

A controlled trial of oral hyposensitization in pollen asthma and rhinitis in children

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Summary

This study describes the effect of an orally administered grass-pollen vaccine, taken pre-seasonally, on the clinical symptoms of fifty-four children with hay fever, asthma or both, during the 1982 grass-pollen season.

Oral mixed grass-pollen vaccine and a matched placebo were randomly allocated to form two matched groups. Although small differences were observed in favour of the active group for both hay fever and asthma, no significant advantage was demonstrated over placebo in terms of symptom scores or additional medication required.

Introduction

Hyposensitization to common inhaled allergens by the oral route has been reported to be of value for children with allergic disease in several uncontrolled studies (Rebien, Wahn & Puttonen, 1980; Stemmann *et al.*, 1979; Wahn, Maier & Geiger, 1976; Wortmann, 1977). A recent controlled trial from Capetown, South Africa (Shore & Weinberg, 1980), comparing oral grass pollen vaccine with placebo in children with seasonal asthma and rhinitis, demonstrated a greater improvement in the vaccine group. Oral hyposensitization appears to have very few side-effects (Wahn *et al.*, 1976), and would have advantages over injection therapy, particularly as it would be more acceptable to children.

The present double-blind study compared oral grass-pollen vaccine with a matched placebo in atopic children with established grass-pollen sensitivity observed during the 1982 English grass-pollen season.

Patients and methods

Children were selected from both St Mary's Hospital Allergy Clinic and Brompton

Hospital Paediatric Respiratory Clinic. They were aged from 5 to 15 years and had seasonal symptoms poorly controlled on conventional therapy. Children who had received hyposensitization within the previous 3 years, and those who had received oral steroids in the past year, were not eligible. All the children had positive allergen challenge tests to mixed grass-pollen solution (Bencard B2 grasses); those with hay fever had nasal, and those with asthma had bronchial challenge tests. Nasal challenge tests were performed using a nasal insufflator for allergen administration into both nostrils. The response was measured by a nasal peak flow meter and a 50% fall in nasal inspiratory peak flow was considered to be a positive result.

Bronchial challenge tests were performed using a method similar to that described by Cockcroft *et al.* (1977). Allergen aerosol was generated by a Wright's nebulizer with an airflow of 8 l/min and the solution was inhaled through a mouthpiece, in doubling concentrations until a fall in both PEFR and FEV₁ of at least 20% from baseline was recorded.

Eligible patients were stratified prior to random allocation on the basis of (i) main diagnosis (hay fever or asthma), (ii) severity of symptoms during the previous pollen season, (iii) drug usage in the previous season, and (iv) positive skin-test results to allergens other than grass pollen. They were randomly allocated either to hyposensitization with the grass-pollen solution (GPS) or to placebo (P).

The trial was approved by the Ethical Committee of the Brompton Hospital where the study was conducted, and informed consent was given by the parents of the children.

Hyposensitization

An aqueous solution of grass pollens, preserved in phenol 0.5% w/vol. identical to Bencard SDV* vaccine for injection, and containing a mixture of twelve grass pollens (B2 grasses, Bencard), was used for the study. The solution was presented in three standard treatment vials of increasing concentration, colour-coded for use at home. The placebo drops were presented in identical vials and consisted of phenol saline drops similar in appearance to the GPS. The vials were presented as follows:

Vial I—1/64 dilution of Vial III.

Vial II—1/8 dilution of Vial III.

Vial III—highest allergen concentration.

Treatment schedule

Each patient started with one drop of Vial I on the 1st day, increasing by 1 drop/day to 15 drops, and the same schedule was followed for Vials II and III. The patient then commenced a maintenance dosage of 15 drops of Vial III twice weekly. Hyposensitization treatment was started in January or February (well before the grass-pollen season) and continued into the early weeks of the season. The children were instructed to take the solution first thing in the morning on an empty stomach, half an hour before breakfast, either on its own, or mixed with a small amount of water or orange juice. The majority of children had maintenance therapy for more than 2 months and some for more than 3 months. However, there was no evidence that the length of time on maintenance therapy influenced effectiveness (data not tabulated).

* SDV is a trade mark of the Beecham group.

The 1982 grass-pollen season, according to the Aerobiology Unit at St Mary's Hospital in central London, lasted for 10 weeks, from 13 May to 21 July.

