

Case report

Successful treatment of occupational allergy to bumblebee venom after failure with honeybee venom extract

Background: Immediate-type allergies to bumblebee stings occur infrequently. Previous studies have demonstrated a high degree of cross-reactivity between honeybee venom (HBV) and bumblebee venom (BBV). It has been proposed that venom immunotherapy (VIT) with HBV is a therapeutic alternative for patients with BBV allergy.

Methods and Results: We present two cases of occupational immediate-type allergies to BBV. Although both nonatopic patients had a negative personal history of previous allergic reactions to honeybee sting, specific IgE antibodies and a positive intradermal reaction to HBV were detected. Despite VIT with HBV, the two developed another severe allergic reaction after incidental bumblebee stings. VIT with BBV, using in one patient a rush protocol and in the other a “conventional” regimen, with escalating doses of 0.01–100 µg of BBV, was performed. Before and during the VIT, the course of IgE and IgG specific antibodies to BBV was analyzed, demonstrating a significant decrease of BBV-IgE and an increase of BBV-IgG. The effectiveness of the treatment was also proven by an in-hospital sting challenge with a live bumblebee.

Conclusions: Our data demonstrate that cross-immunotherapies with HBV do not protect BBV-allergic patients sufficiently. We conclude that BBV-allergic patients should be treated with BBV. A “rush” VIT with BBV is a safe alternative to a “conventional” protocol.

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In contrast to honeybee venom (HBV) and vespid venom (VV) allergy, immediate-type allergies to bumblebee venom (BBV) are rare. The Apidae family (Hymenoptera) includes the genera *Apis* – the honeybees – and *Bombus* – the bumblebees. Bumblebees are not very aggressive, and workers or queens usually sting only when they are threatened (1). Like the Vespidae family, they can usually withdraw their stingers and can sting several times without attachment of the sting apparatus to the victim's skin. Although they preferentially inhabit the temperate zones, bumblebees are widespread with approximately 400–500 species throughout the world. More than 30 species are found in Switzerland. Bumblebees are one of the most hard-working pollinators of wild and cultivated plants. One bumblebee can visit about 4000 different blossoms a day. In recent years, bumblebees (especially *Bombus terrestris*) have been domesticated and used for the pollination of crops such as tomatoes and cherries in greenhouses (2). This expanding bio-industry has probably resulted in an increasing number of reported cases of occupational allergy to BBV (3, 8).

Previous studies have demonstrated a high degree of cross-reactivity between HBV and BBV (4–7). Due to

the phylogenetic relationship and the similar composition of the venoms, it has been proposed that venom immunotherapy (VIT) with HBV is a sufficient treatment for patients who are allergic to BBV (7, 8).

We report on two patients with severe occupational allergy to BBV who were first hyposensitized with purified HBV. Nevertheless, both patients developed another anaphylactic reaction with angioedema after incidental stings by bumblebees during their work. VIT with aqueous and purified BBV extract was performed, using in one patient a “conventional” and in the other a “rush” regimen to achieve the maintenance dose of 100 µg. The efficacy of the bumblebee VIT was proven through an in-hospital insect sting challenge (ICH) with a living bumblebee.

Material and Methods

Case reports

Patient B.I. While working on her thesis about bumblebees, a 31-year-old female biologist was stung about 10 different times by bumblebees without any systemic reactions. She had no personal history of atopic diseases.

In 1995, after a bumblebee sting on her shoulder, she immediately experienced rhinoconjunctival symptoms, vertigo, nausea, generalized pruritus, angioedema, vomiting, wheezing, and dyspnea. According to the classification of H. L. Mueller, the clinical reaction was classified as an allergic reaction of grade III.

Patient P.N. A 22-year-old male nonatopic student of biology used to work with bumblebees when staying with relatives in Belgium. Several stings by bumblebees were well tolerated without subsequent systemic reactions. In 1993, he developed generalized urticaria, rhinoconjunctivitis, nausea, vomiting, and angioedema after a bumblebee sting (allergic reaction grade II–III).

