

Rapid Hymenoptera venom immunotherapy: comparative safety of three protocols

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Summary

We compared 284 sting-allergic patients treated with either a 4 day (group 1), 6 hr (group 2) or 210 min (group 3) rapid venom immunotherapy (RVIT) protocol using honey bee (HB) or yellow jacket (YJ) venom at cumulative doses of 527.6 µg, 226.6 µg and 101.1 µg respectively. The 4 day protocol involved four times as many injections as the 210 min protocol and twice as many as the 6 hr protocol. Desensitization was conducted in a hospital providing full emergency resuscitation facilities. In group 1, 1 × 100 µg boosters were given on days 7, 10, 15 and 45 and, in groups 2 and 3, 2 × 50 µg boosters were given on day 15 and 1 × 100 µg on day 45. The patients in the three groups were comparable with regard to clinical characteristics and immunological reactivity determined by skin tests. All patients had large local reactions. Systemic reactions (SR) occurred in 28.2% of patients in group 1, 28.6% in group 2 and 6.9% in group 3. The mean total cumulative venom dose (s.e.m.) for occurrence of SR was 123.75 (±24.2) in group 1, 183.27 (±28.5) in group 2, and 36.43 (±9.3) in group 3. HB led to more systemic reactions than YJ venom. The rate of SR decreased when the cumulative venom dose was reduced during RVIT. The median dose was 137.6 µg in group 1, 226.6 µg in group 2, and 21.1 µg in group 3. No systemic reactions were observed after the booster injections. The results of this study suggest that short RVIT protocols with low cumulative doses carry a lesser risk of SR.

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Introduction

Venom immunotherapy (VIT) is widely used throughout the world to treat most patients with Hymenoptera sting allergy [1,2]. Since the first desensitization with pure venom was carried out in 1974 [3], protocols of various durations have been devised in an effort to maximize protection, minimize side effects and optimize patient convenience [4–7]. With a slow protocol the time required to reach the maintenance dose of 100 µg generally considered as adequate is several weeks [8,9], with a semi-rush protocol it is several days [5,10–12] and with a rush protocol it is 24 hr [6,13,14]. The rush regimen has the obvious advantage of achieving rapid protection with minimum inconvenience for the patient. Studies using rush protocols [6,13,14] have suggested that they are at least as safe as slower protocols. However, these studies

were based on small groups of patients. In this paper, we compare three RVIT protocols lasting 4 days, 6 hr or 210 min in a large group of 284 sting-allergic patients.

Materials and methods

Patients

The patients in this study were referred to us between 1983 and 1989. Sting anaphylaxis included symptoms such as giant urticaria, generalized pruritus, angioneurotic oedema, laryngoedema, hypotension and shock. Patients with significant cardiopulmonary disease and patients receiving β -blocker drugs were excluded. Clinical characteristics are listed in Table 1.

In all patients venom-specific IgE were demonstrated [15] by skin tests with serial tenfold dilutions of honey bee (HB), yellow jacket (YJ) and wasp (W) venom (Dome Hollister Stier Laboratories, Paris, France), starting at a concentration of 10⁻³ µg/ml. Skin tests were considered positive if reactions occurred at a concentration of 1 µg/

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Table 1. Grade of clinical symptoms in each group of patients

RVIT	Grade of clinical symptoms			
	I	II	III	IV
Group 1				
4-day (n=46)	8 (17.4)*	22 (47.8)	3 (6.5)	13 (28.3)
Group 2				
6 hr (n=21)	3 (14.4)	4 (19)	4 (19)	10 (47.6)
Group 3				
210 min (n=217)	45 (20.7)	90 (41.5)	16 (7.4)	66 (30.4)
P value				
(chi-square test with 2 degrees of freedom)	NS	NS	NS	NS

* Numbers in parentheses are percentages.

ml or less [16]. Immediate systemic reactions were classified according to the system proposed by Mueller [17]. Results of skin tests are shown in Table 2.

