

Reduction of side effects from rush-immunotherapy with honey bee venom by pretreatment with terfenadine

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Summary

In a double-blind placebo-controlled trial on 52 patients with bee venom allergy we studied the effect of a pretreatment with terfenadine 120 mg twice daily on the occurrence of local and systemic allergic side effects from rush-immunotherapy. Large local reactions were significantly reduced by terfenadine pretreatment ($P < 0.01$), while systemic side effects were observed with similar frequencies in both groups. Analysis of individual systemic allergic manifestations showed that cutaneous symptoms like itching ($P < 0.025$) and urticaria/angioedema ($P < 0.05$) were significantly reduced, while respiratory or cardiovascular symptoms were not influenced. A lower consumption of additional anti-allergic medication was found during terfenadine pretreatment ($P < 0.05$). Pretreatment with antihistamines during immunotherapy may thus be helpful in the management of patients with cutaneous side effects.

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Introduction

Immunotherapy (IT) with allergenic extracts is an effective treatment for a number of IgE-mediated allergic diseases, notably rhinitis and asthma due to pollen and mite allergens and anaphylaxis to Hymenoptera stings [1]. Allergic side effects are one of the major problems of this kind of treatment. Fatalities, although rare, have been observed in most countries where this treatment is practiced on a significant scale [2,3,4]. As a direct consequence the British Committee on Safety of Medicines published an update in 1986 which virtually stopped this valuable treatment in the U.K. [2].

Several measures have been proposed to increase the safety of IT: (1) modifications of the injection protocol—as a rule a very slow dose increase causes less side effects [5]. (2) The use of aluminium precipitated or modified allergens—while side effects may be reduced, especially by chemical modification, the efficacy may be impaired as well [5]. (3) Pretreatment with bee keeper gammaglobulin has been shown to reduce side effects of bee venom immunotherapy [6], but is too expensive, however, for

general use in all patients on IT. (4) Pretreatment with antihistamines is cheap and has been claimed to increase the safety of immunotherapy considerably [7,8]. So far no controlled studies to document such an effect have been published.

Allergic side effects are especially often observed during IT with honey bee venom [5]. In a recent study [9], 51% of 86 bee venom (BV) allergic patients with a history of severe systemic reactions developed systemic allergic side effects during BVIT. These were even more frequent in the subgroup of patients in whom treatment was started by a rush-protocol. We, therefore, chose the model of rush-BVIT in order to investigate a possible effect of pretreatment with high dose terfenadine in a double-blind, placebo-controlled trial on 52 bee venom allergic patients.

Materials and methods

Patient selection

The clinical data of the 52 patients are given in Table 1. Eighteen had a history of one and 34 of several severe reactions to honey bee stings of grade III or IV according to H. L. Mueller [10]. All patients had a positive intracutaneous skin test to BV at a concentration of 10^{-3} g/l and a positive RAST to BV before BVIT. Atopy was

Table 1. Clinical data and results of diagnostic tests before VIT in 52 patients with BFV-allergy

Parameter	All patients	P-group	T-group	P
Age				
MV	33.3	30.0	36.6	<0.05†
(range)	(16–69)	(16–60)	(16–69)	
Sex (male/female)	35/17	19/7	16/10	NS‡
Grade of BV reaction III/IV*	28/24	15/11	13/13	NS‡
Atopy				
history	9	4	5	NS‡
≥ 1 pos SPT	9	5	4	NS‡
i.c. skin test with BV				
EPC in g/l				
10 ⁻³	2	1	1	NS§
10 ⁻⁴	18	8	10	
10 ⁻⁶	15	9	6	
10 ⁻⁸	17	8	9	
BV specific IgE				
RAST-class				
0	0	0	0	NS§
1	2	1	1	
2	21	10	11	
3	23	11	12	
4	6	4	2	

* According to H. L. Mueller [9]. MV: arithmetic mean value, NS: not significant.

† P values were calculated by *t*-test.

‡ P values were calculated by χ^2 -test.

