

Short communication

Safety of Hymenoptera venom rush immunotherapy

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We studied 97 consecutive patients who had received Hymenoptera venom rush immunotherapy in our department. There were 53 males and 44 females, whose mean age was 46 years (8–74 years). Most study patients had experienced severe anaphylaxis induced by a Hymenoptera sting: the reaction was Müller stage IV in 48 patients. Skin tests were positive for *Vespula* venom in 85 cases, *Polistes* venom in 23, and bee venom in 23. Radioallergosorbent test values exceeded 0.70 kIU/l in 60 cases. Immunotherapy was performed with *Vespula* venom alone in 73 cases, bee venom alone in five cases, and both *Vespula* and bee venom in 19 cases. A cutaneous reaction was seen at the injection site in most patients. Four patients also had skin manifestations in areas remote from the injection site. Blood pressure elevation was seen in 11 patients, moderate hypotension in two, rhinitis in one, asthenia or headache in seven, visual disorders and vertigo in two, and transient dyspnea in two. Our protocol has proved very safe, epinephrine never being required in the 97 reported cases.

Key words: Hymenoptera; rush immunotherapy; safety; venom.

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The efficacy of Hymenoptera venom rush immunotherapy is well established (1–3). However, adverse effects including anaphylactic reactions have been reported in up to 64% of cases (4–10).

Although these 97 consecutive patients had a history of systemic manifestations of immediate hypersensitivity to Hymenoptera venom (with anaphylactic shock in half the cases), they were able to tolerate subcutaneous administration over 4 days of an amount of Hymenoptera venom corresponding to seven stings.

Material and methods

We studied 97 consecutive patients who received rush immunotherapy within a 1-year period. The 53 males and 44 females had a mean age of 46 years (range: 8–74 years). According to the Müller classification system (11), the severity of the allergic reaction that prompted immunotherapy was stage I in 11 cases, stage II in 20 cases, stage III in 17 cases, and stage IV in 48 cases.

Medications taken at the time of the accidental sting were as follows: β -adrenergic receptor antag-

onists, $n=4$ (propranolol, $n=1$; sotalolol, $n=1$; timolol ophthalmic solution, $n=2$); angiotensin-converting enzyme inhibitors, $n=2$ (perindopril, $n=1$; enalapril-hydrochlorothiazide combination, $n=1$); calcium channel inhibitors (nifedipine, $n=1$); diuretics (altizide-spiroglactone combination, $n=1$); and antiepileptic agents (carbamazepine and a phenobarbital-amphetamine combination in the same patient). β -Adrenergic receptor antagonists were stopped before immunotherapy.

Methods

Skin testing. Control tests were first performed to verify that skin reactivity was normal; 9% codeine phosphate was used as the positive control and diluent as the negative control. Skin reactivity to bee venom (*Apis*) and to *Vespula* and *Polistes* wasp venom (Bayer-Pharma, Hollister-Stier allergen extracts) was tested by performing intradermal tests with increasing concentrations from 10^{-4} μ g/ml to 10^{-1} μ g/ml or induction of a positive reaction, whichever occurred first. Skin tests were considered positive if the diameter of the wheal was at

least equal to that seen with codeine phosphate. A wheal of at least 7 mm 30 min after the injection was the criterion for a positive intradermal test.

Levels of specific IgE. The levels of specific IgE to bee venom, *Vespula* wasp venom, and *Polistes* wasp venom were determined by a commercially available radioimmunologic assay (Pharmacia, Uppsala, Sweden). Results were expressed in kIU/l and categorized into five classes: below 0.35 (class 0), between 0.35 and 0.70 (class 1), between 0.70 and 3.5 (class 2), between 3.5 and 17.5 (class 3), and above 17.5 (class 4).

Specific rush immunotherapy. This treatment was given during a 4-day hospital stay, during which escalating doses of 10^{-3} to 100 μ g of venom were injected subcutaneously (Table 1). The patients who had immunotherapy with two venom extracts received both types at the same time but not at the same site. Maintenance injections (100 μ g) were given during outpatient clinic visits; any adverse effects of maintenance injections were not taken into account in this study.

Clinical surveillance protocol. In this protocol, the condition of the skin, pulse rate, blood pressure, and respiratory rate were recorded before and 30 min after each injection. The need for modifying the immunotherapy protocol or giving corrective treatment was assessed on the basis of local and/or systemic reactions to each injection.

Results

Skin tests

Skin tests were positive for *Vespula* venom in 85 patients, *Polistes* venom in 25, and bee venom in 23.

Specific IgE

Specific IgEs were undetectable in 18 patients, class 1 in 13 patients, class 2 in 33 patients, class 3 in 20 patients, and class 4 in seven patients.

