

Local and systemic reactions during immunotherapy with adsorbed extracts of house dust mite in children

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Background: We retrospectively evaluated the incidence of local and systemic reactions to injections of adsorbed extracts of house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) applied according to a conventional schedule in children.

Method: Eighty-eight patients aged 6 to 15 years, suffering from allergic asthma or asthma together with rhinitis, at various stages of treatment with immunotherapy from January 1989 to November 1997 were included.

Results: Out of 5760 injections, 5542 (96.21%) were not associated with a reaction, 206 injections (3.57%) caused local reactions (144, <20 mm in diameter; 62, >20 mm), and systemic reactions were seen after 12 injections (0.2%). Twelve patients experienced 12 systemic reactions. Of these, 7 patients (58.3%) experienced no local reactions prior to a systemic reaction. Eleven males and one female had systemic reactions. Most of both local and systemic reactions occurred within less than 30 minutes after the injection.

Conclusions: Our study supports the safety of immunotherapy with house dust mites in children. The majority of reactions were local. Although five of 12 patients who experienced systemic reactions had local reactions prior to a systemic reaction, in general the presence of local reactions was not helpful in predicting which patients would develop systemic reactions. Males and patients with asthma together with rhinitis appeared to be at greater risk for systemic reactions.

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INTRODUCTION

Immunotherapy has a long history that dates back to 1911 when Leonard Noon treated patients with grass pollen hay fever by administering subcutaneous injections of grass extract.¹ Specific immunotherapy in children with rhinitis and asthma caused by specific allergens is a well-documented and efficacious treatment. The best results have so far been reported from studies using tree, grass, and ragweed pollen allergens^{2–6} and from studies on dust mite and cat hypersensitivity.^{2,7} Yet, administration of allergen immuno-

therapy is not free of adverse effects. Severe local reactions are common and systemic allergic reactions are not rare.⁸ The incidence of systemic allergic reactions has been extensively studied with a reported range of 1 to 17 reactions per 1000 injections.⁹ The incidence of local allergic reactions range from 0.7% to 4%.^{10–12} Since the allergen preparations vary from study to study, results are difficult to compare.

In our unit, the files of 88 patients with sensitivity to house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) were retrospectively studied. The children had asthma or asthma and rhinitis and received adsorbed extracts of house dust mites of different laboratories by a stepwise schedule. The incidence of systemic and local reactions after 5,760 doses was assessed.

MATERIALS AND METHODS

Patient Selection

Eighty-eight patients, (52 with allergic asthma and 36 with allergic asthma and rhinitis) whose diseases were documented by history and positive immediate skin tests to *D. pteronyssinus* and *D. farinae* were included. The patients were aged 6 to 15 years. Skin tests were performed by the prick method using commercial extracts (Allergopharma Laboratories, Germany and Stallergens Laboratories, France) at a 1/10 IR (index of reactivity) concentration. Normal saline and histamine reagent (10 mg/mL) were used as negative and positive controls respectively. A positive skin prick test was defined as the wheal ≥ 3 mm in diameter. Subjects who had positive immediate skin tests to other extracts in addition to *D. pteronyssinus* and *D. farinae* were not included. The patients were at various stages of immunotherapy from January 1989 to November 1997 at the Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, Cerrahpaşa Medical school, University of Istanbul.

Immunotherapy

The patients received weekly injections of single or combined extracts of *D. pteronyssinus* and *D. farinae* manufactured by Novo-Helisen (Allergopharma Laboratories, Germany), Stallergens (Stallergens Laboratories, France), Alutard (Allergologisk Laboratorium, Denmark) or Bencard (Bencard Laboratories, England). Each treatment consisted of a single injection containing the allergens to which the patient was sensitive. The initial dose was 0.1 mL of 1/1000,000 wt/vol aluminum hydroxide-adsorbed extract

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Table 1. Number of Patients, Injections, and the Type and Severity of the Reactions

Type of Reaction	No. of Reactions	No. of Injections	% of Injections	No. of Patients	% of Patients	Female	Male
No reaction	0	5542	96.21	31	35.22	11	20
1+	90	90	1.56				
2+	54	54	0.94				
3+	32	32	0.55				
4+	30	30	0.52				
Local (total)	206	206	3.57	45	51.14	21	24
Systemic (total)	12	12	0.2	12	13.63	1	11
Total	218	5760		88		33	55

of Novo-Helisen, 0.1 mL of 1/1000,000 wt/vol calcium phosphate-adsorbed extract of Stallergens, 0.2 mL of 1/100,000 wt/vol aluminum hydroxide-adsorbed extract of Alutard and 0.1 mL of 1/1000,000 wt/vol aluminum hydroxide-adsorbed extract of Bencard.

