

Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study

Michael J Radcliffe, George T Lewith, Richard G Turner, Philip Prescott, Martin K Church, Stephen T Holgate



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Abstract

Objective To assess the efficacy of enzyme potentiated desensitisation in the treatment of severe summer hay fever poorly controlled by pharmacotherapy.

Design Double blind randomised placebo controlled parallel group study.

Setting Hospital in Hampshire.

Participants 183 participants aged between 18 and 64 with a history of severe summer hay fever for at least two years; all were skin prick test positive to timothy grass pollen. 90 randomised to active treatment; 93 randomised to placebo.

Interventions Active treatment: two injections of enzyme potentiated desensitisation, given between eight and 11 weeks apart, each comprising 200 Fishman units of β glucuronidase, 50 μ g 1,3-cyclohexanediol, 50 ng protamine sulphate, and a mixed inhaled allergen extract (pollen mixes for trees, grasses, and weeds; allergenic fungal spores; cat and dog danders; dust and storage mites) in a total volume of 0.05 ml buffered saline. Placebo: two injections of 0.05 ml buffered saline solution.

Main outcome measures Proportion of problem-free days; global rhinoconjunctivitis quality of life scores assessed weekly during pollen season.

Results The active treatment group and the placebo group did not differ in the proportion of problem-free days, quality of life scores, symptom severity scores, change in quantitative skin prick provocation threshold, or change in conjunctival provocation threshold. No clinically significant adverse reactions occurred.

Conclusions Enzyme potentiated desensitisation showed no treatment effect in this study.

Introduction

Allergen specific immunotherapy has been in use for many years. A recent World Health Organization position paper concludes that this method relieves symptoms in allergic rhinitis.¹ Prolonged clinical remission accompanied by a persistent alteration in immune reactivity may be induced by this method after many months or years of treatment.² Use of allergen

specific immunotherapy in the United Kingdom diminished considerably after a report by the Committee on Safety of Medicines in 1986 highlighted the risk of serious adverse reactions and death.³ The risks associated with the giving of large doses of allergens and the requirement for many doses of treatment have led to a search for adjuvant linked preparations that might be effective at much lower doses and need fewer treatments; one such method is enzyme potentiated desensitisation.

Although it has been in clinical use for a range of allergic conditions for more than 20 years, enzyme potentiated desensitisation was first proposed as a simple, effective, and safe low dose method of multiple pollen desensitisation for seasonal rhinitis in 1990.⁴ Investigations had previously established that β glucuronidase possesses immune modulating properties in conjunction with certain activators and in the presence of small doses of allergen.⁵⁻⁶ Between 300 000 and 500 000 doses have been given without serious reaction. If, in addition, the treatment could be shown to be effective against multiple allergens it might show considerable advantage over high dosage methods.

In the treatment of patients with pollen allergy six studies using a double blind placebo controlled design have shown that enzyme potentiated desensitisation by a single pre-seasonal injection reduces hay fever symptoms.⁴⁻¹¹ We took the results of these previous investigations into account with a view to developing a more definitive and rigorous method. We aimed to test the hypothesis that in patients with seasonal rhinitis who are predominantly allergic to grass pollen, pre-seasonal enzyme potentiated desensitisation (two injections given eight weeks apart) can improve symptoms when compared with placebo.

Methods

Study population

We recruited participants by advertisement in the local press and by referral from local general practitioners and community pharmacists. We included patients if they were aged between 18 and 64, had a history of hay fever predominantly in June and July for two or more years, were poorly responsive to treatment with antihistamine and intranasal corticosteroid, and had a

School of Medicine, Inflammation and Repair Research Division, University of Southampton, Southampton General Hospital, Southampton SO16 6YD

Michael J Radcliffe
visiting clinical research fellow

Martin K Church
professor of immunopharmacology
Stephen T Holgate
MRC clinical professor of immunopharmacology

School of Medicine, Community Clinical Sciences Research Division, University of Southampton, Royal South Hants Hospital, Southampton SO14 0YG

George T Lewith
senior clinical research fellow

North Hampshire Hospital, Basingstoke RG24 9NA

Richard G Turner
associate specialist in allergy

Faculty of Mathematical Studies, University of Southampton, Southampton SO17 1BJ

Philip Prescott
professor of statistics

Correspondence to: M J Radcliffe
michael@radcliffe.net

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positive skin prick test to timothy grass pollen. We randomised participants to either active treatment or placebo immediately before administering the first of two injections given 8-11 weeks apart between January and March 2001.

