

The Hymenoptera venom study III: Safety of venom immunotherapy

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One thousand four hundred ten (44%) of the 3236 subjects in the Hymenoptera venom study accepted venom immunotherapy (VIT). Time to maintenance averaged 95 days, and the largest number achieved maintenance (147 subjects, 10.4%) at day 56. Ninety-two percent of the treated subjects achieved maintenance, and 84% continued therapy, most subjects (91%) until the study was terminated. One hundred seventy-one subjects (12%) experienced 327 treatment systemic reactions (SRs). The incidence of pruritus and angioedema/urticaria was similar with mild, moderate, or severe SRs. The SR severity did not correlate with the severity of the most recent sting before entry into the Hymenoptera-venom study, the most severe historical sting SR, the most severe SR during venom skin tests, the total dose of venom, the degree of skin test reactivity, or the lowest concentration yielding a positive skin test. Most SRs occurred between 1 and 50 µg and at maintenance; honeybee or wasp venoms were most likely to produce SR. This study, the largest of its kind with the use of standardized extracts, demonstrates (1) that there was good compliance, (2) that various historical and diagnostic criteria did not predict SRs to VIT, (3) that SRs to VIT were most likely to occur between 1 and 50 µg and at maintenance, (4) that honeybee or wasp venoms were most likely to produce an SR, and (5) that VIT is relatively safe. (J ALLERGY CLIN IMMUNOL 1990;86:775-80.)

This article is the third describing the HVS that was initiated late in 1979 by the Committee on Insects of the American Academy of Allergy and Immunology.^{1,2} Data for the 3236 subjects of the study were obtained by analysis of questionnaire and follow-up forms submitted during a 3-year period by 84 fellows and members of the American Academy of Allergy and Immunology. The present article analyzes data on

Abbreviations used

HVS:	Hymenoptera venom study
SR:	Systemic reaction
SRI:	Systemic reaction index
VIT:	Venom immunotherapy
VST:	Venom skin test
GI:	Gastrointestinal

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safety of VIT with standardized Hymenoptera-venom extracts.

METHODS

Design of the questionnaire, forms, and methods used was described in the earlier articles.^{1,2} Follow-up forms were supplied to, and completed by, participating physicians at 6 and 12 months after a subject had entered the study and every 12 months thereafter for the duration of the HVS. Three forms were completed for subjects treated with VIT (Therapeutic Safety and Efficacy Protocol): form A, Venom Therapy; form B, Treatment Reaction Report; and form C, Insect-Sting Follow-Up, described previously.¹

Additional forms (D and E) were provided to the participating physicians to report reactions to therapy or stings between scheduled follow-up visits. Form D reported

TABLE I. SRI*

SR	SRI
Severe	Unconsciousness 0.376
	Shock 0.376
	Drop in blood pressure 0.126
Moderate	Lower airway obstruction 0.050
	Upper airway obstruction 0.050
	GI symptoms 0.013
Mild	Angioedema/urticaria 0.003
	Pruritus 0.003
	"Other" 0.003
Possible total	1.000

*See text for explanation.

TABLE II. Frequency of SRs reported by 171 subjects during VIT

No. of subjects (N = 171)	No. of SRs (N = 327)	% Total SR
117	1	69
28	2	16
12	3	7
3	4	2
2	5	1
2	6	1
4*	7	2
1*†	10	1
2*†	23	1

*SRIs of these seven subjects ranged from 0.003 to 0.016.

†Data not used in all analyses because of large deviation from average number of SRs per subject.

adverse reactions to VIT with questions identical to questions of form B. Form E reported reactions to insect stings with questions identical to questions on form C.

In Table I are listed the values for the SRI for various degrees of severity of SRs.¹ The SRI was designed so that combined values for all mild SRs would be less than the lowest value of any moderate SRs, and the summed values of all moderate SRs, either alone or together with sums of mild SRs, would not equal the value of the least severe SRs (drop in blood pressure). Inclusion of various signs and symptoms under "severe" versus "moderate" in the SR was made to obtain a number reflective of the type and severity of the reaction. It is difficult to determine, in this kind of study, if a subject is having upper and/or lower airway obstruction, whereas it is not as difficult to determine whether the subject is unconscious, in shock, or has a drop in blood pressure. Therefore, lower and upper airway obstructions were given a lower score in the SRI than were unconsciousness, shock, and drop in blood pressure. This difference in scoring is not to be interpreted to mean that

TABLE III. Severity and frequency of occurrence of SRs during VIT

SR	Frequency	SRI range
Mild	193 (59%)	0.003 to 0.005
Moderate	106 (32%)	0.013 to 0.122
Severe	28 (9%)	0.126 to 1.0
Total	327 (100%)	

Chi-square of SRI of 327 SRs during immunotherapy, 0.052.

lower and/or upper airway obstruction cannot be serious and even fatal. Data were compared with Pearson's product-moment correlations.

