

Immediate adverse reactions to immunotherapy in allergy

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We report our experience of adverse reactions to immunotherapy (IT) in patients with insect venom allergy and inhalant respiratory allergy. Adverse reactions included large local reactions, generalized cutaneous reactions or systemic reactions. Among 87 patients treated for venom allergy, 43% had adverse reactions during the course of IT, averaging 2.5 reactions per patient and per course of IT. Nine had systemic reactions, of which 7 required adrenaline administration. Among 52 patients treated with inhalant allergen extracts, 40% had adverse reactions averaging 3 reactions per patient per course of treatment. Ten patients had systemic reactions but only 2 required adrenaline administration. There was no difference between the rate of adverse reactions in the venom and the inhalant treatment groups. IT has an inherent risk which has to be weighed against its benefits.

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Immunotherapy (IT) (hyposensitization or desensitization) was introduced in 1911 (8). IT has gained acceptance since its efficacy has been clearly established in allergic rhinoconjunctivitis (20, 22). Its efficacy in allergic asthma has also been established although it is probably less remarkable (2, 7, 16). IT with pure bee venom and yellow jacket venom reduces the sting reaction rate significantly (10). It is assumed that immunological changes are responsible for the efficacy of IT. However, the mechanism of its effects is not clearly understood (24).

The aim of IT is to administer a high maintenance dose by progressively increasing the allergen concentration. IT is not devoid of side effects, systemic allergic reactions and fatalities have been reported since 1929 (11). The British Committee on Safety of Medicines report described 26 fatalities since 1957 (3) and the Committee on Allergen Standardization of the American Academy of Allergy and Immunology reported 40 fatalities since 1945 (14).

We decided to review our experience of IT in venom-allergic and inhalant-allergic patients.

Patients and methods

Patients were divided into 2 groups: Group I – patients allergic to insect venom, Group II – patients with respiratory allergy. The demographics of the 2 groups are described in Table 1.

Group I. Eighty-seven patients were started on venom IT between 1982 and 1988. Seventy were male and

Table 1. Characteristics of the two groups. Group I: Patients treated for insect venom; Group II: Patients treated for inhalant respiratory allergy

	No. patients	M	F	Mean age	Bee venom	Wasp venom	Bee Wasp
Group I	87	70	17	26	84 one extract	13 2 extracts	10 ≤3 extracts
Group II	52	32	20	35	26	13	13

17 female, mean age 26 years (range 8–66 years), mean duration of treatment was 36.7 months (range 3–66 months). All had a documented systemic anaphylactic reaction following insect sting, consisting of one or more of the following symptoms: generalized urticaria, angioedema, breathlessness, hoarseness, nausea, vomiting, abdominal pain, dizziness, hypotension or collapse. All the patients also had a positive immediate skin test to pure venom as found by prick test or by intradermal test in concentrations up to 1 µg/ml.

IT protocol for venom allergy was started with an injection of 0.001 µg/ml and was increased weekly until a maintenance dose of 100 µg/ml was reached after about 3 months. When a reaction occurred, the dose was cut back by 25 to 50% and was then cautiously increased. If no adverse reaction occurred, the patients achieved the maintenance dose after 20 injections, usually within 3 months. The time interval between single injections was then gradually increased to 6 weeks.

Eighty-four patients were treated with honey bee venom and 13 with wasp venom (Table 1).

Group II. Fifty-two patients were treated with various inhalant extracts between 1985 and 1988. Thirty-two were male and 20 female; mean age was 35 years (range 7–68 years) and the mean duration of treatment was 15 months (range 5–30 months). All patients had seasonal or perennial allergic rhinitis, 10 also had allergic asthma. Patients were given IT when other modes of treatment were not sufficiently effective.

IT was started with 0.05 ml of 1:10000, w/v, of the extracts (Hollister-Stier, Spokane, Washington, USA). The administered concentration and volume were gradually increased until a maintenance dose of 0.5 cc of 1:100 w/v (1000 times the initial dose) was reached. Twenty-six patients received one extract. Thirteen patients received 2 extracts and 13 patients received injections containing 3 or more different extracts. Extract mixtures were prepared for each patient in one to 3 vials containing a mixture of seasonally related allergens. The patients received each allergen mixture in a different syringe. Thirty-four patients were treated with house dust mite (*Dermatophagoides farinae*) extracts, 25 with grass extracts (Bermuda grass – 15, orchard grass – 11, perennial rye grass – 10). Olive pollen extract was given to 11 patients, pigweed extract to 4, mugwort pollen extract to 4 and 4 received various mold extracts.

All patients were observed for 30 min following treatment and reported to the nurse before leaving the clinic. Facilities for cardiopulmonary resuscitation were at our immediate disposal.

Statistical analysis

The χ^2 test was applied to evaluate the statistical difference between the side effects occurring in the 2 groups. A p value ≤ 0.05 was regarded as significant.

