

Rush venom immunotherapy: a 3-day programme for hymenoptera sting allergy

P. NATAF, M. T. GUINNEPAIN and D. HERMAN

*Policlinique Médicale et Allergologie, Hôpital Lariboisière, 2 rue Ambroise Paré,
75475 Paris Cedex 10, France*

(Received 25 April 1983; accepted for publication 21 June 1983)

Summary

In a series of 102 patients consulting for allergic reactions following hymenoptera sting, fifty-two of them, who had experienced one or more severe systemic adverse reactions were selected for rush immunotherapy.

The method employed made it possible to attain the maintenance dose of 100 µg of venom in 3 days. Patient tolerance was excellent, no serious side-effect was observed; immunotherapy never had to be stopped. Clinical effectiveness seems to be very satisfactory, since no abnormal reaction was reported in seven patients who later were spontaneously stung, and in fourteen patients who received an induced insect sting. The level of IgG antivenom antibodies rose regularly from the first month onwards to remain at a stable level.

Because of its safety and effectiveness, it appears that this method should be recommended for immunotherapy in patients who are allergic to hymenoptera stings.

Introduction

The diagnosis and treatment of allergic reactions caused by hymenoptera stings has been greatly changed by the use of insect venoms. Immunotherapy is now effective and reliable (Valentine & Sobotka, 1979). At the same time, less restrictive methods have been sought. Shorter methods of administration have replaced those of traditional immunotherapy which required several months, thereby making it possible at present to attain the maintenance dose in a few weeks (Golden *et al.*, 1980). Weekly injections have been replaced by single or multiple daily injections (Muller *et al.*, 1979; Yunginger *et al.*, 1979).

We wish to present here the results of a technique which makes it possible to attain a safe, effective, maintenance dose in 3 days.

Materials and methods

Patients

This study was made on fifty-two patients chosen from 102 cases with reactions caused by hymenoptera stings. Only those patients who experienced a severe, systemic reaction with cardiovascular collapse were included. The allergic nature of the reactions was confirmed by a positive intradermal skin test using venom taken from the relevant insect, and the presence of specific IgE antibodies as detected by RAST.

There were twenty-nine female and twenty-three male patients, ranging from 15 to 71 years of age (average age: 40.57 years); the allergic reactions had been caused by a bee sting in nine cases, and by a wasp sting in forty-three cases.

Venoms

The same venom extracts were used for skin testing, for determining levels of specific IgE antibodies, anti-venom IgG antibodies and for immunotherapy: Albay purified lyophilized bee venom (*Apis mellifera*) extracts from Dome Hollister Stier Laboratories, and wasp extracts (*Vespa* sp.). Albay pure venom extract contains lyophilized insect venom containing 20% (w/v) mannitol. Diluent for reconstitution and dilution of extract: Albay human serum albumin containing sodium chloride 0.9% phenol 0.4%, normal serum albumin (human) 0.03% sterile water.

Immunologic studies

Specific IgE antibodies. Detection of specific IgE antibodies was performed using the RAST technique (Institut Pasteur, Paris).

IgG. A solid phase radioimmunoassay was developed to measure IgG antibodies to bee and common wasp venom.

In brief, cyanogen-bromide-activated paper discs coupled with bee venom or common wasp venom were incubated with patients' sera. After several washes, discs were incubated with ^{125}I staphylococcal protein A which binds avidly to more than 93% of human IgG. After a new incubation time, the unbound ^{125}I protein A was removed by several washes. The bound ^{125}I protein A was subsequently counted in a gamma well counter and net binding was expressed as the percentage of immunoreactive cpm added.