Both patients showed positive intracutaneous tests and specific IgE to HBV, although neither of them had a personal history of previous allergic reactions to honeybees or other Hymenoptera species. On the basis of the above mentioned findings and the present literature, one must assume a cross-reaction between BBV and HBV. Immunotherapy with purified HBV was performed in both patients.

Patient B.I. received the maintenance dose of HBV (ALK Alutard® 100 000 SQE) for more than 9 months, as she was restung by a bumblebee on her heel. Within 10 min, she manifested an allergic reaction of grade II–III with generalized itching, flush, rhinoconjunctival symptoms, and extensive facial angioedema.

In Patient P.N., the full dose of HBV (Pharmalgen® 100 µg) had been achieved for almost 2.5 years, as he received another accidental bumblebee sting. Nevertheless, he developed an allergic reaction of grade II with flush, generalized pruritus, angioedema, runny nose, and nasal obstruction.

Venoms

The BBV used for diagnosis and treatment is not a standard product. It was provided by ALK Benelux, Groningen, The Netherlands, as aqueous venom extract. The venom of *B. terrestris* was obtained by sac extraction, reconstituted, and dialyzed, and glycerin was added as for commercially supplied vespid venom (VV). HBV and VV vaccines (Pharmalgen and Alutard) were purchased from ALK, Hørsholm, Denmark.

Skin tests

Diagnosis of venom-specific allergy was confirmed with skin tests. In both patients, intracutaneous skin tests were performed with 0.1 ml of 10-fold dilutions of Hymenoptera venoms (VV, HBV, and BBV) on the volar aspect of the forearm. Histamine diphosphate (0.1 mg/ml) was used as positive control, and the diluent buffer as negative control. After 15 min, the wheal and flare diameters were measured and graded.

Specific IgE and IgG antibodies

Serum specific IgE and IgG antibodies against HBV, VV, and BBV were determined in both patients before and during the VIT with HBV and BBV, respectively. The sera were deep-frozen, and all tests were performed at the same time with the same control sera. Specific IgE antibodies to HBV, VV, and BBV were measured with the commercially available CAP method (Pharmacia & Upjohn Diagnostic, Uppsala, Sweden) according to the manufacturer's instructions. Results were expressed in kU/l. For purposes of comparison, the concentration of specific IgE antibodies to BBV was also determined by conventional radioallergosorbent test (RAST, Pharmacia & Upjohn Diagnostic, Uppsala, Sweden) with purified BBV coupled on disks. Results were expressed in Phadebas RAST units/ml (PRU/ml). Levels of specific IgG serum antibodies against BBV were quantified by competitive ELISA (µg/ml).

Venom immunotherapy (VIT)

The same BBV used for analysis was applied for treatment. The protocol for the "conventional" VIT consisted of two weekly injections given over a period of 2 months, starting with a dose of 0.1 µg and increasing stepwise until the maximum dose of 100 µg was reached. The "rush" VIT was performed during a 4-day hospital stay. We began with 0.01 µg of BBV and escalated the dose until reaching the maximum dose of 100 µg. After the maintenance dose of 100 µg was reached, the interval between injections was gradually increased to 4 weeks in the first year, and 5 weeks in the second.

Results

Skin tests

Both patients showed clearly positive intradermal skin reactions to purified and aqueous BBV and HBV extract (Table 1). Intracutaneous testing with VV did not produce any skin reaction up to 1 µg/ml.

Specific IgE and IgG antibodies

The results of total and specific IgE levels before the very first VIT with HBV are shown in Table 1. No specific IgE antibodies to VV were detected (<0.35 kU/l). In patient B.I., we analyzed the course of the BBV-specific IgE and IgG levels. The four measurements dated, respectively, from the time before treatment with HBV (IgE: 6.0 PRU/ml, 23.2 kU/l, IgG: 88 µg/ml), from the VIT with HBV (IgE: 12.0 PRU/ml, 33.5 kU/l,

Table 1. Results of i.c. (intracutaneous) skin tests and IgE levels after first anaphylactic reaction to bumblebee sting and before beginning of VIT

Patient	Total IgE	HBV-IgE	BBV-IgE	HBV i.c.	BBV i.c.
B.I. (1996)	26 kU/l	5.05 kU/l	6.0 PRU/ml, 23.2 kU/l	0.1 µg/ml	0.1 µg/ml
P.N. (1993)	11 kU/l	0.92 kU/l	3.0 PRU/ml	0.1 µg/ml	n.d.