Management and assessment

Coordinator. The children were assessed monthly by the trial coordinator (P.J.C.) throughout the pre-seasonal treatment period, in particular to document any side-effects, and the pollen season, in particular to adjust additional drug therapy as indicated by clinical progress. The schedule for additional drug therapy was, as far as possible, the same for all patients. For hay-fever symptoms, an antihistamine was prescribed initially, sodium cromoglycate (SCG) was added or substituted if this was inadequate to control symptoms and a topical steroid if this too was inadequate. For asthma, inhaled salbutamol (as required) was prescribed and SCG and/or slow-release aminophylline were added if this was inadequate to control symptoms, and inhaled steroids if this too was inadequate. Patients with moderate or severe symptoms could be prescribed SCG or topical steroids immediately. Some patients had mild perennial symptoms and their therapy was reduced to the minimum required to control these symptoms prior to entry into the trial. No child received oral steroids during the study.

Diary card. Subjective assessment of progress was made using a specially designed diary card completed daily by the children or their parents. Children with asthma also recorded their peak flow rate twice daily, using a Mini-Wright peak flow meter. Diary-card recordings commenced at the time the drops were allocated, and continued until the end of the pollen season. Symptoms of rhinitis and asthma were recorded on a 0-3 scale of severity (i.e. none; mild; moderate; severe) in addition to drugs taken, possible side-effects of the trial therapy, respiratory infections, and number of days off school due to illness. Days affected by upper-respiratory infections were excluded from the analysis of the results.

Data analysis

Symptom scores. For both rhinitis and asthma symptoms, two scores were calculated. The first was the mean number of days on which the symptom was present; as the season lasted 10 weeks, the maximum possible score was 70. The second took into account the severity of symptoms (0 = none, 1 = mild, 2 = moderate, 3 = severe); the maximum potential score for a symptom being 210.

As symptom scores were affected by other drugs used in addition to the trial drops it was important to include an assessment of the other drugs taken. Therefore an overall score was calculated based on the severity score to which a score for drug usage was added for each day as follows: 1 for an antihistamine, 1 for nasal SCG, 2 for SCG eye drops, 2 for topical steroid. Thus the maximum possible score was 840 (for a patient taking all four forms of medication each day and having both severe nose and eye symptoms).

A separate drug score was also calculated to compare drug usage allowing for variations in dosage.

(a) *Hay fever.* Total scores were calculated for each day, as follows: for the standard daily dose, antihistamine (b.d.) was scored '4', nasal SCG (q.d.s.) '4', SCG eye drops (t.d.s.) '6', nasal steroids (t.d.s.) '9', and steroid eye drops (t.d.s.) '9'. Scores were reduced proportionately if less than full dosages were used. For example, a child taking antihistamine and nasal SCG, in full dosages every day, would have a weekly score of

56—i.e. $(4+4) \times 7$ and a total seasonal score (10 weeks) of 560, i.e. 56×10 . The scores for twice daily nasal steroids would be 42 and 420, respectively.

(b) *Asthma*. Drug dosage scores were calculated for asthma in a similar manner: inhaled salbutamol (200 μg q.d.s. by rotahaler or aerosol), was scored '4'; slow-release aminophylline (b.d.) '4'; SCG (2 spincap t.d.s.) '6'; inhaled steroids (100 μg t.d.s.) '9', scores being reduced for lower dosage. Thus a child taking SCG 1 spincap t.d.s. and salbutamol inhaler two puffs b.d. would have a weekly score of 56 and a total seasonal score of 560.

Statistical method

Comparisons between all the scores of the two treatment groups in the 10-week period were made using the Wilcoxon rank test.

Results

Of fifty-four children admitted to the study, twenty-eight were allocated to the GPS, and twenty-six to the P series. One P patient was withdrawn because of side-effects. Two GPS patients were excluded before the pollen season (because they failed to attend), and four (one GPS, three P) patients were excluded during the season (because there was insufficient information to assess their progress). There remained forty-seven patients, including sixteen (eight GPS, eight P) with both asthma and hay fever. Thus, forty-four patients (twenty-two GPS, twenty-two P) were assessed in the hay fever series, and nineteen (eleven GPS, eight P) in the asthma series.

Hay-fever series

The majority of the forty-four children (twenty-two GPS, twenty-two P) with seasonal rhinitis were male (Table 1) and aged 10 years or more. Perennial symptoms were common, but these were usually mild and in the majority of cases did not require treatment. The characteristics of the two series were broadly similar.