After performing an electrocardiogram and complete blood count, desensitization was carried out with one of the same venoms used for skin testing (see above). The venom was chosen with reference to the patient's history and skin test results. The initial venom dose for RVIT was the same regardless of the patient's sensitivity. Table 3 shows the number of patients immunized with each venom. Patients allergic to W venom were so few that they were excluded from study.

Rapid venom immunotherapy protocols

RVIT was monitored by the same physician (J.B.) at the Department of Chest Diseases and Allergy in Marseille, France. Three protocols were used: a 4 day (group 1), a 6 hr (group 2) and a 210 min (group 3) protocol (Table 4). Patients were hospitalized for 4 days and those in groups 2 and 3 were admitted for 24 hr. During RVIT, pulse rate and blood pressure were carefully monitored (Vicom-em CMK 211 S, PPG HELIGE). Indwelling intravenous lines were used in all cases. Full emergency resuscitation equipment was readily available. Venom was administered subcutaneously in the upper arms.

In the 4 day protocol, the starting dose of 10^{-4} μ g was followed by increasing doses every 30 min for 3 days. On the fourth day, patients received one 50 μ g and one 100 μ g injection. The cumulative venom dose was 527.6 μ g. If this first phase was successful, booster injections of 100 μ g were given on days 7, 10, 15, 30 and then monthly.

In the 6 hr RVIT, an initial venom dose of 10^{-5} μ g was followed by 10^{-4} , 10^{-3} , 10^{-2} , 10^{-1} , 0.5, 1, 5, 10, 20, 30, 60 and 100 μ g at 30 min intervals. The cumulative venom dose was 226.6 μ g.

In the 210 min protocol, an initial venom dose of 0.1 μ g was followed by 1, 10 and 20 μ g at 30 min intervals and then 30 and 40 μ g at 60 min intervals. The cumulative venom dose was 101.1 μ g.

Patients who completed the 6 hr and 210 min protocols were rehospitalized for two booster injections of 50 μ g on day 15 and one of 100 μ g on day 45. Subsequently monthly 100 μ g boosters were given on an out-patient basis. If two venoms were required, they were administered in separate protocols a few days apart.

We did not challenge our patients with live stings. Nor did we measure the specific IgG. Like Müller [18], we observed that the IgG response induced by immunotherapy is an epiphenomena rather than a decisive protective mechanism. Attempts to define a protective level of venom specific IgG have been disappointing [19]. Also low IgG levels have been observed in some well-protected patients and high IgG levels have been observed in some patients in whom treatment failed.

Results

Between May 1983 and December 1989, 284 patients, ranging in age from 6 to 70, underwent RVIT. The 4 day protocol was performed on 46 patients from May 1983 to April 1985 (group 1), the 6 hr protocol on 21 patients from April 1985 to October 1986 (group 2) and the 210 min protocol on 217 patients from October 1986 to December 1989 (group 3). As shown in Tables 1 and 2, clinical symptoms and immunological reactivity ascertained by skin tests did not differ significantly between the three groups.

Table 5 shows the incidence of SR in the three groups. In group 1, 7/13 patients treated with HB and 26/33 treated with YJ venom completed RVIT without SR or any significant variation in pulse rate or blood pressure. In the remaining 13 patients, mild SR was observed: six with HB venom (46%) and seven with YJ venom (21%). In 10 of these patients the reaction was urticaria, in one it was mild hypotension and in two it was urticaria and mild hypotension.

In group 2, 14 patients underwent RVIT with YJ and seven with HB. In the YJ group, 11 (79%) completed desensitization without SR. In the HB group, 4 (58%) completed desensitization without SR. SR was observed in three patients in each group. With YJ, SR consisted of urticaria in two cases and asthma in the other. With HB, SR consisted of generalized urticaria in one case and generalized urticaria and laryngeal oedema in two cases.

Table 2. Positive skin tests in each group of patients

RVIT	Venom skin tests (μg)				
	1	0.1	0.01	0.001	0.0001
Group 1					
4 day ($n=46$)	11 (23.9)*	7 (15.2)	11 (23.9)	17 (37)	0 (0)
Group 2					
6 hr ($n=21$)	5 (23.8)	7 (33.3)	2 (9.5)	6 (28.6)	1 (4.8)
Group 3					
210 min ($n=217$)	40 (18.4)	39 (18)	45 (20.7)	90 (41.5)	3 (1.4)
P value	NS	NS	NS	NS	NS

* Numbers in parentheses are percentages.

