

Provocation test with a living insect as a diagnostic tool in systemic reactions to bee and wasp venom: a prospective study with emphasis on the clinical aspects

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Summary

The use of the sting challenge (SC) in insect allergy has brought into doubt the widely held belief that clinical data, specific IgE and the skin test are reliable tools in diagnosis and decision making with regard to therapy. We subjected ninety patients, known to have a systemic reaction to SC, in the Intensive Care Unit. Of these patients, 28% once more showed a systemic reaction; 72% had only a local reaction. No statistically significant difference could be demonstrated between positive and negative SC patients with regard to age; sex; the presence of allergic disease(s)—other than allergy to insects—and the severity of the preceding systemic reaction; the sting site and the related time interval; or specific IgE, IgG1, IgG4, their ratios and the skin test. A negative skin test and/or specific IgE, however, does not exclude the possibility of a recurrent systemic reaction. The long-term value of the SC appeared to be good since the results of the revision SC remained unchanged. Skin test and specific IgE are useful as diagnostic tools in establishing the insect concerned. SC provides information on the likelihood of a recurrent systemic reaction.

Introduction

In the studies of Hunt [1] and Parker [2], it was shown that a person who has once experienced a systemic reaction to bee or wasp venom will not always show a systemic reaction to a future sting, with both discongruence and concordance between history, skin test and specific IgE. Since the number of patients studied was rather small (23 *vs* 16), we started a prospective study in which a greater number of patients with a systemic reaction in their history were sting-challenged with a living insect, irrespective of the severity of the preceding systemic reaction(s). A further incentive was that patients informed us that incidental re-stinging did not always result in a subsequent

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Table 1. The number and results of the provocation tests (=SC) performed with regard to the AAACI criteria

No. provocation	AAACI criteria*	Provocation positive group		Provocation negative group	
		No.	%	No.	%
91	+	25	27	66	73
20	-	3	15	17	85
16	+/-	2	13	14	87
127		30	24	97	76

* AAACI in the patients fulfilling the criteria, ninety-one SC were performed in ninety persons: one patient was sting challenged by both bee and wasp. Twenty patients did not satisfy the criteria. Revision SC was performed in fifteen patients, in one of them twice, from both groups.

systemic reaction. The aim of the study, in which particular emphasis was placed on the clinical aspects, was to prove that neither clinical data, skin test nor specific IgE could ever predict the risk and severity of a subsequent systemic reaction, i.e. the outcome of a future sting.

Patients and methods

Patients

In the summers of 1983 and 1984, 114 patients proved eligible for sting challenge (SC) with a living bee (*Apis mellifera*) or wasp (*Vespula germanica*, *V. vulgaris*). Four patients were excluded from the study: one because of pregnancy; three because of severe cardiopulmonary disease and interfering medication (prednisone, β -blockers, vasodilators). They were treated with immunotherapy. Of the remaining 110 patients, none took medication known to interfere with either the outcome of, or recovery from a systemic reaction. Of these, ninety patients satisfied the requirements established by the Committee on Insects of the American Academy of Allergy (AAACI) [3] for the administration of immunotherapy by showing a history of a previous systemic reaction and positive skin test and RAST with insect venom (Table 1). The data from these ninety patients were suitable for statistical analysis.

Their ages ranged from 7 to 70 years with a mean of 36 years (Table 2) and comprised fifty-one females and thirty-nine males. All of them had suffered at least one systemic reaction, the severity of which was expressed in grades I-IV according to the method of Mueller [4] (Tables 2 and 3). According to their history and skin test, seventy-four patients (82%) had been stung by a wasp, fifteen patients (17%) by a bee and one patient by both insects. Allergic disease(s) were present in twenty patients (22%). These included allergic rhinitis, food allergy and allergy to drugs. Two patients had stopped their immunotherapy with purified wasp venom 3 years previously because of pregnancy. All patients provided informed consent before taking part in the study.

