

Food and drug reactions and anaphylaxis

Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections

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Background: Insect venom immunotherapy (VIT) is initiated by a dose increase protocol administered usually over 7 to 9 days. Shorter protocols have the advantage of reducing the patient's stay in the hospital. Very few data are currently available on the safety of shorter VIT dose increase protocols.

Objective: The aim of this study was to investigate whether a reduction in the duration of the VIT dose increase protocol from 7 to 9 days to 2 days causes an increase in the incidence and severity of adverse reactions.

Methods: Between 1992 and 1997 we administered VIT to 1055 patients allergic to bee or wasp venom. We shortened the 7- to 9-day rush protocol stepwise to 2 days by reducing the number of injections and increasing the initial dose and compared the incidence and severity of adverse reactions. The patients were retrospectively divided into 3 cohorts: 20 injections over 7 to 9 days (cohort 1, 317 patients), 10 to 14 injections over 3 to 6 days (cohort 2, 335 patients), and 9 injections over 2 days (cohort 3, 403 patients).

Results: We observed no severe adverse reactions in any of the cohorts during VIT. Adverse reactions were treated in 7.1% of the patients by oral and in 2.9% by intravenous antihistamines and in 0.8% by systemic corticosteroids. The incidence of adverse reactions declined significantly from 22.4% in cohort 1 to 13.7% in cohort 2 and 10.7% in cohort 3 with reduced number of injections ($P < .001$).

Conclusion: The incidence and severity of adverse reactions decline if the VIT dose increase protocol is shortened to 2 days. (J Allergy Clin Immunol 2000;105:1231-5.)

Key words: Venom immunotherapy, insect, honeybee venom, yellow jacket venom, safety, 2-day ultrarush protocol

Abbreviation used

VIT: Venom immunotherapy

The clinical pattern of allergic reactions to insect stings ranges from large local reactions (>10 cm in diameter) and generalized skin reactions to systemic reactions of varying degrees of severity. Epidemiologic studies show that between 2% and 19% of the total populations of Europe and the United States have a history of large local reactions and between 0.8% and 5% of generalized skin or systemic reactions.^{1,2}

Placebo-controlled studies have demonstrated the efficacy of venom immunotherapy (VIT) in preventing anaphylactic reactions to future stings in persons allergic to the venoms of the wasp (*Vespula germanica*, *Vespula vulgaris*) and the honeybee (*Apis mellifera*). According to international recommendations an IgE-mediated systemic reactions resulting from a hymenopteron sting is an indication for VIT in adults.³

Since VIT with pure insect venom was first used in 1974,⁴ various dose increase protocols have been published⁵⁻¹¹ and reviewed.³ The period of time for increase to the generally recommended maintenance dose of 100 μ g venom ranges from 2 days to 16 weeks. Although reports in the literature reveal enormous variations in the incidence of adverse reactions during VIT dose increase, it is nearly impossible to compare these for different VIT protocols because of the different methods used to record the reactions. Nor is there any evidence that the efficacy of VIT, which is claimed to lie in a range of 90% to 95%, is correlated with the protocol of dose increase.

Since 1992 we have been using a lyophilized venom preparation (Alutard SQ/ALK-lyophilisiert SQ, ALK-Abello A/S) in our department. Over a period of 5 years we have gradually reduced the initial 7- to 9-day rush VIT protocol stepwise to 2 days by reducing the number of injections and increasing the dose of the initial injection. We have now been routinely using the 2-day protocol with 9 injections since 1995. In this study we investi-

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gated whether a progressive reduction in the dose increase protocol to only 2 days causes any increase in the number and severity of adverse reactions.

METHODS

Study design

In a retrospective open-cohort study, data on all patients treated with VIT in our department between September 1992 and May 1997 were entered into a database (Microsoft-Excel). Demographic data and case history, specific IgE levels, and the results of skin prick or intracutaneous tests before VIT were recorded. The VIT injections administered during dose increases together with all adverse reactions observed and the medication used to treat these adverse reactions and all data available during VIT maintenance treatment were also recorded. These data were checked for plausibility during the course of the statistical analysis. A source data verification was performed by an external monitor on all data failing to pass the plausibility check.

