

High dose grass pollen tablets used for hyposensitization in hay fever patients

A one-year double blind placebo-controlled study

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Previous, placebo-controlled clinical trials with oral hyposensitization in grass pollinosis have been disappointing. Since the results possibly could be explained by too low doses of ingested allergens, the present study was initiated to evaluate the effect of high doses of allergens. Forty-two adults with symptoms in the grass pollen season and with grass pollen sensitivity demonstrated by skin prick test and conjunctival provocation test were included. Enterosoluble tablets were administered daily for 1 year. Twenty-two patients, who completed the study, received placebo and 17 mixed grass pollen allergens from rye grass, timothy grass, cultivated rye and velvet grass. Evaluated either by self-assessment or by symptom and medicine score before and after treatment, the group receiving pollens did not improve clinically compared the controls. During the study, conjunctival sensitivity decreased equally in the two groups, and changes in specific IgE, allergen-induced histamine release from blood cells and skin prick test were insignificant and with no difference between groups. Five patients, who received pollen allergens, had episodes of urticaria or angioedema, and a further three patients on the same treatment had slight gastrointestinal side effects. In conclusion, enterosoluble grass pollen allergens in contrast to birch pollens did not have any therapeutic effect, even in doses more than 4,000 times higher than those used for subcutaneous hypersensitization. The reason may be degradation of allergens before the immune system is reached.

Key words: grass pollen; hay fever; oral hyposensitization; enterosoluble tablets.

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Oral hyposensitization (OH) in the treatment of allergic disease has been used for more than 80 years (4) and more recent animal studies have demonstrated induction of tolerance in presensitized animals by oral feeding with the antigen in question (2). Several placebo-controlled trials in OH have shown no clinical effect in the treatment of inhalation allergy (3, 7, 14, 17), whereas more optimistic results have been reported from numerous uncontrolled trials (4, 11, 13, 18, 19, 20, 21). Only recently, a beneficial effect has been demonstrated in placebo-controlled studies on the treatment of birch pollinosis in children (10) as well as in adults (15).

The aim of the present study was to evaluate the therapeutic effect of high-dose oral treatment with grass pollen in patients with grass pollen hay fever.

MATERIAL AND METHODS

Patients

Forty-two patients with rhinitis and conjunctivitis during grass pollen season were included. In all patients allergy to grass pollen was verified by a positive skin prick test (SPT), i.e.

showing a reaction to 10,000 biological units (BU) per ml of mixed grass pollen allergens at least equivalent to the size of the histamine control (10 mg/ml). In addition, specific IgE in serum to timothy grass detected by radio-allergosorbent test (RAST) had to be above class 1. Conjunctival provocation with mixed grass pollen allergens should be positive at 10,000 BU/ml or less. Patients were randomized in a double-blind fashion to treatment with either placebo or grass pollen. Groups were comparable with respect to various demographic data (Table 1). None of the patients had previously received hyposensitization with grass pollen and no other kind of hyposensitization was performed during the investigation.

Treatment

The actively treated group received daily enterosoluble tablets containing a mixture of crude grass pollen from rye grass (*Lolium perenne*), timothy grass (*Phleum pratense*), cultivated rye (*Cecale cereale*), and velvet grass (*Holcus lannatus*). The dose was increased weekly with 3-fold increments from 1,000 BU to 10 mio. BU/day within a 10-week period. Top dose being equivalent to approx. 200,000 IU/day as measured by RAST inhibition against timothy grass (international standard). The control group received similar looking tablets containing lactose. Maintenance dose was given daily for 1 year.

Clinical assessment

During the pretreatment grass pollen season, patients recorded symptoms and medicine consumption in a standardized fashion, allowing calculation of total scores as described earlier (14). Recording was repeated during the subsequent season following treatment for 8–9 months. In addition, patients were asked to evaluate the overall effect of treatment after 1 year.

Conjunctival provocation test (CPT) with the purified mixture of grass pollens mentioned above (Pharmalgen Grass Mix, Pharmacia AB) was performed outside the pollen season prior

to treatment and after 1 year as described elsewhere (9).

During the treatment period, medicine consumption and possible side effects were recorded daily.