Dosages were usually increased weekly. The usual maximum dose was 0.8 mL of 1/100 wt/vol extract of Stallergens and 1 mL of 1/100 wt/vol extract of Novo-Helisen, Alutard and Bencard. Once the patient reached the maintenance dose or the maximum tolerated dose, the injection schedule was changed to every 2 and then to every 4 weeks. The maximum tolerated dosage was defined as the largest volume of the most concentrated extract that did not result in a local reaction consistently larger than 2+ (see criteria below) or a systemic reaction.

Study Design

Patients were examined carefully for wheezing before each injection. All of the patients were observed in the allergy outpatient clinic for a period of 20 to 30 minutes after the injection. A record of the date, volume, and concentrations of each allergen or allergen mixture given, the time interval between the injections, and the occur-

rence of local or systemic reactions was kept. Induration and erythema at the injection site was measured and graded. The parents were asked to report any symptoms immediately. Systemic reactions were defined as the occurrence of subjective or objective adverse events. Subjective complaints were those of apprehension, generalized pruritus, feeling of asphyxiation, tightness of the chest, and dizziness. Objective findings were those of itchy watering eyes, sneezing, nasal congestion, rhinorrhea, urticaria, angioedema, cough, wheezing, and tachycardia. Laryngeal or pharyngeal edema with potential airway obstruction and hypotension were included as signs of anaphylaxis. The following criteria were used to grade the local reactions.¹¹ 0 = no reaction; 1+ = induration of <5 mm and/or erythema of <10 mm; 2+ = induration of 5 to 10 mm and/or erythema of 11 to 20 mm; 3+ = induration of 11 to 15 mm and/or erythema of 12 to 50 mm; 4+ = induration of >15 mm and/or erythema of >51 mm in diameter.

Patients received larger dosages of the extract if the local reaction was 2+ or less. If a 3+ local reaction occurred the same dose was repeated at the next

injection and if a 4+ local reaction was observed, the previous dose was applied as the next injection. In case of a mild systemic reaction the next dose was decreased to one half but immunotherapy was discontinued after severe systemic reactions.

Statistical Analysis

Chi-square, Fisher's exact, logistic regression and Kolmogorov-Smirnov tests were used in evaluating the correlations between the variables and the differences between the groups. Differences were considered significant at $P < .05$. 95% confidence interval was calculated for the rates of systemic reactions.

RESULTS

From January 1989 to November 1997, 5,760 extract injections were administered to 88 patients (55 males and 33 females). Of these, 31 patients (35%) experienced neither local nor systemic reactions. There were no local or systemic reactions associated with 5542 injections (96%). In 22 patients, 144 injections (2.5%) were associated with non-significant ($\leq 2+$) local reactions, and in 41 patients 62 injections (1%) were associated with significant ($\geq 3+$) local reactions.

Table 2. Number of Systemic and Local Reactions in Patients with Asthma and Asthma and Rhinitis

	No. of Patients	No. of Injections	Local Reactions	Systemic Reactions	Local and Systemic	%95 CI*
Asthma	52	3348	32	3	2	-0.006-0.12
Asthma and rhinitis	36	2412	30	9	3	0.10-0.39

* CI: %95 confidence interval for the rates of systemic reactions.

Table 3. Characteristics and Treatment Outcome of Patients with Systemic Reactions*

Patient No.	Sex	Age (yr)	Clinical State	Clinical Findings	Time of Onset After Injection (min)	Severity of the Reaction	Number of Previous Injections	Duration Since the First Injection (yr)	Dose of the Injection (mL wt/vol)	Grade of Concurrent Local Reaction	Grade of Previous Reactions After Injections	Any Prior Local Reaction	Interventions Provided for Treatment	Treatment Outcome
1	M	6.5	A + R	Laryngoedema	10	Mild	25	0.58	0.1 (1/1000)	—	4+	Three (4+)	Epinephrine SC.	Improved, IT/stopped
2	M	9	A + R	Generalized urticaria	5	Mild	54	1.2	0.4 (1/100)	—	—	—	H ₂ antihistamine	Improved, IT continued
3	M	12	A	Laryngoedema	5	Mild	52	1.2	0.6 (1/100)	—	—	—	Epinephrine SC.	Improved, IT stopped
4	M	8.75	A + R	Wheezing	5	Mild	31	0.75	0.7 (1/1000)	—	—	—	Aerosolized β -agonist	Improved, IT stopped
5	M	9	A + R	Cough and urticaria	5	Mild	30	0.5	0.6 (1/1000)	4+	—	—	Aerosolized β -agonist, H ₂ antihistamine	Improved, IT stopped
6	M	8.5	A	Wheezing	5	Mild	31	0.66	0.6 (1/1000)	—	—	—	Aerosolized β -agonist	Improved, IT stopped
7	M	10	A + R	Wheezing	20	Mild	60	3.08	0.3 (1/100)	—	—	—	Aerosolized β -agonist	Improved, IT continued
8	M	9.75	A + R	Wheezing	5	Mild	60	2.5	0.8 (1/100)	—	—	—	Aerosolized β -agonist	Improved, IT continued
9	F	8.5	A + R	Anaphylaxis	10	Severe	97	4.5	0.8 (1/100)	—	4+	One (4+)	Epinephrine SC., intubation, IV fluids, Oxygen, Dexamethasone IV, H ₂ antihistamine	Improved, IT stopped
10	M	15	A + R	Laryngoedema	5	Mild	125	3.58	0.6 (1/100)	—	—	One (4+)	Epinephrine SC.	Improved, IT stopped
11	M	12	A + R	Wheezing	25	Mild	60	2.58	0.1 (1/100)	—	—	Two (4+)	Aerosolized β -agonist	Improved, IT stopped
12	M	11	A	Sneezing and itchy watering eyes	15	Mild	61	1.83	0.3 (1/100)	—	—	One (3+)	H ₂ antihistamine	Improved, IT continued

