

A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema

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Summary

A double-blind controlled trial of hyposensitization with tyrosine-adsorbed *Dermatophagoides pteronyssinus* vaccine in 24 children with atopic eczema and immediate hypersensitivity to *D. pteronyssinus* failed to demonstrate superiority over placebo after a standard 8 month course of treatment.

In a second phase, children initially administered active treatment were randomly allocated to continue with active treatment or switched to placebo for a further 6 months. The clinical scores suggest that prolonged hyposensitization may be more effective than placebo but the numbers were too small to permit confident conclusions. A dramatic placebo effect may have served to conceal any additional therapeutic effect from active treatment.

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Introduction

Dermatophagoides pteronyssinus (*D. pteronyssinus*) is the most abundant house dust mite in English homes [1]. Up to 95% of subjects with atopic eczema show strongly positive skin prick tests and high levels of circulating IgE to *D. pteronyssinus* even in the absence of concurrent asthma [2,3]. Further evidence for the role of *D. pteronyssinus* in the pathogenesis of atopic eczema comes from the experimental production of eczematous reactions by epicutaneous testing with *D. pteronyssinus* antigens in skin prick positive individuals with atopic eczema [4–9], and a recent report of increased pruritus and visible inflammation following the prolonged application of *D. pteronyssinus* extract to unabraded eczematous skin in quantities that might be encountered in the home [10]. However, the interpretation of these phenomena in terms of an aetiological role for the house dust mite in atopic eczema remains unclear.

The introduction of measures to reduce house dust mite numbers in patients' surroundings, and of measures to

reduce exposure to faecal antigens has been studied at length in house dust mite-sensitive asthmatics. Though occasional studies have indicated reduction in mite levels and clinical benefit [11], evidence that such measures substantially reduce either the house dust mite population or the prevalence of house dust mite antigen has not been convincing; nor do they generally appear to have been beneficial in terms of disease severity [12]. Properly controlled trials of such procedures have not been undertaken in atopic eczema, though open evaluations have been reported to demonstrate some improvement in patients' disease activity [13–15].

There is some evidence that hyposensitization treatment using injections of small quantities of house dust mite antigen extracts is beneficial in house dust mite-provoked asthma, at least in children [16,17]. A number of uncontrolled studies [18–21] have demonstrated some improvement in atopic eczema following hyposensitization with house dust mite extracts. In addition benefit was noted in concurrent atopic eczema in a double blind controlled study in children with asthma [16]. However, only limited data concerning atopic eczema were collected in that study, and we therefore planned this controlled study specifically to examine the effect of hyposensitization to *D. pteronyssinus* in childhood atopic eczema.

Patients and methods

Patients

Twenty-six children (14 male: 12 female) aged 5–16 years (mean 10.26 years) entered the trial. All had severe atopic eczema, unresponsive to adequate treatment with emollients, mild topical corticosteroids, ichthammol paste bandages, systemic antihistamines, and appropriate elimination diets.

Entry was restricted to patients having a positive skin prick reaction to *D. pteronyssinus* 1.2% (Bencard, Brentford, U.K.), containing the same allergen preparation as used in the hyposensitizing injection. A positive result was a weal equal to or greater than 4 mm in diameter. None of these patients had had previous hyposensitization.

Methods

The study had approval from the Hospital's Standing Committee on Ethical Practice and the parents gave their written informed consent. Patients first entered a 6 week pre-trial assessment to allow stabilization both of concurrent treatments (such as baths, emollients, mild topical corticosteroids and anti-histamines) and of domestic routines that might affect house dust mite populations, or the degree of exposure to house dust mite faeces. Base line diary card data was collected during this period.

Study 1. Entry to the trial was staggered over an 18 month period. At the end of the pre-trial period the patients were randomly allocated to receive either active treatment or placebo. Active treatment consisted of tyrosine adsorbed glycerinated extract of *D. pteronyssinus* (Migen, Bencard, Brentford, U.K.). Subcutaneous injections, from prefilled syringes, were given once a week, increasing progressively to the maximum allergen dose of 400 Noon units (equivalent to 789 international units P1 antigen) after 6 weeks (4, 10, 25, 60, 150 and 400 Noon units respectively) followed by injections of 400 Noon units at 1 month intervals for 6 months.

