic patients (148)	36	112	

than nonallergic subjects, but the possible role of atopy as a risk factor in drug allergy is confirmed by the significantly larger number of atopic patients found among those reacting to both NSAID and AMD than among patients intolerant only of NSAID (odds ratio 2.58). These data agree with a recent report that among subjects with a history of reactions to NSAID, atopy was significantly more frequent ($P < 0.001$) in reactive patients than in those tolerant of challenge with alternative drugs (14).

However, the reports on this issue are conflicting. Some studies indicate that atopy seems to be associated with increasingly severe reactions to penicillin when penicillin-specific IgE antibodies are present (15), but not with the appearance of penicillin allergy (16) or with an increased risk of systemic reactions to drugs (17). By contrast, in a pediatric population, subjects with atopic diseases appeared to have a higher risk of allergic reactions to AMD (18). On the basis of these observations, one can speculate that mechanisms involved in the development of allergic diseases, such as basophil releasability (19), or the genetic phenotype of slow acetylation (20), may play a role in drug allergy, but further studies are necessary to clarify this.

Our data fully confirm the reported higher prevalence of drug allergy among women (5), but this may partly depend on the fact that women are more exposed to drugs, as they tend to consult physicians and use drugs more frequently than men. Sex does not seem to be a real risk factor, as we found no differences in the prevalence of females on matching the TD-negative and TD-positive subgroups.

In conclusion, in subjects allergic to NSAID, the risk of reaction to usually well-tolerated drugs such as acetaminophen and nimesulide is increased by atopy and by history of allergic reactions to AMD. This suggests the need for TD in patients with these characteristics before prescribing alternative NSAID.

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