

Allergy to bumblebees

Hans de Groot

Purpose of review

Field stings by bumblebees are uncommon because of the habitat and nonaggressiveness of these insects. More stings have been reported in the Netherlands because of the increasing use of bumblebees in flowering industries such as tomato growing. The purpose of this review is to summarize the recent literature concerning bumblebee anaphylaxis and describe our own experience with immunotherapy in an occupational group of bumblebee-venom-allergic workers.

Recent findings

Two distinct categories of patients are sensitized to bumblebee venom. First are patients with IgE highly cross-reactive with honeybee venom allergens. Venom immunotherapy with honeybee venom will be adequate in these nonprofessionally exposed bumblebee-allergic patients. These patients react to bumblebee venom as a result of a primary earlier exposure and sensitization to honeybee venom. Secondly, with heavily exposed greenhouse workers or bumblebee workers, frequently stung only by bumblebees, it is recommended to use immunotherapy with purified bumblebee venom, due to the low or absent degree of cross-reactivity with honeybee venom. Otherwise, the best preventive therapy is to avoid further exposure, which means changing profession.

Summary

Immunotherapy with purified bumblebee venom is as well tolerated and effective as immunotherapy with other Hymenoptera venoms.

Keywords

anaphylaxis, bumblebee, cross-reactivity, honeybee, immunotherapy

Introduction

Bumblebee anaphylaxis is rare compared with other Hymenoptera venom allergies caused by stings from vespids and honeybees. In the literature [1–5], the only case reports are found in occupational settings. Bumblebees belong to the genus *Bombus* of the family Apidae. The family Apidae consist of the honeybees (*Apis mellifera*) which are brown and moderately hairy and the bumblebees (genus *Bombus*) which are bigger than honeybees, much more hairy and characterized by distinct yellow or white bands on their abdomen. Approximately 45 bumblebee species exist in North America and about 160 species in other parts of the world. In Europe, the *Bombus terrestris* have been domesticated and used for more than 20 years to pollinate plants grown in greenhouses, such as tomatoes and sweet bell peppers. The bees feed on pollen and nectar collected from the plants and, by foraging, they will pollinate the plants, resulting in more efficient fruit production for the gardeners. Bumblebees are more docile than other bees and greenhouse workers are stung because the bumblebees get stuck between the plants and clothing. The amount of venom released during a sting varies from species to species and within a species. Honeybee stings release approximately 50–140 µg of venom protein per sting; bumblebee stings release 10–31 µg of venom [6].

Earlier observations

Kochuyt *et al.* [4] reports on seven bumblebee-allergic patients working in a bumblebee farm and tomato greenhouse. Two patients had been stung before by honeybees; all patients had a high level of sensitization to honeybee venom. As purified bumblebee venom (BBV) was not available, they started venom immunotherapy (VIT) with honeybee venom. After a follow-up period of 2 months to 3 years, six patients were stung by more than 36 bumblebee stings, only resulting in two large local reactions.

Stern *et al.* [7], however, described two patients with occupational bumblebee anaphylaxis who started VIT with honeybee venom and experienced severe systemic reactions after a sting with bumblebee. After reaching maintenance dose with purified bumblebee venom, protection was demonstrated using in-hospital sting challenges with live bumblebees.

Knowledge of the composition of venoms and structure of allergens is necessary for the appropriate diagnosis and treatment of insect venom allergy. The majority of major

Curr Opin Allergy Clin Immunol 6:294–297. © 2006 Lippincott Williams & Wilkins.

Department of Allergology, Erasmus MC, Rotterdam, The Netherlands

Correspondence to Dr Hans de Groot, Allergologist, PhD, MD, FAAAAI, Erasmus MC, PO Box 2040, 3000 CA, Rotterdam, The Netherlands
Tel: +31 104633970; fax: +31 104634081; e-mail: h.degroot@erasmusmc.nl

Current Opinion in Allergy and Clinical Immunology 2006, 6:294–297

Abbreviations

BBV bumblebee venom
RAST radio allerge sorbent test
VIT venom immunotherapy

© 2006 Lippincott Williams & Wilkins
1528-4050

venom allergens have been cloned and sequenced, and some allergens have been expressed in recombinant form (<http://www.allergen.org>).