RESULTS

During the 3-year period (1979 to 1982) of subject entry, 1410 (44%) of the 3236 subjects in the HVS agreed to undergo VIT. The mean time between the first treatment and achievement of a maintenance dose was 95 days (SD $\pm$ 81.6; range, 7 to 847 days). Maintenance was achieved by the largest number of subjects (147 or 10.4%) at day 56 after beginning treatment.

One thousand two hundred ninety-six (92%) of the 1410 treated subjects achieved maintenance during the 3-year study period. After maintenance had been achieved, 1093 (84%) of these subjects continued receiving VIT, 1000 of whom (77% of the 1296) were still receiving VIT when the study was terminated. Twenty-three of the 296 subjects who left the study did so because of adverse reactions.

Three hundred twenty-seven SRs were reported by 171 subjects who received VIT, an average of 1.9 SRs per subject (Table II). Four of these subjects experienced seven mild to moderate SRs during VIT, one subject, 10 mild to moderate SRs, and two subjects each, 23 mild SRs. Each of the reactions experienced by the seven subjects who experienced seven or more SRs were true SRs. None of the reporting physicians offered any explanation of the large number of reactions experienced by these subjects. Four of the subjects with seven or more treatment SRs achieved maintenance during the study period. Of the 171 subjects who had an SR during VIT, only 10 had an SR during VST, eight of which were hypersensitivity reactions and two, vasovagal or nonanaphylactic.² The severity of the 10 SRs during VST did not correlate significantly with the most severe SR experienced by the 10 subjects during VIT ($r = 0.05$). The mean SRI of all SRs to VIT was 0.052, classified as moderately severe. Fifty-nine percent of the SRs were classified as mild, 32% as moderate, and 9% as severe

TABLE IV. Signs and symptoms of SRs from VIT

		Mild (N = 193*)	Moderate (N = 106*)	Severe (N = 28*)	Total subjects with each individual sign or symptom
Mild	"Other"†	104(54%)	52(49%)	12(43%)	168
	Pruritus	75(54%)	31(29%)	9(32%)	115
	Angioedema/urticaria	72(37%)	33(31%)	9(32%)	114
Moderate	GI symptoms	—	0	11(39%)	11
Severe	Upper airway obstruction	—	63(59%)	9(32%)	72
	Lower airway obstruction	—	53(50%)	3(11%)	56
	Drop in blood pressure	—	—	21(75%)	21
	Shock	—	—	13(46%)	13
	Unconsciousness	—	—	4(14%)	4

0, None reported; —, not included.

*, Total is 327 SRs.

†, "Other" is signs and symptoms that were considered mild by reporting physicians.

TABLE V. Number of subjects with SR by venom-type: honeybee versus all other venom types

Venom type	Subjects		Total	Chi-square	Probability
	With SR	With no SR			
Honeybee	90	134	224		
Yellow jacket	28	206	234	46.16	<0.001
Yellow hornet	1	10	11	3.06	<0.05
Wasp	27	50	77	0.43	NS
Mixed vespid	21	128	149	27.89	<0.001
White-faced hornet	1	5	6	0.54	NS
Total	168	534	702*		

NS, Not significant.

*Seven hundred two subjects were receiving single or mixed vespid venom extracts.

(Table III). The subject with the most severe SR (SRI, 0.897) during VIT developed signs and symptoms of pruritus, a drop in blood pressure, GI symptoms, unconsciousness, shock, and "other" (described as "respiratory failure"). The subject reached maintenance 3 months after this adverse reaction but dropped out of the study 2 years later after a second VIT induced severe SR (SRI, 0.518). The distribution of signs and symptoms of mild, moderate, and severe SRs occurring during VIT is listed in Table IV.

One hundred seventy-one subjects experienced 327 SRs during VIT, 120 (70%) had 210 (64%) SRs before achieving maintenance, and 72 subjects had 117 SRs (36%) the day of, or day after, achieving maintenance. (Twenty-one subjects had treatment SRs before and after maintenance.) Four subjects experienced two severe SRs, and one subject, three severe SRs. Five different individuals, each with one severe SR, did not achieve maintenance during the HVS. At termination of the HVS, two of the latter five individuals

were still receiving therapy, and three had dropped out of the study. All other subjects with severe SRs associated with VIT achieved maintenance. Although 171 subjects experienced SRs to VIT, 134 (78%) of these subjects ultimately achieved maintenance. Of the 37 subjects who did not achieve maintenance, 28 dropped out of the study; 14 (including the above three subjects with severe SRs), because of adverse reactions; three, for financial reasons; one, because of an intercurrent illness; and for the remaining 10 subjects, no reason was listed. The final nine subjects continued treatment but had not attained maintenance at the termination of the HVS.