Specific immunotherapy

Specific immunotherapy was given with *Vespula* venom alone in 73 patients, bee venom alone in five, and both *Vespula* and bee venom in 19.

Cutaneous reaction

A cutaneous reaction at the injection site was seen in 90 patients. Nine patients had a large injection site reaction and four had skin lesions remote from

Table 1. Outline of our venom rush immunotherapy

Day 1	Injected dose (μ g)	Day 2	Injected dose (μ g)
9 h	0.001	9 h	1
9 h 30 min	0.002	10 h 30 min	2
10 h	0.004	12 h	4
10 h 30 min	0.008	13 h 30 min	8
11 h	0.01	15 h	10
11 h 30 min	0.02	16 h	20
12 h	0.04		
12 h 30 min	0.08	Day 3	
13 h	0.10	9 h	20
13 h 30 min	0.20	12 h	40
14 h	0.40	16 h	50
14 h 30 min	0.80		
15 h	1	Day 4	
15 h 30 min	2	9 h	100*

* 50 μ g venom was simultaneously injected subcutaneously in both arms.

the injection site. Other adverse effects included blood pressure elevation in 11 patients, moderate hypotension in two (which did not require epinephrine), rhinitis in one, asthenia or headache in seven, visual disorders and vertigo in two, transient dyspnea in two (more than 30% decrease in peak-flow meter level), and proteinuria with microscopic hematuria in one (with normal urine before treatment). Corrective treatment consisted of dexchlorpheniramine tablets in 11 patients, dexamethasone in four, nifedipine in five, and acetaminophen in two.

Discussion

Our Hymenoptera venom rush immunotherapy protocol proved very safe. Patients with a history of severe Hymenoptera sting-induced anaphylaxis (most with Müller stage IV in this series) were able to tolerate a subcutaneous injection of 100 μ g Hymenoptera venom as early as treatment day 4. Injection site reactions were the rule. The most common systemic adverse effects were blood pressure elevation, headache, and asthenia. Allergic reactions were infrequent and self-limited: none of the 97 consecutive patients included in this study required epinephrine.

Various protocols are currently used to induce desensitization to Hymenoptera venom in order to eliminate the risk of anaphylaxis during a subsequent sting. The adverse event rate is an important factor to consider when selecting a protocol and maintenance dose: Urbanek et al. reported 64% of systemic side-effects, Yunginger et al. 55%, Müller et al. 39%, Thurnheer et al. 38%, and Bousquet et al. 33%. Although 100 μ g is the most widely used maintenance dose in Europe, Reisman & Livingston reported no loss of efficacy with 50 μ g

Table 2. Systemic reactions requiring epinephrine during venom rush immunotherapy (7/1641 patients, never in reported cases)

Patient's initials	Age (years)	Müller grade	Venom type	Injected dose (µg)	Date	Epinephrine use	Further immunotherapy
L.A.	43	IV	<i>Vespula</i>	40	Day 3	Subcutaneous and i.v.	Stop
L.D.	50	IV	<i>Vespula</i>	40	Day 3	i.v.	More progressive until 100 µg
E.L.	26	IV	<i>Apis</i>	100	Month 2	i.v. and inhaled	50 µg/month
S.J.	58	I	<i>Vespula</i> and <i>Apis</i>	100	Month 6	Subcutaneous	Stop
M.P.	70	IV	<i>Vespula</i>	100	Year 7	Subcutaneous	Return to 100 µg/month
H.B.	60	IV	<i>Apis</i>	100	Year 3	Subcutaneous	Return to 100 µg/month
K.T.	44	IV	<i>Vespula</i> and <i>Apis</i>	100	Year 5	Subcutaneous	Return to 100 µg/month

once a month (10). In our opinion, continuous in-hospital surveillance of the patient for several consecutive days at the beginning of the treatment considerably enhances the safety of rush immunotherapy. All our patients were able to tolerate rapid dose escalation as scheduled in the protocol. Maintenance injections performed on an outpatient basis with a 30-min postinjection surveillance period were also well tolerated. Since 1982, we have recorded few adverse events (less than 1%) among the 1641 patients who have received the same Hymenoptera venom rush immunotherapy, without anything particular about the patients or the amount of the venom injected (during rush or maintenance doses). Recent studies have demonstrated that Hymenoptera venom can activate T cells (12), serum complement (13), and platelets (14). These effects may contribute to the pathogenesis of adverse events, which may vary among patients. Adverse event rates have been similar with bee venom and *Vespula* venom; there was a threefold higher number of patients treated with bee venom than with *Vespula* venom in our study (Table 2), as previously reported (4).

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