Intervention

Each active injection consisted of 200 Fishman units of β glucuronidase (derived from the mollusc *Haliotis*), 50 μ g of 1,3-cyclohexanediol, 50 ng of protamine sulphate, and mixed inhaled allergen extracts (pollen mixes for trees, grasses, and weeds; a mix of allergenic mould spores; cat and dog danders; dust and storage mites) in a total volume of 0.05 ml of buffered saline. Placebo and active treatments were both clear colourless solutions.

Measurements and assessments

Sensitivity to grass pollen—At the time of randomisation (October-December 2000) and again six to eight weeks post-treatment (April-May 2001) we performed incremental tests of sensitivity to grass pollen. We did quantitative skin prick tests with serially diluted allergen extracts on the forearm.¹² We did conjunctival provocation tests with successively stronger solutions by following the method of Möller.¹³ We regarded a test as positive, and concluded the procedure, if after inspection for redness and inquiry about eye itch, eye weeping, eye burning, nose dripping, or nose blockage (scoring each as mild=1, moderate=2, and severe=3) a total score of 5 was reached.

Symptoms and rescue drugs—In the autumn before treatment we asked each participant to keep a baseline (out of season) diary of symptoms and all treatment used for two weeks during October, November, or December 2000. We then used the same method as the main record of subjective severity of rhinitis during calendar weeks 20 to 31 inclusive of 2001 (14 May to 5 August inclusive). During these two assessment periods we asked each participant to record a daily global rhinitis symptom score (using a seven point scale from no symptoms to very severe symptoms). In addition, at the end of each week we asked each participant to complete the mini rhinoconjunctivitis quality of life questionnaire.¹⁴ This questionnaire comprises 14 questions within five domains: activities, practical problems, nose symptoms, eye symptoms, and other symptoms. Each is assessed on a seven point severity scale. During

the same period we also asked participants to make a daily record of freely allowed rescue drugs.

Primary and secondary outcomes—The primary outcome measures were proportion of problem-free days and post-treatment overall score for rhinoconjunctivitis related quality of life. We defined a symptom-free day as a day on which the symptom score was either 0 or 1—that is, either no symptoms or very mild symptoms. Secondary outcome measures were change after treatment in daily hay fever symptom severity scores, quality of life scores, conjunctival provocation test score, and quantitative skin prick testing result.

Results

Of a total of 665 patients assessed for eligibility, we randomly assigned 183 participants—90 to the active treatment group and 93 to the placebo group. The remaining 482 patients either failed to meet the eligibility criteria or declined to participate before randomisation (see bmj.com). Withdrawals after randomisation (5/90 active, 2/93 control) left 176 participants (85 active, 91 control) for analysis. In all, 166 participants provided symptom diaries for analysis.

The two groups of participants were well matched for age, sex, and duration and severity of rhinitis (table 1). Rather more participants in the active (31) than in the placebo (20) group had asthma. When we examined duration of asthma the average duration was 4.7 years for the active group and 3.0 years for the placebo group. Assessment of severity of asthma showed a greater number of reports of mild (29 (34%) *v* 19 (21%)) or moderate (9 (11%) *v* 6 (7%)) asthma in the active treatment group. Baseline severity of rhinitis (recorded for two weeks during October to November 2000) did not differ between the two groups, whether assessed by symptom scores, quality of life scores, or proportion of symptom-free days. Baseline sensitivity to grass pollen as measured by the conjunctival provocation test did not differ. Rather more of the placebo group than the active group were sensitised to other pollens (25% *v* 32%), although the distribution of sensitivity to house dust mite (*Dermatophagoides pteromyssinus*) was similar between the groups (27% active *v* 25% placebo). We made adjustments for any baseline differences in the comparative analyses.

The proportions of symptom-free days did not differ between the two groups for any study week (table 2). We calculated the overall quality of life score for each participant from the average of the scores of the 14 questions. The mean overall quality of life scores did not differ between the two groups for any study week (figure). In addition, we analysed adjusted average symptom scores for each of the 12 weeks of the study period by using an analysis of covariance taking age, sex, conjunctival provocation test score, severity of rhinitis history, severity of asthma history, and baseline proportion of symptom-free days as covariates. No significant differences occurred.