§ P values were calculated by contingency table χ^2 -test.

defined (1) by history (allergic rhinitis, allergic bronchial asthma or atopic dermatitis) and (2) by skin prick testing with nine common inhalants (pollen from grass, birch, hazel and artemisia, *Dermatophagoides pteronyssinus*, *D. farinae*, cat hair, dog hair and *Alternaria*; from Allergomed, Switzerland). A 2+ reaction to at least one of these allergens was regarded as skin test evidence for atopy. A total of 26 patients each were randomly assigned to treatment with either terfenadine (T-group) or placebo (P-group). Except for a small but significant age difference, the groups are comparable for all parameters.

Study protocol

BV for IT was obtained from Pharmacia pdf Schweiz AG, Dübendorf, Switzerland. BVIT was initiated by an inpatient rush-protocol with four daily injections [11] reaching a maintenance dose of 100 µg BV after 4 days in patients without systemic side effects. Patients were then dismissed and received further maintenance doses after

5–7 days and at weekly intervals thereafter. Venom injections were alternatively given subcutaneously in the outside of the right and left upper arm 10 cm above the elbow. Patients were under medical observation for 1½ hr after each injection. Blood pressure was measured three times daily and in addition during all systemic allergic side effects.

A total of 26 patients each were randomly assigned to treatment with terfenadine (T-group) or placebo (P-group). The T-group received two daily tablets of 120 mg terfenadine, the first 1 hr before the first injection in the morning and the second at 17.00 hours during the hospital stay. One tablet of terfenadine was given at 17.00 hours on the eve and another one 2 hr before the first and second outpatient injection, whereas no pretreatment was given before the third outpatient injection. The P-group received placebo tablets according to the same time schedule. All medication was packaged and coded by Merrell Dow Pharmaceuticals SA, Switzerland. Neither the investigators nor the patients knew which type of

premedication was given. The code was not broken until all clinical results had been collected.

Blood samples for estimation of specific IgE (BV-IgE) and specific IgG (BV-IgG) antibodies to honey bee venom were collected before immunotherapy, at day 4 or 5, at day 18 or 19 and at week 14 of BVIT.

Registration and management of side effects

Local reactions. The extent of local reactions was registered 1 hr after the last injection of the day and given a score from 0 to 4: (0) no local reaction, (1) less than 5 cm in diameter, (2) 5–10 cm in diameter, (3) extending over elbow, (4) reaching middle of forearm. Local reactions were treated with cold packs if exceeding score 2. Additional preventive treatment with clemastine 1 mg b.i.d., was given. If insufficient, prednisone 50 mg daily was given after the second score 3 reaction.

Systemic allergic side effects. They were classified as subjective (heat sensation, dizziness, itching, fear, tightness of chest, nausea, abdominal pain, etc.) and objective (flush, erythema, urticaria, angioedema, cough, wheezing). Systemic allergic side effects were treated as needed with clemastine 1–2 mg orally or intravenously and adrenaline by inhalation. After each systemic allergic side effect the venom dose was reduced to the last well tolerated dose. The reduced dose was given no less than 3 hr after the reaction. If well tolerated, the normal protocol was then followed. In case of repeated systemic allergic side effects, an additional preventive treatment with clemastine 1 mg b.i.d., was given. If insufficient, prednisone 50 mg daily was instituted.

Skin tests

BV for skin testing was obtained from Pharmacia pdf Schweiz AG, Dübendorf, Switzerland. Intracutaneous skin tests with BV were performed as described previously [11]. The volume of 0.02 ml of each solution containing 10^{-8} , 10^{-6} , 10^{-4} and 10^{-3} g/l was injected intracutaneously in the volar side of the forearm. The test was considered positive when a weal of at least 5 mm in diameter with erythema was observed after 15 min. The lowest concentration resulting in such a reaction was given as the endpoint concentration (EPC).

Specific IgE-antibodies to BV (BV-IgE)

BV-IgE were estimated by the commercially available Phadezym®-RAST (Pharmacia AB, Uppsala, Sweden). The test was performed according to the recommendations of the manufacturer. All tests were done in duplicate. RAST-values are given in RAST classes from 0 to 4 or in Phadebas-RAST units (PRU).

