

Short-term decrease of skin-test sensitivity after rush desensitization in Hymenoptera venom hypersensitivity

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Summary

Thirty-seven patients with a history of systemic anaphylactic stings were desensitized by the rush method. Patients were evaluated by skin testing twice, before and 6 weeks after desensitization. An additional control group of 10 patients, not yet desensitized, were tested for skin test technique reproducibility at 6-week intervals. Results were compared with IgE and IgG antibody levels, and with platelet reactivity towards specific Hymenoptera venom. Before desensitization, the maximum skin-test sensitivity was observed at 10^{-5} µg venom/ml in 56% of patients and decreased to 10^{-1} µg venom/ml after desensitization (48.6% of patients). Decrease of cutaneous tests was observed in 28/37 patients (75%) ($P < 0.001$) and was not associated with significant variations of specific IgE or IgG antibody levels, but was correlated with the decrease of platelet reactivity ($P < 0.05$). Conversely, variations of skin-test sensitivity in the control group was not significant.

Clinical and Experimental Allergy, Vol. 20, pp. 287–292. Submitted 27 September 1988; revised 5 October 1988; accepted 4 December 1989.

Introduction

Evolution of cutaneous tests in Hymenoptera venom hypersensitivity after specific desensitization has been studied very little. Although a spontaneous decrease of cutaneous tests was clearly established in children [1,2] it has not been so well defined in adults. Previous studies made after the beginning of desensitization by venoms found no change in skin-test sensitivity after immunotherapy [3]. More recently, it has been shown that, as in children, cutaneous test sensitivity in adults decreased after 2 or 3 yr of maintenance treatment [4,5], or even several months after discontinuation of venom desensitization [6]. In our work we found that when retesting as early as 6 weeks after rush desensitization, a significant proportion of patients (30/40, i.e. 75%) had decreased skin-test sensitivity, contrary to a control group. We evaluated the correlation with other parameters concomitantly studied: specific IgE and IgG antibodies and platelet reactivity.

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Subjects and methods

Subjects

Thirty-seven subjects, age 11–63 yr, with a history of anaphylactic reactions after Hymenoptera stings were included in this study. Thirty-one were sensitive to *Vespula germanica* and six to *Apis mellifica*. All experienced life threatening reactions. The initial evaluation consisted of a thorough medical and allergy history, venom skin tests, measurements of specific IgE and IgG antibodies and sampling of blood for testing their platelet reactivity. A control group of 10 subjects, age 11–62 yr, were included, nine sensitive to *V. germanica* and one to *A. mellifica* whose, with their informed consent, desensitization was delayed in order to test the reproducibility of the skin test technique. Table 1 presents the main characteristics of the subjects. Clinical reactions were classified in systemic reactions according to Mueller [7] as follows.

- (1) Slight general reaction with generalized urticaria.
- (2) General reaction: any of the above, plus two of the following: angioneurotic oedema, constriction of chest, nausea, vomiting, diarrhoea.

Table 1. Clinical data and cutaneous tests of subjects before and 6 weeks after desensitization, and of a control group at 6 week intervals