Comparison of data recorded by participants relating to weals at the injection site showed significant differences between active and placebo groups for three measurements. Size of swelling ($\chi^2=98.4$, $df=4$, $P<0.0005$), duration of swelling ($\chi^2=98.2$, $df=5$, $P<0.0005$), and itchiness ($\chi^2=29.8$, $df=1$, $P<0.0005$)

Table 1 Baseline data. Values are means (SDs) unless stated otherwise

	Active (n=85)	Placebo (n=91)
No of women	41	46
Age of women (years)	39.8 (10.9)	36.5 (8.6)
No of men	44	45
Age of men (years)	38.6 (11.4)	37.1 (10.5)
Severity of rhinitis*	3.34 (0.70)	3.44 (0.50)
Duration of rhinitis (years)	22.67 (11.46)	19.94 (10.31)
Severity of asthma*	1.55 (0.68)	1.34 (0.60)
Duration of asthma (years)	4.70 (9.18)	2.96 (7.62)
Conjunctival provocation test score (pretreatment sensitivity to grass pollen)	2.81 (0.84)	2.75 (0.90)
SPT positive to house dust mite (%)	23 (27.1)	23 (25.3)
SPT positive to pollens other than grass (%)	21 (24.7)	29 (31.9)

SPT=skin prick test.

*Measured on a four point scale: 1=nil to 4=severe.

were all greater after the first injection in actively treated participants than in controls. Sixty four (72%) participants in the placebo group had no swelling, whereas 56 (67%) of the active group had swellings of at least the size of a 5p coin. These swellings lasted for more than an hour in 71 (84%) participants in the active group but in only 10 (11%) of the control group. Only seven (8%) of the placebo group experienced itchiness compared with 37 (44%) of the active group. We found similar results for the second injection.

Discussion

The primary finding of this study was that two doses of enzyme potentiated desensitisation administered at an interval of eight to 11 weeks in the five months before the start of grass pollination was not efficacious in the treatment of pollen related seasonal rhinitis. We found no significant improvement in the treated group compared with the placebo group for symptom severity score, quality of life score, incremental provocation skin prick test, or conjunctival test. A small but significant increase in adverse events occurred for skin (rash and itch) symptoms after both the first and the second active injection. No difference occurred for any other adverse event recorded.

We had not anticipated the difference in itchiness that we found between active and placebo injections. This is because an invariable observation of physicians using enzyme potentiated desensitisation is that patients report no itching when the weal and flare reaction is inspected 30 minutes after injection. It was for this reason that we did not choose a histamine containing solution as the placebo injection. The fact such a marked difference in reports of itchiness (44% active *v* 8% placebo) occurred may therefore have introduced an element of loss of blinding between the treatments. Patients experiencing itch would have been likely to perceive this as a sign that they had received the active preparation rather than the placebo, having noted that itching was a feature of the positive, though not the negative, skin prick tests that had been carried out at the start of the study. Any effect that this loss of blinding might have had on the outcome would have tended to increase apparent efficacy.

We were also concerned to know why we encountered this unanticipated incidence of post-injection pruritus. In a randomised controlled trial of enzyme potentiated desensitisation versus placebo in 20 patients with seasonal rhinitis, Astarita et al openly

Table 2 Comparison of mean proportion of symptom-free days on scale (0-1) for two treatment groups by week of study

Week	Placebo	Active	Difference (95% CI)
1	0.69	0.74	-0.05 (-0.17 to 0.06)
2	0.58	0.54	0.05 (-0.09 to 0.18)
3	0.46	0.49	-0.03 (-0.16 to 0.10)
4	0.31	0.30	0.01 (-0.11 to 0.13)
5	0.25	0.22	0.03 (-0.08 to 0.14)
6	0.19	0.17	0.02 (-0.08 to 0.11)
7	0.23	0.23	0 (-0.12 to 0.12)
8	0.38	0.33	0.05 (-0.08 to 0.18)
9	0.53	0.49	0.04 (-0.11 to 0.18)
10	0.66	0.64	0.02 (-0.12 to 0.15)
11	0.66	0.69	-0.04 (-0.17 to 0.10)
12	0.77	0.70	0.07 (-0.06 to 0.19)

What is already known on this topic

Enzyme potentiated desensitisation, a low dose multi-allergen immunotherapy method, has been in limited clinical use for hay fever in several countries for some years

