A Clinical Study of 245 Japanese Patients with Bee Sting and Two Cases Administered Rush Hymenoptera Venom Immunotherapy

Yayoi Nagai,1 Naoko Oyama,1 Tomoyasu Hattori 1 Osamu Ishikawa 1 and Masaaki Tamura 2

Background and Aims: We report the results of clinical study into patients with bee sting, and two cases administered rapid venom immunotherapy. Materials and Methods: A total of 245 patients with insect sting received medical treatment at Tone Central Hospital, Japan, between April 2001 and March 2003. Results: Forty-eight patients experienced allergic symptoms of varying severity. Ten patients displayed grade IV anaphylaxis, no obvious correlations were identified between symptom severity and specific IgE-RAST values in response to insect venom. Rapid venom immunotherapy using long-legged wasp hymenoptera venom extract was administered to 2 patients who displayed symptoms of shock. Maintenance dose (100 µg/ml) was reached for 7 days without any adverse reactions. One of the 2 patients subsequently suffered bee sting again, but developed no symptoms of shock. Conclusion: venom immunotherapy is worth trying for patients displaying symptoms of shock following insect envenomation. (Kitakanto Med J 2004; 54: 297-300)

Key Words: stinging insect allergy, anaphylaxis, rapid venom immunotherapy

Introduction

In Japan, 70% of insect stings are caused by long-legged wasps, 20% by yellow jackets, and 10% by honey bees. Frequency of systemic symptoms elicited by insect stings is reportedly 1 ~ 3%,1 and 30-40 patients die from insect envenomation every year in Japan. Over the last 2 years, we have encountered 245 patients with bee stings, with 48 of these displaying allergies to insect stings. We report herein the results of a clinical study into patients with bee sting, and describe the results of rapid venom immunotherapy administered to 2 patients.

Clinical study of 245 patients with bee sting

A total of 245 Japanese patients with insect sting (139 males, 106 females) received medical treatment at Tone Central Hospital in the 2 years from April 2001 to March 2003. Patients presented between April and December, with numbers peaking in August (n = 78) (Fig. 1). Age range of patients was 5-85 years: 35 patients (14.3%) were ≤ 9 years old; 57 patients (23.3%) were 60 to 69 years old; and 47 patients (19.3%) were 70 to 79 years old (Fig. 2).

The most frequently stung sites were exposed areas, comprising: upper arms and hands (n = 122, 49.8%); head-neck region (n = 58, 23.6%); lower legs (n = 42, 17.5%); and trunk (n = 23, 9.4%). In 195 patients who displayed only local symptoms such as swelling, redness and pain, symptoms disappeared within 3 days with the administration of antihistamines and topical corticosteroids. Another 48 patients (37 males, 11 females) exhibited systemic allergic reactions such as urticaria, nausea, dyspnea and shock.

Clinical study of 48 patients with systemic allergy to hymenoptera venom

Mean age of the 48 patients with systemic allergic reaction was 48.8 years (range, 9-82 years) (Fig. 3). According to the classification of anaphylaxis severity described by Mülller (Müller's grade),2 24 patients were classified as grade I, 7 patients as grade II, 7

1 Department of Dermatology, Gunma University Graduate School of Medicine, Maebashi, Japan 2 Division of Dermatology, Tone Central Hospital, Numata, Japan Received : August 6, 2004 Address : YAYOI NAGAI Department of Dermatology, Gunma University Graduate School of Medicine, Showamachi, 3-39-15, Maebashi-shi, 371-8511, Japan
Fig. 1 Month distribution of 245 patients with bee sting

Fig. 2 Age distribution of 245 patients with bee sting

Fig. 3 Age distribution of 48 patients with systemic allergic reactions
patients as grade III and 10 patients as grade IV (Table 1). History of insect sting revealed the current presentation as first sting in 11 patients, second sting in 10 patients, third sting in 8 patients and fourth sting or more in 19 patients.

Specific IgE-RAST values to insect venoms were measured in 26 of these 48 patients. No correlation was evident between severity of systemic allergic reaction and IgE values.