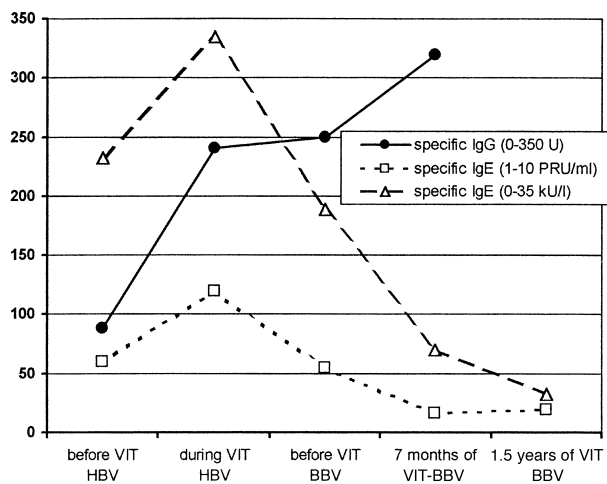


Figure 1. Course of specific IgG ($\mu\text{g/ml}=\text{U}$) and specific IgE antibodies to BBV (RAST: PRU/ml; CAP: kU/l) in patient B.I.

IgG: 240 $\mu\text{g/ml}$), from after the second anaphylactic reaction caused by a bumblebee (before VIT with BBV was initiated) (IgE: 5.5 PRU/ml, 18.9 kU/l, IgG: 250 $\mu\text{g/ml}$), and finally from the VIT with BBV (7 months of VIT IgE: 1.6 PRU/ml, 6.98 kU/l, IgG: 320 $\mu\text{g/ml}$) (1.5 years of VIT: IgE: 1.8 PRU/ml, 3.25 kU/l). The results are summarized in Fig. 1. The VIT with BBV resulted in a significant decrease of specific IgE and an increase of specific IgG to BBV. A similar course of the BBV-specific antibodies was shown by patient P.N., although only two determinations were obtained; before (IgE: 2.39 PRU/ml, IgG: <3.2 $\mu\text{g/ml}$) and during (IgE: 0.49 PRU/ml, IgG: 34 $\mu\text{g/ml}$) the VIT with BBV.

In-hospital sting challenge (IHC)

Four months after reaching the maintenance dose of 100 μg BBV, challenge stings were performed in-hospital under intensive care unit conditions. One live female bumblebee was provoked to sting 2–4 times on the upper leg of patient P.N. and on the forearm of patient B.I., respectively. Both patients experienced a normal local cutaneous reaction (less than 10 cm swelling in diameter) to the bumblebee stings. Neither of the patients showed any systemic reactions or immediate-type symptoms.

Discussion

VIT is a universally accepted and recommended treatment for patients who have experienced systemic IgE-mediated allergic reactions to Hymenoptera stings. Various studies have demonstrated the great bio- and immunochemical similarity of HBV and BBV (5–7). In 1993, Kochuyt et al. performed and described cross-immunotherapy with HBV in a few patients with occupational allergy to BBV (8). Although conventional VIT with HBV has been performed in three cases

before (3), these results have led to the clinical proposition that VIT with HBV is an adequate therapeutic alternative for patients with allergy to BBV.

Our two nonatopic patients experienced a grade III and a grade II–III reaction to BBV, respectively. The sensitization was confirmed by intracutaneous skin tests and RAST with BBV extract. They first underwent VIT with HBV. However, a subsequent sting by a bumblebee led to another anaphylactic reaction. From this clinical finding, one can conclude that cross-immunotherapy with HBV does not sufficiently protect BBV-allergic patients. These two cases demonstrate that BBV must contain other unknown specific and relevant allergens which are important for severe systemic immediate-type reactions. As purified BBV extract is available, we performed both conventional and rush immunotherapy. Both types of protocols were well tolerated, and no side-effects occurred. To our knowledge, patient B.I. is the first patient reported in the medical literature to have undergone rush VIT with BBV successfully.