Table 3. Venom type used in each group of patients

	Mean age $\pm$ s.d.	Honeybee	Yellow jacket
Group 1			
4 day ($n=46$)	37.9 ± 15.9	13	33
Group 2			
6 hr ($n=21$)	40.9 ± 17.9	7	14
Group 3			
210 min ($n=217$)	36.1 ± 16.5	71	146
		$n=91$	$n=193$

In group 3, 202 patients completed RVIT: 146 with YJ venom and 56 with HB venom. No SR was observed with YJ venom. Mild SR with urticaria and/or laryngeal oedema was observed in 15 patients (21%) with HB venom.

With the 4 day and 6 hr protocols, SR occurred at a higher total cumulative dose than with the 210 min protocol. The mean total cumulative dose (s.e.m.) for occurrence of SR and the median dose were $123.75 \mu\text{g}$ (± 28.2) and $137.6 \mu\text{g}$ respectively in the 4 day protocol, $183.27 \mu\text{g}$ (± 28.5) and $226.6 \mu\text{g}$ in the 6 hr protocol, and $36.43 \mu\text{g}$ (± 9.3) and $21.1 \mu\text{g}$ in the 210 min protocol. Most adverse reactions observed with the 4 day protocol occurred on day 2.

Large local reactions were observed in all patients before the end of the rush protocol. These reactions which lasted for 12 to 48 hr were always less severe than the initial reaction. The frequency of local reactions was the same in the three groups but the majority occurred in patients allergic to HB venom. SR during RVIT were

Table 4. Venom immunotherapy protocols

	Venom dosage (μg)					
Timing of injection	D1	D1	D1	D2	D3	D4
0	10^{-1}	10^{-5}	10^{-4}	0.1	10	50
0 hr 30	1	10^{-4}	10^{-3}	1	50	100
1 hr	10	10^{-3}	10^{-2}	2	80	
1 hr 30	20	10^{-2}	0.1	4	100	
2 hr		10^{-1}	0.2	8		
2 hr 30	30	0.5	0.4	10		
3 hr		1	0.8	20		
3 hr 30	40	5	1	40		
4 hr		10		50		
4 hr 30		20				
5 hr		30				
5 hr 30		60				
6 hr		100				
210 min rush		6 hr rush		4 day rush		
<i>Booster injections (Day)</i>						
7				100		
10				100		
15	50		50	100		
	50		50			
45	100		100	100		

always mild with cutaneous (urticaria, angioedema, erythema) and/or respiratory symptoms. Severe hypotension, collapse, and loss of consciousness were not observed. Intravenous injection of H_1 antihistamines brought rapid relief of urticaria and angioedema. To prevent protracted symptoms, corticosteroids were also

Table 5. Incidence of systemic reactions

RVIT protocols	Honeybee	Yellow jacket
(Group 1) 4 day ($n=46$)	6/13 (46%)	7/33 (21.1%)
(Group 2) 6 hr ($n=21$)	3/7 (42%)	3/14 (21.4%)
(Group 3) 210 min ($n=217$)	15/71 (21%)	0/146 (0%)

infused. Unlike Müller *et al.* [20], we do not consider subcutaneous adrenaline at a dose of 0.3–0.5 mg to be a treatment of choice for cutaneous symptoms. For respiratory symptoms (wheezing, cough, inspiratory and expiratory stridor, hoarseness, etc.), 10 puffs of adrenaline were given every 5–10 min in association with intravenous corticosteroids. Mild hypotension was controlled by intravenous corticosteroids. Anaphylactic shock was not observed. Patients with generalized cutaneous and/or respiratory symptoms were kept under observation for at least 3 hr.

As described in Table 4, patients who completed RVIT without experiencing SR returned for booster injections. No SR was observed after injection of 100 µg of venom on days 7, 10, 15 or 30 in group 1 or on days 15 or 45 in groups 2 and 3. Patients who experienced SR during or after RVIT did not receive boosters. Instead a slower protocol was administered.