Immunotherapy

This was undertaken using the venoms corresponding to the patient's sensitivity according to the following protocol (Tables 1 and 2). The patients were confined to hospital for 3 days. Concentrations of venom extract were used ranging from 0.001 to 100 $\mu\text{g}/\text{ml}$; for each of them, increasing concentrations were: 0.1–0.2–0.4–0.8 ml. On the first day, increasing dosages were injected at 0.5-hr intervals from 10.00 to 16.00 h then hourly until 23.00 h. The first dosage was 0.0001 μg venom (0.10 ml of the 0.001 μg concentration). On the 1st day, the last dosage injected was 8 μg . On the 2nd day, the sequence was continued but the frequency of injections decreased. Only six injections were administered, the last one containing 40 μg venom. On the 3rd day, two injections of 50 μg were administered at 12-hr intervals. The maintenance dose of 100 μg was then injected in a single dosage on the 4th, 6th, 9th, 16 and 30th days, and then regularly once a month (for the first twelve patients the maintenance dose was 200 μg).

Table 1. Immunotherapy doses (day 1)

Time	Dose (μg)
10.00	0.0001
10.30	0.0002
11.00	0.0004
11.30	0.0008
12.00	0.001
12.30	0.002
13.00	0.004
13.30	0.008
14.00	0.01
14.30	0.02
15.00	0.04
15.30	0.08
16.00	0.1
17.00	0.2
18.00	0.4
19.00	0.8
20.00	1.0
21.00	2.0
22.00	4.0
23.00	8.0

Table 2. Immunotherapy doses after day 1

Time	Dose (μg)
Day 2	
01.00	10
03.00	10
06.00	20
10.00	20
15.00	40
21.00	40
Day 3	
08.00	50
16.00	50
Day 4	100
Day 6	100
Day 9	100
Day 16	100
Day 30	100
Every month	100

Results

Patient tolerance

No serious side-effect occurred during the first 3-day period involving rapidly increasing dosages. Only localized reactions confined to the points of injection were observed presenting as erythematous papules variable in size, sometimes rather large,

as much as 5–10 cm. In only one case, the occurrence of zones of urticaria distant from the point of injection, on the second day, made it necessary to reduce the frequency of the injections, to attain the maintenance dose in 5 days instead of 3. No systemic reactions were ever observed. There was never any increase in heart rate, nor a decrease in blood pressure, or any digestive or respiratory complications.

Good patient tolerance during the maintenance period of immunotherapy was evaluated during a 6–18-month follow-up (Table 3). Once, a systemic reaction occurred 10 min after an injection, presenting as a generalized urticaria, with a modest fall of blood pressure, from 110 to 90 mmHg. This reaction, which quickly regressed after injection of corticosteroids, did not recur during the following series of injections. A moderate urticarial eruption was observed on two occasions, pruritis four times, diarrhoea twice and delayed-onset localized reactions four times. Fatigue in the evening following the injection was the most frequent finding. All of these reactions were temporary, decreasing in intensity and disappearing at the time of later injections. Immunotherapy never had to be stopped.

Efficacy

This method may be judged as very effective. Seven patients were spontaneously stung again by the insect which had caused an anaphylactic reaction (bee: once; wasp: six times). They only experienced a moderate, localized reaction. An experimentally induced sting test was conducted with fourteen patients (wasp: seven times; bee: seven times). No systemic reaction was observed.

Changes in IgG antibodies during venom therapy

The increase in IgG blocking antibodies following bee venom immunotherapy of seven patients was followed up for 8 months. The average of the observed variations shows a rapid increase of IgG antibodies during the first 2 months of therapy (Fig. 1). Their level remained stable till the 8th month.

A similar brisk increase is obtained after hyposensitization by wasp venom of twenty-three patients (Fig. 2).

