

Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite

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Summary

Thirty-eight adults with allergic rhinitis have been treated with a new partially purified extract of house dust mite (*Dermatophagoides pteronyssinus*) in a double-blind placebo-controlled trial. Patients were randomized to active (Pharmalgen®, *D. pteronyssinus*) and placebo (histamine) treatment by sensitivity to *D. pteronyssinus* on nasal challenge. In the actively treated group nasal symptoms, assessed by visual analogue score, improved ($P < 0.01$), sensitivity on nasal challenge with allergen was reduced ($P < 0.05$) and weal size on skin-prick test with allergen was reduced ($P < 0.01$), compared with the placebo group. These results occurred after 3 months of treatment. Reduction in target organ sensitivity occurred, while the serum level of *D. pteronyssinus* IgE rose in the active group from 14.2 to 22.5 PRU/ml (geometric mean) but did not change significantly in the placebo group. As anticipated, because of the treatment schedule used, a number of generalized allergic reactions were induced by injections, but all responded promptly and easily to treatment. These results suggest this is an effective form of therapy, which now offers us the opportunity to study the immunological mechanisms of hyposensitization and to devise a modified schedule causing fewer reactions.

Introduction

Allergic disease is common: at least one-third of the population are atopic (synthesising IgE antibodies to one or more of the common allergens) and about one-third of these will at some time develop symptoms of allergic disease. *Dermatophagoides pteronyssinus* (house dust mite) is one of the major allergens in the U.K., and causes a variety of allergic disorders, including rhinitis and asthma.

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Although hyposensitization has been used since early this century [1] and is widely practised, overall results are poor. Hyposensitization therapy is unfortunately used indiscriminately and uncritically, in many conditions (e.g. asthma) and with many allergen extracts for which there is no proven evidence of benefit. Whilst clear benefit is sometimes observed in individual patients in clinical practice, controlled studies show convincing evidence of improvement for only a limited number of allergens [2-4]. In the case of hyposensitization to *D. pteronyssinus*, trials in adults with rhinitis and/or asthma give varying results (no benefit [5-8] and benefit [9]) but overall there is little evidence of clinical improvement.

We now have excellent drug therapy for the control of allergic symptoms, but this is ineffective in some patients. Furthermore, whilst drugs suppress or prevent symptoms, reduction in or switch-off of target-organ sensitivity (i.e. cure) would be preferable. This is the aim of hyposensitization therapy. Hyposensitization has not yet been shown to confer long-term cure, but it is of interest that the best results are seen in bee and wasp venom allergy, but only since purified potent extracts (pure venom) have been used [3]. An additional problem is that hyposensitization is potentially dangerous, and while occasional deaths have been reported [10], many more problems go unpublished, and the full extent of the risks of this type of treatment has not been widely publicized until now [11]. These risks highlight the importance of critical evaluation and use of hyposensitization therapy. There is, therefore, a role for hyposensitization but this needs to be clearly defined and appropriate selection of patients, use of extracts of proven value, and administration by experts in the field are essential.

We have carried out a double-blind controlled trial of hyposensitization to *D. pteronyssinus* using a new preparation (Pharmalgen®, ALK, Denmark). This differs from previous preparations in several ways: it is more potent, contains more of the relevant allergenic proteins, is biologically standardized, immunologically characterized and freeze dried. This is a report of the data after the first 3 months of treatment.

Subjects and methods

Sixty patients entered the trial over a period of about 1 year. This report concerns the first 38 of these, 17 females and 21 males, age range 16-55 years, who had completed 3 months of treatment when the first assessment was made. A second assessment will be carried out when all 60 patients have completed 1 year's treatment. The criteria for entry were as follows. All had perennial rhinitis, with or without asthma, with a history suggesting allergy to *D. pteronyssinus*, and no other active perennial allergy. The age range was 16-55 years. No patient had received hyposensitization for 3 years, or systemic steroids for 1 year. All had positive skin-prick tests to Pharmalgen *D. pteronyssinus*, a positive nasal challenge test to Pharmalgen *D. pteronyssinus* and serum IgE antibodies to *D. pteronyssinus*.

