

Predictive Value of Autologous Plasma Skin Test for Multiple Nonsteroidal Anti-Inflammatory Drug Intolerance

Riccardo Asero

Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano, Italy

Key Words

Allergy, drug • Nonsteroidal anti-inflammatory drugs •
Urticaria • Skin testing

Abstract

Background: Recent studies show that patients with multiple nonsteroidal anti-inflammatory drug (NSAID) intolerance are frequently characterized by autoreactivity; this can be detected by autologous serum skin test (ASST). **Objective:** To assess whether the autologous plasma skin test (APST), a test that was recently shown to be more sensitive than ASST, may be usefully employed as a predictive test for multiple NSAID intolerance in patients with a history of single NSAID intolerance. **Methods:** Thirty otherwise normal adults with a history of acute urticaria following the ingestion of one single NSAID underwent an APST before being challenged with a COX-1-inhibiting NSAID other than the offending drug. **Results:** Sixteen patients experienced urticaria following the ingestion of the alternative NSAID and were therefore classified as multiple NSAID reactors; all 16 (100%) scored positive on APST. In contrast only 3/14 patients finally classified as single NSAID reactors were positive on APST ($p < 0.001$). The positive and negative predictive value of APST for multiple NSAID intolerance were 86 and 100%, respectively. **Conclusion:** In patients with a history of acute

urticaria induced by a single NSAID APST can be usefully employed to detect patients that are prone to react to NSAID other than the original offending one.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are probably the most frequent cause of drug-induced urticaria/angioedema. Based on the recent classification suggested by Stevenson et al. [1] two main groups of patients with NSAID-induced urticaria can be distinguished: (1) single drug reactors; otherwise normal subjects whose reactions are now considered as possibly IgE-mediated [1, 2] and (2) multiple drug reactors; these subjects can be either otherwise normal or have underlying chronic urticaria; in these patients, reactions to chemically unrelated substances are most likely based on the inhibition of cyclooxygenase-1 (COX-1) enzyme [1, 2].

In the clinical practice, patients presenting with a convincing history of urticaria induced by chemically distinct NSAID should be directly considered as multiple drug reactors, and submitted to oral challenges with alternative drugs exerting little or no activity on COX-1 (e.g. acetaminophen, tramadol, coxibs). In contrast, the

correct classification of subjects with a history of urticaria induced by a single NSAID requires a more complex workup as they might be either single or multiple NSAID reactors. Testing these patients only with NSAIDs that have little or no COX-1 enzyme-inhibitory activity, a practice that has been largely adopted in the past [3–11], does not allow for the detection of single drug reactors and may lead to unnecessary avoidance of many potentially useful NSAIDs. Very recently, it was shown that about 75% of patients with a history of acute urticaria induced by a single NSAID other than aspirin were able to tolerate aspirin on oral challenge and were therefore true single drug reactors [12]. Clearly, performing oral challenges with alternative strong COX-1 enzyme inhibitors in these patients carries the risk of potentially severe adverse reactions in at least 25% of cases. In this sense, an easily available and inexpensive *in vivo* or *in vitro* test able to predict the possible outcome of oral challenges would be of clinical value.

A significant proportion of patients with chronic urticaria, notably a condition that is often characterized by multiple NSAID intolerance [1], show a wheal-and-flare reaction upon intradermal injection of autologous serum (autologous serum skin test, ASST) [13–17]. In ASST-positive patients histamine-releasing activity has been associated with circulating IgG autoantibodies specific for the high affinity IgE receptor (FcεRI) [18], or for IgE [14, 15], or with not yet characterized serum factors [17]. Interestingly, recent studies showed that also otherwise normal subjects with multiple NSAID intolerance [19] or with multiple drug allergy syndrome [20] are frequently positive on ASST. Further, other studies found that chronic urticaria is often characterized by signs of thrombin generation and that in these patients the autologous plasma skin test (APST) is much more sensitive than ASST to detect an autoreactive state [21, 22]. In experimental animal models, thrombin induces edema through an increase in vascular permeability [23, 24] which can be obtained by a direct effect of thrombin on endothelial cells [25] and indirectly by a thrombin-related release of inflammatory mediators, an effect that is reduced by antihistamines and totally abolished if mast cell granules are depleted [24]. Moreover, thrombin triggers mast cell degranulation [26] and may activate protease-activated receptor-1 on mast cells [27]. Finally, thrombin is able to generate C5a in the absence of C3, thus bypassing the whole first part of the complement cascade [28].

In the light of all these observations, the present study assessed APST as a predictive test for multiple NSAID

intolerance in patients with a history of single NSAID intolerance to be submitted to oral tolerance tests with alternative NSAIDs.