* A, Asthma; A + R, asthma and rhinitis; IT, immunotherapy; SC, subcutaneous; and IV, intravenous.

There were 12 patients (14%) who experienced systemic reactions (0.2%). Of these, 7 patients (58%) experienced no local reaction prior to a systemic reaction. The number of previous injections and the presence of local reactions were not helpful in predicting which patients would develop systemic reactions ($P > .05$). Male patients experienced more systemic reactions than female patients ($P < .05$). The type and severity of the reactions are shown in Table 1.

The distribution of local and systemic reactions among patients with only asthma and those with asthma together with rhinitis is shown in Table 2. There were 52 patients with asthma who received 3,348 injections and experienced 32 local (0.95%) and 3 systemic (0.08%) reactions. There were 36 patients with asthma and rhinitis who received 2,412 injections and experienced 30 local (1%) and 9 systemic (0.4%) reactions. There was no significant difference in the number of local reactions between patients with only asthma and those with asthma and rhinitis ($P > .05$). Patients with asthma and rhinitis experienced significantly more systemic reactions than patients with asthma ($P < .05$).

Seven of the 12 systemic reactions occurred within 5 minutes after the injection; 3 patients had wheezing, 2 patients had laryngoedema, 1 patient had generalized urticaria and 1 patient had cough and urticaria. One patient experienced systemic anaphylaxis and one patient had laryngoedema 5 to 10 minutes after the injection. Three patients experienced systemic reactions 15 to 25 minutes after the injection, one had sneezing and watering eyes, and two had wheezing. Characteristics and treatment outcome of the patients with systemic reactions are shown in Table 3. Of the 62 local reactions, 12 (19%) occurred during dose increases and 50 (80%) during maintenance. Four of the systemic reactions occurred during dose increases and 8 during maintenance.

Local reactions (generally $\geq 3+$) were treated symptomatically with oral antihistaminics and topical application

of ice. Eleven of the 12 systemic reactions were mild, not life-threatening, and readily controlled by immediate treatment. One patient with anaphylaxis required intubation and transport to the intensive care unit. There were no fatalities.

In three of the 12 patients with systemic reactions immunotherapy was continued according to the protocol but was stopped in 9 patients.

DISCUSSION

It has been demonstrated that specific immunotherapy in children with asthma and allergic rhinitis who are sensitive to house dust mites, improve their symptoms and decrease their bronchial hyperreactivity.^{13,14} Immunotherapy is not totally free of complications and immunotherapy with allergen injection can induce a variety of local and systemic reactions. Although the type of the allergen extract affects the rate and severity of the reactions, the majority of the reactions occur during the maintenance period.

In our study using adsorbed extracts of house dust mites, 5,542 (96%) of 5,760 injections were not associated with local or systemic reactions. One hundred forty-four injections were associated with mild local reactions ($\leq 2+$), and 62 injections (1%) were associated with severe local reactions.

Nelson et al¹¹ report the incidence of severe local reactions as 4 per 100 injections of aqueous extracts. Prigal¹² reports an incidence of local reactions from 0.7% to 2.8%, depending on the type of extract. Although the ages of the patients, the type of the extract, dosage and therapeutic regimens differ between these studies, the incidence 1% in our study is similar to that reported by Prigal, but is lower than what Nelson et al found. In our study, 42 (67%) of the 62 severe local reactions occurred within 30 minutes of the injection, and 20 (32%) occurred from 35 minutes to 9 hours after the injection. Of the 62 local reactions, 12 (19%) occurred during dose increases and 50 (80%) during maintenance.

Results from the literature indicate that the rate of systemic reactions

ranges from 1 to 17 reactions per 1000 injections and are observed in 1% to 50% of the patients treated with unstandardized extracts.¹⁵ In other reports, the incidences of systemic reactions during immunotherapy with aqueous and adsorbed extracts vary from 0.062% to 0.37% (Table 4).

