

Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity

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Background: There is scarce information in the literature about a possible association between atopy and certain clinical manifestations of NSAID sensitivity.

Objectives: (1) To evaluate the prevalence of atopy in patients proved to be sensitive to cyclooxygenase inhibitors. (2) To assess cross-reactivity to two alternative NSAIDs, paracetamol (acetaminophen) and nimesulide.

Methods: NSAID-sensitive patients attending an allergy clinic and unselected controls were prick tested with inhalant allergens. Oral challenges with NSAIDs were carried out by the single-blinded (SBOC) method. Clinical data about personal and family history of allergic and atopic diseases were obtained by a careful review of the medical records and by direct questioning by experienced allergists.

Results: Fifty patients had positive SBOCs to the suspected NSAID and only these were studied. A personal history of atopic diseases was present in 41 patients (82%) and 7 controls (14.5%), and a family history in 24 patients (48%) and 6 controls (12.5%). Prick skin tests with aeroallergens were positive in 39 of 45 patients tested (86.6%) and in 14 of 48 controls (29.1%), ($P = .0001$). Skin test positivity rates were higher in patients with cutaneous challenge reactions who responded to only one NSAID (single reactors) in comparison to cross-reactors ($P = .04$). The most frequent clinical manifestations of NSAID sensitivity were (1) cutaneous (angioedema, urticaria) in 34 patients, (2) blended (cutaneous plus respiratory) in 12, (3) respiratory in 3, and (4) anaphylactoid in 1. Aspirin, pyrazolone, paracetamol, and ibuprofen were the drugs more frequently implicated in these reactions. Cross-sensitivity with paracetamol and nimesulide were 32% and 25%, respectively.

Conclusions: The prevalence of atopy is increased in challenge-proven NSAID-intolerant patients. The atopic condition may represent an important risk factor for developing reactions to these drugs. Paracetamol and nimesulide are relatively safe alternative choices in those patients, although their use still carries some risk of unwanted reactions.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are cyclooxygenase inhibitors with analgesic, antipyretic, antiphlogystic, and antithrombogenic properties. Nonsteroidal anti-inflammatory drugs have been used extensively around the world for more than a century. Due to their widespread use it is not surprising to find them among drugs more often involved in adverse

reactions, including hypersensitivity. It has been estimated that the prevalence of allergic or pseudoallergic reactions to NSAIDs in the general population is 0.3% to 0.5%.¹

In a recent article, Stevenson² classified reactions to aspirin and NSAIDs in five patterns: (1) respiratory, (2) cutaneous (angioedema, urticaria), (3) anaphylactoid (cutaneous symptoms plus hypotension), (4) hypersensitivity pneumonitis, and (5) blended reactions.

In 1992, while studying by means of oral challenges aspirin and additive reactions in a group of patients with urticaria/angioedema, we observed a sta-

tistically significant increase of NSAID sensitivity in atopic subjects when compared with nonatopic individuals.³ More recently, we reported our observations on 30 atopic patients who experienced anaphylaxis after eating foods containing high amounts of mites. All of them had positive prick tests to aeroallergens (mites) and surprisingly, 66.6% of them had a personal history of NSAID intolerance, manifested as urticaria or angioedema.⁴ In the meantime, Blanco et al found an 87% prevalence of NSAID sensitivity in patients with severe reactions to ingested mite-contaminated flour.⁵ We have proposed a new aspirin sensitivity triad consisting of sensitivity to aspirin, atopy, and severe allergic reactions to ingested aeroallergens.⁶

An association between atopy and NSAID sensitivity has been suggested by some investigators,^{7–9} but this possible relationship is far from clear in the allergy literature.¹⁰ Years ago, De Weck et al^{11,12} and Phills and Perelmutter¹³ observed positive skin tests to aspiryl-polylysine in patients with anaphylactic-type responses to aspirin. More recently, an IgE-mediated pathogenesis has been suggested for anaphylactoid reactions in patients who show cutaneous symptoms plus hypotension triggered by only one NSAID, generally of the pyrazolone group, without cross-sensitivities with other NSAIDs² and without other risk factors such as atopy.¹⁴

All these observations led us to study in a prospective manner the possible association between atopy and NSAID sensitivity in patients complaining of allergic symptoms presumably caused by these drugs. Furthermore, we have investigated the reaction pattern of these subjects to paracetamol (acetaminophen) and a

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newly introduced NSAID, nimesulide (4-nitro-2-phenoxyethanesulphonamide). Both NSAIDs are generally regarded as safe for use in NSAID-sensitive individuals by physicians and patients in Venezuela.

