Asian Pacific Journal of Allergy and Immunology (1995) 13 : 95-100

Bee Venom Hypersensitivity and Its Management : Patients Perception of Venom Desensitisation

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SUMMARY **The objectives of the study were to review bee venom immunotherapy from the patient's perspective: in particular its benefits and its problems, and to investigate any genetic tendency for bee venom hypersensitivity.**

A self administered, 9 item questionnaire was sent to 219 patients who had undergone either inpatient or outpatient bee venom immunotherapy at Flinders Medical Centre. The clinic records of these patients were also reviewed. The controls for the genetic study were sought from patients, staff and students at Flinders University and Flinders Medical Centre. One hundred and forty-six questionnaires (some incomplete and anonymous) were received. The female to male ratio was 1:2.5. The age at the time of the initial anaphylactic reaction to a bee sting ranged between 2 to 59 years, with 67% of patients being less than 20 years old. Forty percent of patients underwent venom immunotherapy for a period less than 2 years with only 11% maintaining therapy for the recommended period of 5 years or more. Thirty three percent of patients stopped their therapy on their own accord. Bee stings occurring during bee venom immunotherapy (n=56) were generally well tolerated except in 8 subjects, 7 of whom had not reached the maintenance dose. The reduction in systemic reactions to subsequent bee stings was significantly better in the study group receiving bee venom than in an historic control group treated with whole bee extract ($p=0.03$). Fear of bee stings and restricted life styles were improved during or after venom immunotherapy. The frequency of a positive family history of systemic reactions to bee stings in the patient cohort was 31%, whereas in controls it was 15% ($p=0.013$).

Bee venom immunotherapy has dual benefits: patients are protected from subsequent sting anaphylaxis and there is reduced psychological morbidity. However, to be effective, venom immunotherapy requires a prolonged period of carefully supervised treatment and each venom injection can cause local and systemic side effects. Genetic factors appear to be present in those patients who develop immediate hypersensitivity to bee stings.

Immediate hypersensiiivity reactions to common (European) honey bee *(Apis mellifera)* stings are a frequently encountered clinical problem. These anaphylactic reactions are often frightening and potentially fatal, although death from a bee sting is uncommon in Australia with a reported mortality incidence of 0.085/1,000,000 population per year.[1] Victims of such anaphylactic reactions are frequently fearful of subsequent stings and often modify their outdoor life styles. The occurrence and severity of a future reaction is difficult to predict in sensitised subjects, perhaps because the pathogenesis of insect sting anaphylactic reactions, has not been fully elucidated.[2]

The major allergens in honey bee venom are phospholipase A_2, hyaluronidase, a high-molecular weight substance with acid phosphatase activity,and melittin.[3] A key event in the pathogenesis of anaphylaxis is activation of mast cells or basophils, which is induced by insect venom-specific IgE.[2,4] This reaction is a clear example of a Type 1 hypersensitivity reaction due to release of pharmacological mediators, particularly histamine, from mast cells. In addition, the reaction can be aggravated by other factors in the venom, eg melittin which can trigger mast cells non-immunologically.[5]

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Systemic anaphylaxis to bee venom occurs along a continuum of signs and symptoms ranging from trivial systemic responses to severe physiological insults with death sometimes resulting within minutes. Many systemic reactions have frightening but non life-threatening cutaneous manifestations such as urticaria, angioedema, flushing or pruritus. Life-threatening reactions may involve the upper airway, especially the tongue, oropharynx or larynx, with mucosal swelling and airway obstruction. Severe reactions may also involve the lower airway with bronchospasm or cardiovascular system with hypotension and collapse. For subjects with a recent past history of a severe systemic reaction to a bee sting, venom immunotherapy (desensitisation) which is of proven efficacy,[18] is generally recommended. The specific indications for immunotherapy are based on the severity of the reaction, age of subject, associated medical condition and medications, likelihood of continued exposure to stings, proximity to emergency care, and evidence of venom specific IgE.[6-8] Over the last 14 years, since the availability of purified bee venom for desensitisation, more than two hundred individuals with bee venom allergy have attended the immunotherapy clinic at Flinders Medical Centre (FMC). In the present study, the efficacy and safety of the venom immunotherapy and the patients' experiences with desensitisation are evaluated. In addition, the study is extended to investigate any genetic tendency for bee venom hypersensitivity.

METHODS

Patients who had undergone either inpatient (Rush protocol) or outpatient (modified Rush protocol) venom immunotherapy were identified from the records of the Immunology Department at FMC. A questionnaire was sent to all these patients. This 9 item questionnaire was designed to ascertain the clinical manifestations and subject age at the first systemic reaction to a bee sting, duration and adverse effects of immunotherapy, effects on life style both before and after desensitisation, response to field stings occurring during or after desensitisation and finally any family history of bee venom hypersensitivity. Immunotherapy clinic case notes of patients receiving purified bee venom (available from 1981) were also reviewed to record any reactions to subsequent stings noted during the course of venom immunotherapy. Another questionnaire seeking family history of bee anaphylaxis was distributed to 108 subjects from the patients, staff and student population at Flinders University and FMC. This was to establish a control group to investigate any genetic tendency to bee venom hypersensitivity. Chi square and Fisher's exact statistical tests were used to compare groups.

