

Prolonged maintenance interval in Hymenoptera venom immunotherapy

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To decrease the cost, inconvenience, and potential side effects of venom immunotherapy we tested whether the interval between the maintenance injections can be increased. In 30 patients who had been given the standard therapy regimen and who had been sting-challenged after 1 and 2 yr of monthly maintenance injections the maintenance interval was increased from 4 to 6 wk. IgG anti-yellow jacket venom antibodies did not change over the next 9 mo. The incidence of local reactions to venom injections did not increase, and there were no systemic reactions during therapy. After 6 to 9 mo 29 of the 30 patients were sting-challenged with one possible reaction. The success rate, 97%, is the same as that observed with monthly maintenance injections. We conclude that the 6-wk maintenance interval is effective in both clinical and immunologic terms after a period of monthly maintenance therapy.

Anaphylactic sensitivity to Hymenoptera insect stings may result in fatal reactions in susceptible individuals and is an important cause of morbidity in a significant proportion of the population. Immunotherapy with Hymenoptera venoms has been demonstrated to specifically protect affected individuals from systemic sting reactions.¹⁻³ This protection is complete in 97% of those given the recommended dose and regimen; protection is partial in the remaining 3%.⁴⁻⁶ In our early clinical trials a maintenance dose of 100 μ g and a maintenance interval of 4 wk were empirically selected² and have proved effective both clinically and immunologically.¹⁻⁶

Obvious goals in venom immunotherapy are to treat with the minimum amount of venom protein and to require as few physician visits as possible to improve long-term compliance, to reduce the financial

burden, and to minimize the possibility of adverse consequences as a result of large cumulative venom doses. One approach to this problem has proved unsuccessful: reduction of the maintenance dose to 50 μ g is associated with reduced clinical and immunologic efficacy.⁶ We report here the achievement of the above goals by prolongation of the interval between maintenance injections.

MATERIALS AND METHODS

Thirty patients were randomly selected from those continuing treatment among an original group of 81 patients who had been receiving the recommended venom doses and regimen. These 30 patients were representative of our large population of sting-allergic patients with respect to clinical history, previous whole-body extract therapy, age, sex, and skin test sensitivity.⁶ All had reported generalized cutaneous, vascular, or respiratory anaphylactic symptoms following a sting prior to treatment; 80% had a history of life-threatening reactions, defined as significant respiratory distress or hypotension. As judged by previously described criteria^{6, 7} all had positive intradermal skin test results to one or more venoms. All 30 patients had been successfully challenged by an in-hospital sting annually during 2 yr of monthly maintenance venom immunotherapy. The immunization schedule of these 30 patients was then changed so that they received their 100- μ g maintenance doses at 6-wk intervals. After 6 to 9 mo of such treatment they were challenged by an in-hospital sting. Informed consent regarding the potential benefits and risks of the study regimen and of optional supervised in-hospital challenge stings was obtained in accordance with the Johns Hopkins Joint Committee on Clinical Investigation.

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Publication No. 427 from O'Neill Laboratories, The Good Samaritan Hospital.

Supported by Grant AI 08270 from the National Institute of Allergy and Infectious Diseases, the National Institutes of Health.

Received for publication Dec. 15, 1980.

Accepted for publication March 16, 1981.

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*Supported by a fellowship grant from the Medical Research Council of Canada.

All venoms used for diagnosis and treatment were provided by Pharmacia Diagnostics (Piscataway, N.J.) in lyophilized form; they were reconstituted to 100- μ g/ml stock solutions and serially diluted to 10^{-4} μ g/ml in Pharmacia venom diluent. Yellow jacket (YJ), yellow hornet, and white-faced hornet venoms were used individually and where indicated were combined for therapy into a "mixed vespid" solution. Twenty-five patients received yellow jacket or mixed vespid venoms, and two of these also received honey bee venom; five patients received only honey bee venom.

In each patient multiple determinations of venom-specific serum IgG antibodies were performed as described previously.⁸ All had toxicity studies including basic hematologic, biochemical, and urine tests, which showed no changes during the study.

Challenge stings were performed in-hospital with an established intravenous line and emergency resuscitation personnel and equipment standing by. Patients were challenged with stings of honey bees, yellow jackets, or both according to their sensitivity and treatment regimen.

Geometric mean antivenom IgG antibody levels were compared at various time intervals using the rank sum test to derive the two-tailed *p* value from the value of *z*.

RESULTS

One anticipated problem of increasing the interval between maintenance injections was the possibility of adverse reactions. This did not occur. There were no systemic reactions, and the incidence of large local reactions in this group (two reactions per 100 injections) was not greater than that observed with monthly maintenance injections (six reactions per 100 injections).⁴

Twenty-nine patients were sting challenged after 6 to 9 mo of maintenance therapy at 6-wk intervals, 22 with a yellow jacket, five with a honey bee, and two with both insects. No systemic symptoms occurred in 28 patients; one had an unusual reaction with marked anxiety and generalized trembling but without cutaneous, vascular, or respiratory manifestations. This reaction subsided with reassurance after 15 min. One patient was not available for a sting challenge. The 97% efficacy of the 6-wk maintenance interval is compared with that of a 4-wk maintenance interval (Table I). Fifty-six patients (including the 30 in this study) were stung after 1 yr of monthly injections. Forty-two patients (including the 30 study subjects) were stung after 2 yr of monthly therapy. One systemic reaction occurred in each group (98% success). Thus the 6-wk maintenance interval was associated with no reduction in the extent of clinical protection. The 97% success rate is also similar to that seen in our other studies of venom immunotherapy.^{1, 4-6}

The individual yellow jacket venom-specific IgG antibody (anti-YJ-IgG) titers of the 25 patients treated