Discussion

We have presented a technique of rush immunotherapy making it possible to attain the maintenance dose of 100 μ g in 3 days. The fifty-two patients tolerated the period of rapidly increasing dosages very well. Localized reactions at the point of injection were sometimes serious but in only one case, the onset of urticaria made it necessary to decrease the dosage sequence. During later injections, the most frequent side-effect was fatigue, which was often pronounced, during the evening following an injection. The other adverse reactions were negligible, except in one case where a generalized urticaria

Table 3. Patient tolerance during the maintenance period of immunotherapy

Fatigue	Pruritis	Urticaria	Diarrhoea	Generalized reaction	Delayed- onset reactions
27	4	2	2	1	4

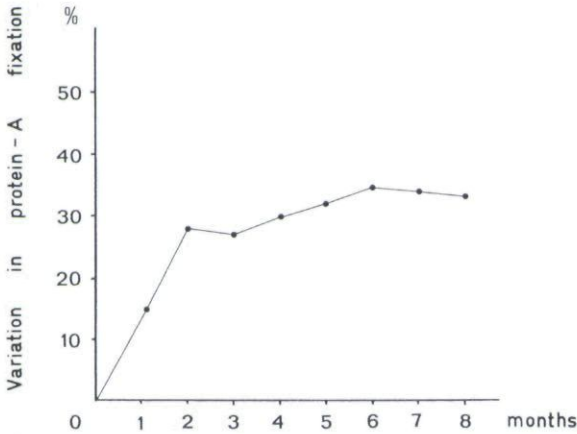


Fig. 1. Quantitative assessment of IgG anti-bee venom in the sera of seven patients treated by rush immunotherapy. The values reported on the graph correspond to the mean of variations of bound protein A percentage, the value observed in the serum of each patient before immunotherapy being used as reference.

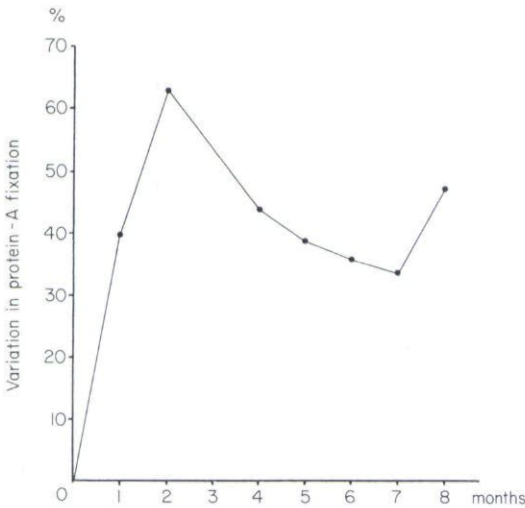


Fig. 2. Quantitative assessment of IgG anti-wasp venom in the sera of twenty-three patients treated by rush immunotherapy. The values reported on the graph correspond to the mean of variations of bound protein A percentage, the value observed in the serum of each patient before immunotherapy being used as reference.

with a fall in blood pressure was observed; this reaction rapidly regressed with therapy and did not recur. In no case did immunotherapy have to be stopped.

The clinical effectiveness of this method was confirmed by spontaneous insect stings and fourteen induced stings which did not cause any complication. These results concur with those already published where the success rate is estimated to be 95% (Lichtenstein *et al.*, 1979).

The level of antivenom IgG antibodies rose significantly from the 1st month onwards, to attain a plateau which was maintained during the maintenance-dose period.

It is agreed to establish a correlation between the antivenom IgG antibodies and the protection afforded although the level of antibodies necessary for protection has not been determined nor is it an absolute value (Reid, Kwasnicki & Cheung, 1982). Grant *et al.* (1981) reported the development of a peak level of IgG antibodies as soon as the total venom dosage of 500 μg is reached. The protective nature of IgG antibodies was demonstrated indirectly by Lessof *et al.*, (1978): five patients who had experienced systemic adverse reactions after the injection of bee venom were protected by the intramuscular administration of gamma globulins obtained from the sera of hyperimmune beekeepers. This passive protection, already observed *in vitro*, demonstrates the direct role of IgG blocking antibodies in the prevention of anaphylactic reactions.

