

Venom immunotherapy for Hymenoptera allergy in a dog

Ana Rostaher* , Ralf S Mueller† , Lena Meile‡, Claude Favrot*  and Nina Maria Fischer* 

*Clinic for Small Animal Internal Medicine, Vetsuisse Faculty University of Zurich, Winterthurerstrasse 260, Zurich, 8057, Switzerland

†Small Animal Medicine Clinic, Centre for Clinical Veterinary Medicine, LMU Munich, Veterinärstr. 13, Munich, 80539, Germany

‡Brünigstrasse 180, Sarnen, 6060, Switzerland

Correspondence: Ana Rostaher, Clinic for Small Animal Internal Medicine, Vetsuisse Faculty University of Zurich, Winterthurerstrasse 260, Zurich, 8057, Switzerland. E-mail: arostaher@vetclinics.uzh.ch

A 1.5-year-old male castrated dog was presented in anaphylactic shock after suffering an apparent bee sting. Immunotherapy with bee venom was initiated based upon history, skin testing and serological testing for allergen-specific immunoglobulin (Ig)E. The dog was maintained on venom immunotherapy for five years and showed no signs of adverse effects from therapy or from repeated bee stings.

Introduction

Anaphylaxis is an immunoglobulin (Ig)E-mediated systemic allergic reaction that is rapid in onset and potentially fatal.¹ Medications, foods and insect venoms are the most common causes of anaphylaxis in people and dogs.^{1,2} It is estimated that $\leq 5\%$ of the human population have had a systemic reaction to an insect sting.^{3,4} In dogs, the incidence of urticaria previously was reported to be 0.12%, with stinging insects being identified in $\leq 40\%$ of cases.² The only efficient treatment in people to prevent further systemic reactions to stinging insects is venom immunotherapy (VIT) and various protocols have been described.^{3,5} By comparison, information in veterinary medicine is quite limited.⁶

Case report

A 1.5-year-old male castrated Kooikerhondje dog was stung by a bee (*Apis mellifera*). The dog was presented to the clinic within 10 min of the onset of acute vomiting and loss of consciousness. A diagnosis of severe anaphylaxis was made; the dog was treated accordingly and recovered uneventfully. The dog had a history of at least one Hymenoptera sting at the age of six months. The prior incident also was associated with severe anaphylaxis.

Six weeks after discharge, the dog underwent skin prick (SPT) and intradermal testing (IDT) with bee and wasp (*Vespula* spp.) extracts (Figure 1). For SPT, a reaction was considered positive when the largest diameter of the wheal was ≥ 3 mm. IDT reactions were graded subjectively as described previously.^{7,8} The IDT was positive for bee and the SPT was negative for bee and wasp venom allergens. An allergen-specific semiquantitative enzyme-linked immunosorbent assay (ELISA) (Laboklin; Bad Kissingen, Germany) was performed and reported high concentrations of serum IgE reactive to bee (reaction

class 5), yellow jacket (reaction class 3) and hornet (reaction class 3), with mild reactivity to paper wasp (reaction class 1). The assay ranges were 0–10, 11–50, 51–75, 76–100, 101–150, >150 Heskia Epsilon Receptor Binding Units (HERBU) for the negative reaction class 0 and the positive classes 1–5, respectively.

Serum tryptase levels (Canine Tryptase ELISA, Chemie Brunschwig; Basel, Switzerland) 30 min after anaphylactic collapse and one year after recovery were similar, with concentrations of 20.8 and 20.7 ng/mL, respectively. Additionally, the same tryptase kit was used to test archived serum from 10 healthy dogs, with an average tryptase concentration of 10.8 ng/mL.

On the basis of case history and allergen testing, immunotherapy with bee venom was prescribed. VIT was conducted according to recommendations from the manufacturer (Table 1). No adverse effects were seen during five years of immunotherapy. After 1.5 years of VIT, the dog was naturally challenged with multiple bee stings, as observed by the owner, with no skin reactions or systemic signs of anaphylaxis.

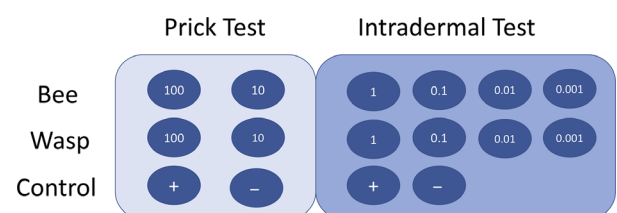


Figure 1. Skin prick test (SPT) and intradermal test (IDT) information. The numbers in ovals represent the tested allergen concentrations in $\mu\text{g/mL}$. The volume of allergens and controls used for testing was one drop for SPT and 0.02 mL for IDT. *Apis mellifera* and *Vespula* spp. allergens for SPT (Soluprick SQ, ALK; Volketswil, Switzerland) and IDT (Pharmalgen, ALK) were used. For positive controls, histamine hydrochloride 10 mg/mL (Soluprick, ALK) was used for the SPT and histamine phosphate 0.1 mg/mL (Artuvet Test Positive control, Artuvet Animal Health; Lelystad, the Netherlands) was used for IDT. For negative controls (Stallergenes Greer; Lenoir, NC, USA), buffered saline with either glycerol (for SPT) or 0.5% phenol (for IDT) was used.

