

Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy

Ulrich Müller, MD, Yvonne Hari, MD, and Emanuel Berchtold, MD *Bern, Switzerland*

Background: Antihistamine premedication has been used to increase safety of specific-allergen immunotherapy. Its influence on the efficacy of this treatment has not been studied so far.

Objective: The goal was to analyze the influence of antihistamine premedication on long-term efficacy of specific-allergen immunotherapy.

Method: Patients included in a double-blind, placebo-controlled trial who received premedication with terfenadine or placebo during initial rush immunotherapy with honeybee venom in 1988/1989 were assessed in a retrospective analysis for the long-term protective effect, as indicated by the tolerance of a bee sting challenge or field sting during immunotherapy.

Results: Of the 52 patients who had participated in the 1988/1989 trial, 47 could be reassessed after an average of 3 years. Of these, 45 were still receiving bee venom immunotherapy. A total of 41 patients were stung by bees while receiving immunotherapy (20 of the terfenadine-premedicated group and 21 of the placebo-premedicated group), 17 with in-field stings and 24 with in-hospital sting challenge. Six (29%) of the patients receiving placebo had a mild-to-moderate systemic allergic reaction, whereas none of the patients receiving terfenadine reacted to the bee sting ($P = .012$).

Conclusions: These results indicate that antihistamine premedication during the initial phase of specific-allergen immunotherapy may enhance the efficacy of this treatment. (*J Allergy Clin Immunol* 2001;107:81-6.)

Key words: Immunotherapy, bee venom allergy, antihistamine premedication, terfenadine

Premedication with antihistamines is used during the initial dose-increase phase of specific-allergen immunotherapy (IT) to increase the safety of this treatment.¹ In a number of double-blind, placebo-controlled studies, such an effect has been documented: both local and systemic, especially cutaneous allergic side effects were significantly reduced in patients premedicated with antihistamines.²⁻⁶ Although most of these studies concerned patients on rush immunotherapy with *Hymenoptera* venoms,^{2,4-6} a similar effect has also been demonstrated for cluster immunotherapy with grass and tree pollen.³ Antihistamines used in these studies were terfenadine, loratadine, cetirizine, and fexofenadine.

Abbreviations used

BV:	Honeybee venom
BV-IgE:	Honeybee venom-specific serum IgE
BVIT:	Honeybee venom immunotherapy
EPC:	Endpoint concentration
IT:	Specific-allergen immunotherapy
P-group:	Patients premedicated with placebo
T-group:	Patients premedicated with terfenadine

The mechanism by which IT induces protection is still not completely understood. During recent years a number of studies have demonstrated significant alteration of allergen-specific T-cell reactivity during venom immunotherapy.⁷⁻¹¹ Whereas all authors observed a reduced T-cell proliferation on allergen stimulation, some also described an alteration in cytokine secretion indicating a switch from a T_H2 to a T_H1 pattern. These changes in T-cell reactivity are generally thought to be important for the protective effect induced by venom immunotherapy. It is well known¹² that T cells have histamine receptors. There is some evidence that the expression of these receptors is altered during immunotherapy.^{13,14} The question therefore arises as to whether antihistamine premedication during the initial phase of IT could alter the long-term effectiveness of this treatment. To answer this question, we retrospectively analyzed the long-term protection from honeybee stings in patients who had participated in a double-blind, placebo-controlled trial analyzing the effect of terfenadine premedication during rush immunotherapy with honeybee venom (BVIT).²

METHODS

Study protocol

In 1988/1989, 52 honeybee venom (BV)-sensitive patients participated in a double-blind, placebo-controlled trial analyzing the effect of terfenadine premedication during BVIT.² All patients had a history of a severe allergic reaction including respiratory and/or cardiovascular symptoms after a honeybee sting. BV allergy was documented by a positive intradermal skin test result at 1 $\mu\text{g/mL}$ or less of BV and BV-specific serum IgE antibodies (BV-IgE) (≥ 0.35 Phadebas RAST units). During an inpatient rush protocol with 4 daily injections, the maintenance dose of 100 μg BV was reached after 4 days in patients without systemic side effects. Further injections of the maintenance dose were given 3 times at weekly intervals and later at monthly intervals. Twenty-six patients each were randomly assigned to treatment with terfenadine (T-group) or placebo (P-group). During the inpatient rush protocol, T-group patients received 2 daily tablets of 120 mg terfenadine, the first 1 hour

From the Medical Division, Zieglerspital, Bern.