Placebo injections (tyrosine suspension alone) were indistinguishable in colour and texture from the active injections, and were administered in exactly the same way. Parents, patients and physicians were unaware of whether placebo or active injections were being administered.

Study 2. In order to assess the effect of longer term maintenance treatment all 13 patients who, on breaking the randomization codes, were found to have had active treatment for the first 12 injections were offered a further 6 month period of once monthly injections. Only seven accepted. These seven patients were allocated randomly

to receive injections of either Migen, 400 units once a month, or placebo.

All injections were given in hospital with immediate access to full cardio-respiratory resuscitation equipment. The majority were administered at the Hospital for Sick Children, Great Ormond Street. One hour before each injection, oral terfenadine (Triludan) was given (30–60 mg according to age). After each injection patients had to stay under medical supervision for at least 2 hr.

Parents were supplied with diary cards to be filled in each day. They were asked to score itching during the day and sleep disturbance due to itch at night on a scale of severity from 0–3. Any reactions to injections were recorded on the diary card.

At the end of the study parents were asked whether they thought that their child's eczema was the same, worse or better than at the start of the study.

Scores for eczema severity were given by the same clinician for all the patients, at each 8 week visit. This clinician was unaware of whether the patient was receiving active treatment or placebo. Special scoring sheets were used, showing the front and back of the body divided into 20 zones of approximately equal area. A score from 0–3 was given for each zone in respect of erythema, surface damage and lichenification, with an estimate of the surface area of the zone affected.

Skin prick tests were carried out at the start and after 12 injections using extracts of *D. pteronyssinus* 1.2%, cat fur, dog hair, mixed grass pollens, hen's egg, and cow's milk (Bencard, Brentford, U.K.). Also assessed at the start and after 12 injections were total serum IgE (in iu/ml), measured by a double antibody radioimmunoassay, and IgE to *D. pteronyssinus*, cat fur, dog hair, mixed grass, whole egg and cow's milk, using a radioallergosorbent method (RAST) (Pharmacia) with results expressed on a scale from 0 (negative) to 4 (very high).

Clinical scores and serum IgE levels were analysed using the non-parametric double sample Mann-Whitney U test to compare the two treatment groups. Frequency tables were analysed using χ^2 test with Yate's correction.

Results

Thirteen children (nine male and four female; mean age 9.38 years) completed the course of 12 active injections and 11 (five male and six female; mean age 11.09 years) completed the course of 12 placebo injections. Of the 13 who received active injections initially, seven agreed to a further six injections at monthly intervals (four active, three placebo). These children did not differ significantly from the six patients who declined entry to Study 2, in terms of initial data (age, severity of eczema, duration of eczema), or in terms of change in scores during Study 1.

Table 1. Details at time of enrolment of the 24 children who completed the course of 12 injections (Study 1)

	Active (n = 13)	Placebo (n = 11)
Mean age (years)	9.38	11.09
Mean age of onset (months)	8.03	11.4
History of		
Aggravation of eczema by dust	5	6
Allergic rhinitis	13	11
Asthma	11	9

Table 2. (a) Mean total circulating IgE (international units) at the start and at the end of the study

	Active (n = 13)	Placebo (n = 11)	
Total IgE (mean)			
Start	6279	12 235	} NS
SD	5267	8551	
Finish	8372	9253	} NS
SD	8148	7617	
	NS	NS	

Table 2. (b) Number of patients within each specific IgE (radioallergosorbent test) grade at the start of the study and after 12 injections (0 = negative; 4 = very high level)

	Active (n = 13)					Placebo (n = 11)				
Grade	0	1	2	3	4	0	1	2	3	4
<i>Start of study</i>										
HDM					13					11
Cat			2	1	10		1		2	8
Dog	1		1	6	5			1	5	5
Timothy grass	1			2	10				2	9
Egg white	6	1	3	2	1	5	2	2	1	1
Cow's milk	6	1	2	2	2	6	2	2		1
<i>After 12 injections</i>										
HDM			1		12					11
Cat		1	1	3	8	1			4	6
Dog	1			4	8		1		3	7
Timothy grass	1			2	10				1	10
Egg white	6	1	2	3	1	3	2	2	2	1
Cow's milk	7		2	3	1	3	4	2		2