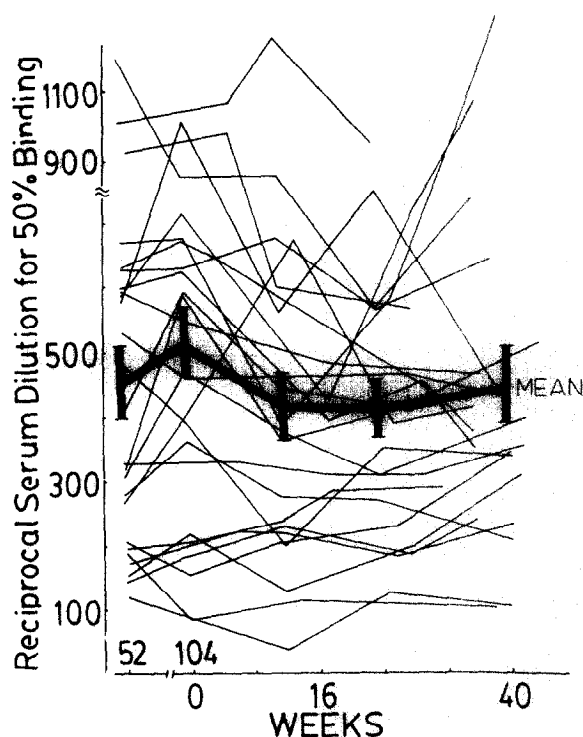


FIG. 1. Yellow jacket venom-specific IgG antibody titers (individual patients and group geometric mean $\pm$ SEM) after 1 yr (52 wk) and 2 yr (104 wk) of monthly maintenance therapy and during the subsequent 40-wk maintenance at 6-wk intervals. IgG titers are expressed as the reciprocal of the serum dilution required for 50% binding.

TABLE I. Clinical efficacy of maintenance venom immunotherapy assessed by challenge sting

Maintenance interval	4 Weeks	4 Weeks	6 Weeks
Duration (wk)	52	104	25 to 36
Number of patients stung	56	42	29
Reactions	1	1	1
Percent efficacy	98	98	97

with yellow jacket venom after 1 and 2 yr (52 and 104 wk) of venom immunotherapy at 4-wk intervals and during the subsequent 6-wk interval study period lasting up to 40 wk is shown in Fig. 1. There was considerable individual variation prior to as well as during the study, but the geometric mean antibody level of the entire group did not change significantly during 40 wk of treatment. The apparent decrease in the mean IgG level in the first 12 wk of the study was not statistically significant ($p > 0.15$). The patient who had the only possible challenge sting-related symptoms had anti-YJ-IgG titers in the highest range.

DISCUSSION

Traditional regimens of allergen immunotherapy have advised weekly injections in the initial induction

phase, followed by maintenance doses repeated at intervals of 2 or 3 wk.⁹ Clinical efficacy has been associated with increased titers of circulating allergen-specific IgG "blocking" antibodies, although the association has not been quantitative.^{10, 11} The rate of decrease of circulating blocking antibody titers¹² suggests that injections at longer intervals could maintain a satisfactory level. In fact, a 6-wk maintenance interval in ragweed immunotherapy has been demonstrated to maintain both clinical improvement and specific IgG levels.¹³ In that case, however, the investigators employed increasing treatment doses during the course of the study. The aim of this trial of venom immunotherapy was to reduce the cumulative antigen load so as to lessen the risk of potential long-term adverse effects, the cost of therapy, and the inconvenience of frequent visits to the physician. Hence the interval between visits was lengthened and the dose held constant at 100 μ g of each venom. From 6 to 9 mo of this treatment was considered to be sufficient to reveal any reduction in clinical or immunologic effectiveness, because blocking antibody levels fall significantly in 3 to 6 mo in the absence of stings or venom injections.¹²

Clinical efficacy remained unchanged at the 97% level previously demonstrated after 4 mo and 1 and 2 yr of therapy. The patients served as their own controls, because they were part of the larger group challenged after 1 and 2 yr of monthly therapy. Many clinicians express concern that longer intervals between allergen injections might be associated with an increased frequency of adverse reactions. This was not observed in the course of this study. No systemic reactions occurred. As we have previously observed with maintenance doses,⁴ large local reactions to injections rarely occurred.

An unexpected observation was the rather wide variation of the venom-specific IgG antibody titer in individual patients (Fig. 1). This occurred prior to as well as during the study. However, the geometric mean antibody titer for the group remained essentially unchanged throughout. We have previously observed that, although the absolute titer of venom-specific IgG antibody has no clear-cut prognostic significance for the individual patient, the mean level of a group of patients does reflect the extent of protection in that group.¹⁻⁶ The only patient who had a challenge sting-associated reaction had anti-YJ-IgG titers well above the group mean. This may support the clinical observation that her reaction was more hysterical than anaphylactic; she has had similar episodes unrelated to insect stings.

The possibility was considered that the challenge sting might have an immunostimulatory effect that

would reverse and obscure any downward trend in the anti-YJ-IgG titer. In fact the IgG antibody level decreased after challenge sting in many patients and remained unchanged in others, compared with the level on the date of challenge sting (shown for each patient in Fig. 1 between weeks 24 and 36). Of those patients who did have an increase of IgG after the sting, some already had increasing levels prior to the challenge sting. Thus the absence of a decrease in IgG antibody titer after 40 wk cannot be attributed to a stimulatory effect of the challenge sting.

We conclude that venom immunotherapy retains full clinical and immunologic efficacy when the maintenance interval is increased to 6 wk after a period of successful 4-wk maintenance treatment. The optimal period of monthly treatment prior to prolongation of the maintenance interval is under investigation, as is the possibility of still longer (8 wk) intervals between injections.

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