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Reprint requests: Prof U. Müller, MD, Zieglerspital, Morillonstrasse 75-91, 3007 Bern, Switzerland.

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before the first injection in the morning and the second at 5 PM. Before the first 2 but not the third and later outpatient injections, 1 tablet of 120 mg terfenadine was given at 5 PM on the evening before and 1 tablet 2 hours before the injection. The P-group received placebo tablets according to the same time schedule. After 3 well-tolerated weekly outpatient injections of the maintenance dose of 100 µg BV, the patient was referred to his family doctor, who continued the treatment with monthly injections of the maintenance dose during the first year and injections every 6 weeks during the second and third years.

All study patients were called in after 3 years of BVIT. Forty-seven could be reached and reassessed between 31 and 60 months. All were questioned for the tolerance of BV injections and results of field stings. Intradermal skin tests with BV and estimation of BV-IgE were repeated. Patients who had not been restung by a honeybee during BVIT were offered an in-hospital sting challenge with a live honeybee.

Skin tests

Intradermal skin tests were performed with Pharmalgen BV (Pharmacia AB, Uppsala, Sweden) as described previously.¹⁵ 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 wheal at least 5 mm in diameter with erythema was observed after 15 minutes. The lowest concentration resulting in such a reaction was given as the end-point concentration (EPC).

BV-IgE

BV-IgE were estimated by the then 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, and the results are given in Phadebas RAST units.

Sting challenge

The sting challenge was performed in an intensive care unit. An intravenous infusion of saline solution was started before the sting, and vital signs, blood pressure, and electrocardiography results were continuously monitored. Adult honeybees (≥ 14 d after hatching) were obtained from the Swiss Institute for Agricultural Research (Bern, Switzerland) for the sting challenge. The insect was placed on the volar side of the patient's forearm. After the sting, the stinger was left in the skin for exactly 1 minute. Patients were closely monitored for allergic symptoms during the following 2 hours.

Statistical analysis

The results of re-exposure to honeybee stings, the incidence of side effects, and the sex distribution between the two groups were compared by the Fisher exact test. The age before immunotherapy was begun, skin test EPC results, and BV-IgE at one particular date were compared between groups by the *t* test for independent variables, longitudinal changes of EPC, and BV-IgE by the *t* test for paired comparisons, respectively. BV-IgE studies were transformed logarithmically for these comparisons.

The study protocol was approved by the ethical committee of the Medical Faculty of the University of Bern, Switzerland.

RESULTS

Clinical data

Of the original 52 study patients, 47 could be assessed after an average of 37.5 months (SD, 3.81; range, 31–60

months) after starting treatment, 24 of the T-group and 23 of the P-group (Table I). Five patients could not be reached or did not agree to be reassessed. All 47 reassessed patients had tolerated 100 µg of BV at the end of the rush phase. In 2 (1 in each group), the maintenance dose had to be reduced to 60 µg during the first year of immunotherapy because of recurrent allergic side effects. In 2 beekeepers (1 in each group) the maintenance dose was increased as usual to 200 µg because beekeepers are often stung by more than 1 bee at a time. Two patients had stopped immunotherapy prematurely: a 21-year-old woman of the T-group stopped treatment after only 4 months because of repeated abdominal pain arising several hours after the injection. This patient had a field sting by a honeybee 14 months after stopping and had a severe systemic allergic reaction again. One patient of the P-group decided to stop treatment after 20 months after experiencing a well-tolerated field sting.

Fourteen of the 47 controlled patients (10 in the P-group and 4 in the T-group) reported objective systemic allergic side effects during the rush ($P = .0485$), and 4 (3 in the P-group and 1 in the T-group) reported side effects at some time after the initial phase of the trial (Table II).

