

Near-fatal anaphylaxis after Hymenoptera venom immunotherapy

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Since Food and Drug Administration licensure in 1979, Hymenoptera venom extracts have been qualified for commercial release on the basis of tests for sterility, moisture content, protein content, and hyaluronidase enzymatic activity. Considering the potential risk for anaphylaxis associated with testing and escalating doses to maintenance, it is remarkable that no deaths have been reported from Hymenoptera venom immunotherapy (VIT). This report describes a case of near-fatal anaphylaxis that occurred in a patient receiving VIT after switching manufacturer's venom extract.

CASE REPORT

A 55-year-old man was stung by a *Polistes* wasp, and he experienced syncope and documented hypoxemia. Our initial intradermal skin test identified only sensitivity to both honeybee venom (HBV; 9-mm induration and 10-mm erythema at 1.0 µg/mL) and *Polistes* wasp venom (PWV; 7-mm induration and 8-mm erythema at 0.1 µg/mL). Intradermal skin tests with the vespids venoms were negative. VIT was administered according to Bayer Corporation's protocol. The subject had been receiving monthly maintenance injections of Bayer HBV and PWV, each at 100 µg, for 13 months without incident. When the national shortage of Bayer PWV occurred, ALK PWV was substituted. Each lyophilized, single-dose vial of 100 µg was reconstituted with 1.2 mL of sterile human serum albumin containing 0.4% phenol and gently rocked to insure complete dissolution. Within minutes after injection of 100 µg of Bayer HBV and ALK PWV (both from new vials) the subject became lightheaded and experienced syncope. Quickly regaining consciousness, he remained hypotensive (74/—) despite being placed in a Trendelenburg position and receiving subcutaneous adrenaline twice, inhaled oxygen, and 1 L of normal saline intravenously. He was taken to an emergency department within 30 minutes of the reaction and was given 200 mg of intravenous hydrocortisone, 300 mg of intravenous Tagamet, and 25 mg of Benadryl by mouth before his blood pressure normalized.

METHODS AND RESULTS

Serum collected at 2 hours after the reaction was evaluated for serum tryptase and found to be elevated at 37.5

Abbreviations used

HBV:	Honeybee venom
PWV:	<i>Polistes</i> wasp venom
VIT:	Venom immunotherapy

µg/mL (normal range for adults, 5.6 to 13.5 µg/mL). HBV- and PWV-specific IgE and IgG antibodies were measured in the same serum specimen by RAST analysis in the Johns Hopkins University DACI Laboratory as previously reported.^{1,2} The IgE anti-HBV and PWV levels were 5 and 12 ng/mL, respectively. The results of repeat intradermal skin tests weeks after the reaction were positive for HBV (10.5-mm induration and 11-mm erythema at 1 µg/mL) and PWV (10-mm induration and 11-mm erythema at 0.1 µg/mL). The levels of IgG anti-HBV and PWV were 2.9 and 9.8 µg/mL, respectively. Levels of IgG anti-venom greater than 3.5 µg/mL have been associated with reduced risk for reaction on re-sting in individuals receiving VIT.¹

RAST inhibition was performed twice to determine the relative potency of the different venom extracts by using the subject's serum as the IgE anti-venom source according to previously described methods.² Previously administered venoms were maintained at 4°C for 6 weeks before testing the residual 0.2 mL. On the basis of the labeled protein content, all new extract vials should have contained 120 µg and were reconstituted with 1.2 mL of phenol saline to a final protein concentration of 100 µg/mL. Table I summarizes the relative potencies of the different venom preparations as measured by RAST inhibition.

DISCUSSION

In this case near-fatal anaphylaxis was totally unexpected with a patient who had achieved maintenance and in whom immunologic protection was considered to be near 100%. Initially we suspected that differences in the potency of the venom from the new company might have been causal. However, it appears from the relative potency data that the HBV from a single source may have contributed to the reaction rather than the new source of PWV. If so, it reminds us that in every case VIT, especially HBV at a maintenance level of 100 µg/mL, may not be protective.³⁻⁵

Why the patient did not experience anaphylaxis to previous HBV injections is unclear. Some may speculate that differences in the RAST-inhibition analyses might be explained by error in reconstitution of the unidose

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TABLE I. Relative venom potencies on the basis of RAST-inhibition analyses

Venom	Source	Status	Lot no	Venom content
				($\mu\text{g/mL}$),* mean $\pm$ 1 SD
PWV	ALK	Freshly reconstituted	01948989	100†
PWV	ALK	Administered at injection	01948989	37 $\pm$ 16
PWV	Bayer	Freshly reconstituted	5219301	85 $\pm$ 17
HBV	Bayer	Freshly reconstituted	5219501	100†
HBV	Bayer	Administered at injection	5219501	210 $\pm$ 25

*Two separate analyses were performed.

†Newly reconstituted venom used as reference and given the reported potency of 100 $\mu\text{g/mL}$.

vial. However, because 1 mL of venom was administered from a vial containing 120 μg of venom and 0.2 mL was left for testing, this is not the explanation. Likewise, it is possible but unlikely that subsequent changes in allergen concentration could have occurred secondary to adherence to the vial itself after reconstitution. Of greatest relevance in this case, and of broader concern, is the issue of extract standardization. The Food and Drug Administration defines acceptable ranges for levels of hyaluronidase (HBV, 40 to 110 U/100 mL; PWV, 45 to

165 U/100 mL) in Hymenoptera venom extracts. Individual manufacturers also use phospholipase measurements (eg, phospholipase A2 in HBV 150 to 400 U/mg and phospholipase A1/2 in PWV 10 to 300 U/mg) as a secondary reference parameter. The actual potency range, as well as the intralot and interlot variation of commercial venom products, should be clearly noted for review by those administering and receiving extracts as an integral part of VIT.

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