Table 1. Pre-treatment characteristics of patients in the hay fever and in the asthma series

	Hay-fever series		Asthma series	
	GPS	P	GPS	P
Sex: male	16	16	9	5
Age (years): less than 10	2	5	2	2
10–12	11	9	7	3
13–15	9	8	2	3
Perennial rhinitis	11	7	8	7
Perennial-rhinitis treatment				
None	15	17	3	1
Antihistamine only	5	3	3	4
Sodium cromoglycate	0	1	1	2
Nasal steroid	2	1	4	1
Total patients	22	22	11	8

The children gave an assessment of their symptoms during the previous (1981) pollen season. The majority considered their symptoms had been moderately severe or severe (twenty-two GPS, twenty P), had had daily symptoms (twenty GPS, twenty-one P) and had required SCG nasal spray or eye drops (five GPS, three P) or nasal steroids (ten GPS, eleven P) in addition to antihistamine therapy. Almost all patients (twenty GPS, twenty-one P) had both eye and nose symptoms and the majority (eighteen GPS, thirteen P) considered last season had been worse than average and (sixteen GPS, fifteen P) that their symptoms were getting worse over the years. The two series were thus well matched.

Seasonal assessment of hay-fever symptoms

The mean number of days on which symptoms were present was lower for all the symptoms in the GPS series (Table 2). The symptom showing the largest difference between the two series was nasal stuffiness but none of the differences were statistically significant ($P > 0.1$). The mean number of days with nasal, eye or any hay-fever symptoms assessed week by week during the season was consistently lower in the GPS series but this was not related to the pollen count and did not change as the season progressed.

If the severity of symptoms was taken into account (Table 2 and Fig. 1) there was very little difference between the two series. The overall scores (Table 2 and Fig. 1) were lower in the GPS series throughout the season but the difference was not statistically significant ($P > 0.1$).

Scores (see Patients and methods) for additional medication were calculated allowing for variations in dosage (for one GPS patient drug dosages were not available). Most patients took additional drugs only intermittently and six (three GPS,

Table 2. Assessment of hay-fever symptom scores, severity scores and overall scores during the pollen season (13 May 1982–12 July 1982, a 70-day period) based on twenty-two GPS and twenty-two P patients

Score	Assessment	Mean score	
		GPS series	P series
Number of days with symptom: (maximum 70)	Sore eyes	34.5	38.5
	Stuffy nose	31.6	43.2
	Sneezing	33.4	37.5
	Runny nose	30.7	34.1
	Any nasal symptoms	48.7	53.1
	Any hay-fever symptoms	51.5	56.7
Severity score for symptom*: (maximum 210)	Sore eyes	53.0	54.1
	Stuffy nose	48.3	62.4
	Sneezing	52.2	53.7
	Runny nose	45.0	47.4
	Any nasal symptoms	81.0	80.9
	Any hay-fever symptoms	89.6	87.6
Overall score including drug usage*		197.9	226.2

* See text for definitions.

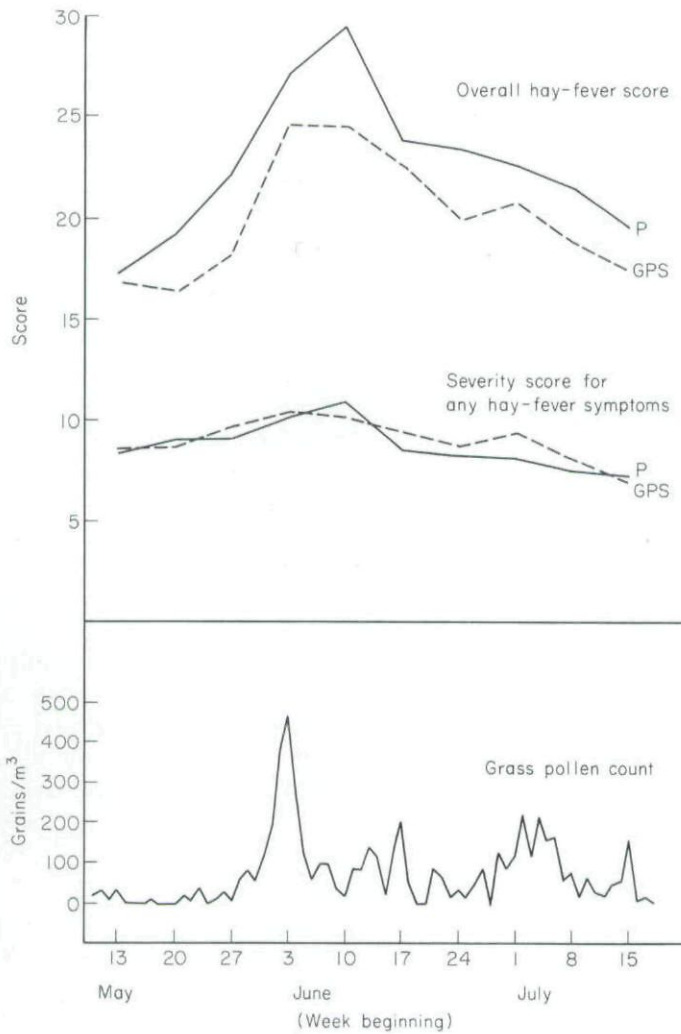


Fig. 1. Assessment of hay fever by week (see Patients and methods section for definitions).

three P) took no drugs at all; fifteen (7 GPS, eight P) patients took antihistamines only, a further fifteen (ten GPS, five P) SCG and eight (two GPS, six P) nasal steroids.