Seventeen patients (8 in the P-group and 9 in the T-group) were re-exposed to a field sting during immunotherapy, and 24 (13 in the P-group and 11 in the T-group) who had not been re-exposed before agreed to an in-hospital sting challenge during the 3-year control (Table II). Forty-one patients (21 of the P-group and 20 of the T-group) were thus re-exposed by either a field sting or a sting challenge. The patient who stopped immunotherapy after 4 months was excluded because she was only re-exposed more than a year after stopping BVIT. The 2 patients receiving reduced maintenance doses were not challenged, and 3 further patients declined a repeat challenge. Re-exposed patients did not differ between groups regarding age, sex, grade of severity of pretreatment reaction, and pretreatment skin sensitivity as well as pretreatment BV-IgE. Six systemic allergic reactions were observed in the P-group: 1 patient had cutaneous erythema and pruritus, and 5 patients had urticaria and angioedema. No severe systemic allergic symptoms were observed. No systemic allergic symptoms occurred in any of the patients of the T-group. The difference in sting tolerance between the 2 groups is significant ($P = .012$). Even if the patient of the T-group who stopped immunotherapy after only 4 months and then had a systemic allergic reaction to a field sting by a honeybee more than 1 year later is considered to represent treatment failure, the difference between the 2 groups remains significant ($P = .042$).

Diagnostic tests

Skin sensitivity and BV-IgE estimated during the reassessment in comparison with pretreatment data are given in Table I and Figs 1 and 2. A highly significant decrease in skin sensitivity and BV-IgE was observed in both groups. Although the decrease in skin sensitivity was somewhat less pronounced in the T-group, no signif-

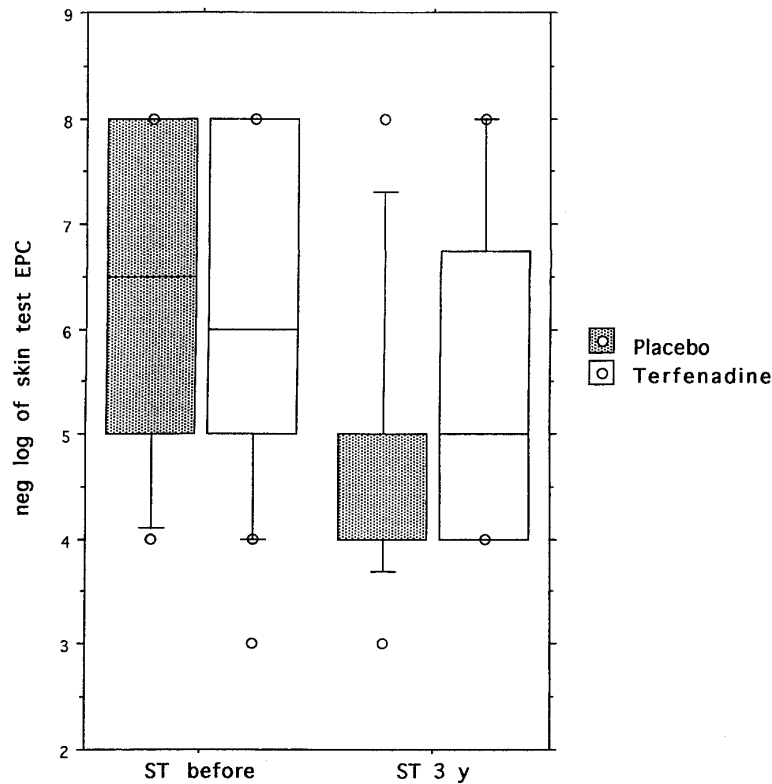


FIG 1. Box plots showing skin sensitivity (negative logarithm of skin test EPC) before and after 3 years of BVIT in patients premedicated with terfenadine or placebo during the initial rush protocol.

