

Multiple NSAID Intolerance in Chronic Idiopathic Urticaria Is Correlated with Delayed, Pronounced and Prolonged Autoreactivity

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Abstract

Autologous serum skin test (ASST) reactivity is positive in up to 60% of patients with chronic idiopathic urticaria (CIU). About 21 to 30% of patients with CIU have intolerance to acetyl salicylic acid (ASA) and/or other chemically unrelated non-steroidal anti-inflammatory drugs (NSAIDs). To investigate the relationship between ASA/NSAID intolerance and ASST reactivity, a case-control study was performed in 110 patients with CIU and 60 healthy controls. A positive ASST was defined as an erythematous wheal with a diameter of ≥ 5 mm more than the saline-induced response. Patients were assessed at 10-minute intervals for a minimum of three hours. ASA/NSAID intolerance was ascertained by a placebo controlled-provocation test with offending drug (s). Forty-two patients with CIU (38.2%) had autoreactivity whereas only two of the controls (3.3%) displayed early and weak skin responses ($P < .0001$). ASA/NSAID intolerance was demonstrated in 30 (27.3%) patients with CIU. The prevalences of autoreactivity were 93.3% (28/30) and 17.5% (14/80) in patients with and without ASA/NSAID intolerance, respectively ($P < .001$). Thirteen of the 25 ASST-positive patients (52%) who had single ($n: 7$) or multiple ($n: 6$) NSAID intolerance showed early (before or at 30 min) and mild autoreactivity of short duration, whereas 15 of the remaining 17 ASST-positive patients (88.2%) who all had multiple NSAID intolerance showed delayed (later than 30 min) and prolonged autoreactivity ($P < .05$). These findings suggest that a common mechanism may be responsible for the pathogenesis of both delayed autoreactivity and multiple NSAID intolerance in CIU. It might be further speculated that delayed, prolonged, and pronounced autoreactivity may be a possible predictor for multiple NSAID sensitivity in CIU.

Key words: chronic idiopathic urticaria; ASA/NSAID intolerance; autologous serum skin test; delayed autoreactivity

Introduction

Chronic idiopathic urticaria (CIU) is a common form of urticaria defined as erythematous wheals with or without angioedema occurring daily or at least three days a week for more than six weeks (1). It is well

known that a considerable proportion (21 to 30%) of patients with CIU are intolerant of acetyl salicylic acid (ASA) and a number of chemically unrelated non-steroidal anti-inflammatory drugs (NSAIDs) (2, 3). Cross-reactivity among NSAIDs is usually seen in patients with CIU, but also in otherwise healthy persons. Cyclooxygenase (COX)-1 pathway inhibition appears to be involved in the cutaneous adverse reactions due to NSAIDs in cross-reactive patients, by causing diversion of arachidonic acid metabolism from prosta-glandin formation to leukotrienes (LTs) (4). However, the causes and underlying

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ing mechanism of the cross-reactivity to various NSAIDs are probably more complex than this, because weak COX-1 inhibitors like acetaminophen (paracetamol), and preferential and selective COX-2 inhibitors including nimesulide and rofecoxib may also evoke flares of hives/angioedema and even anaphylaxis (3, 5–7).

Asero et al. (7) recently demonstrated an association between ASA intolerance and an increased risk for acetaminophen- and/or nimesulide-induced urticaria. They also reported a high prevalence of autologous serum skin test (ASST) reactivity in the majority of the otherwise healthy subjects, who have a history of multiple drug reactivity (urticaria after ingesting several, chemically unrelated NSAIDs and other drugs). Therefore, they suggested that autoreactivity may represent a common pathogenic background for multiple NSAIDs sensitivity and hypothesized that the offending drugs in multiple NSAID intolerance could cause acute urticaria episodes by enhancing the activity of circulating histamine-releasing factors which might be insufficient to initiate the attacks alone (5). In this report (5) and some recent studies (8–10), wheal-and-flare reactions to ASST were usually observed to appear before 30 min and to fade immediately, in disagreement with the original description of autoreactivity in CIU, indicating that the maximal skin responses usually had developed by 1.5–2 h and remained positive for an average of 8 h (11). On the other hand, an extensive literature search revealed that there has been no clinical study focusing on the characteristics of autoreactivity in CIU associated with ASA/NSAID intolerance.

The current case-control study aimed to compare the prevalences of positive autoreactivity between CIU patients with and without NSAID intolerance, and healthy controls. Clinical characteristics of the skin reactions were evaluated in all participants with regard to time kinetics and maximal intensities of wheal-and-flare reactions as well.