There were five respondents who confirmed the occurrence of an adverse reaction to therapy but failed to report the symptoms of the reaction and did not include an SRI on the form. Therefore, the SRs these respondents had were included in the total number of SRs but not included when characteristic data on SRs were analyzed. Two subjects had 23 SRs each, and

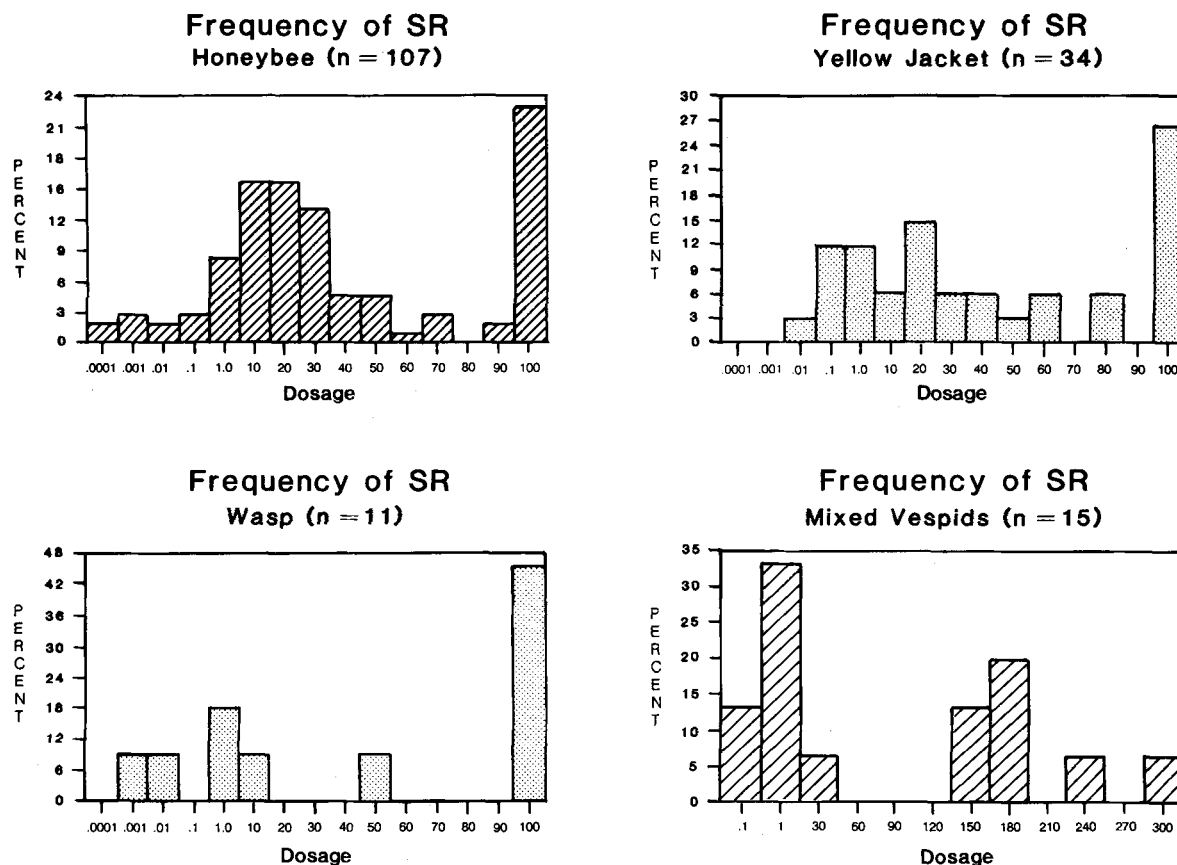


FIG. 1. Most SRs occurred between 1 and 50 µg and at 100 µg for honeybee venom. Similar patterns occurred with wasp and yellow jacket single venom administration, but fewer subjects received these venoms. The SR frequency for subjects receiving mixed vespid treatment was similar to that of other venoms, up to 50 µg or less with an increase in frequency occurring in 130 to 200 µg range.

one subject had 10 SRs during VIT. Data for these three subjects were excluded from subject-based analysis (correlations, chi-square) because of the high frequency of SR, that is, outside the 99% confidence interval (mean, 1.91; SE, 0.15). Therefore, the data for analysis of SRs and not the number of SRs consisted of 322 SRs. Subtracting the three subjects with 10 or more SRs from the original 171 leaves 168 subjects.