MATERIALS AND METHODS

Patients

Fifty patients, aged 8 to 63 years (average age 29.7 ± 12.7 years), 38 females and 12 males, fulfilled the following study criteria for inclusion. (1) Presence of allergic symptoms suspected from the clinical history to be caused by NSAIDs. (2) Positive single-blinded oral challenge with the suspected NSAID. (3) Written informed consent for allergy evaluation was obtained from every patient and the protocol was approved by the Ethics and Research Committee of the participating institution. Forty-eight unselected healthy adults, 41 females and 7 males, from the general population were used as the control group. Mean age for these subjects was 36.6 ± 11.2 years (range 20 to 65 years).

Data about personal and family history of allergic diseases including asthma; rhinitis/sinusitis; conjunctivitis; atopic dermatitis; and food, drug, and insect hypersensitivity were gathered from the medical records and personal interview with the investigators.

Skin Tests

Immediate-type hypersensitivity prick skin tests were carried out with inhalant allergens including house dust, *Dermatophagoides farinae*, cockroach, weed, tree and grass mix, cat, dog, feathers, *Penicillium*, *Aspergillus*, *Cladosporium*, *Alternaria*, and *Rhizopus* (Center Laboratories, Port Washington, NY). Glycerosaline solution and histamine phosphate, 1 mg/mL, were used as negative and positive controls, respectively. A wheal 3 mm larger than glycerosaline control was regarded as positive.

Oral Provocation Tests

Single blinded oral challenges (SBOC) controlled with placebo were carried

out with the suspected NSAIDs, according to the protocol described by Stevenson et al.¹⁵ Drug doses used in the provocation tests are summarized in Table 1. Once performed, positive reacting patients were subsequently submitted to SBOC with paracetamol and/or nimesulide. According to protocol, patients were challenged in hospital setting with appropriate access to emergency procedures.

Statistical Analysis

For comparison of atopy and skin test sensitivity prevalences Chi-square test with a significance level of $P < .05$ was used.

RESULTS

Atopy and Allergy Prevalence

Data about personal and family history of atopic and allergic diseases in our patients and controls are presented in Table 2. Forty-one patients (82%) and 7 controls (14.5%) ($P = .0001$) had a personal history of an atopic disease, whereas in 24 patients (48%) and 6 controls (12.5%) there was a family history of such conditions ($P = .0001$). In 6 patients (12%), 5 out of them atopic, and in 3 controls there was a family history of NSAID sensitivity (P was not significant). Nine patients (18%) had previous experiences of drug allergies (5 to penicillin, 2 to radiocontrast media, 1 to Vitamin B₁₂, 1 to Vitamin C and 1 to trimetoprim-sulfamethoxazol). One control subject had penicillin allergy history (2%), ($P = .02$). Twelve patients (24%) had

histories of food allergies (shellfish 5 patients, fish 4, pork 1, egg 1, mango 1) whereas 3 control individuals (6.2%) had food allergy history (chocolate 1, shellfish 1, and chocolate, eggs, fish and pork the third one) ($P = .03$). No history of insect allergy was present in patients or controls.

Immediate Type Skin Tests

Prick tests with inhalant allergens were positive in 39 patients out of 45 tested (86.6%) and in 14 control subjects (29.1%) ($P = .0001$) (Table 2). Thirty-nine patients reacted to *Dermatophagoides farinae*, 29 to house dust, 19 to cockroach, 13 to cat, 11 to dog, 9 to tree mix, 9 to grass mix, 6 to molds, 6 to feathers, and 3 to weed mix extract. In control subjects, skin tests were positive for *D. farinae* in 13, house dust in 9, cockroach in 5, cat, dog, grass and molds in 2, and tree mix in 1 (Table 3).