Skin-prick tests

These were carried out in duplicate mirror image rows along the forearm with Pharmalgen *D. pteronyssinus* 100 000, 10 000 and 1000 biological units (BU)/ml, histamine chloride (1 mg/ml) as positive control and albumin diluent as negative control. Morrow Brown needles were used, and the same operator carried out all skin tests. The weals were outlined and permanent records obtained by transfer onto sticky tape. The area of the weal was calculated by planimetry.

Nasal challenge tests

Nasal airflow obstruction was assessed by measuring the peak nasal expiratory flow (PEFR) [12], sneezing and secretions. Drugs acting on the nose, beclomethasone nasal spray or chlorpheniramine or terfenadine tablets, were stopped 72 hr before the tests. Each patient was trained to perform the PEFR manoeuvre until repeatable measurements were obtained. Albumin (0.1 ml), as control solution, was applied to the mucosa of the inferior turbinate of one nostril with the head tilted back, and the nostril was closed by pinching for 1 min. The number of sneezes, degree of secretions (scale 0–4) and nasal PEFR were measured (baseline PEFR). Similar measurements were made after a series of concentrations of Pharmedin *D. pteronyssinus* were applied to the nasal mucosa. A positive result was taken as a fall in nasal PEFR > 20%, plus either sneezing or secretions. We devised a scoring system, the cumulative score (maximum = 38), which took into account not only the concentration of allergen to give a positive result, but also the degree of sneezing, degree of secretions and actual percentage fall in nasal PEFR. The concentration of *D. pteronyssinus* needed to reach the end-point was scored from 2 to 26, as follows: 1000 BU/ml = 26; 3200 BU/ml = 20; 10 000 BU/ml = 14; 32 000 BU/ml = 8; and 100 000 BU/ml = 2. Sneezing was graded as none, slight (1–5 sneezes) or severe (> 5 sneezes) and scored 0, 2 or 4; secretions were graded similarly and scored 0, 2 or 4; and the actual percentage fall in peak flow was scored 1 point for each 10% beyond the 20% fall required as the end-point (i.e. 21–30% = 1, 31–40% = 2, etc.). The scoring system was thus heavily weighted towards the allergen concentration (maximum of 26 points) but did take account of the other parameters, which vary from patient to patient.

Nasal symptoms. These were assessed by visual analogue scores. A standard method was used, whereby patients are shown a 10-cm line one end of which represents no symptoms, the other severe symptoms, and minimal, slight and moderate are indicated 1, 4 and 7 cm along the line. The patient is asked to mark with a cross a position representing the severity of his symptoms over the previous 2 weeks. This was done before and after 3 months of treatment. The patient was not shown his previous record. From these records the position of the cross was measured, and symptoms converted to a scale from 0 to 100%.

Diary cards were kept throughout the study. Daily records of drug consumption were kept, and morning and evening nose and eye symptoms were recorded as a weekly average. The diary cards were not analysed until 12 months of treatment were completed.

Concomitant medication. This was restricted either to beclomethasone nasal spray or the short-acting oral antihistamines, chlorpheniramine or terfenadine.

Serum IgE antibodies

Total IgE and *D. pteronyssinus* IgE were measured by radioimmunoassay (Phadebas IgE PRIST® and Phadebas RAST®, Pharmacia AB, Sweden).

Treatment extract

The Pharmedin *D. pteronyssinus* extract is relatively purified, many of the low molecular weight impurities in crude mite extract having been removed. It contains about 15% dry weight of the major allergen *Der p* I (old name antigen P1). 100 000 BU is equivalent to approximately 260 000 IU of the international standard of *D. pteronyssinus*, when assessed by RAST inhibition (manufacturers in-house data). In

order to express the potency in relation to a widely used desensitizing preparation, 100 000 BU Pharmalgen® is equivalent to about 1 000 000 standardized quality (SQ) units of Alutard® (ALK, Denmark), i.e. Pharmalgen is about ten times more potent than Alutard. It was provided freeze dried, in vials of four strengths: 100, 1000, 10 000 and 100 000 BU/ml when reconstituted. The diluent contained human serum albumin, 0.3 mg/ml.

The histamine placebo was also given in graded doses: increasing volumes from vials of four strengths containing 0.001, 0.003, 0.01 and 0.03 mg/ml histamine chloride. The dose range was 0.0007–0.03 mg (equivalent to 70–100 000 BU of the active preparation).