IgE and IgG antibody levels and the ratio IgG:IgE

Blood sampling for determination of specific IgE, IgG1 and IgG4 (RAST) was

Table 2. Comparison between patients with a positive or negative sting challenge (SC) with regard to the number of patients subjected to SC, the stinging insect, mean age and range, sex, severity of the preceding systemic reaction and the reaction following SC, and the sting of the preceding systemic reaction

Provocation test	No. patients	Insect	Mean age in years (range)	Sex		Severity of reaction leading to provocation				Severity of reaction following provocation				Sting site		
				♂	♀	I	II	III	IV	I	II	III	IV	Head	Trunk	Extr.
+	18	Wasp	36 (10-53)	8	10	5	5	5	3	13	2	2	1	5	4	7
+	7	Bee	33 (8-43)	3	4	1	3	2	1	4	—	3	—	4	—	1
+	25	Wasp and bee	35 (8-53)	11	14	6	8	7	4	17	2	5	1	9	4	8
—	57	Wasp	40 (7-70)	24	33	10	22	18	7	—	—	—	—	14	4	25
—	9	Bee	35 (9-62)	5	4	—	5	4	—	—	—	—	—	4	—	3
—	65*	Wasp and bee	39 (7-70)	28	37	10	27	22	7	—	—	—	—	18	4	28
+/-	90	Wasp and bee	36 (7-70)	39	51	—	—	—	—	—	—	—	—	27	8	36

*One male was sting challenged by both insects, both with a negative result.

Table 3. Severity grades of the systemic reaction following a sting by a bee or wasp (from H. L. Mueller [4])

Severity grade	Systemic reaction
I	Mild: generalized urticaria and or erythema, fear, itching
II	Moderate: arbitrary symptoms from grade I and two or more of the following: generalized oedema, nausea, vomiting, dizziness, tightness in the chest, abdominal pain, diarrhoea
III	Severe: arbitrary symptoms from grades I and II and two or more of the following: dyspnoea, bronchus obstruction, dysphagia, hoarseness, drowsiness, slurred speech, swoon
IV	Very severe: arbitrary symptoms from grades I, II, III and two or more of the following: cyanosis, hypotension, collapse, incontinence, unconsciousness

performed, at the latest, immediately before SC and, at the earliest, 1 year prior to SC. Determination was carried out in the Central laboratory of the Blood Transfusion Service in Amsterdam. The IgE value was expressed from 1+ to 5+ according to the percentage of bound radioactive labelled anti-IgE (RIA) and corresponded with: class 1 (1+): 2–5%; class 2: 6–10%; class 3: 11–20%; class 4: 21–40%; class 5 (5+): > 40%. A specific IgE value of 1+ or more was considered positive both for bee and wasp venom.

The specific IgG1 and IgG4 values were determined according to the Phadebas® IgG RAST method. Specific IgG1 and IgG4 values of > 10 (RAST) U/ml were considered positive.

The ratios of IgG1/IgE and IgG4/IgE were calculated from the corresponding IgE, IgG1 and IgG4 values determined. None of the patients had a subsequent sting in the period between blood sampling or skin testing and SC

Skin tests

Skin testing was performed at least 4 weeks, and at most 1 year, prior to SC and consisted of an intracutaneous injection of 0.1 ml of a solution with purified insect venom in increasing concentrations commencing with 0.000001 (10^{-6}) mg/litre. The bee venom (Pharmalgen Bee Venom vaccine in NSA diluents) and wasp venom (Pharmalgen Wasp Venom vaccine in NSA diluents) were purchased from Pharmacia Diephuis Groningen. All patients were skin tested with both venoms. The skin test was considered positive when an induration of ≥ 5 mm and an erythema of ≥ 10 mm or an induration + erythema ≥ 20 mm resulted from a concentration of ≤ 1.0 mg/litre [5–8].

Sting challenges (SC)

The time period between the sting that led to a visit to the out-patient department and the SC was between 3 weeks and 15 years and was 1 year or less in 75% of the patients. Sting challenge was performed with the insect(s) of which the purified venom had elicited a positive skin test. All SC were performed in the Intensive Care Unit (ICU). An i.v. catheter was inserted into the arm not to be stung. Medication, medical and nursing staff were on hand. The insects were caught from a nearby nest or apiary using forceps and were applied to the dorsal aspect of the lower arm. Almost all insects stung within a few seconds. Every insect caught was killed, whether it stung or not. The patients remained in the ICU for 1 hr and spent the next 2 hr in the waiting-room where