Clinical Reactions to NSAIDs

Drugs causing symptoms in these patients, by history or as confirmed by means of SBOC, are shown in Table 4. Thirty patients had experienced reactions to more than one NSAID. Most frequently involved drugs were aspirin, pyrazolone, paracetamol, and ibuprofen. Clinical manifestations are summarized in Table 5, where it can be observed that 22 patients experienced facial angioedema (44%), 9 angioedema plus difficult breathing (18%), 6 urticaria alone (12%), 6 angioedema plus urticaria (12%), 3 urticaria plus breathlessness (6%), 3 isolated dyspnea (6%), and 1 was considered to be anaphylactoid (cutaneous symptoms plus hypotension). According to Stevenson's classification, 34 patients (68%) showed cutaneous reactions, 12 (24%) "blended" reactions, 3 (6%) respiratory reactions, and 1 (2%) was anaphylactoid.

In order to ascertain if there were differences in their personal or familiar atopic history or skin test positivity frequencies, we classified patients as single drug reactors and multiple drug reactors ("cross-reactors"). No statistically significant differences in atopic history or positive skin tests preva-

Table 1. Drug Doses Used for Oral Challenges

Drug	Dose* (<12 yr)	Dose* (>12 yr)
Aspirin	100	250, 500
Pyrazolone	250	500
Paracetamol	180	500, 1000
Nimesulide	50	100
Ibuprofen	100	200
Diclofenac	ND	50
Ketoprofen	ND	50
Naproxen	ND	250

* mg.

ND: not done.

Table 2. Atopic History and Immediate-Type Skin Tests

Clinical Condition	Atopic/Allergy History	Control Group (%) n = 48	NSAID Sensitive Patients (%) n = 50	P Value*
Rhinitis	P†	4 (8.3)	18 (36)	.002
	F	2 (4.1)	11 (22)	.02
Rhinitis + asthma	P	0 (0)	16 (32)	.0001
	F	0 (0)	4 (8)	NS‡
Asthma	P	3 (6.2)	3 (6)	NS
	F	4 (8.3)	8 (16)	NS
Rhinitis + conjunctivitis	P	0 (0)	4 (8)	.04
	F	0 (0)	0 (0)	NS
Atopic dermatitis	P	0 (0)	0 (0)	NS
	F	0 (0)	1 (2)	NS
None	P	41 (85.4)	9 (18)	.0001
	F	42 (87.5)	26 (52)	.0001
Atopic disease	P	7 (14.5)	41 (82)	.0001
	F	6 (12.5)	24 (48)	.0001
NSAID sensitivity	F	3 (6.2)	6 (12)	NS
Allergy to other drugs	P	1 (2.0)	9 (18)	.02
Food allergy	P	3 (6.2)	12 (24)	.03
Skin test positivity	—	14/48 (29.1)	39/45 (86.6)	.0001

* Chi-square test.

† P: personal and F: familial.

NS: not significant.

Table 3. Immediate Hypersensitivity Skin Tests in Controls and Patients

Antigen	Controls (n = 48)	Patients (n = 45)	P Value*
<i>D. farinae</i>	13	39	.0001
House dust	9	29	.0001
Cockroach	5	19	.001
Cat	2	13	.003
Dog	2	11	.01
Grass	2	9	.04
Molds	2	6	NS†
Tree mix	1	9	.01
Feathers	0	6	.02
Weed mix	0	3	NS

* Chi-square test.

† NS: not significant.

lences were observed when all reactions were compared. When patients were classified according to the clinical pattern of the reaction, however, skin test positivity was significantly more prevalent in single reactors showing urticaria or angioedema (cutaneous group of Stevenson's classification, see reference 2) (Table 6).