Treatment regime

As this was a new and potent extract, it was difficult to know what the ideal regime would be, but on the grounds that better efficacy is achieved if larger doses of allergen are given [13, 14] we aimed to give the maximum tolerated dose. We chose to use aqueous extracts, while the dose was being increased, although we were aware this would cause many more reactions than a depot preparation. This was because with a potent extract, being given in high dose, we felt it would be safer if reactions were to occur immediately, when the patient was under our care. No patient followed the planned regime without modification, but sensitivity to the extract varied greatly from patient to patient.

Patients were randomized on the basis of sensitivity on nasal challenge to the actively treated group (Pharmalgen *D. pteronyssinus*) or the placebo group (histamine). A modification of the semi-rush technique was used. Injections were given at 1–2 week intervals, using albumin diluent (i.e. aqueous extracts) in gradually increasing concentrations. The initial dose was 70 BU (20+50) and the planned top dose was 100 000 BU. The dose was increased until a reaction occurred, reduced and slowly increased again, usually to a much higher dose, until a second phase of reaction was encountered. The dose below this (designated the maximum tolerated dose) was used for maintenance injections, in depot diluent, which were given monthly for the remainder of the year. The histamine placebo was also given in increasing concentrations. After the first 3 months of treatment, in which only aqueous extracts were used, the mean dose reached in the active group was 17 000 BU and in the placebo group 43 000 BU.

Before each injection, patients were assessed for suitability to receive an injection, and to determine the dose to be given. The peak flow rate was also measured in all patients. The regime was modified if there was a history of recent respiratory infection or worsening of asthma (dose usually omitted, and the same dose given next visit) or any intercurrent illness (dose halved or omitted). The dose was reduced if the peak flow had fallen > 10% below the patient's baseline, even in the absence of clinical change. The dose was reduced if a generalized allergic reaction had occurred to the previous injection (the reduction depending on the type and severity of the reaction) or the same dose was repeated if a large local reaction had occurred.

Results

Assessments were made 1 month before and 3 months after the start of treatment. The weal size on skin-prick test with Pharmalgen *D. pteronyssinus* 100 000 BU/ml (Fig. 1) fell in the actively treated group [mean $\pm$ SD (mm²) before treatment 53.9 $\pm$ 25.6; after treatment 29.1 $\pm$ 12.5], but did not change significantly in the placebo group

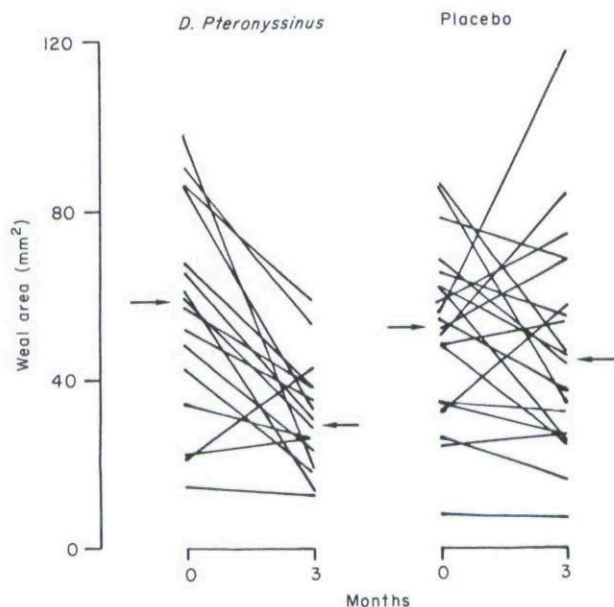


Fig. 1. Weal area on skin-prick test with Pharmeden® *D. pteronyssinus* (100 000 BU/ml) in the active and placebo-treated groups, before and 3 months after the start of treatment. Medians are indicated by arrows.

(49.8 ± 23.9 and 44.3 ± 26.4 ; $P < 0.01$; Student's *t*-test when comparing the difference in change between the groups).