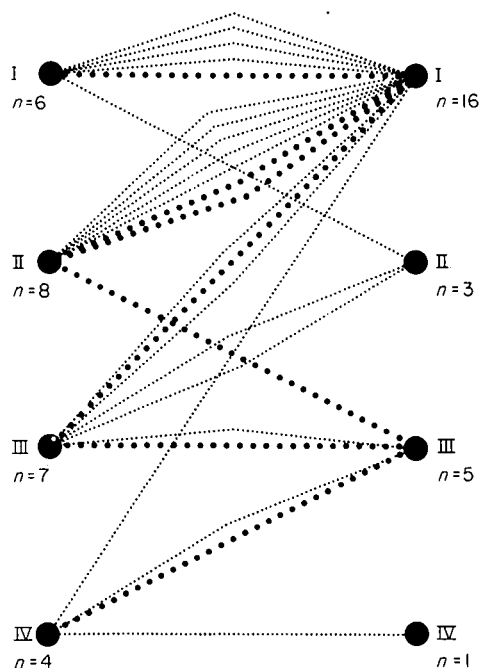


Fig. 1. Severity (according to H. L. Mueller [4]) of the preceding systemic reaction (left) and the reaction following SC (right) in twenty-five patients who developed a systemic reaction following SC. Seven were stung by a bee (●●●); eighteen by a wasp (.....). For ease of survey the sixty-five patients with a negative SC (Table 2) are omitted.

they were also able to reassure the patients waiting to undergo SC. If no systemic reaction appeared, the patients were discharged without treatment.

Depending on the severity of the systemic reaction following SC, the treatment advised was the prescription of an emergency kit containing syringes, i.m. needles and Clemastine ampulles 2 mg (Epipen, containing 0.5 ml adrenaline 1:1000, was not at that time available in Holland), or desensitization with pure insect venom according to the super-rush procedure [9].

Statistical analysis

Depending on the specific situation, one of the following tests was used: Chi-squared test, Student's *t*-test or Wilcoxon-Mann-Whitney's test. In each situation to be tested, a significance threshold of 5% was selected. When appropriate, one-tailed or two-tailed testing was performed. The nature of the test used is indicated with each test result.

Results

Of 100 SC performed on ninety patients with positive skin test and specific IgE, twenty-six (26%) produced a systemic reaction in twenty-five patients (28%). Of twenty-five positive sting challenge (PSC) patients, five presented with an allergic disease (20%) and of sixty-five negative sting challenge (NSC) patients, fifteen presented with an allergic disease (23%). Of these patients with allergic disease(s), 25% showed a PSC, the patients without allergic disease(s) showed a PSC in 29%.

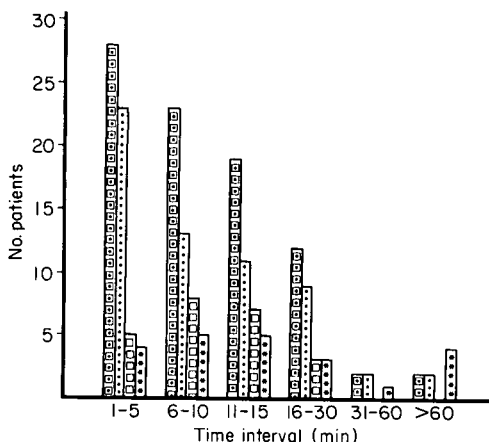


Fig. 2. The first three rows of each column show the time interval from the sting and onset of the preceding systemic reaction in ninety patients (□□□). Of these, sixty-five patients showed a negative SC (●●●) and twenty-five a positive SC (◐◐◐). The extreme right-hand row in each column shows the time interval between the sting and onset of the systemic reaction following SC (***).

The interval between the last systemic reaction to a sting and the SC was more than 1 year in 27% of the PSC patients and 26% of the NSC patients. Of patients with this interval, 30% had a positive SC. Of the patients with an interval of 1 year or less, 27% had a positive SC. Not even with one-tailed testing could statistical analysis demonstrate any difference between PSC and NSC patients for age (Student's *t*-test: $P > 0.05$); sex ratio (χ^2 : $P > 0.05$); the presence of allergic disease(s) (χ^2 : $P > 0.05$); or the severity of the preceding systemic reaction according to the history (χ^2 : $P > 0.05$); its sting site (χ^2 : $P > 0.05$) or the time interval between the sting and the onset of the preceding systemic reaction (χ^2 : $P > 0.05$). Nor was there any difference between PSC and NSC patients for the interval (≤ 1 year or > 1 year) between the preceding systemic reaction and the SC (χ^2 : $P > 0.05$). Comparison of the severity of the systemic reaction prior to, and following, SC showed a reduction in eighty patients (89%) (χ^2 : $P < 0.05$) (Fig. 1). In two patients (2%) there was an increase and eight (9%) showed an identical systemic reaction. In 98% of these patients, therefore, there was no progression in severity.

The time required to develop the preceding systemic reaction was ≤ 15 min in 87% of the PSC patients and in 80% of the NSC patients. That was also the case in 64% of PSC patients following SC. Of the latter, the interval was > 30 min in 22% and > 60 min in 18%. When compared with the preceding systemic reaction, the time interval was extended in 65%, shorter in 15% and the same in 20% of twenty PSC patients (χ^2 : $P < 0.05$) (Fig. 2).