Table 3. Number of patients in each treatment group exhibiting positive immediate skin tests (weal equal to or greater than 4 mm) to a variety of antigens at the start of the study and after 12 injections

	Active (n = 13)	Placebo (n = 11)
<i>Start of study</i>		
HDM	13	11
Cat	12	11
Dog	11	10
Timothy grass	12	10
Egg white	4	3
Cow's milk	2	2
<i>After 12 injections</i>		
HDM	12	11
Cat	9	9
Dog	6	7
Timothy grass	10	9
Egg white	2	1
Cow's milk	1	0

Two children both female, were withdrawn, one because she refused to continue the injections and the other because of an adverse reaction after the third injection. Both were receiving placebo. Their data was not included in the analysis.

Analysis of the characteristics of the children completing the study showed that at the start subjects in the two groups showed small differences in terms of age, age of onset and history of aggravation of eczema by house dust (Table 1). Actively treated patients and controls were recruited at similar times of the year. There were no significant differences between the two groups in total serum IgE, RASTs (Tables 2a and 2b) or skin prick tests (Table 3). The clinical scores for erythema and lichenifica-

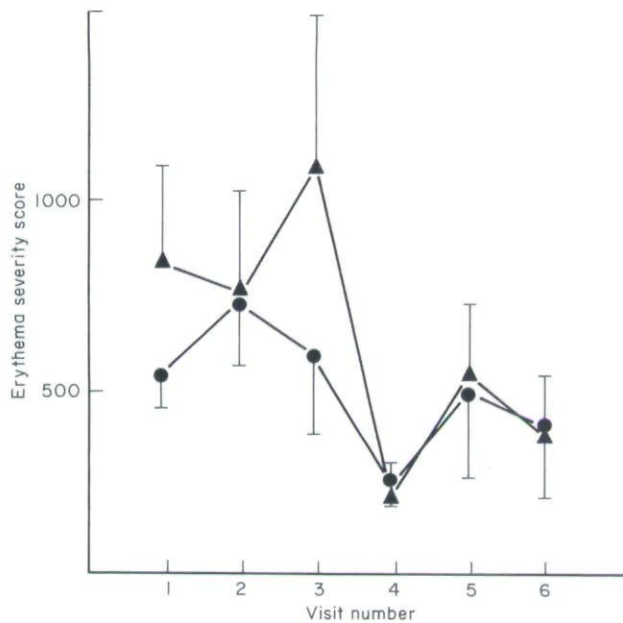


Fig. 1. Mean erythema severity score and standard error of the mean (s.e.m.) for visits 1–6 (13 active, 11 placebo) showing no significant difference between active and placebo groups. ●, active. ▲, placebo.

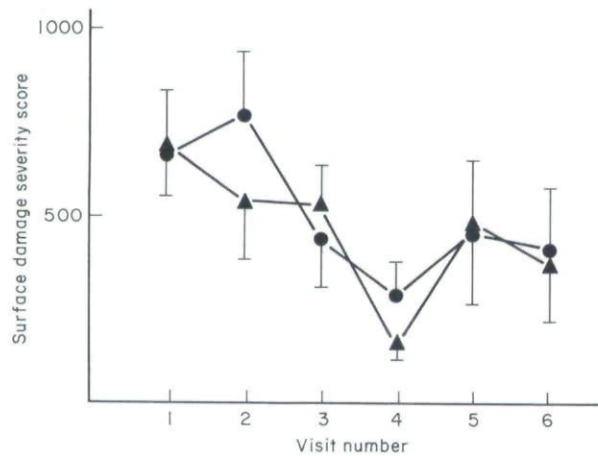


Fig. 2. Mean surface damage severity score and s.e.m. for visits 1–6 showing no significant difference between active and placebo groups. ●, active. ▲, placebo.

tion were slightly higher at the start in patients subsequently receiving active treatment (Figs 1 and 3). These differences did not achieve statistical significance.