Patients

A total of 966 patients treated with VIT and a total of 1055 VIT treatments were evaluated. Hypersensitivity to honeybee or yellow jacket venom had been confirmed by skin tests and an increased level of specific IgE antibodies. Fifty-nine patients received two VIT treatments, 52 of them because sensitization to both types of venom had been diagnosed. In 6 patients allergic to wasp venom and in 1 patient allergic to bee venom, the dose increase protocol had to be initiated twice because the patients had not been adhering to the injection interval for maintenance therapy. Wasp VIT was administered to 933 patients, 428 male (45.9%) and 505 female (54.1%) with a median age of 39 years (range 2 to 84 years). Bee VIT was administered to 122 patients, 70 male (57.4%) and 52 female (42.6%), with a median age of 37 years (range 4 to 76 years). In 1005 of the total of 1055 treatments administered, the patients had a history of a generalized reaction more severe than a simple urticaria, showed a positive reaction to the skin prick test, and had increased levels of specific IgE. In the remaining 50 treatments there was no clear indication for VIT that was administered at the patients' request.

Skin prick tests were classified as positive if reactions had occurred at concentrations of 1 to 100 $\mu\text{g/mL}$ (logarithmic steps) and intracutaneous tests as positive if reactions had occurred between 10^{-5} $\mu\text{g/mL}$ and 1 $\mu\text{g/mL}$. Venom-specific IgE was analyzed by the CAP-FEIA (fluorescence enzyme immunoassay) method (Pharmacia) in accordance with the manufacturer's instruction with concentrations of ≥ 0.35 kU/mL (CAP class 1) being classified as positive. The patients' history of clinical symptoms after insect stings was recorded in a standardized questionnaire.

VIT

The treatment used in 1992 was a well-established VIT dose increase protocol involving 20 injections administered subcutaneously in the upper arm and an initial injection of 0.001 μg of venom. The injections were given at 30- to 60-minute intervals, with the last 2 injections (100 μg of venom each) at intervals of 2 to 4 hours. Patients were kept under medical observation for at least 30 minutes after each injection. Adverse reactions attributable to the injections were documented in the case reports that were analyzed retrospectively in the study. When objective allergic reactions occurred, the therapy was interrupted and restarted on the following day at a reduced venom concentration (1-3 concentrations earlier in the dose increase protocol). Maintenance injections of 100 μg were given on days 7, 14, 28, 42, 63, and 84 and then monthly on an out-patient basis. In the following years the rush protocol was subsequently shortened by reducing the number of injections and by

increasing the dose of the initial injection. Since 1995 we have been exclusively using the 2-day rush protocol with 9 injections on 2 consecutive days. The first 7 injections with a cumulative dose of 151.11 μg of insect venom are administered on day 1 and the last 2 injections of 100 μg of venom each on day 2.

Adverse events

Allergic reactions were classified as either local reactions, generalized skin reactions (urticaria, wheals, exanthema, erythema, itch, prickle, reddening, flush), swelling/angioedema, nasal symptoms, ocular symptoms, tightness of the throat, coughing, dyspnea, vomiting, nausea, circulatory disturbances, heat/cold (sweat, chill, fever), headache, tiredness/weakness, and other symptoms. The three categories of generalized skin reactions, systemic reactions, and other allergic reactions were then compared, and cases where oral or intravenous antiallergic treatment had to be administered were classified into subcategories.

Statistical analysis

SAS software (SAS, Research Triangle Park, NC) was used to analyze the data. For evaluation of the adverse reactions attributable to the VIT treatment, the patients were divided into 3 cohorts depending on duration of treatment and number of injections administered. Patients who had received 20 injections over a period of 7 to 9 days were allocated to cohort 1, those who had received 10 to 14 injections over 3 to 6 days to cohort 2, and those who had received the final 2-day rush protocol with 9 injections to cohort 3. The chi-square test was used to analyze the incidence of adverse reactions attributable to the VIT injections in the 3 cohorts. The influence of cofactors on the prognostic risk of adverse reactions was analyzed by a stepwise logistic regression analysis and expressed as odds ratios with 95% confidence intervals.