The severity of a subject's SR after the most recent sting before entry into the study did not correlate with the most severe SR experienced by that subject during VIT ($r = 0.03$). The severity of a subject's most severe SR before entrance into the HVS also failed to correlate with the severity of the most severe SR experienced by that subject during VIT ($r = 0.03$). Neither the size of skin test reaction to venom nor the lowest concentration yielding a positive venom skin test (micrograms per milliliter) correlated with the most severe SR during VIT ($r = 0.01$ for each).

There was no correlation between the administered total dose in micrograms and the SRI value associated with its administration ($r = -0.01$). The relationships between dosage for single venoms and mixed vespids and the frequency of SRs are displayed in Fig. 1.

More subjects who had SRs from VIT received honeybee more than any other venom. One-tailed chi-square analyses were conducted to ascertain whether a subject receiving single honeybee VIT was more likely to have an SR than a subject receiving a different type of venom (Table V). An SR was more likely to be associated with honeybee VIT than with yellow jacket (chi-square, 46.16; $p < 0.0001$), yellow hornet (chi-square, 3.06; $p < 0.05$), and mixed vespid (chi-square, 27.89; $p < 0.001$). Wasp and white-faced hornet venom did not differ significantly from honeybee venom. The results with white-faced hornet venom may be due to the small number of subjects in this group.

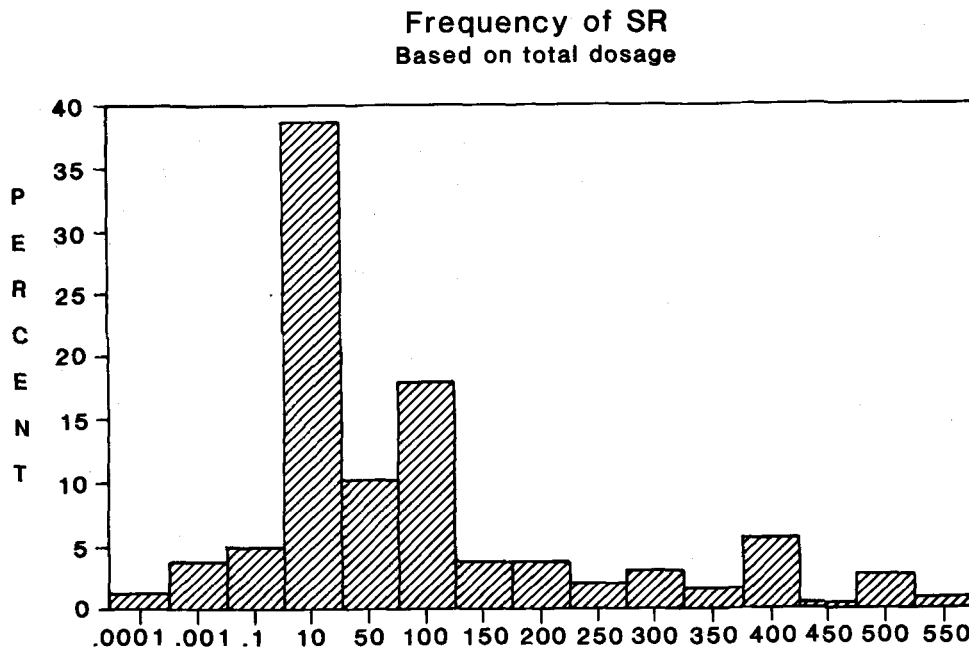


FIG. 2. SRs were analyzed based on total dosage (single and multiple venoms). A similar pattern was observed as with single venom administration with most SRs in the 0.1 to 200 µg range.

Most SRs occurred between 1 and 50 µg and at 100 µg (maintenance) for honeybee venom. Similar patterns occurred with wasp and yellow jacket single venom administrations, but fewer subjects received these venoms. The SR frequency for subjects receiving mixed vespid treatment was similar to that of other venoms, up to 50 µg or less with an increase in frequency occurring in the 130 to 200 µg range. This treatment mixture had three times the concentration of other venoms, and full maintenance was not achieved until 300 µg. SRs were analyzed based on total dosage (single and multiple venoms, Fig. 2). A similar pattern was observed with most SRs in the 0.1 to 200 µg range.