Only five (one GPS, four P) patients had total drug scores of more than 500, and nineteen (ten GPS, nine P) had scores less than 100. The median score for the active series was 114, and for the placebo series 145. There was thus a suggestion that patients in the GPS series took less extra drugs than those in the placebo series, but the difference was not statistically significant ($P > 0.1$).

Asthma series

There were nineteen patients with seasonal asthma (eleven GPS, eight P) (Table 1) and there were differences in the pre-treatment characteristics between the GPS and placebo series, in particular in the perennial and seasonal treatment taken. Inhaled steroid therapy was used by four patients in the GPS series, but only one in the placebo

Table 3. Assessment of seasonal asthma scores and severity scores during the pollen season (13 May 1982–21 July 1982, a 70-day period) based on eleven GPS and eight P patients

Score	Assessment	Mean score	
		GPS series	P series
Number of days with symptom: (maximum 70)	Night wheeze	17.6	22.6
	Morning wheeze	24.0	26.8
	Episodes of wheeze	19.8	31.3
	Restricted activity	9.4	6.2
	Any asthma	34.3	40.8
Severity score for symptom*: (maximum 210)	Night wheeze	21.6	33.6
	Morning wheeze	32.2	36.5
	Episodes of wheeze	25.1	41.0
	Restricted activity	11.5	8.5
	Any asthma	45.5	58.2

* See text for definitions.

series. Analysis of the mean number of days with asthma symptoms (Table 3) suggests a small advantage in favour of the active series, most marked in the number of episodes of wheezing. When symptoms were graded according to severity there was again a difference in favour of the GPS series for all symptoms with the exception of restricted activity. Both the morning and evening average daily peak flow recordings (expressed as a percentage of baseline recordings for 1 month prior to the season) were consistently higher in the GPS series. None of these differences between the series were statistically significant ($P > 0.1$).

Scores for additional drugs were calculated allowing for variations in drug dosage (see Patients and methods section) most patients took medication only intermittently. Five (two GPS, three P) children required only a bronchodilator, seven (four GPS, three P) took SCG in addition, and seven (five GPS, two P) needed inhaled steroids. Eight (six GPS, two P) children had drug scores greater than 400 for the season, and four (two GPS, two P) had scores less than 100. The median scores were 408 for the GPS series, and 248 for the P series.

End-of-season assessment

The forty-four children (twenty-two GPS, twenty-two P) with hay-fever symptoms were asked at the end of the study about their symptoms and drug usage during the season, compared with previous seasons; fifteen children (nine GPS, six P) reported that their symptoms were much better and they had used less treatment compared with previous seasons; a further five (one GPS, four P) children were much better and had had the same amount of treatment. Only three children (one GPS, two P) reported that their symptoms had been worse, all three having used more treatment.

Possible side-effects

Possible side-effects were reported in twenty-seven (fourteen GPS, thirteen P) of the fifty-four (twenty-eight GPS, twenty-six P) children who started treatment. Most of the symptoms were similar to those of hay fever (eight GPS, six P) and two (one GPS, one

P) of them also had mild asthma. One patient in the placebo series was withdrawn because of severe vernal conjunctivitis.

Discussion

Pre-seasonal hyposensitization therapy for rhinitis and asthma has been used extensively since the original observations of Noon (1911) and Freeman (1911). There has been a consensus of agreement that subcutaneous therapy with ragweed or grass pollen in sensitive subjects is effective in reducing the severity of symptoms in rhinitis (Frankland & Augustin, 1954; Lowell & Franklin, 1963; Franklin & Lowell, 1965) and to a lesser extent in asthma (Johnstone & Dutton, 1968; Lichtenstein, 1978). Although most studies have been performed in adults, it is thought that the response to hyposensitization may be better in children (Johnstone & Dutton, 1968). However, other long-term control studies in children have failed to show any advantage over placebo therapy (Fontana, Holt & Mainland, 1966).