Methods

Patients and Skin Tests

Thirty adult patients (mean age 44.2 years, range 18–70 years; M/F 8/22) with a history of recent (1–3 months before) acute urticaria with or without angioedema following the ingestion of a single NSAID were studied. No patient had a history of spontaneous urticaria/angioedema or of urticaria/angioedema following the ingestion of drugs other than the reported one. Clinical features and offending drugs are shown in table 1. Offending drugs included pyrazolone drugs (n = 12), propionic acid derivatives (n = 6), aspirin (n = 4), nimesulide (n = 4), diclofenac (n = 2), piroxicam (n = 1), and acetaminophen (n = 1).

Before the start of oral tolerance tests all patients underwent an intradermal injection of 0.05 ml of sterile, fresh autologous plasma anticoagulated with Na citrate (APST), as previously described [21]. Readings were taken at 20 min. Only an unequivocal wheal-and-flare formation at the site of plasma injection in the absence of any skin reaction at the site of intradermal injection of an equivalent amount of saline was considered a positive response.

Tolerance Tests

All patients underwent oral tolerance tests with one COX-inhibiting NSAID other than the offending one. Patients with a history of urticaria following the administration of a NSAID other than aspirin were challenged with aspirin [12]; two provocative doses of aspirin (first dose 125 mg; second dose 375 mg) were given 1 h apart. Patients with a history of urticaria following the ingestion of aspirin were challenged either with a propionic acid derivative (ketoprofen; provocative doses 20 g and 60 mg) [29] or with diclofenac (provocative doses 25 and 75 mg). Patients were observed for 2 h after the last dose. Only the appearance of clear-cut urticaria with or without angioedema was considered as a positive reaction; urticaria was controlled by intravenous chlorphenamine 10 mg and the patient was observed for 1 further hour. The second provocative dose was not administered in the case of a positive reaction to the first dose.

Patients reacting on challenge with a strong COX-1 inhibitor were offered further oral challenge tests with drugs exerting little or no COX-1 inhibition, including acetaminophen (provocative doses 125 and 375 mg), tramadol (25 and 25 mg), nimesulide (25 and 75 mg), and/or etoricoxib (20 and 70 mg) in order to detect at least one safe drug to be used when needed. These further tests were carried out at least 2 weeks after the positive challenge. All patients gave an informed written consent before the start of the diagnostic procedure.

Statistics

Proportions were compared by two-tailed χ^2 test with Yates' correction. Probability (p) values of less than 0.05 were considered significant.

The positive predictive value (PPV) and negative predictive value (NPV) of APST were calculated using Goldman's method

Table 1. Clinical features, offending drugs, tolerance test results, and APST results

No.	Sex	Age years	Offending drug	Challenged drug	Further challenges	APST
1	M	54	Naproxen	ASA (Neg)	ND	Negative
2	F	23	ASA	Ketoprofen (Neg)	ND	Negative
3	F	41	ASA	Diclofenac (Neg)	ND	Negative
4	F	42	Ketoprofen	ASA (Neg)	ND	Negative
5	F	57	Feprazone	ASA (Neg)	ND	Negative
6	M	63	Nimesulide	ASA (Neg)	ND	Negative
7	F	21	Ketoprofen	ASA (Neg)	ND	Negative
8	F	37	Ketoprofen	ASA (Neg)	ND	Negative
9	F	54	Acetaminophen	ASA (Neg)	ND	Positive
10	M	41	Feprazone	ASA (Neg)	ND	Negative
11	F	66	Noramidopyrine	ASA (Neg)	ND	Positive
12	F	51	Diclofenac	ASA (Neg)	ND	Negative
13	F	27	Nimesulide	ASA (Neg)	ND	Positive
14	F	70	Feprazone	ASA (Neg)	ND	Negative
15	M	39	ASA	Ketoprofen (Pos)	E/A/T (Neg)	Positive
16	F	30	ASA	Ketoprofen (Pos)	E/T (Neg); N (Pos)	Positive
17	F	18	Feprazone	ASA (Pos)	ND	Positive
18	F	68	Feprazone	ASA (Pos)	A/T (Neg); E/N (Pos)	Positive
19	F	49	Feprazone	ASA (Pos)	T/N/A (Neg)	Positive
20	F	21	Nimesulide	ASA (Pos)	E (Neg)	Positive
21	M	44	Naproxen	ASA (Pos)	A/N/E/T (Neg)	Positive
22	F	36	Noramidopyrine	ASA (Pos)	N (Pos)	Positive
23	F	39	Noramidopyrine	ASA (Pos)	E/T/N (Neg)	Positive
24	M	55	Diclofenac	ASA (Pos)	A/N/E/T (Neg)	Positive
25	F	31	Feprazone	ASA (Pos)	A/N/E/T (Neg)	Positive
26	F	62	Feprazone	ASA (Pos)	A/E (Neg)	Positive
27	F	50	Naproxen	ASA (Pos)	N (Neg)	Positive
28	M	70	Noramidopyrine	ASA (Pos)	A/N/E/T (Neg)	Positive
29	F	35	Piroxicam	ASA (Pos)	A/E/T (Neg); N (Pos)	Positive
30	M	32	Nimesulide	ASA (Pos)	E (Neg); A (Pos)	Positive

ASA = Aspirin; Neg = tolerated; Pos = not tolerated; ND = not done; A = acetaminophen; E = etoricoxib; T = tramadol; N = nimesulide.