Discussion

Desensitization is highly effective in preventing anaphylaxis to insect stings in patients with proven Hymenoptera sensitivity. The goal of VIT is to administer increasing doses of venom up to a maintenance dose of 100 µg. The duration of the protocol ranges from a few weeks to several days. Some authors have reported lower SR rates (0–10%) with slow protocols [21–23] than faster ones while others have reported that there is no difference [24]. In order to gain further insight into this question, we compared a 210 min protocol with a 4 day and 6 hr protocol and found the 210 min protocol to be the safest. Out of 217 patients who underwent the 210 min protocol only 15 patients (6.9%) had mild SR. All these reactions occurred with HB. No SR was observed with YJ.

Yunginger *et al.* [5] treated 20 HB venom-sensitive patients using a 3 day RVIT designed to attain a maximum single dose of 200 µg. Systemic anaphylactic reactions occurred in 17 patients including 11 cases in which subcutaneous epinephrine was required. Live challenge was tolerated by 11 out of 19 patients. This high

incidence of SR may be due to the fact that boosters were not administered between the initial RVIT and the sting challenge, one month later. In contrast, Nataf *et al.* [7], using a 3 day RVIT in which two injections of 50 µg were administered on the third day, encountered only one mild urticaria out of 52 patients: nine treated with HB and 43 with YJ.

Van Der Zwan *et al.* [6] who treated 11 wasp-venom-sensitive patients with a 6 hr protocol reported no SR. Live challenge at least 4 weeks after treatment suggested complete protection. The higher rate of SR with a similar 6 hr protocol in our series may be due to the larger number of patients treated and to the venom used, i.e. HB and YJ.

The 210 min regimen achieved protection rapidly with minimal risk. This is particularly true with YJ venom. Bernstein *et al.* [13] reported a rush venom protocol in which a cumulative venom dose of 58.55 µg was administered in 2 hr and 30 min. Out of 33 patients, four (12%) experienced mild SR consisting of urticaria and angioedema. The fact that three of these reactions occurred with HB venom and one with HB and mixed vespid suggests that the risk of SR is higher with HB than other venoms. As previously reported [6,25], VIT with YJ appears to be safer than with HB especially for rush protocols.

The higher rate of SR associated with the 4 day and 6 hr protocols may have been due to relatively large cumulative doses, 527.6 µg and 226.2 µg, respectively. In two earlier studies involving a 10 day protocol with a cumulative venom dose of 560 µg [21] and a 3 day protocol with venom doses ranging from 69 to 5667 µg [5], SR rates of 38 and 80%, respectively, were reported. The incidence of SR decreases with lower cumulative doses like those used in Bernstein's study [13] and in our 210 min protocol. The mechanism involved is unknown. Venom injection might induce clinical tolerance on day 1 and subsequently hyposensitization to the injected venom, as suggested by the absence of general reaction after booster injections on day 15. Clinical tolerance could also explain why in Lichtenstein *et al.*'s study [26] no reactions were observed in the 40 sensitized patients challenged with HB or YJ venom administered in doses of 1 µg, 10 µg and 100 µg at 30 min intervals.

In conclusion, this study indicates that a 210 min VIT protocol with a low cumulative dose is safe. Since October 1986, we have been using the 210 min protocol routinely in our Department of Chest Diseases. Immediate SR have been mild and responded readily to properly supervised treatment. Although no late reactions have been observed so far, we advise patients to stay in hospital during the night following RVIT.