RESULTS

Cohorts for VIT dose increase protocols

In the statistical analysis the patients were allocated to 3 cohorts as described under Statistical analysis. Details of the different treatment protocols and of the allocations to the 3 cohorts are shown in Table I. The VIT dose increase protocols in cohort 1 ($n = 317$) involved 20 injections over a period of 7 to 9 days (median 8 days) and were used by us in 1992. In 26.5% of the treatments using this protocol the number of injections was greater than 20 and in 15.1% less than 20, depending on the patient's tolerance level. All subsequent VIT dose increase protocols longer than the 2-day protocol ultimately used were allocated to cohort 2 ($n = 335$), which consequently represents the interim phase of stepwise reduction from the initial 7- to 9-day protocol to the final 2-day protocol. It contains subgroups of patients treated with a different number of injections over a gradually decreasing period of treatment. The duration of these protocols was 3 to 5 days (median 5 days) in 77% of the patients (maximum 10 days). In 72.2% of the patients the numbers of injections were 10, 11, 12, or 14. All patients treated with the final 2-day protocol of 9 injections were allocated to cohort 3 ($n = 403$). In 86.1% of these patients we were able to administer this protocol without any deviations. In 76.7% the injections were administered over 2 days and in 13.9% over 3 days. This 2-day protocol has been used in our department since 1995.

TABLE I. Treatment protocols for up-dosing of VIT

Day	VIT dose (μ g of venom)					
	Cohort 1		Cohort 2			Cohort 3
1	0.001	0.001	0.001	0.001	0.001	0.01
	0.004	0.01	0.01	0.01	0.1	0.1
			0.1	0.1	1	1
					10	10
					20	20
2						40
						80
	0.008	0.1	1	1	40	100
	0.02	1	5	10	60	100
	0.04	2	10	20	80	
3	0.08	4		40		
	0.2	8	20	60	100	
	0.4	10	40	80	100	
	0.8	20	60			
			80			
4	1	40	100	100		
	2	60	100	100		
	4	80				
	8					
5	10	100				
	20	100				
	40					
6	60					
	80					
7	100					
	100					
Cumulative	431.553	425.111	416.111	411.111	411.11	351.11

TABLE II. Clinical data of VIT-treated patients

	VIT cohorts					
	Bee venom			Wasp venom		
	1	2	3	1	2	3
Total (No.)	33	32	57	284	303	346
Age (y)						
Minimum	4	9	7	3	3	2
Maximum	76	64	70	84	78	75
Median	40	33	37	40.5	39	38
Sex (No.)						
Male	23	19	28	128	143	157
Female	10	13	29	156	160	189
Atopics (No.)	2	9	13	72	69	70
Adverse reactions to index sting						
Local	1	1	1	0	2	5
Urticaria	1	2	3	4	12	18
Systemic	31	29	53	280	289	323

Patients

Table II shows the clinical data on the patients in the 3 cohorts. There were no statistically significant differences among the 3 cohorts with regard to age, sex, severity of reaction to field stings, specific IgE antibody levels, skin sensitivity to insect venoms, and total IgE levels as analyzed by the chi-square test.

Adverse reactions

All symptoms documented during VIT treatment were

included in the analysis. No life-threatening anaphylactic reactions and no severe cases of hypotension, collapse, or unconsciousness were observed. Most of the adverse reactions were mild and disappeared without treatment.

A total of 224 patients complained of some type of adverse reaction (21.2%). Generalized skin reactions (itch, flush, urticaria) were reported in 124 cases (11.8%) and systemic reactions in 160 cases (15.2%). A drop of less than 20% in blood pressure was observed in 7 patients (0.7%) and was not treated with epinephrine.

