

Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria

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Background: Recent studies have found that most otherwise normal subjects with a history of acute urticaria induced by several nonsteroidal anti-inflammatory drugs (NSAIDs) show a wheal-and-flare reaction on intradermal injection of autologous serum. This phenomenon has been previously observed in patients with chronic urticaria (CU) and suggests a possible common background in CU and NSAID-induced urticaria. A relationship between these 2 conditions is further suggested by the fact that up to 30% of patients with CU have a worsening of their skin disorders after the ingestion of chemically unrelated NSAIDs.

Objective: I sought to assess whether otherwise normal subjects with multiple or single NSAID intolerance show a propensity to have CU.

Methods: Two hundred eighty otherwise normal patients with an unequivocal history of acute urticaria induced by NSAIDs seen during the last 10 years were studied. On the basis of both clinical history and oral challenge tests with at least 2 alternative NSAIDs, the patients were classified as having single or multiple NSAID intolerance. All the patients were re-evaluated within the end of 2002, 1 to 10 years after the first visit, to assess the onset of CU. One hundred allergic adults without a history of CU and of drug allergy followed up for 1 to 10 years were used as control subjects.

Results: One hundred fifty-nine and 121 patients were finally considered as having single or multiple NSAID intolerance, respectively. At the follow-up visit, 93 (33%) of 280 patients had CU. The prevalence of CU was very similar in subjects with single or multiple NSAID intolerance (48/159 [30%] vs 45/121 [37%], respectively; $P =$ not significant). Only 1 (1%) of 100 atopic control subjects had CU during the follow-up period ($P < .001$). Among single NSAID reactors, patients who had CU had a significantly higher prevalence of intolerance to aspirin than those who did not have CU (36/48 [75%] vs 41/111 [37%], $P < .001$), whereas the latter had a markedly higher prevalence of intolerance to pyrazolone drugs (52/111 [47%] vs 10/48 [21%], $P < .01$). Altogether, only 12 (15%) of 82 patients intolerant to drugs other than aspirin versus 36 (47%) of 77 aspirin reactors had CU ($P < .001$).

Conclusion: NSAID intolerance might precede the onset of CU by years. Both multiple and single NSAID reactors with a his-

tory of aspirin-induced urticaria seem at higher risk for CU than patients with a history of single intolerance to NSAIDs other than aspirin. (*J Allergy Clin Immunol* 2003;111:1095-8.)

Key words: Drug allergy, nonsteroidal anti-inflammatory drug intolerance, chronic urticaria

It is generally accepted that up to 30% of patients with chronic urticaria (CU) might have a worsening of their skin disorder after taking several chemically unrelated nonsteroidal anti-inflammatory drugs (NSAIDs).¹⁻³ In contrast, the possibility that otherwise normal subjects might have multiple intolerance to NSAIDs (defined as distinct episodes of acute urticaria after the ingestion of chemically unrelated NSAIDs) has been much more debated. The latest edition of one of the most authoritative textbooks of allergy states that, "After earlier exposure to a specific acetylsalicylic acid (ASA) or NSAID, otherwise normal-appearing individuals may develop urticaria, angioedema, or anaphylaxis on re-exposure to the same drug. In this type of reaction cross-reactivity between ASA and NSAID does not occur."⁴ However, during the last decade, a number of studies aiming to assess the tolerance to alternate drugs in otherwise normal subjects with a history of urticaria induced by an NSAID found that some patients reacted to chemically distinct NSAIDs as well.⁵⁻¹⁰ In a study that specifically addressed this issue, 94 (36%) of 261 subjects without CU were finally classified as having multiple intolerance to NSAIDs on the basis of clinical history, challenge tests with alternative substances, or both.¹¹ In view of these studies, Stevenson et al¹² recently proposed a new classification system for allergic and pseudoallergic reactions to NSAIDs; such classification included a subgroup of otherwise normal subjects with a history of acute episodes of urticaria induced by several chemically distinct NSAIDs. A recent study found that these subjects have a very high prevalence (>90%) of positive skin reactions on intradermal injection of autologous serum (autologous serum skin test [ASST]); interestingly, ASST results were positive in 30% of subjects with a history of urticaria induced by a single NSAID as well.¹³ That study suggested that, at least in some patients, a state of autoreactivity might play a role in the pathogenesis of adverse reactions to NSAIDs. ASST results are frequently positive in patients with CU,¹⁴ and this test is generally considered as a simple means of detecting patients with circulating histamine-releasing factors,¹⁵ such as IgG autoantibodies specific for the high-

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TABLE I. Clinical features of the study population

	Single intolerance	Multiple intolerances	<i>P</i> value
No.	159	121	
Sex (M/F)	48/111	27/94	NS
Mean age, y (range)	33.1 (5-80)	39.7 (8-72)	<.001
Patients with CU (%)	48 (30)	45 (37)	NS
Mean follow-up in patients with CU, mo (SD)	71.5 (38.6)	50.0 (37.0)	NS
Mean follow-up in patients without CU, mo (SD)	68.6 (39.7)	59.2 (38.1)	NS

NS, Not significant.