Neither the participating physicians nor the authors classified any SR to VIT as vasovagal. One VIT SR was a large local reaction but was included as an SR because it was reported as such. There were no late-onset or serum-sickness reactions reported.

DISCUSSION

During the 3-year period of the HVS (1979 to 1982), 44% (1410/3236) of sting-allergic subjects agreed to undergo VIT and began treatment. The mean interval between the date of first VIT and the date of achievement of the maintenance dose was 95 days with a modal interval at day 56 (8 weeks) into treatment when 10.5% of the immunized subjects achieved maintenance. The maintenance dose was based on the

package insert for the products and defined as 100 µg of each venom or 300 µg of mixed vespid. The mean interval to maintenance observed in HVS is similar to the interval observed for other schedules of VIT that require 9 to 24 weeks for reaching maintenance.³ The mode interval of 8 weeks is similar to the interval of 9 weeks recommended in the package insert for the venom products^{4,5} and to the interval revealed in a review of the VIT literature.⁶ The HVS physicians were thus able to adhere to the recommended product labeling and to use a schedule typical of other studies. Ninety-two percent of the treated subjects in the HVS achieved maintenance. The high percentage of subjects reaching maintenance is noteworthy and similar to rates reported for prior clinical trials,⁷ suggesting that the published clinical trial experience is applicable to practice. Eighty-four percent of subjects who reached maintenance elected to continue VIT. Seventy-seven percent of subjects achieving maintenance continued to receive venom at last report (December 1982). Of the 296 subjects reaching maintenance who elected not to continue, 8% dropped out because of adverse reactions. This finding illustrates that most subjects who began receiving VIT reached maintenance (92%) and that dropout was not highly influenced by adverse-reaction experience.

Twelve percent of subjects who received VIT (1410) experienced an SR (average, 1.9 SR per subject) (Table II). This rate is consistent with the median

SR rate of 14% reported in a review of nine venom-treatment regimens requiring 4 or more weeks to reach maintenance, demonstrating that the HVS clinical experience is typical of experiences previously reported.³ In contrast, the rate of SR observed for VIT is less than half the rate observed with a maximal tolerated dose of short ragweed immunotherapy,⁸ demonstrating the comparative safety of VIT. Most SRs were mild (59%); nevertheless, moderate to severe SRs accounted for 41% of all SRs (Table III). Most reactions (64%) occurred before reaching maintenance, a result similar to that of other studies.³ This finding may indicate that some treatment subjects are at higher risk for such reaction before reaching maintenance. However, it could also reflect the number of injections necessary to reach maintenance versus injections administered while subjects were receiving maintenance, a factor not accounted for in the HVS.

Rates of pruritus and angioedema and "other" manifestations were similar for all SR categories (Table IV). Therefore, the presence or absence of these signs or symptoms does not appear to predict whether SR from VIT will be mild, moderate, or severe. Symptoms of upper and lower airway obstruction were more frequently reported during SRs of moderate severity than during SRs in the severe category. This may mean that the "anaphylactic shock organs" in the former group of subjects are primarily respiratory, whereas in the latter, they are cardiovascular. Such patterns have been observed with fatalities associated with skin testing and immunotherapy.^{9,10} Hypotension was most frequently observed in the severe category, whereas GI symptoms were observed only with severe SRs and not with moderately severe SRs.

There was no significant correlation between the following parameters: (1) the SRI of the most recent sting before entry into the study and the most severe SR experienced during VIT, (2) the severity of the most severe historical sting-induced SR before entry into the study and the most severe SR during VIT, (3) the severity of a subject's SRI during VST and the most severe SR during VIT, (4) the degree of VST reactivity or the lowest concentration yielding a positive VST with the most severe SR during VIT, and (5) the venom dose administered and SRI. Data on the previous dose before the VIT SR, maintenance intervals, and the presence of local reactions to VIT were not obtained. Also, in contrast to other experiences,⁹ there was no late onset or serum sickness reported.

Most SRs from VIT occurred after doses between 1 and 50 µg and at maintenance (Figs. 1 and 2). The

highest frequency of reactions occurred with honeybee or wasp venoms (Table V), but of the parameters examined, there were no indicators predictive of the risk of the severity of SRs during VIT. All subjects undergoing VIT should be treated by physicians experienced in VIT and in the emergency treatment of anaphylaxis, as specified in the package inserts.^{4,5} This is especially true since fatalities have been reported from allergen immunotherapy, although none have been reported secondary to VIT.^{10,11} HVS, the largest survey of its kind, has demonstrated relative safety of immunotherapy with standardized venom extracts when they are used by physicians trained in their use according to the approved package inserts.^{4,5}

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