References

- 1 Lichtenstein LM, Valentine MD, Sobotka AK. Insect allergy: the state of the art. *J Allergy Clin Immunol* 1979; 64:5-12.
- 2 Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978; 299:157-61.
- 3 Lichtenstein LM, Valentine MD, Sobotka AK. A case for venom treatment in anaphylactic sensitivity to hymenoptera sting. *N Engl J Med* 1974; 290:1223-7.
- 4 Müller U, Thurnheer U, Patrizzi R, Spies J, Hoigne R. Immunotherapy in bee-sting hypersensitivity. *Allergy* 1979; 34:369-78.
- 5 Yunginger JW, Paull BR, Jones RP, Santrach PJ. Rush venom immunotherapy program for honeybee sting sensitivity. *J Allergy Clin Immunol* 1979; 63:340-7.
- 6 Van Der Zwan JC, Flinterman J, Jankowski IG, Kerchaert JAM. Hyposensitization to wasp venom in six hours. *Br Med J* 1983; 287:1329-31.
- 7 Nataf P, Guinépain MR, Herman D. Rush venom immunotherapy: a 3-day program for hymenoptera allergy. *Clin Allergy* 1984; 14:269-75.
- 8 Ramirez DA, Londono SA, Evans R. Adverse reactions to venom immunotherapy. *Ann Intern Med* 1981; 47:435-9.
- 9 Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of hymenoptera venom immunotherapy. *Ann Intern Med* 1980; 92:620-4.
- 10 Urbanek R. Rush hyposensitization of children allergic to hymenoptera venom. In: Johansson SGO, ed., *Diagnosis and treatment of IgE-mediated diseases*. Amsterdam: Excerpta Medica, 1986.
- 11 Bousquet J, Fontes A, Bobinet-Levy M, Aznar R, Michel FB. Combination of passive and active immunotherapy in the treatment of honeybee venom allergy. *J Allergy Clin Immunol* 1987; 79:947-54.
- 12 Müller U, Morris T, Bischof M, Friedli H, Skarvil F. Combined active and passive immunotherapy in honeybee sting allergy. *J Allergy Clin Immunol* 1986; 78:115-23.
- 13 Bernstein DI, Mittman RJ, Kagen SL, Korb L, Berstein IL, Enrione M. Clinical and immunologic studies of rapid venom immunotherapy in hymenoptera-sensitive patients. *J Allergy Clin Immunol* 1989; 84:951-9.
- 14 Birnbaum J, Vervloet D, Charpin D, Arnaud A. Désensibilisations accélérées aux hyménoptères. *Rev Fr Allergol* 1986; 4:212-13.
- 15 Golden DBK, Schwartz HJ. Guidelines for venom immunotherapy. *J Allergy Clin Immunol* 1986; 77:727-8.
- 16 Müller U. Insect sting allergy: clinical picture, diagnosis and treatment. Stuttgart: Gustav Fischer, 1990:66-108.
- 17 Mueller HL. Diagnosis and treatment of insect sensitivity. *J Asthma Res* 1966; 3:331-3.
- 18 Müller U, Hecbling A, Bischof M. Predictive value of venom-specific IgE, IgG and IgG subclass antibodies in patients on immunotherapy with honeybee venom. *Allergy* 1989; 44:412-18.
- 19 Yunginger JW. The immune response to venom immunotherapy. In: Levine M, Lockey RE, eds. *Monograph on insect allergy*. USA: Library of Congress, 1986:63-5.
- 20 Müller U, Mosbech H, Blaauw P *et al.* Emergency treatment of allergic reactions of hymenoptera sting. *Clin Exp Allergy* 1991; 21:281-8.
- 21 Ramirez DA, Londono SA, Evans R. Adverse reactions to venom immunotherapy. *Ann Allergy* 1981; 47:435.
- 22 Reisman RE. Insect allergy. In: Middleton E, ed. *Allergy, principles and practice*. St Louis: Mosby, 1983:1361.
- 23 Rocklin RE, Alfano N, Sobotka AK, Rosenwasser LJ, Findlay SR. Low incidence of systemic reactions during venom immunotherapy. *J Allergy Clin Immunol*, 1982; 69:125.
- 24 Thurnheer U, Müller U, Stoller R, Lanner A, Hoigne R. Venom immunotherapy for hymenoptera sting allergy. *Clin Allergy* 1983; 38:465-75.
- 25 Bousquet J. Allergy to hymenoptera venom. *Allergy Today* 1985; 3:10-18.
- 26 Lichtenstein LM, Kagey-Sobotka A. Immunotherapy for insect sting allergy: where we are and how we got there. *Clinical Trends, ACI News*, 1989:39-42.

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