In order to determine the long-term predictive value of the SC and exclude seasonal influences, revision SC was performed in fifteen of the original 110 patients under identical conditions, in one of them twice. In thirteen patients, the result was identical (eleven NSC; two PSC), two PSC patients showed no further systemic reaction (χ^2 : $P < 0.05$) (Table 1).

Similarly, statistical analysis could not demonstrate any difference between PSC and NSC patients for specific IgE, IgG1 and IgG4 (and their ratios) and for skin test

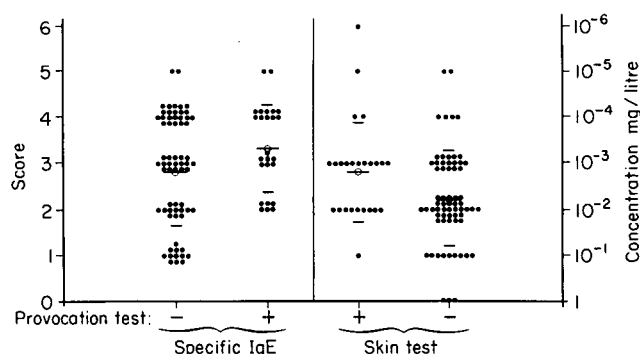


Fig. 3. Specific IgE and skin test with means and standard errors in ninety patients with positive or negative SC.

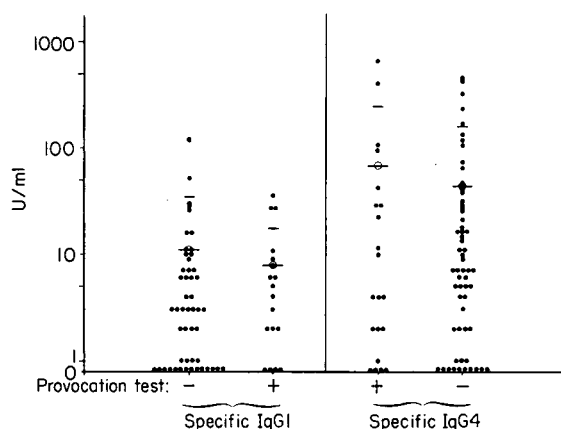


Fig. 4. Specific IgG1 and IgG4 with means and standard errors in ninety patients with positive or negative SC.

(Wilcoxon-Mann-Whitney: $P > 0.05$) (Figs 3 and 4).

Three (NSC) patients only showed a positive skin test with the threshold concentration of 1.0 mg/litre. Two of them, stung by a wasp, had been previously admitted to a hospital because of (documented) anaphylactic shock. The other, a beekeeper, had showed a systemic reaction II in the past when stung by a bee.

Of the twenty patients who did not satisfy the AAACI requirements, four showed a negative skin test. In three of them, no specific IgE could be demonstrated either: one had a PSC III and two had a NSC. Two out of sixteen patients with a positive history and skin test, but no demonstrable specific IgE, showed a PSC II.

Discussion

Notwithstanding the results of others [10] we demonstrated an equal risk of a systemic reaction in patients with and without allergic disease(s). In contrast to the studies of Schwartz [11] and Barnard [12], we have already shown that the severity of a systemic reaction following an insect sting is not increased in patients with allergic disease(s) [13].

The fact that no difference could be found between PSC and NSC patients for the interval since the last systemic reaction and the SC, casts some doubt on the concept that there is a decline in sensitivity over the years if stings are avoided.

Specific IgE and the skin test are only useful in the identification of the allergen and even in this they might fail [7], as illustrated in our twenty patients with a positive history but negative specific IgE and/or skin test. Mueller [14] suggests a spontaneous loss of allergy. Sobotka [15], however, points out that it is the mast cell/basophil-bound specific IgE and not the serum specific IgE that is of importance.

Since it is impossible to predict the outcome of a future sting, the course of action should be determined on the basis of those patients who have already shown a potentially life-threatening systemic reaction, even though Lessof [16] and Rubenstein [17] believe that a preceding systemic reaction is not a condition *sine qua non* to succumb following an insect sting. The time-lag between the onset of the systemic reaction and proper treatment will determine to what extent low perfusion state or respiratory distress will contribute to secondary effects, which do not respond to epinephrine, and, furthermore, influence morbidity and mortality. Prophylactic measures prevent those risks. In selecting these patients, we and others [1,2,7,18,19] proved that a classic history, a positive skin test and specific IgE are inadequate. The percentage of adults who appear to show no risk of a subsequent systemic reaction, despite the presence of all of these selection criteria, varies from 30 to 70% [1,2,9,20-22] and agrees with the 72% found in our study. Differences may well result from the inclusion or exclusion of local reactions and the number of patients studied.