TABLE I. Clinical and laboratory data before and after 3 years of BVIT

	Before IT			During reassessment (re-exposed patients)		
	Placebo	Terfenadine	P	Placebo	Terfenadine	P
No. of patients	26	26		23 (21)	24 (20)	
Time of reassessment after start of IT (mo)						
Arithmetic mean value	—	—		38.18	36.74	NS
SD/range	—	—		5.47/31-60	2.07/35-43	
Age at start of IT (y)						
Arithmetic mean value	30.15	36.6	< .05	30.7 (31.6)	37.5 (34.1)	< .05 (NS)
Range	16-60	16-64		16-60 (16-60)	16-64 (16-56)	
Sex (M/F)	19/7	16/10	NS	17/6 (16/5)	14/10 (12/8)	NS (NS)
Severity of reaction before IT (grade III/IV)*	15/11	13/13	NS	13/10 (11/10)	13/11 (11/9)	NS (NS)
Skin sensitivity (negative log EPC)						
Arithmetic mean value	6.08	5.8	NS	4.55 (4.57)	5.04 (5.1)	NS (NS)
Range	3-8	3-8		3-8	4-8	
BV-IgE (PRU)						
Geometric mean value	3.81	4.55	NS	1.18 (1.22)	1.21 (1.11)	NS (NS)
Range	0.43- > 17.5	0.8 - > 17.5		< 0.35-7.7	< 0.35-17.4	

NS, Nonsignificant; PRU, Phadebas RAST units.

*According to Mueller.²⁶

icant differences between groups were found, when mean values of skin test EPC or BV-IgE before or at the 3-year assessment were compared.

The increase of BV-IgG during the first 3 months of immunotherapy has been presented previously² and was found to be similar in both groups (data not shown).

DISCUSSION

Venom immunotherapy is known to be highly effective: during treatment with *Vespula* venom 95% to 100% of patients no longer react to *Vespula* stings, and during treatment with BV around 80% of patients are completely pro-

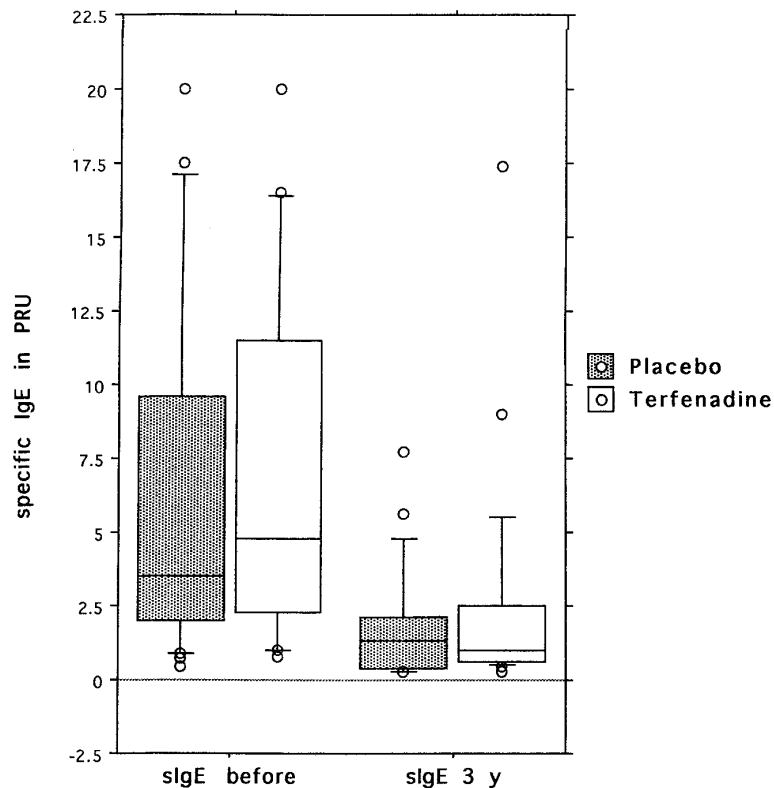


FIG 2. Box plots showing BV-IgE serum levels (Phadezym RAST) before and after 3 years of BVIT in patients premedicated with terfenadine or placebo during the initial rush protocol. PRU, Phadebas RAST units.