Subjects	Age (yr)	Sex	Insect	Clinical score*	Skin test† (μg/ml)	
					Before	After
Treated group						
1	54	F	V	4	10 ⁻⁵	10 ⁻²
2	35	M	V	4	10 ⁻⁵	Neg.
3	58	M	HB	2	10 ⁻⁵	10 ⁻³
4	61	F	V	4	10 ⁻⁵	10 ⁻¹
5	16	F	V	2	10 ⁻⁵	10 ⁻²
6	16	F	HB	3	10 ⁻⁵	10 ⁻¹
7	52	F	V	4	10 ⁻⁵	10 ⁻²
8	55	M	V	1	10 ⁻⁵	10 ⁻¹
9	27	F	V	4	10 ⁻⁵	10 ⁻⁴
10	57	M	V	2	10 ⁻⁵	Neg.
11	49	F	V	1	10 ⁻⁵	10 ⁻²
12	53	F	V	2	10 ⁻⁵	10 ⁻²
13	11	M	HB	2	10 ⁻⁵	10 ⁻¹
14	50	F	HB	1	10 ⁻⁵	10 ⁻¹
15	13	F	V	1	10 ⁻⁵	10 ⁻¹
16	40	F	V	3	10 ⁻⁵	10 ⁻²
17	49	M	V	2	10 ⁻⁵	10 ⁻²
18	58	F	V	3	10 ⁻⁵	10 ⁻¹
19	44	M	HB	4	10 ⁻⁵	Neg.
20	22	M	V	2	10 ⁻⁵	10 ⁻²
21	49	F	HB	4	10 ⁻⁵	10 ⁻²
22	27	M	V	1	10 ⁻⁴	Neg.
23	63	F	V	4	10 ⁻³	10 ⁻¹
24	37	F	V	1	10 ⁻³	10 ⁻²
25	56	F	V	2	10 ⁻³	10 ⁻²
26	46	M	V	2	10 ⁻³	10 ⁻²
27	34	M	V	4	10 ⁻²	10 ⁻¹
28	19	M	V	2	10 ⁻¹	10 ⁻¹
29	18	M	V	4	10 ⁻¹	10 ⁻¹
30	37	F	V	3	10 ⁻¹	10 ⁻¹
31	10	F	V	3	10 ⁻¹	10 ⁻¹
32	27	M	V	3	10 ⁻¹	10 ⁻¹
33	52	F	V	4	10 ⁻¹	Neg.
34	59	M	V	3	10 ⁻¹	10 ⁻¹
35	63	M	V	4	10 ⁻¹	10 ⁻¹
36	64	F	V	4	10 ⁻¹	10 ⁻¹
37	41	F	V	1	10 ⁻¹	10 ⁻¹
Control group						
1	11	M	V	2	10 ⁻⁵	10 ⁻⁵
2	53	M	V	2	10 ⁻⁵	10 ⁻⁴
3	32	F	V	4	10 ⁻⁴	10 ⁻³
4	41	M	V	3	10 ⁻³	10 ⁻²
5	13	M	HB	1	10 ⁻²	10 ⁻³
6	62	F	V	4	10 ⁻²	10 ⁻²
7	44	M	V	4	10 ⁻¹	10 ⁻¹
8	39	M	V	1	10 ⁻¹	10 ⁻¹
9	30	F	V	1	10 ⁻¹	10 ⁻¹
10	55	M	V	2	10 ⁻¹	10 ⁻¹

*Clinical reactions were classified in systemic reactions as described in subjects and methods.

†Minimum venom concentration required to obtain a positive test (weal ≥ 5 mm).

V, Vespula; HB, honey-bee.

(3) Severe general reaction: any of the above, plus two of the following: dyspnea, dysphagia, hoarseness.

(4) shock reaction: fall in blood pressure and/or unconsciousness.

All 37 patients were desensitized towards the related venom.

Venom skin testing

The following technique was employed throughout the entire study. Standardized honey-bee and yellow-jacket venoms were supplied by Laboratoires des Stallergènes (Fresnes, France) and were reconstituted in albumin-containing buffer to yield the required venom concentration. Preparation of venom dilutions was carried out just before skin testing, excluding loss of allergenic potency. The same batches of venom extracts were used over the whole time of the study (batch no. 60936).

Skin tests were performed intradermally by injection of approximately 0.02 ml of serially diluted venoms between 10^{-5} and 10^{-1} $\mu\text{g/ml}$. Positive responses were defined as a minimum 2+ reaction as defined by Norman [8] (weal size 5×5 mm or greater). Negative controls (diluent) and positive controls (histamine, 0.5 mg/ml) were also included. Skin tests were performed before desensitization and 6 weeks after rush immunotherapy, i.e. 3 weeks after the last injection of venom for the treated group, and at 6 week intervals for the control group. All skin tests were performed and interpreted by the same investigator.

Antibody measurements

Specific IgE antibodies (RAST-Pharmacia, Uppsala, Sweden) were measured successively before and 6 weeks after rush desensitization, before the skin testing, and expressed as 0–4 scores. Measurements of venom-specific IgG antibodies were performed by radioimmunoprecipitation in the liquid phase according to the method described by Sobotka [9] and results were expressed as a percentage of bound radioactivity (between 0 and 100%).