[30]. PPV and NPV were defined as $TP \times P / TP \times P + FP(1 - P)$, and as $TN(1 - P) / TN(1 - P) + FN \times P$, respectively, where P = prevalence (multiple NSAID reactors/total patients), TP = true positive (multiple NSAID reactors positive on APST), FN = false negative (multiple NSAID reactors negative on APST), TN = true negative (single NSAID reactors negative on APST), and FP = false positive (single NSAID reactors positive on APST).

Results

Sixteen (53%) patients (M/F 5/11; mean age 42.4 years) experienced urticaria following the administration of a strong COX-1 inhibitor other than the offending NSAID reported by history, and were therefore classified as mul-

tipl NSAID reactors (table 1, No. 15–30). After the positive challenge, 15 of these patients agreed to undergo oral tolerance tests with drugs exerting little or no effect on COX-1. Acetaminophen, tramadol, etoricoxib and nimesulide were tolerated in 9/10 (90%), 11/11 (100%), 11/12 (92%), and 6/10 (60%) cases, respectively (table 1).

Fourteen (48%) patients (M/F 3/11; mean age 46.2 years) tolerated the drugs challenged (table 1, No. 1–14). No difference in mean age and gender was found between single and multiple NSAID reactors.

APST scored positive in 16/16 (100%) multiple NSAID reactors versus 3/14 (21%) single NSAID reactors; the association between positive APST and multiple NSAID reactivity was statistically significant ($p < 0.001$). The PPV

and NPV of APST for multiple NSAID intolerance were 86 and 100%, respectively. No difference in total serum IgE or blood eosinophil count was found between patients scoring positive or negative on APST.

Discussion

It is generally accepted that the pathogenesis of multiple NSAID intolerance is associated with the inhibition of COX-1 enzyme, whereas single drug reactions are considered as possibly IgE-mediated [1, 2]. However, apart from COX-1 inhibition, recent studies show that clinical conditions characterized by urticaria following the ingestion of several, chemically unrelated drugs, such as the multiple drug allergy syndrome [20] and multiple NSAID intolerance [19], are commonly associated with autoreactivity. Further, studies in patients with chronic urticaria have shown that the intradermal test with autologous plasma (APST) is able to detect an autoreactive state much more efficiently than the ASST suggesting that some factor that is lost during the clotting process is involved in such skin reaction [21]. In effect, subsequent investigations demonstrated the activation of the tissue pathway of coagulation resulting in thrombin formation in patients with chronic urticaria [22]. Although specific studies are still missing, it is very likely that similar mechanisms may be involved in disorders other than chronic urticaria but also characterized by autoreactivity. To date, an increased thrombin generation has also been observed in patients with multiple drug allergy syndrome [31]. In the present study, the APST was used as a predictive test in a group of otherwise normal patients with a history of acute urticaria following the ingestion of one single NSAID before challenges with alternative, chemically

unrelated COX-1 inhibiting NSAID with the aim to assess whether the detection of an autoreactive state could be usefully employed to predict multiple NSAID intolerance. The results unequivocally demonstrate that autoreactivity is associated with multiple NSAID intolerance: 100% of multiple NSAID reactors versus 21% single drug reactors scored positive on APST. The fact that some single NSAID reactors scored positive on APST is not surprising, as this was observed in a very similar proportion of patients in a previous study [19]. Although it cannot be excluded that the 3 APST-positive patients finally classified as single NSAID reactors would have reacted on a challenge with COX-1-inhibiting drugs other than aspirin, this seems very unlikely. Follow-up studies will be needed to ascertain whether these APST-positive subjects are also prone to develop multiple NSAID intolerance. About 20% of patients with chronic urticaria, another condition often characterized by autoreactivity, may experience a flare-up of hives when they take COX-inhibiting NSAID [1]; recent studies have shown that NSAID intolerance (notably, also to one single NSAID) might precede the onset of chronic urticaria by years [32]. The finding that also single NSAID reactors may score positive on APST might be related to such a tendency.

Not unexpectedly [21], the proportion of multiple NSAID reactors positive on APST exceeded that of multiple NSAID reactors who scored positive on ASST in a previous study [19]; in effect, of 6 multiple NSAID reactors that underwent both APST and ASST in this study (No. 15–21, table 1), 1 (No. 16) scored negative on ASST.

In conclusion, in view of its excellent NPV and good PPV, APST may be usefully employed as a means to detect NSAID-intolerant patients that are prone to react to chemically unrelated anti-inflammatory drugs.

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