TABLE III. Adverse reactions from VIT

Adverse reactions	Patients with adverse reactions (%)							
	Bee-VIT cohorts (n = 122)				Wasp-VIT cohorts (n = 933)			
	1	2	3	Statistical significance*	1	2	3	Statistical significance*
Total	33.3	28.1	15.8	$P = .135$	29.9	19.5	14.7	$P < .001$
With dose reduction	21.2	12.5	10.5	$P = .356$	5.3	4.0	7.5	$P = .140$
And systemic reaction	9.1	3.1	8.8	$P = .562$	4.2	3.3	4.9	$P = .591$
And drug treatment	15.2	12.5	7.0	$P = .448$	3.9	2.6	6.9	$P = .026$
With generalized skin reactions								
Overall	24.2	28.1	15.8	$P = .351$	11.6	9.9	10.1	$P = .760$
Orally treated	15.2	6.3	5.3	$P = .231$	3.9	4.0	4.3	$P = .951$
Intravenously treated	3.0	6.3	3.5	$P = .770$	1.1	0.7	3.2	$P = .028$
With systemic reactions								
Overall	18.2	12.5	8.8	$P = .424$	22.9	13.9	11.0	$P < .001$
Orally treated	6.1	6.3	3.5	$P = .796$	7.4	3.3	2.6	$P = .007$
Intravenously treated	6.1	0.0	3.5	$P = .387$	2.5	1.7	2.9	$P = .577$

*Chi-square test.

TABLE IV. Factors influencing risk for development of adverse reactions during VIT

Factor	Odds ratio	95% Confidence interval	Statistical significance
Female sex	2.247	1.621-3.114	$P = .0001$
Cohort 1 to cohort 3	0.361	0.246-0.529	$P = .0001$
Dyspnea (index sting)	1.697	1.245-2.313	$P = .0008$
Cohort 1 to cohort 2	0.564	0.388-0.820	$P = .0027$
Urticaria (index sting)	0.689	0.500-0.951	$P = .0235$
Age (>50 y)	0.704	0.492-1.007	$P = .0550$

Most of the systemic reactions reported, such as dizziness (n = 35), cardiovascular sensations (n = 35), shortness of breath (n = 31), headache (n = 23), nausea (n = 22), sense of constriction of the chest (n = 21), and tickle in the throat (n = 16), were attributed to emotional factors because they were accompanied by hypertension. Antihistaminic drugs to treat adverse reactions were given orally in 75 (7.1%) and intravenously in 31 treatments (2.9%). Intravenous corticosteroids were used in 8 treatments (0.8%), in most cases to treat an urticaria. A temporary reduction of the venom dose after adverse reactions was documented for 70 treatments (6.6%); 56 of these cases (5.3%) had to be treated with an additional drug therapy. Altogether, adverse reactions were less frequent in patients treated with wasp VIT (20.9%) than with bee VIT (23.8%). There was a significant difference in the incidences of generalized skin reactions to wasp VIT and bee VIT at 10.5% and 21.3%, respectively ($P < .001$). There was no similar significant difference in the incidences of systemic reactions, which were 15.5% for wasp VIT and 12.3% for bee VIT ($P = .347$). Adverse reactions requiring intravenous drug treatment were more frequent during bee VIT (4.9%) than during wasp VIT (2.8%).

The frequency of untreated ($P < .001$) and orally treated systemic reactions ($P = .007$) observed with the shorter dose increase protocols was significantly lower, but this was not the case with generalized skin reactions (Table

III). The frequencies of adverse reactions to bee and wasp VIT were comparable. The differences among the 3 cohorts were significant for wasp VIT but not for bee VIT. The reason for this was the smaller number of patients receiving treatment for allergy to bee venom. There were significant differences among the 3 cohorts in generalized skin reactions requiring intravenous drug treatment ($P = .028$) but not in systemic reactions ($P = .577$). Late reactions 10 to 14 hours after the last injection were observed in 3 patients exhibiting tachycardia and hypertension accompanied by shivering. Both patients were treated with intravenous antihistamines and corticosteroids.