Immunological changes have been described following injection therapy (Turner *et al.*, 1984) but these often do not correlate quantitatively with clinical improvement and their relevance is uncertain. There is a wide divergence in individual response to therapy and occasional severe side-effects, notably anaphylaxis, do occur (Ewan, 1980; Rands, 1980). The dosage is empirical, absorption uncertain and mode or site of action once absorbed is unknown. Doubts as to its effectiveness and the lack of scientific knowledge as to why it should work, has made this approach to treatment unpopular in the U.K. although it remains a widely used method in many countries. On the whole, the development of highly effective and safe pharmacological therapy has made further study of hyposensitization superfluous, but where disease is poorly controlled on conventional therapy, a review of hyposensitization remains appropriate.

Oral or sublingual hyposensitization has been used in Europe and the U.S.A. for many years, mainly by individual allergists (Dickey, 1971) whose claims of the effectiveness of this form of treatment have been, at best, anecdotal. Various uncontrolled studies (Wortmann, 1977; Wahn *et al.*, 1976; Rebien *et al.*, 1980) have claimed value, especially in children, but there is a lack of evidence from controlled studies to support these claims. Advantages over injection therapy are increased acceptability, particularly to children and lack of reported side-effects. Thus, if it could be shown to be clinically effective in a controlled study, it could command a place in the treatment of childhood allergic diseases. However, there is even less information on the site and degree of absorption and on the possible mode of action for oral than for injection therapy.

The theoretical basis for oral therapy is largely from animal studies of antigen absorption. Antigen can be absorbed intact through columnar mucosal cells directly into the blood stream and distributed throughout the body (Hemmings & Williams, 1978; Warshaw, Walker & Isselbacher, 1974; Warshaw & Walker, 1977). It is possible that atopic children have a greater mucosal leak to antigen than the normal population (Jackson & Lessof, 1981). However, the absorption of antigen via mucosal cells covering the Peyers Patches in the gut (Owen & Jones, 1974; Owen, 1977) may be of greater importance and it is by this route that the antigen is presented directly to immune lymphocytes. Presentation of small amounts of antigen to T lymphocytes within these gut lymphoid organs may either result in a state of systemic tolerance to antigen or initiate immunization with local specific antibody production (Swarbrick, Stokes & Soothill, 1979). Tolerance could develop as a result of a fall in specific IgE

production either by a decline in T helper mechanisms or a stimulation of T suppressor cells involved in the production of IgE (Jarrett, 1977). Alternatively, stimulation of T lymphocytes in the gut-associated lymphoid system (GALT) has been shown to increase the production of IgA by T helper cells with suppression by T suppressor cells of the production of IgG and IgM antibody (Elson, Heck & Strobes, 1979). These lymphocytes of the GALT system could theoretically migrate to the lung or nasal passages where local IgA synthesis could be modulated and hence the response to antigen at these distant sites, also influenced. Direct absorption of antigen through the gut wall in large amounts has been shown also to induce T suppressor cells (Jarrett, 1977) but it is unlikely that sufficient antigen would be absorbed during oral hyposensitization to produce this response.

This study has failed to show a significant advantage for oral pollen hyposensitization therapy, either for hay fever or asthma and this suggests that the vaccine has at best a small effect. However, it is debatable whether, if the observed difference had been shown to be statistically significant with larger numbers of patients it would be considered clinically worthwhile. There were other factors in this study that we feel should be considered in assessing the results. First, although the two groups were well matched on the basis of previous seasonal drug usage, it is possible that this was not an accurate reflection of symptom severity. Secondly, as there are effective alternative medications which it would be unethical to withhold if a patient's symptoms were not controlled by the vaccine, symptom scores in isolation (without taking into account the drugs used) may well not demonstrate a genuine difference between the series. However, even allowing for drug scores, although there was a suggestion in the rhinitis series that the actively treated group required less additional medication, there was still no significant difference between the series. Thirdly, the 1982 pollen season was unusual, with very high peaks interspersed with very low pollen counts, so that there was little chance for a therapy having only a small effect to show a sustained advantage. Despite high counts, symptoms were mild and this suggests unusual antigenic characteristics of the pollen itself. A therapy which might reduce symptom severity rather than relieve symptoms completely would therefore have less chance to show an effect. It is possible that a greater response will be demonstrated if the treatment is continued for a 2nd year, as suggested by previous hyposensitization studies (Engstrom & Kraepelin, 1957; Lichtenstein, Norman & Ishizako, 1974). Our patients are being followed up for a second season.

Oral hyposensitization has proved to be well accepted and safe, but from the limited evidence of this study, it should not be recommended for use in routine clinical practice at present. However, we consider that it is worthy of further investigation, particularly to optimize dosage and site of absorption, and this may lead to the development of an effective and safe treatment for children with allergic disease.

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