Study 1

Both active and placebo treatment groups showed substantial improvement in terms of diary card data and

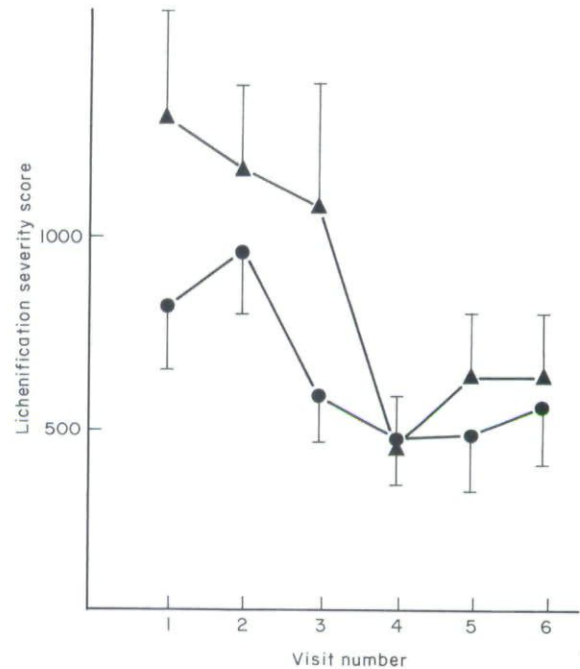


Fig. 3. Mean lichenification severity score and s.e.m. for visits 1–6 showing no significant difference between active and placebo groups. ●, active. ▲, placebo.

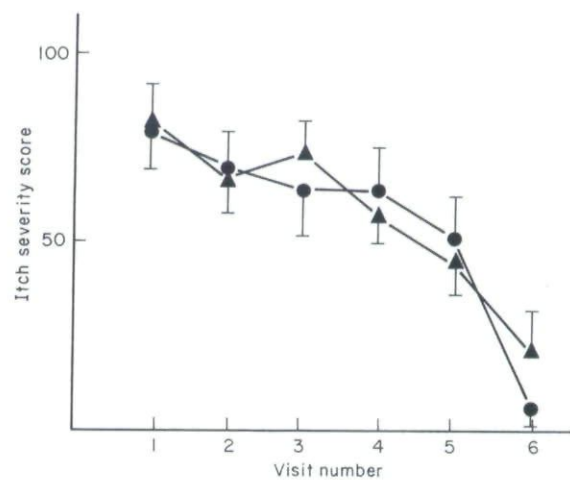


Fig. 4. Mean itch severity score and s.e.m. for visits 1–6 showing no significant difference between active and placebo groups. ●, active. ▲, placebo.

clinical scores but statistical analysis showed no difference between the two groups in terms of erythema, surface damage, lichenification or itch at the end of the 6 month study period (visit 6) (Figs 1–4 and Table 4). There was no difference between the two groups in changes in use of topical steroids.

Table 4. Study 1. Mean scores and *P* values (Mann Whitney U test) for erythema, surface damage and lichenification for visit 2 (start of treatment) and visit 6 (end of first 12 injections)

	Visit 2		Visit 6	
<i>Erythema</i>		s.e.m.		s.e.m.
Active (13)	724	176.01	396	176.9
Placebo (11)	766	252.98	387	148.53
	<i>P</i> =0.800		<i>P</i> =0.643	
<i>Surface damage</i>				
Active (13)	775	162.13	408	178.28
Placebo (11)	536	125.13	366	131.48
	<i>P</i> =0.295		<i>P</i> =0.907	
<i>Lichenification</i>				
Active (13)	951	163.23	544	150.14
Placebo (11)	1162	204.06	605.91	181.74
	<i>P</i> =0.4137		<i>P</i> =0.685	

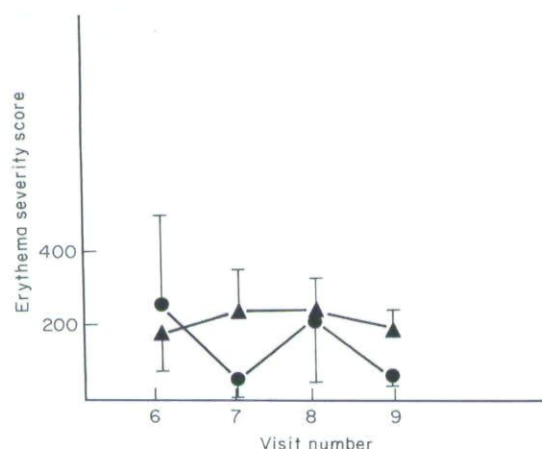


Fig. 5. Mean erythema severity score and s.e.m. for visits 6–9 (four active, three placebo) showing a significant difference between active and placebo groups at visit 9 (*P*=0.049). ●, active. ▲, placebo.