Six small scale clinical studies have previously shown efficacy, although no large scale study has previously been undertaken

What this study adds

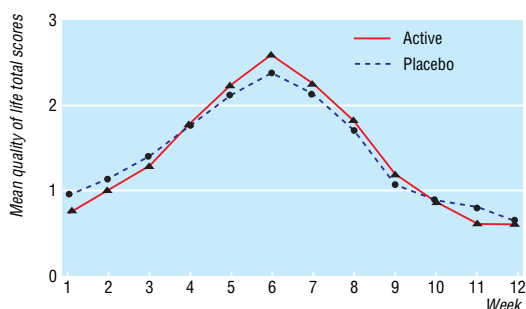
The enzyme potentiated desensitisation allergen immunotherapy method had no treatment effect in this study

The desensitising potency of the treatment might be subject to variation

treated a further 10 patients with the allergen mixture alone devoid of the enzyme.⁹ Weal and flare skin response to the injection was invariably accompanied by pruritus in all 10 patients treated with the allergen mixture alone but in none of the 10 patients given the active treatment and in none of the subjects treated with placebo. This unexpected attenuation of weal and flare pruritus supports the suggestion that the enzyme-diol mixture does possess immune modulating properties. The apparent absence of this attenuation in 44% of the actively treated participants in our trial means that we cannot entirely exclude the possibility that the active material used, although stringently prepared to a good manufacturing practice standard, might have been subject to a loss of desensitising potency.

We considered other possible explanations for finding no treatment effect for enzyme potentiated desensitisation whereas six other placebo controlled studies have had positive findings,^{4 7-11} but we were unable to reach a conclusion. Our study population seems to have been of similar average age, although insufficient data were available from the other studies to allow us to establish if the participants were more severely affected or if they were more likely to be sensitive to multiple pollens.

In conclusion, allergen immunotherapy with enzyme potentiated desensitisation had no treatment effect in this rhinoconjunctivitis study involving a total of 183 volunteers. In the light of evidence of efficacy



Mean overall quality of life score by treatment group for weeks 1 to 12 of the study

from six previous clinical trials of enzyme potentiated desensitisation in seasonal rhinitis, we searched for any reason why we were unable to detect a treatment effect but were unable to find one, except for the suggestion that the desensitising potency might be subject to variation. This possibility should be taken into account in the design of any future trial. In the meantime, the evidence of efficacy from the previous clinical trials of enzyme potentiated desensitisation in seasonal rhinitis should be viewed with caution.

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Competing interests: MJR was funded by a grant from McEwen Laboratories and has received fees for lecturing and consulting from the same source. GTL is funded by a grant from the Maurice Laing Foundation. STH has consultancies with several pharmaceutical companies in relation to asthma research and

receives grants and support for clinical trial work from various companies; none of these represents a competing interest with the work described in this paper.

Ethical approval: Southampton and South West Hampshire local research ethics committee.

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Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India

Lakshmi Rahmathullah, James M Tielsch, R D Thulasiraj, Joanne Katz, Christian Coles, Sheela Devi, Rajeesh John, Karthik Prakash, A V Sadanand, N Edwin, C Kamaraj

Abstract

Objective To assess the impact of supplementing newborn infants with vitamin A on mortality at age 6 months.

Design Community based, randomised, double blind, placebo controlled trial.

Setting Two rural districts of Tamil Nadu, southern India.

Participants 11 619 newborn infants allocated 24 000 IU oral vitamin A or placebo on days 1 and 2 after delivery.

Main outcome measure Primary outcome measure was mortality at age 6 months.

Results Infants in the vitamin A group had a 22% reduction in total mortality (95% confidence interval 4% to 37%) compared with those in the placebo

group. Vitamin A had an impact on mortality between two weeks and three months after treatment, with no additional impact after three months.

Conclusion Supplementing newborn infants with vitamin A can significantly reduce early infant mortality.

Introduction

Ocular signs of vitamin A deficiency are associated with increased mortality among children aged 6 months or older. Supplementation with vitamin A can significantly reduce total mortality, but the impact is only clear in children aged 6 months or older. It was assumed that breast feeding protected infants from vitamin A deficiency, but recent evidence has challenged this. Infants are born with low stores of



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Aravind Centre for Women, Children and Community Health, Madurai, Tamil Nadu, India
Lakshmi Rahmathullah
director

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