RESULTS

Of 219 questionnaires sent to patients, 146 replies were received. Not all questions were satisfactorily completed for every patient and hence the sample size varies according with each question. Demographic analysis revealed there were 103 males, 41 females and 2 unspecified. The patients range in age between 4 to 73 years (mean 26 years). Sixteen patients did not specify their age.

Initial anaphylactic reaction to a bee sting

The symptoms experienced during the first systemic reaction and their frequency are presented in Table 1. Other symptoms reported but not shown on Table 1 included vomiting, widespread itch, irritation in ears, numbness, dizziness, sensation of body heat, whole lower limb swelling, tiredness, central chest pain and muscle spasm. The age at initial anaphylaxis ranges from 2 years to 59 years (mean 17 years) with 67% experiencing their first reaction before the age of 20 years.

The lifestyle changes following initial anaphylactic reaction

After the first major bee sting reaction, 22% of patients restricted outdoor activities, 77% of them became more fearful of bees and 29% of subjects modified their life style. The life style changes are summarised in Table 2.

Desensitisation

Questionnaire

The mean age for the commencement of desensitisation was

Table 1. Symptoms of initial sting-anaphylaxis in the 146 patients.

Symptoms	No. patients
Swelling near the sting	114
Generalised hives or redness	85
Facial swelling	88
Tongue or throat swelling with sense of impending respiratory obstruction	79
Asthma or wheezing	66
Faintness or collapse	67
Other	29

Table 2. Summary of life style changes following first or subsequent major bee sting reaction (n=42 patients)

Life style changes	No. patients*
Wear covered shoes and clothes outside, especially during spring and summer	19
Keep away from flowering plants, clover lawn	9
Carry medications such as anti-histamine, self injected adrenaline	7
More careful when walking bare feet/with thongs, or before eating or drinking	5
Ensured completed coverage when riding motor cycle or keep window closed when driving	3
Avoid wearing colourful clothes	2

* some patients have indicated multiple life style changes.

Table 3. Summary of adverse side effects of desensitisation.

Adverse side effects*	No. patients
Possible systemic reaction	7
Systemic reaction	10
Other	
Malaise	5
Nausea	1
Uterine contraction	1

* not including large local reaction

21 years, (range 3 to 66 years) with 58% starting before the age of 20 years. The mean duration of immunotherapy was 3 years and ranged from 2 months to 6 years. Prior to 1981 in Australia, whole bee extract (WBE) was utilised in immunotherapy programs and 22 patients received this therapy. From 1981, pure bee venom (PBV) replaced WBE. Of those patients who had ceased their venom immunotherapy, 40% underwent desensitisation for a period of less than 2 years whilst only 11% continued for the recommended 5 years or more. One third of all patients who had ceased their immunotherapy did so on their own volition.

A total of 24 patients from 123 replies reported that immunotherapy had caused them some adverse side effects (Table 3). There was no significant difference in the degree of side effects of immunotheapy between the patients on WBE therapy and the patients on PBV therapy ($p=0.303$).

Clinical record analysis

Subjects complained frequently that the desensitising injections cause large local reactions although only 59 instances were recorded (since 1981) where the local reaction measured over 20 cms. Minor systemic reactions (pruritis, urticaria, facial swelling, discomfort in throat) were noted on 113 occasions while major systemic reactions (bronchospasm, pharyngeal/laryngeal oedema, hypotension) occurred on 39 occasions and of these 11 required intramuscular adrenaline for reversal. No subject with a severe reaction required hospitalisation.

Subsequent bee sting following desensitisation

Questionnaire

Of the questionnaire respondents, sixty-one patients had a subsequent sting during or after a course of desensitisation with 17 reporting major systemic reactions. Of these 17, 7 patients had received WBE therapy and 10 had received PBV therapy. In patients on PBV therapy, significantly fewer systemic reactions were noted on subsequent stings when compared with patients on WBE therapy ($p=0.030$).