Paraclinical measurements

Prior to treatment, timothy-specific serum-IgE-antibodies were determined by Phadebas RAST® (Pharmacia Diagnostics AB, Sweden). Parallel measurements of histamine release from whole blood cells exposed to various concentrations of Grass Mix were done in a micro assay (12). Duplicate SPTs with a 1 mm lancet from Dome/Hollister-Stier (5) were performed with Grass Mix 1,000, 10,000, and 100,000 BU/ml before and during treatment, and changes in sensitivity were evaluated by parallel line assay (6, 8).

The same batch of grass pollen allergens was used throughout the study for all CPT- and SPT-sessions. The material was kept in a freeze-dried form and reconstituted within 8 h prior to use.

Statistics

Chi-squared and (for 2 × 2 tables) Fisher's exact tests were used to evaluate differences in clinical improvement between groups. Assessment of test results were done by one and two sample t-test after logarithmic transformation.

RESULTS

Clinical parameters

In the group receiving grass pollen, one patient left the study due to side effects (see below) and two others for various practical reasons. All patients in the placebo group completed the study. No significant differences in improvement could be demonstrated between groups, either in medicine consumption or in symptoms. In both groups less than half of the patients had a reduction of 10% or more in symptom score (Fig. 1). Scores for various cate-

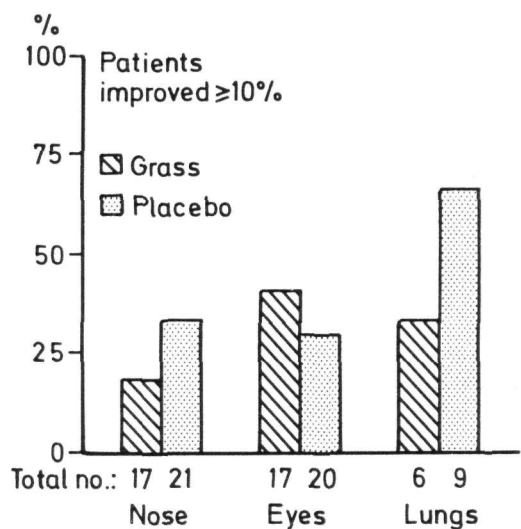


Fig. 1. Proportion of patients with improvement in seasonal symptom scores of 10% or more following 9-10 months of treatment. Figures below indicate the total number of patients reporting the symptoms in question. $P > 0.05$ (Fisher's exact test).

gories of medicine tended to decrease to approximately half the pretreatment value in both groups (Fig. 2). Combined medicine and symptom scores did not disclose any therapeutic effect either (Table 2). Self-assessment based on answers from 35 patients indicated a higher improvement rate compared to log books but with no significant difference between groups (Table 3). Mean sensitivity in CPT was not significantly affected by the treatment. It decreased 70% in the pollen-treated compared to 77% in the placebo group.

Paraclinical results

No significant differences could be demonstrated between groups before or after treatment as measured by SPT, RAST or histamine

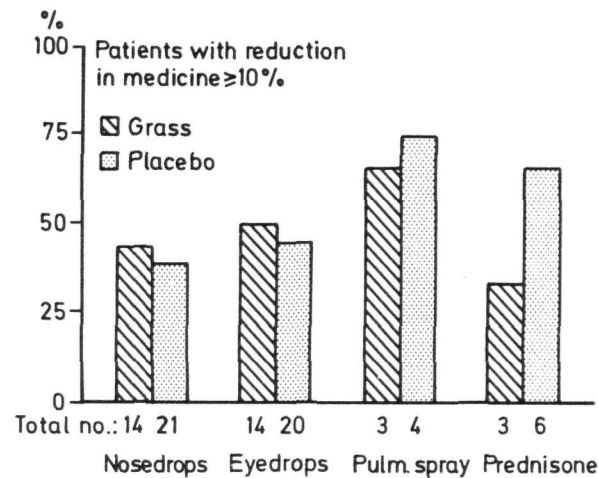


Fig. 2. Proportion of patients with improvement in medicine consumption of 10% or more following 9-10 months of treatment. Figures below indicate the total number of patients taking the various types of medication. $P > 0.05$ (Fisher's exact test).

release from blood cells. Changes during treatment were non-significant and there was no difference in change between groups.