We analyzed risk factors for the occurrence of adverse reactions by logistic regression analysis calculated as odds ratios with 95% confidence intervals (Table IV). We calculated a higher risk of adverse reactions for women and for development of dyspnea after an insect sting. We calculated a lower risk for development of adverse reactions for patients aged more than 50 years, for patients to have urticaria after an insect sting, and for the shift from cohort 1 to cohort 2 and from cohort 1 to cohort 3.

DISCUSSION

This study analyzes the adverse reactions observed in patients receiving VIT treatment during a stepwise decrease in duration of the dose increase protocol over a period of several years. Local reactions were observed in nearly all patients during VIT. No severe anaphylactic reactions were observed in a total of 1055 cases during dose increase and none of our patients required treatment with epinephrine. Adverse reactions were in most cases mild and did not require specific antiallergic drug therapy. A total of 8 patients were treated with intravenous corticosteroids and 31 patients with intravenous antihistamines. One patient required medication with β -sympathomimetics, sedatives, and antihypotensive drugs. The higher incidence of adverse reactions in patients receiving bee VIT compared with those receiving wasp VIT is in agreement with the findings in other reports.¹²⁻¹⁴

A comparison of adverse reactions to different dose increase protocols shows that the incidence of adverse reactions decreased with the number of injections. Adverse reactions were observed in most cases after a median single dose of 80 µg of venom and a median cumulative dose of 151 µg of venom. The single venom dose inducing side effects (20 µg in cohort 1, 70 µg in cohort 2, 80 µg in cohort 3) was significantly lower for protocols involving a higher number of injections ($P < .001$). The cumulative dose associated with adverse reactions was 52 µg in cohort 1, 178 µg in cohort 2, and 151 µg in cohort 3.

After a comparison with 3 different dose increase regimens, Birnbaum et al¹¹ concluded that the rate of systemic reactions in rush VIT decreases with the reduction of the cumulative venom dose. A cumulative dose of 101.5 µg of insect venom was administered over a period of 210 minutes, 2 injections of 50 µg were given on day 15, and the first booster of 100 µg was given on day 45, with the patients being rehospitalized for the injections.

In comparison with the dosage regimens used by Birnbaum et al, the cumulative dose of insect venom in our 2-day ultrarush VIT regimen was higher at 151.5 µg on day 1, as also was the last dose administered on day 1 (80 µg). The shortest overall period for administration of the 7 injections was 210 minutes. On day 2, the maintenance dose of 100 µg of venom was administered twice with a 2- to 4-hour interval.

Our data suggest a correlation between the incidence of systemic reactions and the number of injections administered, whereas the cumulative venom dose seems to play only a minor role. Systemic reactions appear to be rare when the number of injections is reduced. However, a lower cumulative venom dose did not prevent systemic side effects. These results are in line with our subjective observation that local reactions are less intense when the 2-day protocol with 9 injections is used. The venom may be distributed faster by an increase in blood circulation at the area of injection, which may be the cause of systemic reactions.

Reports in the literature reveal a high variation in the incidence of side effects (including severe anaphylactic reactions) attributable to VIT.^{3,15-25} It is difficult or even impossible to compare these reports of incidence of adverse reactions with different VIT protocols because the investigators use different classification systems for the severity of adverse reactions. In comparison with the published data, the figure of 6.6% of patients with adverse reactions necessitating temporary reduction of the venom dose in our study appears to be very low. This low rate also shows that objective adverse reactions were relatively rare.

In conclusion, this study demonstrated the safety of our 2-day VIT protocol with a cumulative dose of 351.11 µg of insect venom. This protocol has been in routine use in our department over recent years and no severe adverse reactions have been observed so far. Because late reactions (as described in detail in the section Adverse reactions) were observed in 2 patients, we have been routinely discharging our inpatients early on the morning of the third day. We are currently conducting a prospective study of the safety and efficacy of our VIT protocol.

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