Specific IgG-antibodies to BV (BV-IgG)

BV-IgG were estimated by an ELISA technique as described previously [11]. Briefly polystyrol tubes activated with glutaraldehyde were coupled with 1 µg of BV per tube. Patient sera were diluted 1:50. The marker to detect BV-IgG was a conjugate of protein A (Pharmacia Fine Chemicals, Uppsala, Sweden) and alkaline phosphatase (Sigma Chemical Co, St Louis, Missouri, U.S.A.). Results are given in µg/ml and were calculated by comparison with a standard curve obtained by serial twofold dilution of a beekeeper reference pool with a known content of BV-IgG (kindly determined by Professor G. Hamilton, Baltimore, U.S.A.).

Statistical evaluation

The χ^2 -test was used to compare groups regarding sex, grade of previous reaction, atopy, incidence of systemic side effects and use of additional medication. The distribution of RAST-classes, skin test EPC and local reaction scores was analysed by contingency table χ^2 -test. The number of single doses of additional medication in the two groups was compared by the Mann-Whitney *U*-test. Age, number of injections until maintenance dose, the duration of the rush phase and differences between BV-IgE and BV-IgG at one particular date between groups were compared by the *t*-test for independent variables. Longitudinal changes of BV-IgE and BV-IgG within groups were compared by the *t*-test for paired comparisons.

Results

Treatment protocol

The maintenance dose of 100 µg BV was reached in all 52 patients in the rush phase. The mean number of BV injections to achieve the maintenance dose was 13 in the T- and 14 in the P-group, and the duration of the rush phase was 4.1 days for the T- and 4.4 days for the P-group. These differences are not significant. Except for 1 patient the maintenance dose of 100 µg was then repeated three times during the outpatient phase. In one patient in the T-group the maintenance dose had to be reduced to 60 µg because of a SE following the last inpatient injection.

Local reactions to BV injections (Fig. 1)

The local reaction scores during the 4 days of rush-hyposensitization in the two groups are shown in Fig. 1. Contingency table χ^2 -test reveals a significant difference in the distribution of the local reaction scores in the P- and T-groups ($P < 0.01$). Figure 1 shows that this is due to a shift towards higher scores in the P-group.

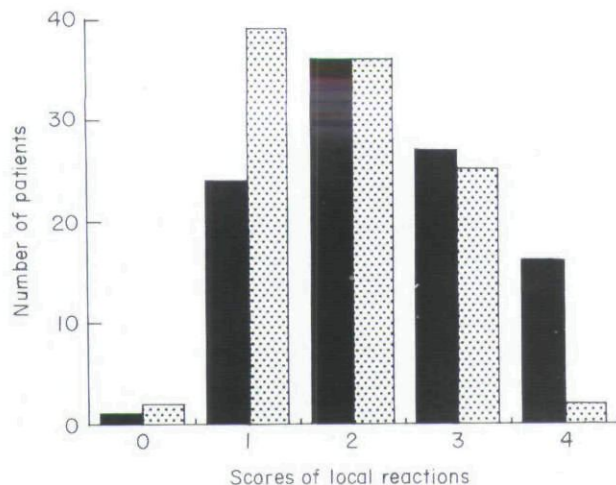


Fig. 1. Local reactions during BVIT: for scores see text. Comparison by contingency table χ^2 -test shows significantly higher LR scores for the P-group than for the T-group ($P < 0.01$). ■, placebo. □, terfenadine.

Systemic side effects to BV injections (Table 2)

In the P-group eight patients and in the T-group nine patients did not develop systemic allergic side effects at any time during the study and 15 in each group had subjective systemic allergic side effects, while objective systemic allergic side effects were observed in 11 P- and seven T-patients. All these differences are not significant. However, if individual systemic allergic side effects are analysed, it is obvious that P-patients developed more frequent itching ($P < 0.025$) and urticaria/angioedema

($P < 0.05$) than T-patients. No significant difference was found regarding the incidence of flush/erythema, gastrointestinal or respiratory symptoms. The third outpatient injection, which was given without pretreatment, resulted in one systemic allergic side effect in the P- and three in the T-group. This difference is not significant. All these reactions were subjective and consisted of heat sensation in two, itching in one and tightness of the chest in one.