Platelet activation test

Blood was collected on ACD-C [10] before and 6 weeks after desensitization. Platelet-rich plasma was obtained by centrifugation ($120 \times g$ for 15 min) and then platelets were washed three times by repeated centrifugation ($2000 \times g$ for 15 min) in saline supplemented with citric acid (36 mM), glucose (5 mM), calcium (2 mM), magnesium (1 mM), serum albumin (0.35%) and PGE₁ (100 nM) [11]. Platelets were suspended at a concentration of $30 \times 10^8/\text{ml}$ in Eagle's minimum essential medium (EMEM, Institut Pasteur Production, Paris, France). Suspensions of 50 μl

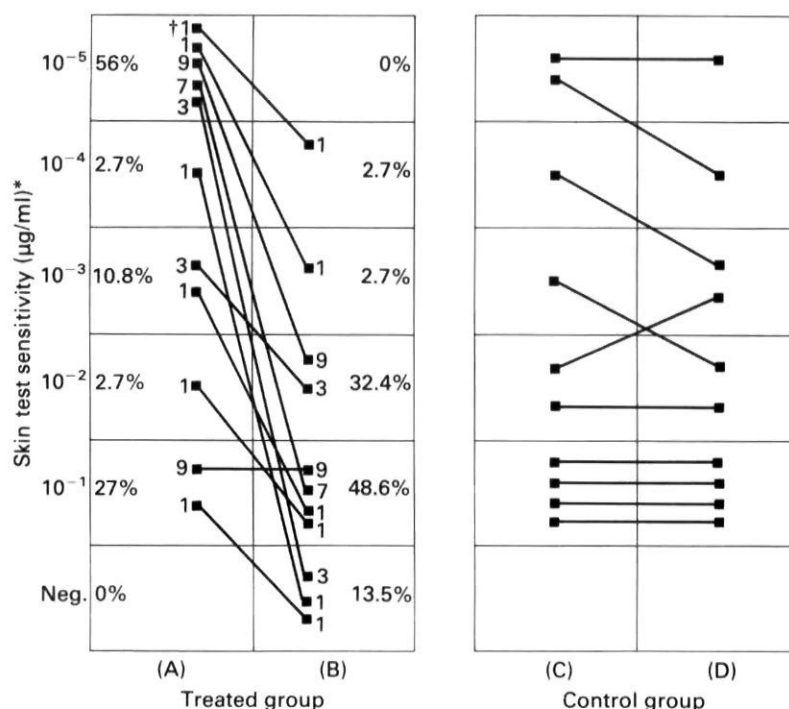


Fig. 1. Changes in skin-test sensitivity of the treated group 6 weeks after desensitization and of the control group at 6 week intervals. * Minimum venom concentration required to obtain a positive skin test (weal ≥ 5 mm). (A) Before desensitization; (B) 6 weeks after desensitization. † Numbers in columns A and B (treated group) refer to the exact number of subjects exhibiting the same modification in skin-test reactivity. For example, seven subjects sensitive before desensitization at 10^{-5} µg/ml were found, after desensitization, to be positive at a dose of 10^{-1} µg/ml. (C) First skin testing; (D) second skin testing 6 weeks later. Changes in cutaneous test sensitivity were significant in the treated group ($P < 0.001$), but not in the control group ($P = 0.34$).

were incubated in flat-bottomed microplates (Nunc, Roskilde, Denmark) with 50–100 *Schistosoma mansoni* schistosomula, 10% pooled sera from normal donors, and in the presence of the related allergen (honey-bee or yellow-jacket venom) in a final volume of 200 µl. Allergens were reconstituted in EMEM and aliquots of 100 µl, corresponding to 10 µg of venom, were frozen at -20°C .

For each platelet cytotoxicity test, venom allergens were diluted at concentrations varying from 10^{-5} to 10^{-1} µg/ml at the same time as the *in-vitro* test. Platelet reactivity was estimated by the release of cytotoxic mediators, as shown by the killing of parasite larvae. After 24 hr at 37°C and 5% CO_2 in air, motionless and dark dead larvae were clearly distinguishable from mobile and refringent living schistosomula by optical microscopy, which allowed a definition of a percentage of parasite cytotoxicity [12].