The sensitivity on nasal challenge (Fig. 2) fell in the actively treated group and rose in the placebo group ($P < 0.05$, Mann-Whitney *U*-test, for the difference between the groups) after 3 months of treatment. Nasal symptoms (Fig. 3), assessed by visual analogue score, diminished in both groups but significantly more in the actively treated group [mean $\pm$ SD (%) 66.8 ± 23.2 to 28.8 ± 15.8] compared with the placebo group (50.2 ± 31.0 to 39.3 ± 35.1 ; $P < 0.01$, Mann-Whitney *U*-test). The *D. pteronyssinus* IgE level in the serum (Table 1) rose in the actively treated group ($P < 0.05$) and fell slightly (not significantly) in the placebo group. The difference between the groups was significant ($P < 0.005$, Student's *t*-test). Similar changes were seen in total IgE, which rose in the active group ($P < 0.02$), but not significantly in the placebo group.

In the actively treated group 205 injections were given and 31 generalized allergic reactions occurred (15%). Eight of these were considered serious or potentially serious, and consisted of 'anaphylactic type' reactions. Symptoms varied but included some of the following: conjunctival flare; intense erythema of the face; angioedema of the face, ear lobes, or neck; or acute dyspnoea due to asthma, glottal or laryngeal oedema. All such reactions began within seconds or minutes of the injection, and were immediately treated with adrenaline 0.5 ml of 1:1000 strength subcutaneously. Some patients were also given oxygen, nebulized salbutamol and intramuscular hydrocortisone. Incipient reactions were always treated promptly and aggressively, and all patients recovered rapidly. Other generalized reactions were asthma alone (7), asthma with urticaria or erythema (5), rhinitis (3), erythema or pruritus (5) and erythema with other symptoms (3). All occurred within 15 min of the injection. Although these figures sound alarming, all patients responded easily and quickly to treatment, and even the most severe reaction had almost completely subsided within 20 min. In the placebo group, 13 reactions occurred in 244 injections (5%), but these were mild—generalized pruritus

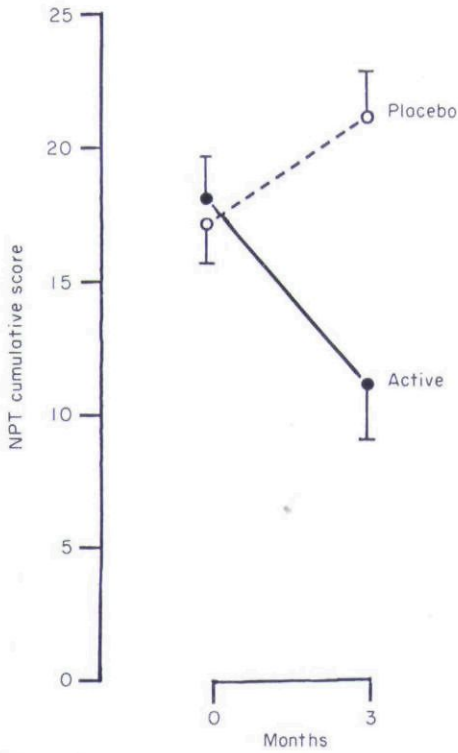


Fig. 2. Cumulative score (max = 38) on nasal provocation test (NPT) with Pharmedin® *D. pteronyssinus* (mean ± s.e.) in the active and placebo-treated groups, before and 3 months after the start of treatment.

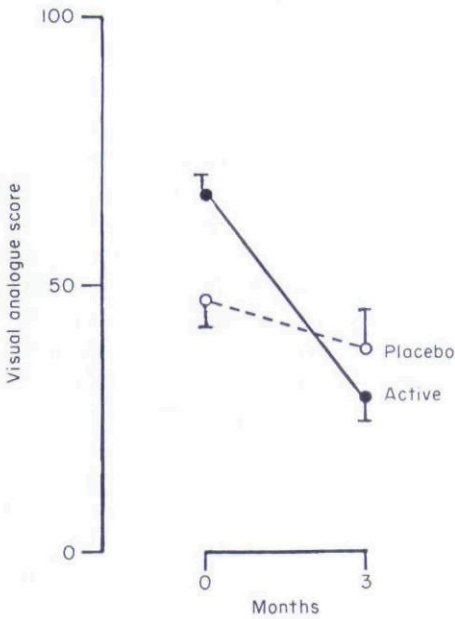


Fig. 3. Nasal symptoms (mean ± s.e.), assessed by visual analogue score (%), in the active and placebo-treated groups, before and after treatment.