Use of additional medication (Table 3)

All systemic allergic side effects to BV injections were essentially mild and easily managed. The comparison of the number of patients treated with clemastine, prednisone and adrenaline shows no significant difference between groups. The number of single doses given is, however, significantly higher for clemastine tablets ($P < 0.03$) and prednisone tablets ($P < 0.05$) in the P-group. Because of repeated systemic allergic side effects which could not be prevented by additional antiallergic medication, one patient in the P-group got an infusion of 7 g of beekeeper gammaglobulin [11] on the fifth hospital day. He did not develop any further systemic allergic side effects thereafter.

Specific IgE-antibodies (Fig. 2)

RAST-values increased significantly from before BVIT to day 18/19 in both T- and P-patients. They decreased significantly from day 18/19 to week 14 in both groups as well. There was no significant difference between before rush and week 14 in the P-group, but still a significantly

Table 2. Systemic side effects to BV injections

Parameter	P-group (number of patients)	T-group (number of patients)	P
Subjective side reactions			
Itching	13	5	< 0.025
Heat, dizziness, tiredness, indisposition	5	10	NS
Fear, tightness	4	5	NS
Nausea, abdominal pain	0	1	NS
All subjective side reactions	15	15	NS
Objective side reactions			
Flush, erythema	7	6	NS
Urticaria, angioedema	6	1	< 0.05
Cough, wheezing	2	3	NS
All objective side reactions	11	7	NS

P values were calculated by χ^2 -test. NS: not significant.

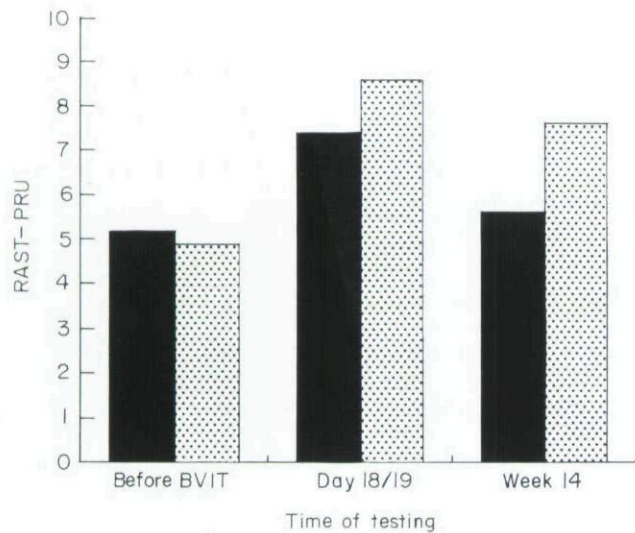


Fig. 2. Geometric mean values of BV-specific IgE during BVIT: BV-IgE increase significantly from before BVIT to day 18/19 in both the P-group ($P=0.012$) and the T-group ($P=0.0007$) and decrease significantly from day 18/19 to week 14 in the P-group ($P=0.008$) and in the T-group ($P=0.013$). There is no significant difference between before BVIT to week 14 in the P-group ($P=0.28$); but still a significant elevation in the T-group ($P=0.003$). There is no significant difference between the groups at any time.

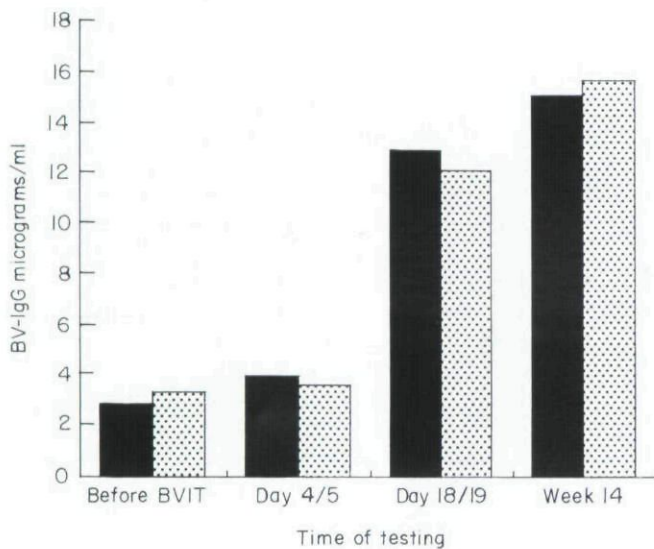


Fig. 3. Geometric mean values of BV-specific IgG during BVIT: there is no change of specific BV-IgG from before BVIT to day 4/5 in both groups. They increase significantly from before BVIT to day 18/19 in the P-group ($P=0.00005$) and in the T-group ($P=0.00005$) and the increase is still significant from day 18/19 to week 14 in the T-group ($P=0.0042$); there is no further significant increase in the P-group ($P=0.054$) in the same period. There is no significant difference between groups at any time. ■, placebo. □, terfenadine.