TABLE II. Prevalence of CU by follow-up duration

Follow-up (mo)	Prevalence of CU
12	15/42 (36%)
24	11/34 (32%)
36	13/31 (42%)
48	7/24 (29%)
60	5/23 (22%)
72	10/22 (45%)
84	4/11 (36%)
96	7/26 (27%)
108	6/14 (43%)
120	15/53 (28%)
Total	93/280 (33%)

Abbreviations used

ASA: Acetylsalicylic acid

ASST: Autologous serum skin test

COX: Cyclooxygenase

CU: Chronic urticaria

NSAID: Nonsteroidal anti-inflammatory drug

affinity IgE receptor Fc ϵ RI or for IgE.¹⁶⁻²⁰ All these observations suggest that, at least in some patients, NSAID intolerance and CU might have a common background. The present follow-up study aimed to assess whether a history of acute urticaria induced by NSAIDs in otherwise normal subjects represents a risk factor for CU.

METHODS**Patients**

Two hundred eighty otherwise normal patients (75 male and 205 female patients; age range, 5-80 years) with an unequivocal history of recent acute urticaria induced by NSAIDs seen at the allergy unit of Bollate Hospital during the last 10 years were studied. No patient had a history of prior urticarial episodes other than those caused by NSAIDs. All subjects reporting spontaneous episodes of pruritus, urticaria, or both were excluded. Because both patients and their family physicians asked for safe alternative drugs, on the basis of clinical history all patients underwent single-blind, placebo-controlled oral challenges with at least 2 anti-inflammatory drugs other than the offending ones. In patients with a history of urticaria induced by aspirin, other cyclooxygenase (COX) inhibitors, or both, substances to be challenged were chosen among drugs considered as generally safe on the basis of previous studies, namely acetaminophen, nimesulide, tramadol, rofecoxib, and flectafenine.^{6-8,21-24} On the basis of previous reports, patients with a history of a single adverse reaction induced by pyrazolones (including feprazone and noramidopyrine), nimesulide, or acetaminophen were challenged

with aspirin first, and tolerance to other drugs was assessed only in case of an adverse reaction to ASA.^{5,25-31} Procedures and doses used to carry out challenges have been described in detail elsewhere.^{11,22,25,32} Only the appearance of clear-cut urticaria within 6 hours after the challenge was considered a positive test result. On the basis of both clinical history and challenge test results, patients were finally classified as having single or multiple NSAID intolerance. Patients were left free to use drugs that were tolerated on oral challenges whenever necessary and were recommended to present at the allergy center in the event of spontaneous urticaria. Those who had not yet undergone a control visit by the end of 2001 were contacted by telephone; patients suspected of having CU were offered a free control visit during 2002. All the patients were finally re-evaluated 1 to 10 years after the first visit. CU was defined as the spontaneous recurrence of hives with or without angioedema for more than 6 weeks.

One hundred atopic adults (41 male patients and 59 female patients; mean age, 29 years; age range, 14-57 years) who were followed up at the allergy center for 1 to 10 years (mean, 41 months) were used as control subjects. None of them had a history of CU or of acute urticaria induced by any drug.

Statistical analysis

Means were compared by using the 2-tailed Student *t* test. Proportions were compared by using the χ^2 test with the Yates correction. *P* values of less than 5% were considered statistically significant.

RESULTS

On the basis of both clinical history and oral challenge test results, 159 and 121 patients were finally considered as having single or multiple NSAID intolerance, respectively. Clinical details are summarized in Table I. The 2 groups had a similar sex distribution, but single NSAID reactors were significantly younger than patients with multiple NSAID intolerance. At the follow-up visit, 93 (33%) of 280 patients had CU. The prevalence of CU was very similar in subjects with single or multiple NSAID intolerance (48/159 [30%] vs 45/121 [37%], respectively; *P* = not significant). The onset of CU did not depend on follow-up duration (Table II), and in both subgroups with single or multiple NSAID intolerance, patients with or without CU did not show any difference in follow-up duration (Table I). Only 1 (1%) of 100 atopic control subjects had CU during the follow-up period (*P* < .001 by comparison with both subgroups of patients).

In the subgroup with multiple NSAID intolerance, no difference in the prevalence of intolerance to single NSAIDs was observed between patients who had CU and patients who did not have CU (Table III).