The above, together with the failure of the skin test as a diagnostic tool when SC is replaced by 50 μ g of pure insect venom [1], demonstrates that only SC serves as an adequate criterion for selection.

Those opposed to this diagnostic tool cite three risks. Firstly, the possibility of a (late) fatal reaction: when explained to our patients, all expressed a preference for SC in the ICU rather than awaiting a subsequent in-field sting. Secondly, the risk of sensitization by the SC [5], but the same argument could also apply to a desensitization course. Thirdly, the fact that patients with a severe systemic reaction would probably be excluded from SC, this leading to a falsely high percentage of NSC. This assumes that the chance and course of a subsequent systemic reaction will depend on the severity of the preceding systemic reaction. This is confirmed by Lichtenstein [5] who observed that patients who displayed only cutaneous symptoms showed an identical or less severe reaction to a subsequent sting. Also Blaauw [7], Reisman [22] and Schuberth [23] demonstrated that the risk of a subsequent systemic reaction was particularly small in cases where there was a history of a systemic reaction I. These patients rarely showed a more severe reaction, unlike patients with a history of a systemic reaction III or IV. From the severity of the reactions in our population prior to and following SC, it can be seen that nearly all patients had a similar or less intense reaction, irrespective of the severity of the preceding systemic reaction (Fig. 1). Boon [24] and Parish [25], in retrospective studies, found that those patients who died as a result of an insect sting, 38% (of 50) and 34% (of 299), had a time interval between sting and onset of the subsequent systemic reaction of ≥ 60 min; 16% of Boon's patients and 4% of Parish's patients showed a time interval of ≥ 5 hr. Although all patients in our study with a severe systemic reaction (III or IV) following SC had a time interval of ≤ 15 min, it seems reasonable, in view of the above, to observe the patient for at least 3 hr following SC and to instruct the patient for the following 24 hr since the possibility of a late severe

reaction cannot be excluded.

The SC should only be withheld from patients with serious cardiopulmonary disease and/or vital interfering medication.

As a consequence, the indications for desensitizations as proposed by the AAACI [3] are no longer valid. Only patients with serious cardiopulmonary disease and a positive history, who cannot safely be submitted to SC, and PSC patients III and IV should be advised to undergo desensitization. For PSC patients I and II, management depends on the result(s) of revision SC. They should also be prescribed an emergency kit.

Although our results thus far have shown a good long-term predictive value for the negative (and to a lesser extent, for the positive) SC, one should be aware that the SC is no more than an indicative device. This is illustrated by the fact that four NSC patients had each previously showed two systemic reactions; in one of them, diminishing in severity with time, but progressive in two others. Of the latter, one was a beekeeper with remarkably high values for specific IgG1 (29 U/ml) and specific IgG4 (140 U/ml), which could have give some protection previously lacking. The reason(s) why the other patient with a progressive history did not show any further systemic reaction to SC is a matter for speculation, since her values for specific IgG1 (3 U/ml) and specific IgG4 (5 U/ml) were low.

A possible explanation of the discrepancy between the immunological parameters and the clinical data is the presence of non-IgE mediated reactions [16], lability of the kinin and/or complement system [26], cellular immunity [27] (which so far seems to be reserved for large local reactions), poorly recognized antigens, quantitative factors such as the amount of venom and the possible role of cross-binding of mast cell/basophil receptors [9,28], toxic and pharmacologic influences [5], spontaneous loss of sensitivity [14,29,30] and variability in the release of mediators [31]. Sting site (and vascularization), season and age of the stinging insect do not seem to be relevant [2,12,13].

Conclusions

Neither clinical data, specific IgE, IgG1 and IgG4, nor skin test can predict the risk and severity of a subsequent systemic reaction. A good and reliable diagnostic tool continues to be essential, despite the spontaneous tendency of a systemic reaction to remain stable or reduce in severity with time. The SC with a living insect fulfills the requirements of such a tool. It remains the only selection criterion with regard to immunotherapy. It forces reconsideration of the current AAACI/criteria and enables considerable reduction in the number of patients who need to be subjected to (costly) immunotherapy.

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This article is dedicated to the memory of the late Dr J. W. Imhof and is a result of his persisting and inspiring scientific interest and the way in which he transmitted this to his assistants.

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