The therapeutic benefit was established through the re-exposure to a live bumblebee sting in the intensive care unit. Neither of our patients showed an allergic reaction to the IHC. IHC is a controversial but mostly reliable indication of effective VIT. The course of specific IgE and IgG antibodies to BBV corresponds to data about VIT in bee- or vespid-allergic subjects (9–11). The specific IgE levels decreased remarkably, indicating a lower sensitization and better tolerability. A significant induction of blocking IgG antibodies was observed. These changes in concentrations of specific antibodies were not clearly demonstrable in patient B.I. during the VIT with HBV. It is well known that neither IgE nor IgG is alone responsible for the protective effect of VIT, although they are still important and accepted clinical markers for its course and effectiveness. For the determinations of specific IgE to BBV, the RAST correlated with the CAP method, although the latter showed much higher values.

In conclusion, our two patients show that cross-immunotherapy with HBV in BBV-allergic patients is not a sufficient protection against subsequent systemic reactions after bumblebee stings. Our data indicate that immunotherapy with BBV is the only safe therapeutic alternative in bumblebee-allergic patients who cannot avoid exposure. A rush protocol is a safe method of performing BBV-VIT. If BBV is not available for VIT, the only options remaining during the active season for bumblebees are strict avoidance of bumblebee stings and an emergency kit containing epinephrine in a ready-to-use syringe, antihistamines, and corticosteroids.

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References

1. MÜLLER UR. Insect sting allergy. Stuttgart: Gustav Fischer, 1990.
2. VON HAGEN E, AICHORN A, FADINI A. Hummeln – Bestimmen, Ansiedeln, Vermehren, Schützen. 4th ed. Augsburg: Naturbuchverlag, 1994.
3. DE GROOT H, DE GRAAF-INT VELD C, GERTH VAN WIJK R. Allergy to bumblebee venom. I. Occupational anaphylaxis to bumblebee venom: diagnosis and treatment. *Allergy* 1995;**50**:581–584.
4. REISMAN RE, MÜLLER UR, WYPYCH JI, LAZELL MI. Studies of coexisting honeybee and vespid-venom sensitivity. *J Allergy Clin Immunol* 1984;**73**:246–252.
5. HOFFMANN DR. Allergenic cross-reactivity between honeybee and bumblebee venoms. *J Allergy Clin Immunol* 1982;**69**:139.
6. STAPEL SO, WAANDERS-LIJSTER DE RAADT J, VAN TOORENENBERGEN AW, DE GROOT H. Allergy to bumblebee venom. II. IgE cross-reactivity between bumblebee and honeybee venom. *Allergy* 1998;**53**:769–777.
7. HOFFMANN DR, JACOBSON RS. Allergens in Hymenoptera venom. XXVII. Bumblebee venom allergy and allergens. *J Allergy Clin Immunol* 1996;**7**:812–821.
8. KOCHUYT AM, VAN HOEYVELD E, STEVENS AEM. Occupational allergy to bumblebee venom. *Clin Exp Allergy* 1993;**23**:190–195.
9. WILSON AB, DEIGHTON J, LACHMANN PJ, EWAN PW. A comparative study of IgG subclass antibodies in patients allergic to wasp or bee venom. *Allergy* 1994;**49**:272–280.
10. REISMANN RE, WYPYCH J, ARBESMAN CE. Stinging insect allergy: detection and clinical significance of venom IgE antibodies. *J Allergy Clin Immunol* 1975;**56**:443–449.
11. WYSS M, SCHEITLIN T, STADLER BM, WÜTHRICH B. Immunotherapy with aluminium hydroxide adsorbed insect venom extracts (Alutard SQ): immunologic and clinical results of a prospective study over 3 years. *Eur J Allergy Clin Immunol* 1993;**48**:81–86.