In the subgroup with single NSAID intolerance (Table IV), approximately one half of the patients were intoler-

TABLE III. Comparison between multiple NSAID reactors who did and did not have CU

Offending drugs	Whole population (n = 121)	CU (n = 45)	No CU (n = 76)	P value
Aspirin	92 (76%) [4]	37 (82%) [2]	54 (71%)	NS
Indomethacin	3 (2%)	1 (2%)	2 (3%)	NS
PAD	42 (38%)	16 (36%)	26 (34%)	NS
Diclofenac	22 (18%)	7 (16%)	15 (20%)	NS
Ketorolac	8 (7%)	3 (7%)	5 (7%)	NS
Piroxicam	23 (19%)	4 (9%)	19 (25%)	NS
Pyrazolones	60 (50%)	24 (53%)	36 (47%)	NS
Morniflumate	2 (2%)	0 (0%)	2 (3%)	NS
Acetaminophen	31 (26%) [23]	11 (24%) [8]	20 (26%) [15]	NS
Nimesulide	37 (31%) [26]	16 (36%) [14]	21 (28%) [12]	NS
Floctafenine	5 (4%) [5]	1 (2%) [1]	4 (5%) [4]	NS
Rofecoxib	7 (6%) [7]	3 (7%) [3]	4 (5%) [4]	NS
Tramadol	3 (2%) [3]	1 (2%) [1]	2 (3%) [2]	NS

Values in square brackets indicate the number of patients whose intolerance was detected during challenge tests. Pyrazolones include feprazone and noramidopyrine.

NS, Not significant; PAD, propionic acid derivatives.

TABLE IV. Comparison between single NSAID reactors who did and did not have CU

Offending drugs	Whole population (n = 159)	CU (n = 48)	No CU (n = 111)	P value
Aspirin	77 (48%)	36 (75%)	41 (37%)	<.001
Indomethacin	0	0	0	NS
PAD	5 (3%)	1 (2%)	4 (4%)	NS
Diclofenac	5 (3%)	0	5 (5%)	NS
Ketorolac	0	0	0	NS
Piroxicam	3 (2%)	1 (2%)	2 (2%)	NS
Pyrazolones	62 (39%)	10 (21%)	52 (47%)	<.01
Morniflumate	1 (1%)	0	1 (1%)	NS
Acetaminophen	1 (1%)	0	1 (1%)	NS
Nimesulide	5 (3%)	0	5 (5%)	NS
Floctafenine	0	0	0	NS
Rofecoxib	0	0	0	NS
Tramadol	0	0	0	NS

NS, Not significant; PAD, propionic acid derivatives.

ant to aspirin (77/159 [48%]), and more than one third were intolerant to pyrazolones (62 [39%]); the remaining offending drugs were diclofenac, propionic acid derivatives, and nimesulide (5 patients each); piroxicam (3 patients); and acetaminophen and morniflumate (1 patient each). A history of aspirin-induced urticaria was significantly more frequent among patients who had CU than among those who did not have CU (36/48 [75%] vs 41/111 [37%], $P < .001$), whereas the latter showed a markedly higher prevalence of intolerance to pyrazolone drugs (52/111 [47%] vs 10/48 [21%], $P < .01$; Table IV). Altogether, only 12 (15%) of 82 patients intolerant to drugs other than aspirin versus 36 (47%) of 77 aspirin reactors had CU ($P < .001$, Table IV).

DISCUSSION

Greater than one third of patients with multiple intolerance to NSAIDs had CU at the end of the follow-up period. Altogether, this finding is not particularly surprising. The association between multiple NSAID intolerance

and CU has been known for many years,¹⁻³ and the findings of this study simply suggest that in a proportion of patients with CU, the onset of the spontaneous skin disorder might be preceded by intolerance to anti-inflammatory drugs by years. From the pathogenic point of view, otherwise normal subjects with a history of urticaria after the ingestion of chemically unrelated NSAIDs react to offending drugs nonspecifically, probably through an inhibition of COX, as suggested by their cross-intolerance to chemically unrelated NSAIDs not involved in a previous reaction.⁹ The present study suggests that subjects with multiple NSAID intolerance should be regarded as potentially having CU.

In contrast, the findings in patients with single NSAID intolerance were rather unexpected. Two kinds of patients could be clearly identified in this subgroup: (1) those with a history of urticaria after the ingestion of aspirin and (2) those with a history of urticaria caused by drugs other than aspirin. The former showed a propensity to have CU that was very similar to the propensity observed in patients with multiple NSAID intolerance.

Because, as in most previous studies, challenge tests with alternative substances were carried out with either weak COX-1 inhibitors (nimesulide, rofecoxib, and flectafenine) or drugs that do not exert any inhibitory effect on COX (acetaminophen and tramadol) and all these patients tolerated them, one might infer that many aspirin-intolerant patients would have probably reacted against alternative drugs had they been challenged with stronger COX-1 inhibitors. In other words, it is possible that these patients were misdiagnosed multiple NSAID reactors. In contrast, most patients in group 2 behaved as if they had a true IgE-mediated drug allergy. Isolated hypersensitivity reactions to NSAIDs, possibly mediated by IgE, have been reported for several anti-inflammatory/analgesic drugs, including pyrazolones,^{25,32,33} acetaminophen,²⁸⁻³¹ aspirin,³⁴ ketorolac,³⁵ celecoxib,³⁶ and nimesulide.²⁶ In subjects characterized by specific immune-mediated adverse drug reactions, one would not expect the onset of CU.

From a practical point of view, this study suggests that patients reporting urticaria after taking drugs other than aspirin should undergo an oral tolerance test with aspirin to establish whether they have a true single NSAID intolerance (allergy). Those reacting to aspirin on oral challenge would be included among multiple NSAID reactors and as such should be considered at higher risk for CU.

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