Side effects

No patients on placebo tablets complained of severe symptoms or other possible side effects with a duration of more than 2 weeks. In the actively treated group, five patients with no previous skin symptoms developed attacks of urticaria or angioedema, all having received the planned maintenance dose for 4 to 13 weeks. In two of these patients, symptoms were preceded by vigorous physical activity, one had had an injection of local anaesthetics, one had received a β -receptor-antagonist, whereas the last could not report on any external cause which could be related to the skin symptoms.

Table 1
Basic data on inclusion

Treatment	Age		Sex		Pollen asthma N	CPT*	SPT**
	mean	range	M	F			
Grass	27	(15-38)	13	7	3	3.3	3.4
Placebo	27	(17-38)	14	8	4	3.0	3.4

* Mean sensitivity in conjunctival provocation test expressed as concentration in BU/ml (log-transformed) eliciting positive response
** Mean sensitivity in skin prick test expressed as concentration in BU/ml (log. transformed) giving reaction equivalent to 10 mg/ml histamine

One patient continued on the same dose and reacted again before leaving the study. In the four other patients the dose was reduced to 50 % during the rest of the study and no relapse occurred. One patient with urticaria and two further patients reported slight abdominal distension during various periods with a total of at least 2 weeks. In the two patients with abdominal symptoms alone, results from CPT did not change, and the scores deteriorated during season. All five patients with urticaria showed improvement in CPT, mean increase being a 7.9-fold increase in tolerated concentration compared to 2.6 in the rest of the actively treated and 4.4 in the placebo group (differences were non-significant, $P > 0.05$). In parallel, log books indicated an aggravation in one and unchanged symptoms in the three other assessable patients. As in the whole material, RAST and SPT did not change significantly in this subgroup.

DISCUSSION

Compared to the beneficial treatment effect of OH shown in adults with birch pollinosis (15), the results of this grass pollen trial were surprising as no changes in SPT, CPT, clinical and serological parameters emerged after 1 year of

OH. This observation, however, agrees well with a previous similar study (14) using much lower doses of grass pollen allergen. In the birch pollen study (15), a significant change was found in symptom scores, self-assessment, CPT, SPT as well as birch-specific IgE- and IgG-antibodies. Despite the lack of serological changes in the present study, five of our actively treated patients actually had urticaria and/or angioedema and – even more surprisingly – after several weeks on the maintenance dose. At least in one case it seemed most unlikely that anything beside grass pollen induced the reaction. Urticaria during OH is well known (1, 16, 20). In a successful birch OH study (15), urticaria was observed in one case during up-dosing but after a short reduction period, the patient succeeded in reaching maintenance dose without further side effects.

The cumulative dose in the present study was more than 3,000 mio. BU of grass pollen allergen within only 1 year. On average, the patients received a 20 times higher dose per day, expressed in BU, than the birch pollen patients in the study previously reported (15). Compared to conventional subcutaneous OH, the accumulated grass pollen dose was more than 4,000 times higher in the present study. The formulation of the enterosoluble tablets did not differ from that in the birch pollen study. Therefore it is likely that the tablets did dissolve in the upper intestine. Preliminary studies indicate that the allergenic components of birch pollen are more stable in intestinal fluid than those of grass pollen. It could be speculated that, after being released in the intestine, the grass pollen allergens disintegrate at a high rate, impairing the penetration of the intestinal wall. Therefore no immunological response is achieved.

Before starting further trials using grass pollen in OH, a new formulation of grass pollen should be developed. Such a formulation should be at least as stable in intestinal fluid as birch pollen.

Table 2

Assessment based on log books combining changes in medicine consumption and symptom scores. Unchanged status indicates changes < 10 % in both medicine and symptoms or changes of these parameters in opposite directions. $P > 0.05$

Treatment	Improved (%)	Unchanged (%)	Aggravated (%)
Grass	4 (24)	6 (35)	7 (41)
Placebo	6 (29)	2 (10)	13 (62)

Table 3

Self-assessment after 1 year of treatment. $P > 0.05$

Treatment	Improved (%)	Unchanged (%)	Aggravated (%)
Grass	7 (44)	7 (44)	2 (13)
Placebo	11 (58)	3 (16)	5 (26)

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