Table 4. Nonsteroidal Anti-Inflammatory Drugs Causing Adverse Reactions in 50 Patients

Drug	n (%) History*	n (%) SBOC†
Aspirin	40 (80)	36 (72)
Pyrazolone	20 (40)	4 (8)
Paracetamol	14 (28)	5 (10)
Ibuprofen	7 (14)	2 (4)
Diclofenac	5 (10)	1 (2)
Ketoprofen	3 (6)	1 (2)
Glafenin	2 (4)	0 (0)
Naproxen	1 (2)	1 (2)
Flurbiprofen	1 (2)	0 (0)
Octafenin	1 (2)	0 (0)
Tiaprofenic acid	1 (2)	0 (0)
Piroxicam	1 (2)	0 (0)
Ketorolac tromethamine	1 (2)	0 (0)

* Twenty patients (40%) sensitive to one drug, 14 (28%) to two drugs, 12 (24%) to three drugs, and 4 (8%) to four NSAIDs.

† SBOC: single-blinded oral challenge.

Oral Provocation with Alternative NSAIDs

Fifty patients were submitted to SBOC with paracetamol, whereas 32 patients were challenged with nimesulide. Six-

teen patients (32%) gave positive reactions to paracetamol and oral provocations with nimesulide were positive in 8 (25%). Oral challenges for both drugs were carried out in 32 patients, with negative results for both drugs in 16, positive for both drugs in 2, positive only for paracetamol in 8, and positive for nimesulide but not for paracetamol in 6 patients. Three patients (6% of those challenged) did not react to 500 mg of paracetamol but reactions were observed at the higher dose tested, 1000 mg.

DISCUSSION

The aim of this study was to confirm our previous observations regarding an association between NSAID sensitivity and atopy in a prospective design in unselected patients who consulted because of allergic symptoms suspected to be precipitated by the administration of NSAIDs. Our results show an increased frequency of personal (82% of patients) and family history (48%) of atopic diseases in this group of patients. The proportion of atopic individuals in the general population worldwide has been estimated to be 30% to 50%,¹⁶ whereas in Venezuela atopic disease frequency varies between 12.2% and 23.7%.¹⁷

Atopy was confirmed to be 86.6% in these NSAID-sensitive patients by means of immediate-type skin tests, a figure which is higher than the atopy prevalence in our general population and significantly increased when compared with atopic history and skin test positivity frequencies in the control group. In this regard we must mention that the prevalence of skin test reactivity to *Dermatophagoides* in the general population, the most important inhalant allergen in this country, is 14.5%.¹⁷ This frequency varies in atopic subjects between 7.3% and 54% depending on the socioeconomic level of the individuals.¹⁸

We have also compared the proportion of NSAID-sensitive patients in the general population, known to be 0.3% to 0.5%,¹ to its prevalence by history in 100 non-selected atopic patients older than 12 years from our allergy clinics,

and we found that it was 23%. Taken together, our results suggest that there is an unexpected association between these conditions, a fact not clearly established in the literature. This finding would be rather surprising, taking into account that atopic diseases are mediated by IgE, whereas NSAID sensitivity is likely due to cyclooxygenase inhibition and increased production of sulfidopeptide leukotrienes. A positive correlation has been demonstrated between the potency of analgesics in inhibiting cyclooxygenase activity in vitro and their potency to exacerbate asthma in vivo in aspirin-sensitive patients.¹⁹

It could be proposed that patients reacting to multiple NSAIDs (“cross-reactors”) would have cyclooxygenase-dependent reactions, whereas those reacting to only one NSAID (“single-reactors”) would have IgE-mediated reactions. Although we did not find differences in skin test positivity when single reactor and cross-reactors were compared as a whole, single reactor patients showing cutaneous challenge reactions to NSAID had an increased skin test reaction rate. Atopic patients, therefore, would have an increased risk for developing cutaneous reactions to individual NSAIDs, which is in agreement with the findings by Quiralte et al of an increased frequency of NSAID-triggered periorbital angioedema in atopic individuals.⁸

The association between atopy and NSAID sensitivity remains unexplained. Since most of our atopic patients are allergic to mites, we have speculated on three possibilities. (1) Do these patients have an increased predisposition for mediator release after exposure to multiple triggering factors of a diverse nature? (2) Are there cross-reactions between mite components and NSAIDs? (3) Do mites contain some chemical constituents able to inhibit prostaglandin synthase?²⁰ All these questions hopefully will be addressed in the future. Quiralte et al have proposed that the presence of an atopic disease might predispose patients to certain clinical manifestations

Table 5. Clinical Manifestations of NSAID Sensitivity

Clinical Presentation	Patient Number (%)	Reaction Pattern*			
		C	R	B	A
Facial angioedema	22 (44)	X			
Angioedema + dyspnea	9 (18)			X	
Urticaria	6 (12)	X			
Angioedema + urticaria	6 (12)	X			
Urticaria + dyspnea	3 (6)			X	
Dyspnea	3 (6)		X		
Anaphylactoid	1 (2)				X
Total	50 (100)	34 (68)	3 (6)	12 (24)	1 (2)

C: cutaneous, R: respiratory, B: blended, A: anaphylactoid.