Table 1. Changes in total and specific IgE levels before and after 3 months of hyposensitization

		Baseline	3 months	Probability
Total IgE	Active	252	402	$P=0.02^*$
(kU/l)	Placebo	291	311	n.s.*
<i>D. pteronyssinus</i>	Active	14.2	22.5	$P=0.05^*$
IgE (PRU)	Placebo	18.2	16.0	n.s.*
				$P=0.005^\dagger$

* Comparisons within group.

† Comparisons between groups.

and erythema in 10, rhinitis in 2 and asthma in one—and none required treatment with adrenaline.

Localized allergic reactions were not a problem. Thirteen (6%) moderate indurations (2.5–5 cm diameter) were seen in the actively treated group but there were no large (> 5 cm diameter) indurations. A small number of flares were seen in both groups [seven (3%) in the active group and four (2%) in the placebo group].

Discussion

This double-blind study of a new desensitizing preparation has demonstrated reduced sensitivity to allergen in the nose and in the skin, and a reduction in nasal symptoms in patients with allergic rhinitis, after only 3 months of a planned 12-month treatment. The effect on asthma is not yet known. This preparation differs from previous preparations in a number of ways, importantly in being relatively purified and containing more (~15%) of the major allergen, *Der p* I (R. Einarsson, pers. comm., [15]). Furthermore, the preparation is biologically standardized, there is no batch-to-batch variation and, because it is freeze dried, it is stable so the same preparation could be used for diagnostic tests and for treatment.

Previous controlled trials of hyposensitization to *D. pteronyssinus* in adults have generally failed to demonstrate efficacy [5–8]. More detailed analysis of one study where some benefit was demonstrated [9] shows that different methods of assessment gave different results. There was no improvement in symptoms, assessed by diary score-cards, whereas a significant improvement was seen when a questionnaire was used (but only in three out of seven questions asked) and on nasal challenge. This highlights the problem of interpretation of such clinical trials, and it would seem that reduction of sensitivity on allergen challenge without improvement in symptoms cannot necessarily be considered as clinical benefit. These studies used conventional crude extracts, which contain small amounts of the major allergens, whereas the preparation used in this study differs in purification and potency. It is of interest that the introduction of pure venom extracts, for immunotherapy of bee-sting allergy, resulted in high cure rates (95%), whereas the old whole-bee-body extracts, which contained very little of the major allergens in venom, gave no better results than placebo injections [3]. It is likely that the response to hyposensitization is related to the dose of the relevant allergen.

Although effective drugs are available for rhinitis and asthma, the use of several topical preparations (e.g. eye drops, nasal sprays and inhalers) sometimes combined with oral preparations throughout the year is clearly inconvenient and patient

compliance is often poor. Furthermore, prophylactic nasal sprays are usually ineffective in the presence of marked nasal obstruction, a feature of perennial allergic rhinitis. Long-term reduction in target organ sensitivity to the allergen by hyposensitization would therefore be highly desirable.

The observed incidence of side-effects is not simply because the preparation is potent but is a result of the regimen used. Firstly, soluble aqueous extracts (rather than a depot preparation) were used, and these carry greater risk of immediate systemic reactions because of rapid release of allergen into the circulation. However, with a new and potent preparation, we preferred to have reactions occurring early when the patients were still under our care. In this series, prompt recognition of the early signs of a generalized allergic reaction and immediate treatment resulted in rapid resolution of symptoms in all patients. The apparently frequent use of adrenaline was because of this policy, and not because any patient was difficult to treat. Secondly, the hyposensitization regimen followed was aggressive, and involved giving the highest dose tolerated (determined by induction of systemic reactions) by each individual. The maximum tolerated dose in highly sensitive patients was as low as 1000 BU (whereas others reached 60 000 BU), but this was sufficient to effect a dramatic reduction in symptoms and target organ sensitivity on challenge. It is therefore probable that a lower dose regimen, using depot diluent, might be as effective, but give fewer side-effects, and studies on this are planned.

Having demonstrated a clinically effective regime, we are now in a position to study the immunological changes associated with therapy, and this may give a clue to the mechanism of hyposensitization. In this study reduced sensitivity to allergen occurred in two target organs, nose and skin, without a fall in the level of specific IgE antibody in the circulation. Mechanisms other than suppression of IgE antibody are implicated, and immunological studies, particularly of cellular events, are in progress.

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