Treatment

The method used for immunotherapy was rush desensitization, as described by Nataf [13]. The maintenance dose of 100 µg was usually reached in 4 days, repeated 1 week, 2

weeks and 3 weeks later, and then at monthly intervals. All investigations were performed before the third injection of venom after the rush, i.e. 3 weeks after the last injection of venom.

Statistical analysis

Data were analysed by the two-way analysis of variance and results expressed as mean $\pm$ s.e.m. Correlations were studied by a linear regression using the least-squares method.

Results

Skin testing

In the treated group, cutaneous tests were studied before and 6 weeks after desensitization (Fig. 1). Maximum skin-test sensitivity was observed at 10^{-5} µg venom/ml before rush desensitization (56% of subjects) and at 10^{-1} µg venom/ml after rush desensitization (48.6%). Before desensitization, two groups could be distinguished: a group of subjects with highly sensitive cutaneous tests positive at a concentration of 10^{-4} or 10^{-5} µg venom/ml

Table 2. Time course evolution of skin tests*

Subjects†	Before	Time after desensitization*		
		6 weeks	1 yr	2 yr
3	10 ⁻⁵	10 ⁻³	n.d.	10 ⁻¹
4	10 ⁻⁵	10 ⁻¹	Neg.	Neg.
5	10 ⁻⁵	10 ⁻²	10 ⁻¹	10 ⁻¹
7	10 ⁻⁵	10 ⁻²	n.d.	10 ⁻¹
8	10 ⁻⁵	10 ⁻¹	10 ⁻¹	10 ⁻¹
11	10 ⁻⁵	10 ⁻²	10 ⁻¹	10 ⁻¹
12	10 ⁻⁵	10 ⁻²	10 ⁻²	10 ⁻¹
13	10 ⁻⁵	10 ⁻¹	10 ⁻¹	Neg.
16	10 ⁻⁵	10 ⁻²	n.d.	Neg.
17	10 ⁻⁵	10 ⁻²	10 ⁻¹	10 ⁻¹
20	10 ⁻⁵	10 ⁻²	10 ⁻²	10 ⁻¹
24	10 ⁻³	10 ⁻²	n.d.	10 ⁻¹
27	10 ⁻²	10 ⁻¹	10 ⁻²	Neg.
34	10 ⁻¹	10 ⁻¹	10 ⁻¹	10 ⁻¹
35	10 ⁻¹	10 ⁻¹	Neg.	Neg.
37	10 ⁻¹	10 ⁻¹	10 ⁻¹	10 ⁻¹

*Minimum venom concentration ($\mu\text{g/ml}$) required to obtain a positive skin test (weal ≥ 5 mm).

†Numerals refer to subjects from Table 1.

and a group of subjects that demonstrated less sensitive tests positive at concentrations of 10⁻³, 10⁻², or 10⁻¹ μg venom/ml. No relationship was observed with the age of the allergic accident. After desensitization the highly sensitive group showed a dramatic decrease of cutaneous test sensitivity, the threshold of which was $< 10^{-2}$ $\mu\text{g/ml}$ in 20/22 subjects (91%) and negative in 4/22 (18%). Conversely, in the less sensitive group 9/15 subjects (60%) showed the same skin-test sensitivity as before desensitization, 4/15 (26.6%) showed a 10-fold decrease, 1/15 (6.6%) a 100-fold decrease and 1/15 (6.6%) became negative. In the control group, 1/10 showed a 10-fold increase (10%), 6/10 (60%) the same skin-test sensitivity and 3/10 (30%) a 10-fold decrease. A decrease of skin-test sensitivity was significant only for the treated group ($P < 0.001$). Moreover 16 subjects have been extensively followed up. In these subjects none were negative after the rush, 2/16 (12%) were negative 1 yr after treatment and 5/16 (31%) were negative 2 yr later (Table 2).