Patients and Methods

Study population: The study was carried out on 110 adult patients (66 women and 44 men; mean age $\pm$ SD, 36.4 ± 6.67 years) with CIU, defined as recurrence of hives with or without angioedema for at least six consecutive weeks, and 60 healthy volunteers (38 women and 22 men; mean age $\pm$ SD, 33.8 ± 4.5) without dermatographism. Patients with physical urticaria, those with urticaria associated with any known causes including hepatic, psychiatric, endocrine diseases, chronic infection, parasitoses, malignancies or other major systemic diseases, and those with asthma were excluded from the study. The duration of urticaria ranged from 3 to 120 months (median: 18 m). A careful interview was carried out in order to define patients with CIU who experienced exacerbations after taking ASA or any other NSAID. Control subjects were also asked whether or not they had any history of ASA/NSAID intolerance. ASST was done before aspirin/NSAID challenge. At the time of the ASST and oral provocation test with offending drug(s), none of the patients had ingested any H_1 antihistamines during the previous seven days and, if the person was on steroid therapy, it was withdrawn at least two weeks before the tests.

Skin tests: All subjects underwent intradermal testing with 0.05 mL of sterile fresh autologous sera and with saline as a negative control. All sera from patients with CIU were collected during the active phase of the disease. Venous blood was drawn into sterile vacutainers without clotting accelerator, allowed to clot at room temperature for 30 min, and centrifuged at 1250 g for 5 min. Sera were immediately used for intradermal tests. A skin prick test with histamine 10 mg/mL was used as the positive control. Readings were taken at 10-minute intervals for at least three hours. A positive test was defined as an erythematous wheal in the absence of any reaction to the negative control with saline or larger by a diameter of ≥ 5 mm than the response to the negative control. The intensity of each positive reaction was graded by comparison with the skin reaction to the positive control. Because a prick test response to histamine usually disappears

Table 1. Offending NSAIDs with positive oral challenge test results

	No. of subjects receiving tolerance test	Single NSAID intolerance (n)	Multiple NSAID intolerance (n)
Aspirin	170 (110 patients, 60 controls)	5	18
Acetaminophen	4	1	3
Pyrazolones	7	—	7
Nimesulide	6	1	5
Naproxen sodium	5	1	4
Piroxicam	2	—	2
Diclofenac	5	—	5
Rofecoxib	2	1	1
Indomethacin	2	—	2
Benzydamine hydrochloride	3	—	3

Table 2. Comparisons of autoreactive cases with and without NSAID intolerance who showed early and delayed responses to ASST

	Cases with NSAID intolerance (n: 28)	Cases without NSAID intolerance (n: 14)
Early reactors (n: 25) (before or at 30 min)	13 (52%)	12 (48%)
Late reactors (n: 17) (after 30 min)	15 (88.2%)	2 (11.8%)

P < .05, Fischer's exact test

after 30 minutes, the diameter of the wheal-and-flare reaction caused by histamine in each case was recorded as reference for the grading of any possible delayed reaction. Wheal and flare reactions whose areas were larger than that of the positive control were graded as 4+, those with an intensity equal to the control as 3+, those 50 to 100% of the control as 2+, and those measuring less than 50% of histamine but larger than saline-induced response were graded as 1+.

Oral challenge tests: After informed consents were obtained, the study subjects who had a history of ASA/NSAID intolerance underwent a single blind, placebo-controlled oral tolerance test with the offending drug(s), as previously described in detail (4–7). Placebo and active drugs, prepared in identical opaque capsules, were challenged at least one week apart, because there is usually a refractory period lasting at least five days after a reaction (4). Even if there was no history of ASA/NSAID intolerance, an oral challenge test with aspirin was still performed in all study subjects including the con-

trols, in order to disclose any subclinical ASA sensitivity. The doses were equivalent to 25, 50, and 100% doses of the challenged drugs, and were given at least one hour apart. Cases were reassessed for at least two hours after the last provocative doses. In patients with CIU, test results were regarded as positive if skin lesions (wheals and angioedema) were ≥ 20 of baseline (4). In controls, the appearance of an unequivocal urticarial rash and/or angioedema was considered as a positive response. All subjects were also evaluated on the following day, in order to detect any possible late reaction.

Statistics: The statistical significances between groups were determined by unpaired-t test, chi-squared test, and Fisher's exact test, depending on the sample sizes. All tests were two-sided, and a *p* value less than 0.05 was considered significant.