Study 2

In the seven patients receiving a further 6 months of treatment there was a greater improvement seen in the clinical scores of the four actively treated patients than in the three placebo treated patients (Figs 5–8). The differences in scores at the final visit just achieved statistical significance in the case of erythema and lichenification, but not surface damage (Table 5).

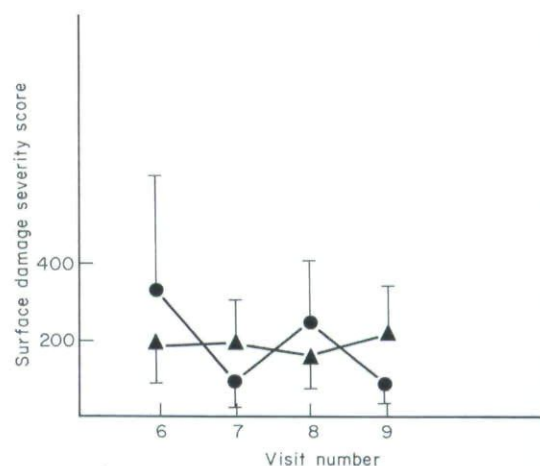


Fig. 6. Mean surface damage severity score and s.e.m. for visits 6–9 showing no significant difference between active and placebo groups. ●, active. ▲, placebo.

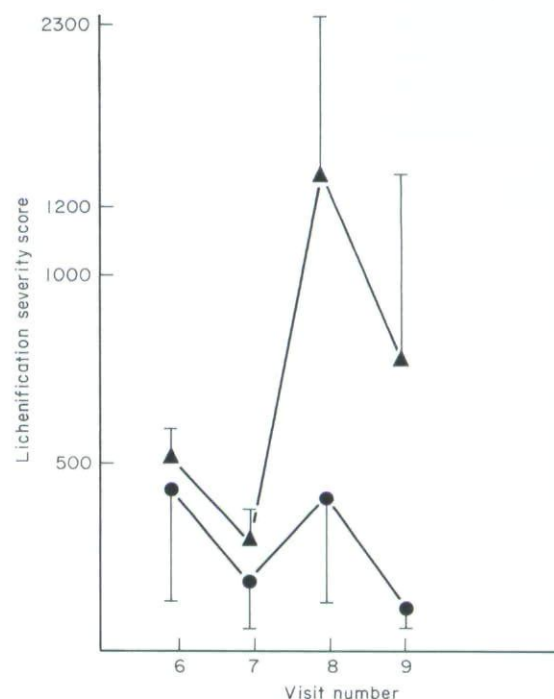


Fig. 7. Mean lichenification severity score and s.e.m. for visits 6–9 showing a significant difference between active and placebo groups at visit 9 (*P*=0.0415). ●, active. ▲, placebo.

Analysis of total circulating IgE, IgE to *D. pteronyssinus*, and skin prick test responses at the start of the study and after 12 injections showed no significant difference between the two groups.

Parents responses to the question 'is your child's

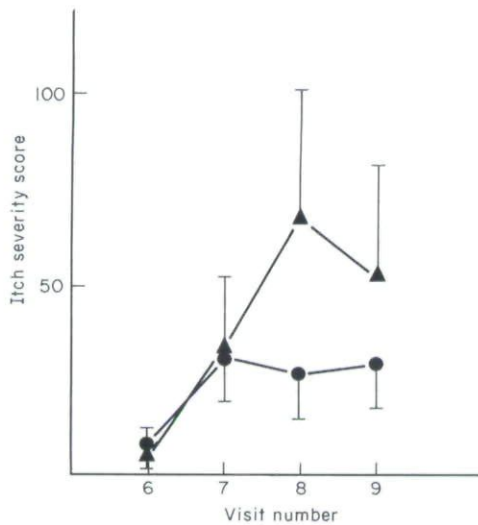


Fig. 8. Mean itch severity score and s.e.m. for visits 6–9 showing no significant difference between active and placebo groups. ●, active; ▲, placebo.