Results

Efficacy

Group I. Thirty-five patients were stung by the insect they were known to be allergic to, 75 times. This was corroborated by the patients' evidence. Four had systemic reactions, 3 while on maintenance dose. Two patients had diffuse cutaneous reactions and the other 2 had transient shortness of breath.

Group II. The effects of IT were reassessed after 12 months and, if considered ineffective by the patient or by the physician, further treatment was discontinued. No objective criteria could be used.

Adverse effects

Adverse reactions to IT were divided into 3 types:

1. Large local reaction only, at the site of injection with a diameter of swelling of ≥ 5 cm.

2. Generalized skin reaction including feeling of warmth, erythematous rash, urticaria and swollen lips or eyelids.

3. Systemic reaction, as described above for the indications to start IT in insect sting allergy.

Table 2 shows the adverse effects in the 2 groups.

Group I. Thirty-seven patients had 93 adverse reactions to the venom IT. Eighteen patients had a total of 25 large local reactions and 15 patients had 37 generalized cutaneous reactions. Nine patients had 29 systemic reactions, 13 being severe enough to require adrenaline administration. Three patients received subcutaneous adrenaline 1:1000 0.3–0.5 ml during one episode. Three more patients had 2 such episodes and one patient received adrenaline for 4 different episodes of systemic reaction.

Group II. Twenty-one patients had a total of 61 adverse reactions to the inhalant IT. Eight patients had 18 large local reactions. Four patients had one episode each of diffuse cutaneous reactions and 10 had 39 episodes of systemic reactions, most of them presented as an asthmatic reaction. Only 2 needed adrenaline to alleviate their symptoms – one of them only once and the other 6 times. Four of 10 patients who had systemic reactions were asthmatics.

None of the patients in the 2 groups required a second dose of adrenaline or intravenous fluid, and there was no need for hospitalization.

There was no statistically significant difference between the rate of total adverse reactions between the 2 groups. There was also no difference between the 2 groups when diffuse cutaneous and systemic reactions only were compared.

Table 2. Distribution of the types of reactions to immunotherapy within the two groups of patients

	Large local	Generalized cutaneous	Systemic	Total	Adrenaline
Group I					
No. patients	18	15	9	37	7
No. reactions	25	37	29	93	13
Group II					
No. patients	7	4	10	21	2
No. reactions	18	4	39	61	7

Discussion

Immunotherapy is a life-saving procedure for insect sting anaphylaxis and a valuable adjunct to the treatment of respiratory allergy in cases where avoidance of the offending allergens and administration of medications are insufficient. The efficacy of IT is dependent on adequate dose administration since low-dose treatment was found to be ineffective (17). Since the procedure involves administration of an increasing amount of the allergen, immediate hypersensitivity reactions occur even when a cautious protocol of administration is employed.

The IT for insect venom allergy was found to be beneficial in Group I since only 5% (4/75) of those who were resting had systemic reactions compared with 50%, which represents the rate in untreated venom-sensitive patients (5, 10).

Forty-three percent (37/87) of the patients treated with venom had an adverse reaction during the course of treatment but only 10% (9/87) had systemic reactions. The percent of adverse reactions was similar among patients treated with inhaled extracts - 40% (21/52), 19% (10/52) of them had systemic reactions. The similarity in the frequency of immediate reactions to venom allergens compared with inhaled allergen demonstrates that there is no greater risk with venom therapy than with inhaled allergen IT. Four of the 10 asthmatic patients had systemic reactions compared with 6 in the 46 patients with allergic rhinitis only. This is consistent with an increased incidence of systemic reactions, shown by others (3, 14), in asthmatics. All the systemic reactions were readily controlled and none of the patients required further treatment. Most reactions were controlled with no treatment or by oral antihistamines alone. It is noteworthy that patients had a tendency to recurrent reactions, usually of the same type, during the course of IT.

This report presents a retrospective experience with immunotherapy in a clinical set-up. Most other publications have dealt with side effects of immunotherapy during a controlled study. The rate of reactions in our experience is similar to that found in most other studies. The reaction rate for grass IT is between 5 and 44% (1, 19, 21) and with mite IT between 7 and 50% (6, 12, 13, 26). Venom IT systemic reactions are described in 5 to 40% of the treated patients (10, 25). Reaction rates may be as high as 80 to 100% using mold allergens (4), ragweed allergens (15) and animal dander extracts (23). It appears that the more sensitive the patients are and the higher the dose aimed for, the higher the rate of adverse reactions. If one is determined to get a good clinical response a high concentration of maintenance dose should be achieved and this rate of reaction cannot be avoided. Novel approaches to

device modified allergens that would be less allergenic and yet retain their immunogenicity, such as polymerized allergens (9) or allergoids (2), should be pursued.

The large majority of life-threatening reactions and most fatalities occurred within 30 min of the injections. Thirty minutes is the minimal recommended period to observe the patients after administering the shot (18). All necessary measures should be taken to reduce the risk to the point where deaths will not occur and make this well-established treatment available to all patients who can benefit by desensitization. However, currently adverse effects might occur even if all precautions are taken.

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