In our study the incidence of systemic reactions was 2 per 1000 injections. All systemic reactions occurred within 25 minutes after the injection. Of the 12 systemic reactions, 10 were associated with the respiratory system. One patient had generalized urticaria and one had anaphylaxis with hypotension. Four of the systemic reactions occurred during the time of dose increases and 8 during maintenance.

When compared with other reports of systemic reactions after injections of aluminum adsorbed allergen extracts, the incidence of 0.2% found in our study is similar to those reported by Vervollet et al,¹⁶ Tabar et al,¹⁷ and Walker et al.⁴ Nelson et al¹¹ report a similar incidence of 0.3% after injections of aqueous extracts but Tinkelman et al¹⁸ report a lower incidence of 0.062%. Our study confirms the safety of immunotherapy using house dust mite extracts in children with a total reaction rate of 3.79%. The majority of the reactions were local and systemic reactions occurred after only 0.2% of the injections. Although five of the 12 patients who experienced systemic reactions had local reactions prior to the systemic reaction, the presence of local reactions was not predictive of a systemic reaction. Males and patients with asthma and rhinitis appeared to be at greater risk for systemic reactions.

REFERENCES

1. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1: 1572-1574.
2. Bousquet J, Michel F-B. Specific immunotherapy in asthma: is it effective? *J Allergy Clin Immunol* 1994;94:1-11.
3. D'Amato G, Kordash TR, Liccardi G, et al. Immunotherapy with Alpare in patients with respiratory allergy to Parietaria pollen: a two year double-blind placebo—controlled study. *Clin Exp Allergy* 1995;25:149-158.
4. Walker SM, Varney VA, Gaga M, et al. Gross pollen immunotherapy: efficacy and safety during a 4-year follow-up study. *Allergy* 1995;50: 405-413.
5. Litwin A, Pesce J, Fischer T, et al. Regulation of the human immune response to ragweed pollen by immunotherapy: a controlled trial comparing the effect of immunosuppressive peptic fragments of short ragweed with standard treatment. *Clin Exp Allergy* 1991;21:457-465.
6. Hedlin G, Silber G, Naclerio R, et al. Comparison of the in-vivo and in-vitro response to ragweed immunotherapy in children and adults with ragweed—induced rhinitis. *Clin Exp Allergy* 1990;20:491-500.
7. Hedlin G, Graff-Lonnevig V, Heilborn H, et al. Immunotherapy with cat and dog dander extracts: V. Effects of 3 years of treatment. *J Allergy Clin Immunol* 1991;87:955-964.
8. Lin MS, Tanner E, Lynn J, Friday GA. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. *Ann Allergy* 1993;71: 557-652.
9. Greenberg MA, Kaufman CR, Gonzalez GE, et al. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. *J Allergy Clin Immunol* 1986;77;6:865-870.
10. Thompson RA, Bousquet J, Cohen S,

Table 4. Studies on Reactions to Immunotherapy Using Aqueous and Aluminum Adsorbed Extracts

Study	Type of Extract	Incidence of Systemic Reactions (per injection)
Nelson, et al ¹¹	Aqueous	0.3%
Tinkelman, et al ¹⁸	Aqueous	0.062%
Tabar, et al ¹⁴	Alum adsorbed	0.37%
Vervollet, et al ¹⁶	Alum adsorbed	0.1%
Walker, et al ⁴	Alum adsorbed	0.2%

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- et al. Allergen-specific immunotherapy. Report of a WHO-IUIS working group. *Lancet* 1989;1:259–261.
11. Nelson BL, Dupont LA, Reid MJ. Prospective survey of local and systemic reactions to immunotherapy with pollen extracts. *Ann Allergy* 1986;56:331–334.
12. Prigal SJ. A ten-year study of repository injections of allergens: local reactions and their management. *Ann Allergy* 1972;30:529.
13. Warner JO, Price JF, Soothill JF, Hey EN. Controlled trial of hyposensitisation to *Dermatophagoides pteronyssinus* in children with asthma. *Lancet* 1978;2:8096, 912–915.
14. Bousquet J, Calvayrac P, Guérin B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. In vivo and in vitro parameters after a short course of treatment. *J Allergy Clin Immunol* 1985;76:734–744.
15. Hejjaoui A, Ferrando R, Dhivert H, et al. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol* 1992;89:925–933.
16. Vervolet D, Khairallah E, Arnaud A, et al. A prospective national study of the safety of immunotherapy. *Clin Allergy* 1980;10:59.
17. Tabar AL, Garcia BE, Rodriguez A, et al. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. *Allergy (Denmark)* 1993;48:450–453.
18. Tinkelman DG, Cole WQ, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995;95(1 pt 1):8–14.
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