Bumblebee venom contains phospholipase A2 (Bom p 1), serine protease (Bom p 4), hyaluronidase, acid phosphatase and several allergens not found in honeybees [8]. The primary amino acid sequence of bumblebee venom phospholipase shows 53.7% identity with that from honeybee venom, with 33% additional conservative changes. Mellitin is a peptide specific for honeybee venom, whereas a protease of tryptic amidase specificity was found only in bumblebee venom and not in other Hymenoptera venoms.

About 75% of sera from patients allergic to honeybee react in radio allerge sorbent test (RAST) with bumblebee venom, and 85% of sera from patients with histories of allergy to bumblebee stings demonstrate positive RAST responses to honeybee venom. These observations can be caused by true double sensitization or by cross-reactive IgE recognizing similar epitopes of different common venoms. The distinction between the two is important for the choice of venom(s) for immunotherapy. Stapel *et al.* [9] demonstrated in sera from patients who worked in a bumblebee farm by RAST-inhibition and immunoblot analysis the existence of bumblebee-specific epitopes. Even within the bumblebee subspecies, differences were found between European and American bumblebee species, recently confirmed by Hoffman *et al.* [10] using three-dimensional modeling.

The Dutch experience with occupational bumblebee anaphylaxis

The growing use of bumblebees in Dutch greenhouses for pollination has resulted in an increasing number of anaphylactic reactions to their stings in the gardeners. In our outpatient clinic, we have seen 42 consecutive patients with a history of bumblebee anaphylaxis. The group consisted of 22 workers in tomato horticulture, 17 workers on a bumblebee farm and three city gardeners. Anaphylaxis occurred after 8.5 stings of the bumblebees (range 1–25 stings). The city gardeners were stung in the past by vespids and honeybees without any sign of anaphylaxis.

The diagnosis of bumblebee anaphylaxis was confirmed according to international guidelines [11^{••}]. Intracutaneous testing was performed with 0.02 ml of stepwise incremental 10-fold dilutions of purified bumblebee venom (*B. terrestris*, 1 µg/ml, ALK Abello, Nieuwegein, The Netherlands), ranging from a venom concentration of 0.0001 to 1.0 µg/ml. After 20 min, wheal and flare reactions were measured with the grading system of standardized plus signs devised by Norman [12]. As

control solutions, dilution buffer and histamine diphosphate (0.1 mg/ml) were used. Subsequently, confirmation of the IgE-mediated reaction to bumblebee venom and sensitization to *Vespula germanica* and *Apis mellifera* were detected by RAST (Pharmacia, Uppsala, Sweden).

The general characteristics, severity of the sting reaction according to Mueller [13] and sensitization to the three venoms are summarized in Table 1.

Stapel *et al.* [9] and Hoffman *et al.* [10] demonstrated significant species group-specific epitopes on bumblebee venom proteins, using the sera of the Dutch patients.

Table 1 General characteristics of 42 consecutive patients with occupational bumblebee venom

Grade	Age	IgE <i>B. terrestris</i>	IgE <i>A. mellifera</i>	IgE <i>V. germanica</i>
Workers in bumblebee farm				
I	52	12.2	0.36	n.d.
I	27	0.45	4.5	0.85
I	22	12.8	n.d.	n.d.
II	52	2.5	<0.35	<0.35
II	27	0.45	<0.35	<0.35
III	24	10.5	9.19	0.76
III	43	1.05	0.86	0.45
III	44	13.5	3.95	19.6
III	42	15.2	1.59	0.49
III	29	9.99	19.8	10.5
III	32	9.16	6.25	<0.35
III	22	43.1	n.d.	n.d.
IV	58	3.22	n.d.	n.d.
IV	43	8.4	n.d.	n.d.
IV	38	8.58	3.17	<0.35
IV	30	56.5	1.59	0.46
IV	28	2.4	6.87	0.37
Workers in tomato greenhouse				
II	37	5.3	n.d.	n.d.
II	42	50	12.2	1.17
II	61	3.3	n.d.	n.d.
II	60	12.5	n.d.	n.d.
II	51	15.3	<0.35	<0.35
II	57	83.7	19.5	4.1
III	34	6.7	2.8	<0.35
III	55	17.5	<0.35	<0.35
III	38	11.3	<0.35	0.56
IV	49	10.8	0.7	<0.35
IV	41	35.4	9.68	4.77
IV	44	15.3	5.34	2.71
IV	51	48	33.8	0.46
IV	37	3.28	n.d.	n.d.
IV	57	0.95	n.d.	n.d.
IV	39	5.75	<0.35	<0.35
IV	34	44.5	16.3	4.18
IV	55	27.3	12.2	2.02
IV	59	0.38	<0.35	<0.35
IV	59	19.4	61.2	36
IV	69	0.94	<0.35	<0.35
IV	34	80.7	>100	2.16
City gardeners				
II	25	2.94	27.9	14.2
III	25	12.8	60	4
IV	60	12.9	49.7	2.53