TABLE II. Results of re-exposure during BVIT

	Placebo	Terfenadine	P
No. of patients re-exposed	21	20	
By field stings	8	9	
By challenge	13	11	NS
Duration of IT at re-exposure (mo)			
Arithmetic mean value	29.8	30.4	NS
Range	3-60	6-39	
Systemic allergic reaction at re-exposure field sting/challenge	6 3/3	0 —	.012
Systemic allergic side effects of IT			
During rush	10	4	.0485
Later	3	1	NS

NS, Nonsignificant.

tected. The remainder usually have only minor systemic allergic symptoms.^{16,17} Allergic side effects to venom injections, especially to BV,^{17,18} may occur quite frequently. BVIT is therefore a relevant situation in which to study measures to reduce side effects from immunotherapy injections, such as the use of antihistamine premedication.

In the original study by Berchtold et al,² a significant reduction of local reactions and systemic allergic symptoms like urticaria and angioedema was seen with terfenadine premedication. More severe systemic allergic reactions were infrequent, so the effects of antihistamine premedication could not be properly assessed.

Patients of this study were further analyzed in a retrospective way for the long-term protection induced by BVIT. After an average of 3 years, 47 of 52 patients could be reassessed. Of these, 41 were re-exposed to honeybee stings during immunotherapy. To our surprise a significant difference was found between the 2 groups: none of 20 patients who had been given antihistamine premedication initially, but 6 of 21 given placebo, had a systemic allergic reaction to the re-exposure by either a field sting or a sting challenge. This highly significant difference suggests that antihistamine premedication during the initial dose-increase phase may have enhanced

the long-term efficacy of BVIT. What could be the mechanism by which antihistamine premedication resulted in such an effect? Skin sensitivity and BV-IgE were not different between groups at any time, and a highly significant decrease of these parameters was observed in both groups during BVIT. BV-IgG had already previously been shown² to increase significantly and to a similar extent in both groups during the first 3 months of BVIT. The IgG response late during immunotherapy was not further studied because no association between this parameter and protection has been found in previous studies.¹⁹⁻²¹ A change in skin sensitivity or venom-specific serum antibodies induced by antihistamine premedication can therefore not be responsible for the observed effect. The lack of difference in BV-IgE and skin sensitivity strongly supports the contention that these are not useful surrogate markers of clinical efficacy.

On the other hand, profound changes in T-cell reactivity are observed during BVIT: T-cell proliferation after allergen stimulation is strongly reduced, and cytokine secretion by T_H2 cells is downregulated.⁷⁻⁹ Histamine released endogenously during the early phase of rush BVIT may well be responsible in part for these effects; an immunomodulatory role of histamine has been known for many years.¹² Histamine downregulates mitogen- and antigen-induced lymphocyte proliferation. According to recent work on T lymphocytes from bronchoalveolar lavage fluid of patients with asthma,²² this effect is mediated by H2 receptors because it could be blocked by H2 antagonists. The observation that expression of histamine receptors on T lymphocytes is strongly reduced during ultrarush BVIT¹⁴ is an indication for a role of histamine in immune regulation during this treatment. Recently, it has been reported²³ that terfenadine specifically inhibits T_H2 cytokine secretion from human peripheral T-cell cultures in vitro. This indicates that H1 receptors are also involved in the modulation of the T-cell response, possibly in an at least partly antagonistic way; their stimulation may block the expression of T_H1 cytokines such as IL-2,²⁴ which in turn inhibit T_H2 activation. H1 antagonists such as terfenadine then would restore the down-regulating role of T_H1 cytokines on the T_H2 response. The preventive effect of the potent H1 antagonist cetirizine on the development of asthma in small, atopic children reported in the ETAC (Early Treatment of the Atopic Child) study²⁵ may be another indication for an important role of H1 receptors on T lymphocytes in the regulation of the atopic immune response.

In conclusion, these results indicate that antihistamine premedication does not reduce but may rather enhance the effectiveness of BVIT. This finding might be of considerable interest, especially if confirmed during IT for other IgE-mediated allergies like asthma or allergic rhinitis caused by pollen, mites, or animal dander. In vitro studies looking at T-cell responsiveness and especially at alterations of histamine receptor expression during early IT, with and without antihistamine premedication, could increase the understanding of the mechanism of this effect.

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