The search for a well-tolerated, effective, and less restrictive treatment has made it possible to propose many variations in relation to traditional immunotherapy. Golden *et al.* (1980) injected 15 μg of venom in three doses on the 1st day, then one injection every 2 weeks to attain the maintenance dose of 100 μg in 6 weeks. Lichtenstein *et al.* (1979) attained the maintenance dose in 6 weeks but at a cost of about 10% serious complications. Muller *et al.* (1979) proposed four daily injections and obtained excellent results but poor patient tolerance rate (39% systemic reactions). In twenty patients who were allergic to bee venom, Yunginger *et al.* (1979) tried a rapidly administered technique of immunotherapy using increasing dosages injected ever 0.5–1.0 hr for 2 or 3 days to attain a dosage of 200 μg . Judging patient tolerance to be inadequate (eleven cases out of nineteen), they prefer to adopt the technique of weekly injections.

In our series of fifty-two patients, tolerance may be described as excellent, since only once the sequence of increasing dosages at the time of rush had to be slowed down because of the occurrence of urticaria on the 2nd day of administration.

During later injections, only one systemic reaction was observed and it did not recur. It seems that the very low initial dosage and the rapid frequency of injections until the maintenance dose are factors for good patient tolerance.

The maintenance dose of 100 μg may be recommended. It corresponds to twice the dose of venom injected by the insect when it stings. Comparing the effectiveness of maintenance doses of 50 and 100 μg in twenty-three desensitized patients, Golden *et al.* (1981) induced four systemic adverse reactions following a sting in the first instance and did not observe any such reactions in the second case.

It appears that the interval of 4 weeks between injections has to be accepted although Golden *et al.* (1981) were able to lengthen this period to 6 weeks without difficulty: the induced-sting test remained negative and the immunologic data unchanged. Further studies are needed to confirm these points.

References

- GOLDEN, D.B.K., KAGEY-SOBOTKA, A., VALENTINE, M.D. & LICHTENSTEIN, L.M. (1981) Prolonged maintenance interval in hymenoptera venom immunotherapy. *Journal of Allergy and Clinical Immunology*, **67**, 482.
- GOLDEN, D.B.K., KAGEY-SOBOTKA, A., VALENTINE, M.D. & LICHTENSTEIN, L.M. (1981) Dose dependence of hymenoptera venom immunotherapy. *Journal of Allergy and Clinical Immunology*, **67**, 370.
- GOLDEN, D.B.K., VALENTINE, M.D., KAGEY-SOBOTKA, A. & LICHTENSTEIN, L.M. (1980) Regimens of hymenoptera venom immunotherapy. *Annals of Internal Medicine*, **92**, 620.
- GRANT, J.A., GOLDBLUM, R.M., RAHR, R., THEUSON, D.O., FARNAM, J. & GILLASPY, J. (1981) Enzyme

- linked immunosorbent assay (ELISA) for immunoglobulin G antibodies against insect venom. *Journal of Allergy and Clinical Immunology*, **68**, 112.
- LESSOF, M.H., SOBOTKA, A.K. & LICHTENSTEIN, L.M. (1978) Effects of passive antibody in bee venom anaphylaxis. *Johns Hopkins Medical Journal*, **142**, 1.
- LICHTENSTEIN, L.M., VALENTINE, M.D. & SOBOTKA, A.K. (1979) Insect allergy: the state of the art. *Journal of Allergy and Clinical Immunology*, **64**, 5.
- MULLER, U., THURNHEER, U., PATRIZZI, R., SPIESS, J. & HOIGNE, R. (1979) Immunotherapy in bee sting hypersensitivity. Bee venom versus whole body extract. *Allergy*, **34**, 369.
- REID, M.J., KWASNICKI, J.M. & CHEUNG, N.V. (1982) A quantitative enzyme-linked immunosorbent assay for honeybee venom-specific immunoglobulin G. *Journal of Allergy and Clinical Immunology*, **70**, 191.
- YUNGINGER, J.W., PAULL, B.R., JONES, R.T. & SANTRACH, P.J. (1979) Rush venom immunotherapy program for honeybee sting sensitivity. *Journal of Allergy and Clinical Immunology*, **63**, 340.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.