n.d., not done; IgE, values in kU/l.

Table 2 Severity of bumblebee anaphylaxis and follow-up in 42 consecutive patients

Grade	Number	Start immunotherapy
I	3	1
II	9	7
III	11	6
IV	19	14

They advised these occupational patients to be treated with the appropriate species group, which was responsible for the primary sensitization, the *B. terrestris*. Selecting the patients who needed VIT is mainly based on the clinical history: it is indicated in patients with a history of severe systemic reaction including respiratory and cardiovascular symptoms and documented sensitization to the respective insect [14**]. Higher-risk subjects are those who are likely to receive frequent stings in their occupation. Some patients quit their job and they are not at an increased risk of being re-stung by bumblebees in the future (see also Table 2). All patients were provided with an EpiPen autoinjector; oral and written instructions were given by the doctor or a trained nurse about the use of the pen. As the other patients could not avoid bumblebees, VIT was started. Activities in which the risk of re-sting was high were forbidden until the maintenance dose of VIT was reached [15].

Immunotherapy with purified bumblebee venom extract (obtained by electric stimulation and provided by ALK Abello, Nieuwegein, The Netherlands) was started very carefully in the first two patients [5]. No severe reactions were seen and we subsequently treated the next 26 patients with a modified semi-rush protocol, followed by monthly injections with approximately 100 µg of purified bumblebee venom [15]. All patients showed a 10–100-fold decrease in skin test reactivity after 1 year of immunotherapy, confirmed by RAST.

Challenge tests [16] using live insects were performed in the first two patients according to the European guidelines. No systemic reactions were seen – only large local reactions. Subsequently, 56 field stings were experienced in 15 of the 28 patients who were still working with bumblebees. Five patients suffered from large local reactions; in two patients a systemic reaction (grade I/II and grade II) was observed, although less severe than the index sting reaction (respectively grade IV and grade III). No epinephrine was used in these reactions.

The protection rate is estimated to be 96% in BBV; this is comparable to that of other VIT. In prospective (uncontrolled) studies [14**] with in-hospital sting challenges during the course of immunotherapy, a treatment failure was found for vespids in 0–9% of the patients and for honeybees in approximately 20% of the patients. In the

patients who reacted, the symptoms were usually much less severe than before the injection therapy, indicating a partial success in these ‘failures’. In follow-up studies, more than 80% of the patients remained protected when re-stung up to 7 years after stopping immunotherapy.

All patients reached maintenance dose in 6 weeks without severe side effects. During the induction phase (336 injections), we registered 14 (4.2%) local reactions (5–10 cm) and two (0.6%) systemic reactions, consisting of shortness of breath in an asthmatic atopic gardener who did not use his asthma medication as instructed by his physician. After stabilization of the bronchial hyperreactivity with inhalant corticosteroids, no additional side effects were seen in this patient. During the maintenance phase (1272 injections), we encountered 14 (1.1%) local reactions and no systemic side effects. In an EAACI-multicenter study [17], systemic reactions were found in 20% of patients, corresponding to 1.9% of injections during the dose-increase phase and 0.5% during the maintenance phase.