Clinic record analysis

Furthermore, analysis of the records of all individuals attending the bee venom immunotherapy clinic since 1981 revealed that 56 patients reported a further sting during the course of PBV immunotherapy. Forty-eight of these patients reported local swelling without any systemic reaction. Seven out of the remaining 8 patients who developed systemic reactions had not achieved a regular maintenance dose (100 μg) when the further sting was encountered, ie they either had a sting within 2 months of commencing the immu-

Table 4. Family members with bee venom hypersensitivity

Category	Total	No.	%
Patient cohort	67	21	31
Negative controls	99	15	15

p=0.013

Relationship	Patient cohort*	Negative controls*
Mother	2 (8%)	2 (13%)
Father	13 (50%)	1 (6%)
Sister	4 (15%)	4 (25%)
Brother	5 (19%)	4 (25%)
Daughter	1 (4%)	2 (13%)
Son	1 (4%)	3 (18%)

*some patients have indicated more than one family members with bee venom hypersensitivity.

notherapy or did not comply with the program. The last patient, although having reached a maintenance dose, developed severe dysphagia 5 hours after the sting (with Teldane being the only initial treatment). Furthermore, this patient had another bee sting subsequently without any adverse reaction.

Effects of desensitisation on life style

The patients were asked to assess the effects of immunotherapy injections on their life style. Forty-seven percent of patients found that the therapy allowed them to participate more freely in outdoor activities and 51% of them said that it reduced their fear of bees, whereas 30% reported an improvement inlife style. No significant differences in frequency of improvement in outdoor activities, reduced fear of bees and altered life style between patients on WBE therapy and patients on PBV therapy were observed ($p=0.924$, $p=0.256$ and $p=0.141$, respectively).

Family history of bee venom hypersensitivity

To investigate the genetic tendency of bee venom hypersensitivity, 108 controls were randomly obtained from the Flinders University and FMC. They included students, staff members and patients from orthopaedic outpatient clinic at FMC. There were 48 males, 59 females and 1 unspecified. Nine of the controls reported systemic reactions to a bee sting (classified as positive controls) leaving 99 subjects in the negative control group, ie the group which had never suffered any major anaphylactic reaction to a bee sting.

Thirty-one percent of the bee venom sensitive patients reported family members with histories consistent with bee sting anaphylaxis compared with 15% in the negative control group ($p=0.013$, Table 4) and 33% in the positive control group. Table 4 also lists the numbers and percentage of the relationship between subject and family members with bee sting anaphylaxis for both the patients and the negative controls.

DISCUSSION

The clinical picture of an anaphylactic (systemic) reaction to a honey bee *Apis mellifera* sting may vary from mild urticaria to profound cardiovascular collapse and respiratory distress.[9-11] In the present study, these features have been confirmed. Most patients experienced the first systemic reaction to a bee sting when young, with 67% of our subjects being less than 20 years of age and only 8% more than 39 years of age. Many of our patients reported marked anxiety and fear of bees and/or restricted life style and as such, alleviation of this fear can be considered as one of the specific indications for venom immunotherapy in bee sensitive individuals, especially in those younger individuals who, however, rarely die from bee sting anaphylaxis.[1,12,13]

Immunotherapy with purified bee venom, although highly efficacious, is costly to both the patients and to health care providers with current regimens usually being a course of sixteen to eighteen weeks of weekly injections followed by monthly maintenance injections (venom maintenance dose 100 μg) for 3-5 years. Untreated bee sensitive patients with past generalised reaction have a 27% to 61% risk of a repeat systemic reaction with future stings.[14] Patients with generalised reactions who have received venom immunotherapy for 1 or 2 years have approximately a 25% risk of a generalised reaction, whereas in patients who have received venom immunotherapy for 5 years or more, the risk drops to approximately 2%.[14,15] In our own patient group, 40% of patients underwent immunotherapy for a period of less than 2 years, with one third of the total group ceasing immunotherapy of their own volition whereas there were only 11% of patients who continued therapy for at least 5 years or longer. Reasons for poor com-

pliance were not sought. However, patient motivation may lessen with time, corresponding to reduced anxiety about future stings. Side effects of immunotherapy may also contribute to poor compliance. Large local reactions and minor systemic reactions (urticaria, facial swelling, mild throat swelling) occurred reasonably commonly during venom immunotherapy in keeping with the experience of other[16] and were easily treated. Major systemic reactions (bronchospasm, pharyngeal/laryngeal oedema, hypotension) occurred infrequently (39 instances over 14 years) and required intramuscular adrenaline for reversal on only 11 occasions. No subjects required hospitalisation.

Statistical tests on the effects of subsequent stings during/after immunotherapy, between patients with WBE therapy (pre 1981 and of unproven efficacy) and the patients with PBV therapy (post 1981) agree with the earlier studies that immunotherapy with PBV is clinically more efficacious.[17,18] In addition, reviews of the outpatient records from the immunotherapy clinic since 1981 (when PBV was introduced and replaced WBE) revealed that any subsequent stings were, in the majority of patients, well tolerated without any severe adverse reactions. Only 8 (14%) out of 56 patients who had a further sting during/following immunotherapy, developed a systemic reaction. However, these reactions cannot be seen as a failure of PBV since with one exception the sting occurred in the program before a maintenance dose of venom had been achieved.