Rapid venom immunotherapy

Rapid venom immunotherapy was administered to 2 patients who strongly requested preventive therapy. Rapid venom immunotherapy was conducted as proposed by Yukawa et al.3 Briefly, immunotherapy was initiated by subcutaneous injection of long-legged wasp hymenoptera venom extract (HVE) diluted 10-fold from minimum skin test positive concentration (0.1 ml of 0.1 µg/ml HVE) on day 1. This dose was increased 2-fold at 2-h intervals for a total of 4 subcutaneous injections per day. In this way, dose was increased up to the maintenance dose of 1.0 ml of 100 µg/ml HVE on day 7. This maintenance dose was estimated as double that typically resulting from hymenoptera envenomation.

Venom immunotherapy resulted in fist-sized erythema at the injection site on day 5 in both patients. However, no general symptoms developed. As of the time of writing, both patients have received a maintenance injection, 1 ml of Wasp-HVE, once a month on an outpatient basis. No obvious symptoms have developed other than localized erythema at the injection site. One of the patients experienced multiple insect stings after 3 courses of maintenance injections, but developed no systemic allergic reactions.

Discussion

Hymenoptera venom comprises amines, enzymes and low molecular weight peptides, although exact composition varies from species to species. Enzymes such as phospholipase and hyaluronidase and low molecular weight peptides such as antigen 5 appear to represent the cause of allergic reactions. Hamilton et al. reported that cross-reactions between yellow jacket and long-legged wasp venom are common, and that cross reactivity between species is highest for hyaluronidase, antigen 5 and phospholipase, in descending order.5

In bee stings, the immediate allergic reaction is clinically the most dangerous, and anaphylaxia occasionally leads to death. Empirical treatments encompass administration of antihistamines, corticosteroid hormone preparations, bronchodilators, vasopressors and anticonvulsants. In contrast, venom immunotherapy represents a desensitization treatment for patients with stinging bee allergy. Rapid venom immunotherapy is indicated for patients with several systemic symptoms. If the kind of bee that stung the patient is known, HVE of the identified bee should be selected, unless the bee is known but cannot be specified by IgE RAST or skin test, when either yellow jacket or long-legged wasp HVE could be indicated.5 If sting by a honey bee cannot be excluded, HVE of honey bee should be used.

Venom immunotherapy can be roughly divided into 3 types: slow; stepwise; and rush regimens, according to differences in administration intervals. Although all types of venom immunotherapy are equally effective, rush regimen displays greater immune responses and fewer adverse reactions than slow regimen.6 Furthermore, Brehler et al. reported that ultra-rush immunotherapy, in which maintenance dose is reached in 2 days, is safer than conventional methods.7

Systemic allergic reactions during venom immunotherapy pose several problems. Sturm et al. reported frequency of systemic allergic reaction as 0 ~60%.8 They noted that the wide variation among reports might be due to the different severity index of adverse effects, use of antihistamines prior to treatment, or method of administration. With the 4-day rush regimen, frequency of systemic symptoms is about 6.9%, lower than described in previous reports.8 In our patients, no systemic reactions developed during rapid venom immunotherapy, and local reactions at the injection site gradually disappeared. With this method, maintenance treatment for 5 years is recommended,9 as risk of systemic reactions remains at 5 ~15% for 5–10 years after cessation of venom immunotherapy. Unlike the progressive decline in immunological markers with skin test and IgE levels, risk of systemic allergic reactions never decreases.10 To prospectively assess risk of recurrent systemic reaction, long-term follow-up studies are required.

The possible mechanisms of venom immunotherapy include declines in 1) production of specific IgE antibodies; 2) activity of liberating histamines from mast cells; 3) T-cell proliferation activity against specific antigen; 4) production of cytokines from antigen-specific Th1 or Th10 cells; or 5) conversion
from Th2 cells to Th10 or Th1 cells. In addition, therapy may induce tolerance depending not only on specific action of venom antigens on T cells, but also on a secondary non-specific action of monocytes.

Venom immunotherapy is covered by health insurance in various countries around the world, but not in Japan. If the treatment were to be covered in Japan, problems such as troublesome import procedures and patient expenses would be resolved. Conversely, therapy involves a risk of anaphylaxis due to injection of hymenoptera venom. Fortunately, self-administered epinephrine became available in Japan in 2003. Establishment of standard protocols for treating stinging bee allergy is desirable.

References