* According to Stevenson, DD (see reference 2).

Table 6. Skin Test Results According to Reaction Pattern in Single and Cross-Reactors

Challenge Reaction*	Single Reactors		Cross-Reactors	
	n	ST + (%)	n	ST + (%)
Cutaneous	17	16 (94.1)	19	12 (63.1)†
Blended	2	1 (50.0)	6	5 (83.3)
Respiratory	0	0 (0.0)	1	1 (100.0)
Anaphylactoid	0	0 (0.0)	1	1 (100.0)
All reactions	19	17 (89.4)	27	24 (88.8)‡

* According to Stevenson, DD.²

† *P* = .04, Fisher’s exact test.

‡ *P* n.s.

of NSAID intolerance⁸ and Hoigne and Szczeklik have postulated that severe reactions to aspirin occur more often in atopic than in nonatopic subjects.²¹

Because atopy represents a genetic predisposition to develop specific IgE and allergic diseases, there might also be a related or common genetic control for the development of both atopy and NSAID sensitivity. In the last few years important advances have been made in relation to the genetic control of atopy and asthma. One set of genes, located on chromosome 5q, governs bronchial hyperresponsiveness and total serum IgE and is related to asthma susceptibility.²² Chromosome 5q22-q35 is especially rich in genes that are implicated in allergic inflammation, including those for growth factors and their receptors (GM-CSF, FGFA, other colony-stimulating factors and receptors), the lymphocyte-specific glucocorticoid receptor 1, the beta-adrenergic receptor, and cytokines such as IL-3, 4, 5, 9 and 13.^{23–26} The second

candidate region controlling atopy has been mapped to chromosome 11q13, the location of the gene encoding the beta subunit of the high-affinity IgE receptor (FcεRI).^{27,28}

LTC4 synthase, a 18-kD membrane protein present on eosinophils, basophils, mast cells, monocyte/macrophages and platelets, is the terminal enzyme critical for the biosynthesis of LTC4, the parent compound of cysteinyl leukotrienes known to be involved in asthma pathogenesis.^{29–31} Recently, the LTC4 synthase gene has been localized to human chromosome 5 in the region 5q35 in the proximity of the cluster of cytokine genes.³² Since both “atopic” genes and LTC4 synthase gen are closely located in the same chromosomal region, it is provocative to postulate that this co-localization would be responsible for the increased prevalence of atopy in NSAID-sensitive individuals observed in the present study.

The frequency of adverse reactions to the different NSAIDs varies between countries depending on the prescription patterns and the availability of medications. We are now evaluating the prevalence of NSAID intolerance history in atopic children and have found that this is an age-related problem increasingly observed after the age of 10 years, mostly in the form of facial angioedema.³³

Since NSAID sensitivity is observed with such a high prevalence in atopic subjects attending an allergy service, clinicians are often led to the search of alternative analgesic and anti-inflammatory drugs.

In Venezuela, physicians have used paracetamol and more recently nimesulide for NSAID-intolerant patients. We have observed in this work that about one-third of those individuals will have reactions to paracetamol, and about one-fourth of them will react to nimesulide. Similar results have been reported by other investigators.^{34–36} We recommend oral challenges in order to assess clinical tolerance before advising about drug choice in this patient population.

Since it has been shown that pretreatment with 5-lipoxygenase inhibitors and LTD4 receptor antagonists inhibit the acute asthmatic response to aspirin,^{37,38} it will be interesting to study in the near future the effect of pretreatment with these agents on cutaneous and anaphylactoid reactions triggered by aspirin and other NSAIDs.

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