Results

Twenty-five out of the 110 patients with CIU (22.72%) had autoreactivity, but only

Table 3. The intensities of ASST reactions in patients with and without NSAID intolerance*

Intensity of the reaction	Cases with NSAID intolerance		Cases without NSAID intolerance	
	Early reactors (n: 13)	Late reactors (n: 15)	Early reactors (n: 12)	Late reactors (n: 2)
4+	2	15	—	—
3+	9	—	6	1
2+	1	—	4	1
1+	1	—	2	—

$P < .05$, chi-squared test, *, Each patient had either an early or late response only

two of the controls (3.3%) were reactive to ASST when the test results were read ≥ 30 min ($P < .001$). Skin reactions in the patient group reached a maximal intensity at an average of 20 min (range, 15–30 min) and usually faded before 40 min. Control cases showed weak (1+) reactions, which initiated early (at 10 and 15 min) and faded before or at 20 min. Further observations disclosed a delayed reactivity, which appeared after 30 min, with a maximal intensity at an average of 90 min (ranging from 40 to 180 min) in 17 additional cases with CIU, but in none of the controls. Thus, test positivity in CIU patients increased to 38.2% ($P < .0001$). Wheal-and-flare reactions remained positive for an average of 7 h (range: 3–24 h) in the late reactors. Saline injection did not elicit any reaction in any of the participants while all of them reacted positively to histamine.

While none of the controls had any history of intolerance to ASA/NSAIDs, 30 of the patients with CIU (27.3%) did have a positive history. Oral tolerance test results revealed that nine cases with CIU had single NSAID intolerance and the remaining 21 cases had multiple NSAID intolerance. Aspirin sensitivity was the most prevalent as a single agent or associated with other drugs (Table 1). Nine patients with multiple NSAID intolerance were also intolerant to food additives, especially to foods high in salicylates, and had an additional history of aggravation of urticaria after taking various antibiotics [penicillins (n: 6), co-trimoxazole (n: 3), β -lactams (n: 2) and quinolones

(n: 1)]. The remaining patients were unaware of any additional intolerance to other chemicals like antibiotics or food additives. Interestingly, two control cases that showed weak reactions to ASST were also found to be intolerant to the challenge with the highest test doses of aspirin, but not to other NSAIDs. The prevalence of positive autoreactivity was 93.3% (28/30) in patients with ASA/NSAID intolerance and significantly higher than that [17.5% (14/80)] in patients without ASA/NSAID intolerance ($P < .001$). While 13 of 25 CIU patients (52%) who showed early and mild autoreactivity of short duration had single (n: 7) or multiple (n: 6) NSAID intolerance, 15 of 17 patients (88.2%) who showed late and prolonged reactivity all had intolerance to two (n: 8) or more (n: 7) NSAIDs ($P < .05$) (Table 2).

Late reactive and NSAID intolerant cases were all found to have the strongest (4+) wheal and flare reactions to autologous sera whose areas exceeded those of the positive control with histamine (Table 3). Further interview revealed that late reactors' urticaria plaques continued usually more than 24 hours and that they experienced angioedema attacks more frequently than did early reactors.

Discussion

NSAIDs induce urticaria and/or angioedema in two clinical settings; in otherwise normal subjects who experience the attacks only when a specific NSAID is ingest-

ed, and in patients with CIU who experience a flare after taking any NSAID and occasionally after other drugs like antibiotics. IgE-mediated immune reactions seem to be involved in the former setting, while a non-specific, patient-related, and drug-induced activation of mast cells and basophils may be responsible for the cross-reactivity among different NSAIDs in patients with CIU (3–5, 7). The susceptibility to NSAID intolerance in CIU has been demonstrated to vary with the degree of urticaria activity (2). Multiple drug reactivity in CIU cannot be explained by only a mechanism dependent on COX-1 inhibition, because weak COX-1 blockers, selective or preferential COX-2 inhibitors, and drugs other than NSAIDs are also able to induce urticarial reactions to oral challenges after the lowest doses. An IgE-mediated cross-reaction against the offending parent drugs or their metabolic breakdown products also seems unlikely because of the completely different chemical structures of these drugs (4–7).

It is well known that a rather high proportion (up to 60%) of patients with CIU have an autoreactivity, because they show a wheal-and-flare reaction upon intradermal autologous serum injection (1, 2, 8, 9). Skin reactivity to autologous sera is also associated with higher urticaria activity, *i.e.*, a higher frequency of daily symptoms and concurrent angioedema, and it usually disappears during remissions (1, 11). The nature of the skin reactivity to ASST is still controversial. Because pretreatment with antihistamines or the mast cell-degranulating chemical compound 48/80 substantially reduces the skin response, it is thought to be mast cell dependent and mediated by histamine (12). Circulating functional IgG autoantibodies specific either for the high-affinity IgE receptor, FcεRI, or for IgE have long been accused of this reactivity (13). Nevertheless, Fagiolo et al. (10) have recently shown that heat-decomplemented/IgG depleted sera retain their ability to induce wheal-and-flare reactions, suggesting that autoreactivity could depend on yet unidentified non-Ig re-