Conclusions

Bumblebee anaphylaxis is a rare phenomenon due to the nonaggressiveness of these insects as compared with yellow jackets. People at risk are those who are occupationally exposed to bumblebees, such as bumblebee farm workers, scientists studying these creatures or greenhouse gardeners who use these insects for pollination. VIT with honeybee venom will be adequate in nonprofessionally exposed bumblebee-allergic patients. For occupational bumblebee anaphylaxis, the best preventive therapy is to avoid further exposure, which means changing profession. VIT is advised in people who will continue to work with bumblebees. Due to the low or absent degree of cross-reactivity with honeybee venom in these patients, we advise the use of purified bumblebee venom. All patients reached maintenance dose in 6 weeks without severe side effects. Efficacy was demonstrated, first with in-hospital sting challenge and subsequently with field stings with bumblebees. The efficacy was comparable to honeybee and yellow jacket VIT.

Acknowledgements

We acknowledge Dr K.Y. Tan and Dr M.W.H.M. Roovers, both allergologists, for providing data of bumblebee-allergic patients. Furthermore, Dr A.E.J. Dubois, allergologist, for critically reading the manuscript.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 304).

- 1 Barnard JH. Severe hidden delayed reactions from insect stings. *N Y State J Med* 1966; 66:1206–1210.

- 2 Donovan BJ. Anaphylactic shock and strong cardiac stimulation caused by stings of the bumble bee of *Bombus terrestris*. NZ Entomol 1978; 6:385–389.
 - 3 Van der Zwan JC, van der Linden PW, de Maat-Bleeker F, *et al*. Anaphylactic systemic reactions after a bumblebee sting. Allergy 1992; 47:52.
 - 4 Kochuyt AM, van Hoeyveld E, Stevens EAM. Occupational allergy to bumble bee venom. Clin Exp Allergy 1993; 23:190–195.
 - 5 De Groot H, de Graaf-in't Veld C, Gerth van Wijk R. Allergy to bumblebee venom I: occupational anaphylaxis to bumblebee venom – diagnosis and treatment. Allergy 1995; 50:581–584.
 - 6 Hoffman DR, Jacobson RS. Allergens in Hymenoptera venom: XII – how much protein is in a sting? Ann Allergy 1984; 52:276–278.
 - 7 Stern A, Wuthrich B, Mullner G. Successful treatment of occupational allergy to bumblebee venom after failure with honeybee venom extract. Allergy 2000; 55:88–91.
 - 8 Hoffman DR, Jacobson RS. Allergens in Hymenoptera venom: XXVII – bumblebee venom allergy and allergens. J Allergy Clin Immunol 1996; 97: 812–821.
 - 9 Stapel SO, Waanders-Lijster de Raadt J, van Toorenenbergen AW, de Groot H. Allergy to bumblebee venom II: IgE cross-reactivity between bumblebee venom and honeybee venom. Allergy 1998; 53:769–777.
 - 10 Hoffman DR, El-Choufani SE, Smith MM, de Groot H. Occupational allergy to bumblebees: allergens of *Bombus terrestris*. J Allergy Clin Immunol 2001; 108:855–860.
 - 11 Bilo BM, Rueff F, Mosbech H, *et al.*, the EAACI Interest Group on Insect •• Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. Allergy 2005; 60:1339–1349.
- A systematic review from the European Academy of Allergy and Clinical Immunology focusing on the diagnosis of Hymenoptera venom allergy.
- 12 Norman PS. Skin testing. In: Rose NR, Friedman H, editors. Manual of clinical immunology, 2nd ed. Washington, DC: American Society for Microbiology; 1980. pp. 189–193.
 - 13 Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res 1966; 3:331–333.
 - 14 Bonifazi F, Jutel M, Bilo BM, *et al.*, the EAACI Interest Group on Insect Venom. •• Prevention and treatment of Hymenoptera venom allergy: guidelines for clinical practice. Allergy 2005; 60:1459–1470.
- This updated review from the EAACI summarizes recent publications on prevention and treatment of Hymenoptera venom allergy, as well as the evidence of the conclusions graded according to the new guidelines.
- 15 De Jong NW, Vermeulen AM, de Groot H. Allergy to bumblebee venom III Immunotherapy follow-up study (safety and efficacy) in patients with occupational bumblebee-venom anaphylaxis. Allergy 1999; 54:980–984.
 - 16 Rueff F, Pryzbilla B, Muller U, Mosbech H. The sting challenge test in Hymenoptera venom allergy. Allergy 1996; 51:216–225.
 - 17 Mosbech H, Muller U. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. Allergy 2000; 55:1005–1010.