Table 3. Use of additional medication

Parameter	P-group	T-group	P
Prophylactic and therapeutic use of drugs			
No. of patients	13	7	NS‡
Use of Clemastine p.o.			
No. of patients	8	3	
No. of single doses	43	7	
Mean no. of doses per patient	1.65	0.27	0.03†
Use of Clemastine i.v.			
No. of patients	1	1	
Use of prednisone p.o.			
No. of patients	8	3	
No. of single doses	17	7	
Mean no. of doses per patient	0.65	0.27	0.045†
Use of epinephrine			
No. of patients	3	4	
No. of single doses	3	6	
Mean no. of doses per patient	0.12	0.23	NS†

† P values were calculated by Mann-Whitney- U Test, ‡ P values were calculated by χ^2 -test, NS: not significant.

increased specific IgE-level in the T-group. There was no significant difference between groups at any time.

Specific IgG-antibodies (Fig. 3)

BV-IgG increased significantly in both groups from before BVIT to day 18/19. The further increase to week 14 only reaches significance in the T-group.

Discussion

The efficacy of immunotherapy with Hymenoptera venoms is well documented [5,12,13]. However, and IT with BV especially induces side effects in a large proportion of patients, not only during conventional protocols but even more so during rush protocols [5,14,15]. Rush-BVIT is therefore a good model to investigate the claimed protective effect of a pretreatment with antihistamines before IT-injections [7,8].

In this double-blind, placebo-controlled study we found a significant reduction of the severity of local reactions to BV-injections. The occurrence of systemic allergic side effects on the whole, whether subjective or

objective, was not influenced. The frequency of cutaneous symptoms—itching, urticaria and angioedema—was, however, reduced significantly by terfenadine pretreatment. Other systemic symptoms pointing to gastrointestinal (nausea, abdominal pain), respiratory (wheezing, cough) or cardiovascular (dizziness, flush) involvement were not significantly influenced by pretreatment with antihistamines. This finding is not surprising, when the well documented role of mediators other than histamine is considered in the pathogenesis of respiratory and cardiovascular symptoms of IgE-mediated allergic reactions [5,16,17]. Because of the relatively low number of respiratory and cardiovascular symptoms in this study, a type II error (i.e. not noticing a significant difference which would be detected in a larger number of patients) cannot be excluded, however. Not only the relatively low number of patients studied but also the fact that placebo treated patients got significantly more additional medications, both antihistamines and corticosteroids, may further have concealed a possibly significant difference regarding respiratory and cardiovascular symptoms. Most likely the excess of additional medication will also have diminished the difference between groups regarding cutaneous side effects.

One of the reservations made concerning antihistamine pretreatment during IT is that it suppresses minor allergic reactions which could be a warning signal for more severe ones and thus an indication for a more careful increase or even a reduction of the allergen dose. In this study, there are no data to substantiate this reservation. The number of injections and the days until reaching the maintenance dose were similar in placebo and terfenadine treated patients. Finally severe allergic side effects were not observed after the third outpatient injection, the first one without antihistamine-prophylaxis, in the T-group. The number of observations is too small though to refute the above mentioned reservation completely.

Rocklin [18] has shown that antigen specific T-suppressor cells induced by immunotherapy bear H2-receptors which may be important in the modulation of the specific IgE-response. It seems possible, therefore, that pretreatment with antihistamines can influence the immune response during allergen specific immunotherapy. In this study, however, we could not find a significant alteration of either the IgE- or the IgG-response in the T-group.

We conclude that pretreatment with antihistamines may be very helpful in the management of patients who develop large local reactions or cutaneous symptoms like urticaria and angioedema during BVIT. Most likely it will, however, not influence the incidence of more severe, gastrointestinal, respiratory or cardiovascular side effects.

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