Table 5. Study 2. Mean scores and *P* values (Mann Whitney U test) for erythema, surface damage and lichenification for visit 6 and visit 9 for the patients in Study 2

	Visit 6		Visit 9	
<i>Erythema</i>		s.e.m.		s.e.m.
Active (4)	270	243.6	71	28.75
Placebo (3)	196	100.38	195	47.69
	<i>P</i> =0.475		<i>P</i> =0.049	
<i>Surface damage</i>				
Active (4)	335.5	308.5	81	37.21
Placebo (3)	200	108.66	216	127.16
	<i>P</i> =0.4755		<i>P</i> =0.184	
<i>Lichenification</i>				
Active (4)	448	320.18	116	56.39
Placebo (3)	508	75.69	768	481.09
	<i>P</i> =0.2888		<i>P</i> =0.0415	

Table 6. Parents' assessment of eczema severity after 12 injections compared to severity at the start of the study

	Active (<i>n</i> = 13)	Placebo (<i>n</i> = 11)
Better	8	9
Same	4	2
Worse	1	0

eczema the same, worse or better compared to the start of the study?" showed no significant difference between the two groups (Table 6).

Adverse reactions

Only one possible adverse reaction was observed during either study. The patient complained of faintness and dizziness, starting 4 hr after the third injection. Because it was thought that this could be a systemic reaction attributable to the treatment she was withdrawn from the study. Following breakage of the randomization code she was found to have been receiving placebo. On questioning, local discomfort and redness and swelling at the injection site, lasting from 1–2 days, were noted by six subjects having active and six having placebo injections.

Discussion

Our results suggest that in the treatment of atopic eczema hyposensitization to *D. pteronyssinus*, using the standard regime established for atopic asthma, over an 8 month treatment period, does not demonstrate any superiority compared to placebo.

However, a striking feature of our study was the magnitude of benefit seen in patients treated with placebo. There can be little question that this response was great enough to have concealed most of the additional therapeutic effect that might have resulted from active treatment. The placebo effect observed in this study was greater than we have recorded in any other therapeutic study we have undertaken in atopic eczema, both in its degree and its duration. We believe that this may be related to the physically unpleasant nature of the treatment and to the rather ritualistic procedures involved in its administration, for example, the preparation of adrenaline, checking of resuscitation equipment and the close observation for the subsequent 2 hr. This phenomenon certainly serves to cast doubt on the validity of anecdotal observations of benefit from hyposensitization [18–21].

We used the standard dosage regime for Migen because this had been successful in a previous asthma study [1] and because higher doses increase the risk of adverse reactions. The quantity of the major allergen *Der p* I given in the top dose of Migen (400 Noon units) is 789 international units (iu), compared to approximately 4000 iu introduced intracutaneously in skin testing (Manufacturer's information).

The trend towards improvement in the four patients receiving active treatment for a further 6 months in Study 2, compared to the three subjects receiving placebo is interesting, but the numbers are too small to permit firm conclusions. The statistical power of the present study to

show, say, a 50% superiority of activity over placebo therapy was very low ($P < 0.25$), because of the small patient numbers, but more particularly because of the large variance of the scores. Therefore, by virtue both of the very substantial placebo effect, and the low power of the study, it is not possible to conclude confidently that *D. pteronyssinus* hyposensitization according to our protocol is ineffective.

We had intended to recruit larger numbers of children into this study, but recruitment was discontinued when new guidelines were published by the Department of Health [22]. Because of the recommendations that all injections be given only with immediate access to full resuscitation facilities we arranged for all the injections to be administered in hospital, rather than by their general practitioner as originally intended. Because this involved travelling considerable distances for many children, and because of the new recommendation that all patients must stay under observation for 2 hr after each injection, new patients were deterred from entering into the study.

Our data failed to show any definite benefit from a standard *D. pteronyssinus* hyposensitization regime in children with atopic eczema, but they do suggest that further studies would be justified. It is clear that patient numbers should be larger, and we would especially recommend long treatment periods, of at least one year in duration.

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