In this study, 31% of the patients and 33% of the positive controls had family members with a history of bee sting anaphylaxis. In contrast, only 15% of the negative controls had a family history of bee sting anaphylaxis. In 50% of patients with a positive family history of bee venom anaphylaxis, the father was identified as the bee sensitive subject. A maternal link was only identified in 8%. Overall, there was a male predominance in our cohort of patients and their bee allergic relatives. These factors are of interest, suggesting a male related factor in the genetic aspects of bee venom sensitivity.

In summary, venom immunotherapy benefits patients not only by effectively preventing sting anaphylaxis, but also by preventing the psychologic morbidity that often interferes with normal activities, especially in young individuals throughout the warm weather seasons. In the present study, venom desensitisation allowed a freer participation in outdoor activities and reduced fear of bees in at least 47% and 51% of patients, respectively.

Finally, there appears to be a genetic aspect in the pathogenesis of bee venom hypersensitivity. To date no previous study has shown such a genetic tendency although Frey and Litwin[19] in United States have found similar findings in *Hymenoptera* (including honey bee) sensitivity. In order to make a conclusive statement about the genetic tendency in bee venom hypersensitivity, additional studies with larger samples of patients as well as controls are needed.

ACKNOWLEDGEMENTS

We would like to thank The Asthma Foundation of South Australia for providing financial support and patients and staff members of the Immunotherapy and Rheumatology Clinics at FMC.

REFERENCES

1. Harvey P, Sperber S, Kette F, Heddle RJ, Roberts-Thomson PJ. Bee-sting mortality in Australia. Med J Aust 1984; 140 : 209-11.
2. Bochner BS, Lichtenstein LM. Anaphylaxis. N Engl J Med 1991; 324 : 1785-90.
3. Reisman RE. Insect stings. N Engl J Med 1994; 331 : 523-7.
4. Reisman RE, Dvorin DJ, Randolph CC, Georgitis JW. Stinging insect allergy : natural history and modification with venom immunotherapy. J Allergy Clin Immunol 1985; 75 : 735-40.
5. Roitt IM, Brostoff J, Male DK. Immunology. Mosby 3rd Ed. 1993 (Chapter 19).
6. Hamilton RG, Wisenauer JA, Goldnen DBK, Valentine MD, Adkinson NF. Selection of *Hymenoptera* venoms for immunotherapy on the basis of patient's IgE antibody cross-reactivity. J Allergy Clin Immunol 1993; 92 : 651-9.
7. Reisman RE, Livingstone A. Venom immunotherapy : 10 years of experience with administration of single venoms and 50μg maintenance doses. J Allergy Clin Immunol 1992; 89 : 1189-95.
8. Frew AJ. Injection immunotherapy. Br Med J 1993; 307 : 919-23.
9. Roberts-Thomson PJ, Harvey P, Sperber S, Kupa A, Heddle RJ. Bee sting anaphylaxis in an urban population of South Australia. Asian Pac J Allergy Immunol 1985; 3 : 161-4.
10. Golden DBK, Valentine MD. Insect sting allergy. In : Franklin E.C. ed. Clinical immunology update. Edinburgh : Churchill Livingstone, 1981; 169-96.
11. Lantner R, Reisman RE. Clinical and immunological features and subsequent course of patients with severe insect sting anaphylaxis. J Allergy Clin Immunol 1989; 84 : 900-6.
12. Schuberth KC, Licktenstein LM, Sobotka AK, Szklo M, Kwiterovich KA, Valentine MD. Epidemiologic study of insect allergy in children : effect of accidental stings in allergic children. J Paed 1983; 102 : 361-5.
13. Valentine MD, Schuberth KC, Kagey-Sobatka A. *et al.* The value of immunotherapy with venom in children with allergy to insect stings. N Engl J Med 1991; 123 : 1601-3.
14. Keating MJ, Kagey-Sobtka A, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. J Allergy Clin Immunol 1991; 88 : 339-48.
15. Golden DBK, Johnson K, Addison BI, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Clinical and immu-

nologic observations in patients who stop venom immunotherapy. J Allergy Clin Immunol 1986; 77 : 435-42.

16. Reisman RE. Venom hypersensitivity. J Allergy Clin Immunol 1994; 94 : 651-9.
17. Muller U, Thurnheer U, Patrizzi R, Spiess J, Hoigne R. Immunotherapy in bee sting hypersensitivity : bee venom vesus whole bee extract (Abstract). Allergy 1979; 34 : 369-78.
18. Hunt KJ, Valentine MD, Sobtka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. (Abstract) N Engl J Med 1978; 299 : 157-61.
19. Freye HB, Litwin CM. *Hymenoptera* sensitivity occurring in families. Allergy-Proc 1994; 15 : 53-6.