actants. They have also hypothesized that putative histamine releasing factor(s) could act directly on the cutaneous microvasculature, bypassing mast cells and basophils (10). Another explanation for autoreactivity might be the involvement of vasoactive factors generated during clotting on a background of intrinsic mast cell releasability in CIU (1). Wedi et al. (14) recently demonstrated that sera from a subgroup of severe CIU patients positive on ASST induce not only histamine liberation, but also basophil activation marker CD63 surface expression and *de novo* production of LTs, which are 100 times more potent than histamine (15). Moreover, serum-induced basophil CD63 expression and LT production have been found to be more frequent in patients with severe urticaria (14).

Our results in a case population from Turkey revealed a lower incidence (38.2%) of autoreactivity in CIU when compared to those of the previous studies from other countries (2, 8–10, 13, 14, 16). However, the positivity of ASST in NSAID intolerant CIU patients (*i.e.*, sensitivity of the test) was 43.3% (13/30) and 50% (15/30) for the early reactors and late reactors, respectively. Furthermore, more than two-thirds (15/21) of the patients with multiple NSAID intolerance, who were late reactors, also displayed more pronounced and prolonged skin reactions, implying the role of histamine-independent mechanisms. Another notable finding in our study was that two control subjects, who were demonstrated to be aspirin-intolerant with the provocation test, also reacted positively on ASST, although they had only weak reactions. This observation suggests that some ASST positive healthy subjects may also have a subclinical aspirin/NSAID sensitivity.

Asero et al. (2) recently showed that the prevalences of NSAID intolerance were identical in the subgroups of CIU patients who were distinguished based on different *in vivo* and *in vitro* histamine releasing activities of their sera. They concluded that NSAID intolerance in CIU might not de-

pend on the mechanism of histamine release, whether induced by autoantibodies or by other hitherto undefined factors. As no *in vitro* histamine releasing assay from basophils could be performed in our study, it is unclear what proportion of our cases had functional autoantibodies with *in vitro* histamine releasing activity. Sabroe et al. (8) recently reported that ASST can be used as a predictive clinical test to indicate the presence of functional autoantibodies with a sensitivity of approximately 70% and a specificity of 80% if test positivity is defined as a pink, serum-induced wheal with a diameter of ≥ 1.5 mm than the saline-induced response at 30 min. They also observed a higher sensitivity (93%) but a lower specificity (48%) of ASST when readings are taken at 60 min, in other words, an increased proportion of autoreactivity in patients without autoantibodies to Fc ϵ RI and/or IgE. This observation also supports the opinions suggesting that delayed response to ASST might not depend on histamine-releasing autoantibodies.

Although there is agreement on the increased mast cell releasability in CIU, the reasons for the chronic activation of mast cells and, possibly, basophils in CIU patients are currently unclear (1, 17). It also remains to be explained which mechanisms underlie the increased LT₄ *de novo* production after ASST in patients with severe CIU (14). A putative mechanism for NSAID-induced exacerbation in CIU has been proposed to be an increased activity of LTC₄ synthase (2), which is a key enzyme for the production of cysteinyl leukotrienes, because a fivefold increase in LTC₄ synthase positive cells has been shown in the majority of the patients with aspirin-induced asthma (18). On the other hand, some anecdotal case reports (19–23) and study results (24, 25) have shown that LT receptor antagonists montelukast and zafirlukast were effective in the treatment of CIU, particularly in the control of severe urticaria/angioedema exacerbations related to cold, pressure, food additives, and NSAIDs. More recently, all of the

patients with NSAID sensitive CIU have been found to be among the complete responders to montelukast therapy with an increased tolerability to NSAIDs. Furthermore, ASA/NSAID sensitive and autoreactive cases, also including the late reactors to ASST, were all non-reactive at the end of the therapy period (26).

In our study, multiple NSAID intolerance in CIU was found to be correlated with delayed, pronounced, and prolonged autoreactivity, whereas single NSAID intolerance was associated with immediate and milder skin reactivity. Similarly to that in the otherwise healthy subjects, single NSAID intolerance in CIU may result from type I hypersensitivity. However, intolerance to various NSAIDs of different chemical structures seems unlikely to be related to this type of reaction. In conclusion, a common and yet undefined mechanism(s) other than histamine release might be responsible for the pathogenesis of both delayed autoreactivity and multiple NSAID intolerance in CIU. It might be further speculated that delayed, prolonged, and pronounced autoreactivity may be a possible practical clinical test for predicting multiple NSAID sensitivity in CIU. Further and more detailed clinical, biochemical, and genetic studies are required to clarify these hypotheses.

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