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Table 1. Bee venom immunotherapy protocol of the patient used in the case

Time	Dose increase
Week 1	0.1 µg
Week 2	0.2 µg
Week 3	0.5 µg
Week 4	1.0 µg
Week 5	3.0 µg
Week 6	5.0 µg
Week 7	10 µg
Week 8	20 µg
Week 9	40 µg
Week 10	60 µg
Week 11	80 µg
Week 12	100 µg
Maintenance doses	
Months 4–12	100 µg aqueous allergen solution every four weeks
Years 1–2*	100 µg alum allergen solution every four weeks
Years 2–5*	100 µg alum allergen solution every six weeks

The lyophilized allergens for the aqueous solution were diluted with 0.5% phenol-buffered saline rather than human serum albumin as recommended by the manufacturer, to avoid a potential adverse immunological reaction.

*The dog was switched from aqueous allergens to an alum-based allergen solution, both from the same manufacturer (Alutard, ALK; Volketswil, Switzerland) using the same dosing regimen. This was the consequence of a change in market availability of the venom allergens after the first year of venom immunotherapy.

Discussion

In people, SPT with venom allergens is reported to be not only less sensitive than IDT, but also less likely to cause adverse events.⁴ Therefore, the dog described here underwent SPT first, and yielded negative results. Follow-up IDT showed sensitivity to bee venom and not wasp allergens. Venom-specific serum IgE testing disclosed positive results to bee and several species of wasp, indicating a possible cross-reactivity between these allergens as reported previously for people.³ However, cross-reactivity due to specific IgE antibodies directed against carbohydrate epitopes cannot be ruled out as the cause of this co-reactivity.⁴ Co-sensitization was considered to be unlikely owing to the animal's history. Therefore, because the bee venom IgE level was reactive class 5 (and other venom types were only classes 1 or 3), a diagnosis of bee venom hypersensitivity was made in light of concurrent IDT results and the case history.

Data on the safety and efficacy of VIT is very scarce for dogs.⁶ In this case, the induction period with gradually increasing doses over a three month period, followed by monthly 100 µg venom injections, was accomplished without any adverse effects. Apparently, VIT was successful in this dog as demonstrated by a lack of clinical response to natural re-exposure to bee stings. It is worth noting that IDT reactivity and serum IgE concentrations

reflect exposure to venom allergens and do not provide prognostic information.³ Therefore, these tests were not repeated in this case.

Human serum tryptase has been described as a predictor of anaphylaxis severity, with a cut-off for severe response of 11.4 ng/mL.³ The tryptase concentration in our case was well above the normal reference range. There are no published data on normal serum tryptase levels for dogs. Therefore, we used the same tryptase kit to test archived serum from healthy dogs, which had an average tryptase level lower than the case studied and also lower than the severity cut-off for human anaphylaxis. Therefore, we conclude that this dog's tryptase concentrations were most likely significantly elevated and remained elevated one year after the event.

In summary, this case provides reasonable evidence of venom-induced anaphylaxis and favourable response to VIT. These findings should be confirmed in larger randomised clinical trials. In addition, it would be interesting to evaluate serum tryptase concentrations as a possible risk factor for severe reactions in dogs with anaphylaxis, as it has been described in people.

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Résumé – Un chien castré de 1,5 ans a été présenté pour choc anaphylactique après avoir été piqué par une abeille. L'immunothérapie avec le venin d'abeille a été initié en fonction des commémoratifs, des tests cutanés et des tests sérologiques pour les immunoglobulines (Ig)E spécifiques d'allergènes. Le chien a été maintenu sous immunothérapie au venin pendant cinq ans et n'a montré aucun effet indésirable du traitement ou à la suite d'autres piqûres d'abeilles.

Resumen – Un perro macho castrado de 1,5 años se presentó en shock anafiláctico luego de sufrir una aparente picadura de abeja. La inmunoterapia con veneno de abeja se inició basándose en el historial, las pruebas cutáneas y las pruebas serológicas para la inmunoglobulina (Ig)E específica de alérgenos. El perro se mantuvo con inmunoterapia con veneno durante cinco años y no experimentó efectos adversos con la terapia o con repetidas picaduras de abeja.

Zusammenfassung – Ein 1,5 Jahre alter Rüde wurde nach einem vermeintlichen Bienenstich mit einem anaphylaktischen Schock vorgestellt. Eine Immuntherapie mit Bienengift wurde basierend auf der Anamnese, dem Hauttest und der Serologie auf Allergen-spezifisches Immunglobulin (Ig)E initiiert. Der Hund wurde fünf Jahre lang mit Bienengift Immuntherapie behandelt und zeigte keine Nebenwirkungen durch die Therapie oder durch wiederholte Bienenstiche.

要約 – 1.5歳の去勢雄犬は、明らかな蜂刺されに苦しんだ後、アナフィラキシーショックで紹介された。アレルギー特異的免疫グロブリン (Ig) Eの病歴、皮膚検査、血清学的検査に基づいて、蜂毒による免疫療法が開始された。犬は5年間毒免疫療法を受け続け、治療や繰り返しの蜂刺されによる悪影響はなかった。

摘要 – 一只1.5岁的雄性去势犬在遭受明显的蜜蜂蜇伤后出现过敏性休克。根据病史、皮肤试验和过敏原特异性免疫球蛋白(Ig)E的血清学检测,开始蜂毒免疫治疗。该犬接受毒液免疫治疗5年,未因治疗或反复蜂蜇伤而出现不良反应。

Resumo – Um cão macho castrado de 1 ano e meio de idade foi apresentado em choque anafilático após aparentemente ter sido picado por abelha. Iniciou-se a imunoterapia com veneno de abelha baseado na história clínica, testes alérgicos cutâneos e sorológicos para imunoglobulina (Ig)E alérgeno-específica. O cão foi mantido em imunoterapia com veneno por cinco anos e não apresentou nenhum efeito adverso do tratamento ou de novas picadas de abelha.