Venom-specific IgE

RAST scores were compared before and 6 weeks after desensitization. No significant change was observed: 20/37 (54%) had the same RAST score, 6/37 (16.2%) had increased RAST levels and 11/37 (29.7%) had decreased

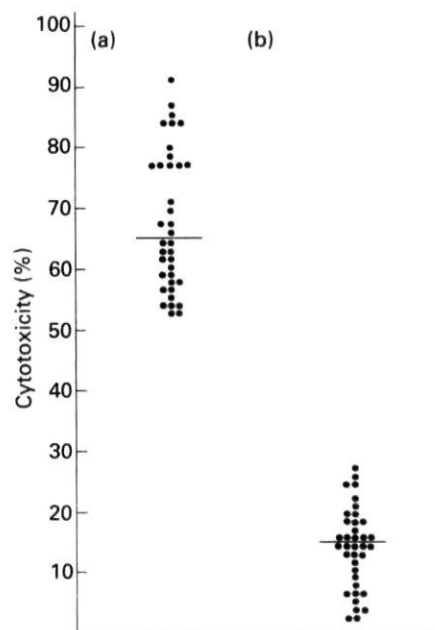


Fig. 2. Allergen-induced anti-parasite cytotoxicity of platelets studied before (a) and 6 weeks after (b) rush desensitization. Cytocidal platelet functions were estimated against *Schistosoma mansoni* larvae, after overnight incubation, by the percentage of dead larvae. Platelet cytotoxicity results were given in the presence of 10⁻⁴ μg venom/ml.

RAST levels (data not shown). No correlation was observed between variations of RAST and decrease of skin-test sensitivity after desensitization.

Venom-specific IgG

Specific IgG were studied at the same time as other parameters. Before desensitization the mean IgG level was $20.3 \pm 3.8\%$ with a range of 0–66%. After desensitization, the mean IgG level was $42.6 \pm 4.6\%$ with extreme values of 8 and 77% (data not shown). The difference was statistically significant ($P < 0.05$; $n = 24$), but no correlation could be shown between variations of specific IgG and decrease of skin-test sensitivity after desensitization.

Platelet activation test

As previously observed [12], the allergen-specific platelet cytotoxicity decreased significantly 6 weeks after rush desensitization (Fig. 2) and persisted months or years after immunotherapy. The mean percentage of allergen-induced platelet cytotoxicity was $67.4 \pm 1.6\%$ in untreated subjects and $14.9 \pm 0.9\%$ after treatment ($P < 0.001$; $n = 37$). A significant correlation was found between decrease of cutaneous test sensitivity and decrease of platelet cytotoxicity ($r = 0.4$; $P < 0.05$) (Fig. 3).

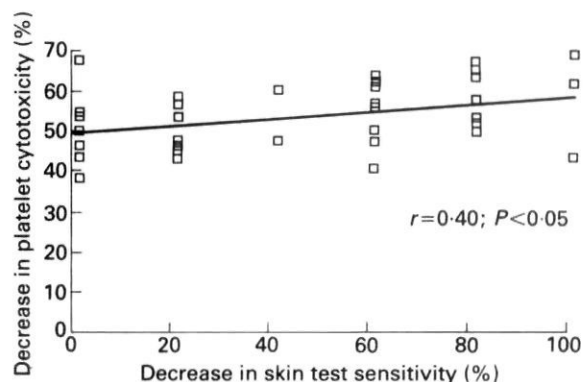


Fig. 3. Correlation between decrease of skin-test sensitivity and decrease of platelet cytotoxicity. The percentage decrease of platelet cytotoxicity was expressed as platelet cytotoxicity (%) before desensitization subtracted from platelet cytotoxicity (%) after desensitization. For skin-test sensitivity, the percentage decrease was evaluated to 20% for each 10-fold concentration decrease. The correlation was statistically significant ($P < 0.05$).

Discussion

Cutaneous tests, evaluated by end-point titration, decreased as early as 6 weeks after the beginning of immunotherapy. Although this decrease of cutaneous tests is not a recognized parameter in allergic respiratory diseases [8] it has been described for venom immunotherapy mainly in children [1,2] and occasionally in adults [4,5], generally after several years of immunotherapy. In these studies, skin tests were usually performed with diluted venom concentrations beginning at 10^{-3} $\mu\text{g}/\text{ml}$. In our study, we began skin tests at a lower venom concentration (10^{-5} $\mu\text{g}/\text{ml}$) and the decrease of the cutaneous response thereby appeared more obvious. This decrease of skin-test sensitivity was statistically significant compared to a control group. The rate of sensitivity loss was greater for the group with highly sensitive cutaneous tests before immunotherapy than for the group with lower skin sensitivity, but no correlation could be established in either group with the clinical score. In our study, many subjects were followed up for several months and even years after the beginning of desensitization. Skin-test sensitivity remained stable or continued to decrease, but to a lesser extent. The significance of this decrease of cutaneous tests was investigated by comparison with *in-vitro* parameters. This decrease might have reflected a loss of venom-specific IgE, but no significant change in RAST levels was observed at the same time. The hypothesis that increased amounts of venom-specific IgG induced by venom immunotherapy were responsible for the decrease of the venom skin test appeared unlikely, because, despite an increase in IgG antibodies after desensitization, the mean level of specific IgG after desensitization was not different in the highly sensitive group ($39.7 \pm 6.8\%$) and in

the less sensitive group ($46.1 \pm 6.1\%$) ($P > 0.05$), and no correlation could be established with the decrease of skin-test sensitivity. Moreover, some subjects with high venom-specific IgG antibodies before desensitization had highly sensitive skin tests and others, exhibiting low levels of IgG antibodies after desensitization, had low or negative cutaneous tests.

The decrease of cutaneous tests was also compared to another biological parameter: the platelet activation. The interaction of specific IgE bound to the platelet membrane with the relevant antigen has been shown to induce a potent and selective activation process [14]. It has been suggested, therefore, that platelets might interfere in immediate-type allergic reactions perhaps as secondary cells, triggered at the site of the reaction by mediators released from other inflammatory cells (e.g. platelet-activating factor [15]), or as primarily reacting cells initiating a reaction in the presence of allergen [16]. The IgE-dependent activation of platelets has not yet revealed the release of specific platelet mediators. Stimulation of platelets in the presence of the specific allergen through the IgE type II receptor of low affinity [16] has been described in patients sensitive to Hymenoptera venom [12]. This platelet reactivity was abolished after rush desensitization and was not correlated with specific IgE and IgG antibodies. Although the exact role of platelets in immediate hypersensitivity reactions remains to be defined, platelets appeared as marker cells of desensitization. Some experimental data were in favour of the involvement of a lymphokine. First, a circulating suppressive factor of platelet cytotoxic functions has been described in sera from desensitized patients [17], which was different from IgG and IgE antibodies, and whose characteristics were very similar to a newly described lymphokine: platelet activity suppressive lymphokine (PASL) [18]. Secondly, the lymphocyte supernatants from patients desensitized towards Hymenoptera venom were able to suppress the IgE-dependent platelet activation [19]. The physicochemical characterization of this lymphokine also showed the same characteristics as PASL [20]. Indeed, although the exact mechanism cannot be clearly established at this time, we observed that the decrease in platelet reactivity after rush desensitization occurred in parallel with the decrease of skin-test sensitivity. The platelet reactivity was abolished for all the venom concentrations tested from 10^{-5} to 10^{-1} $\mu\text{g}/\text{ml}$, but no difference in platelet reactivity was found among the subjects, as for cutaneous tests, which may suggest that platelets were more sensitive than cutaneous mast cells to rush desensitization. As a linear correlation was found between decrease of skin-test sensitivity and decrease of platelet reactivity ($P < 0.05$), it is suggested that, as for platelets, a lymphokine might also act on mast

cells but in a less effective manner. This hypothesis, however, needs further investigations.

These data show a marked decrease of cutaneous tests 6 weeks after rush venom desensitization, unrelated to IgE or IgG antibody levels, but associated with a decrease of the platelet reactivity, perhaps in relation with the production of lymphocyte-derived products.

Acknowledgments

The authors wish to acknowledge Mr H. Vorng, Mrs J. Lejosne and Mrs C. Laine for expert technical assistance, Mr G. Ville and Mrs L. Guilloux for specific IgG antibody dosages, and Mrs C. Zeiske and Mrs C. Colson for secretarial assistance. This study was supported by INSERM (Réseau de Recherche Clinique sur la participation des cellules inflammatoires au cours des affections respiratoires à composante immunologique n°850027).

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