

Orally Administered Grass Pollen

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In 1900 it was claimed that oral administration of ragweed could be used for the hyposensitization of hay fever patients. Several uncontrolled trials have been published, all showing an effect of oral hyposensitization. Only one study was controlled and showed no effect of oral hyposensitization. It was decided to undertake controlled clinical trials to determine the safety and effectiveness of orally administered enteric-coated grass pollen tablets in patients with hay fever. The actual grass pollen dose in the first trial was 30 times the dose that is normally recommended for preseasonal oral pollen hyposensitization using pollen aqueous solution or pollen powder. The safety study will be described here. Twelve young adults with a history of grass pollen hay fever positive skin prick test and positive nasal provocation test with extracts of timothy grass pollen were randomly allocated to one of the treatment groups with four patients in each group taking enteric-coated Conjuvac Timothy tablets or enteric-coated Whole Timothy pollen tablets or enteric-coated placebo tablets. The study was double blind. Preseasonally, the patients received 342,500 PNU and in total they received 4,500,000 PNU during 6 months. The patients receiving active treatment did not have any side effects. No significant changes were shown in the skin and nasal reactivity to grass pollen during the study. Neither were there any changes in timothy-specific IgE, IgG, total IgE nor histamine liberation from basophils.

Key words: grass pollen; hyposensitization; immunotherapy; safety study; oral administration.

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One hundred years ago it was reported that the American Indians could reduce the intensity of allergic skin reactions due to poison ivy simply by eating the leaves of a related plant (*Rhus* leaves) (10).

In 1900 it was claimed (6) that oral administration of ragweed could be used for the hyposensitization of hay fever patients. For many years oral hyposensitization with various allergens has been used in certain countries (West Germany, Switzerland, Austria and Spain) in the treatment of allergic asthma and rhinoconjunctivitis. Several uncontrolled trials have been published, all showing an effect of oral hyposensitization (2, 4, 7, 8, 9, 11, 16, 18, 19). One controlled study has shown no effect of oral hyposensitization (15).

It was decided to undertake controlled clinical trials to determine the safety and effectiveness of orally administered enteric-coated grass

pollen tablets in patients with hay fever. The actual grass pollen dose in the first trial was 30 times the dose that is normally recommended for preseasonal oral pollen hyposensitization (19). It was also important in a safety study to test the mechanical and pharmaceutical tolerance of the enteric-coated grass pollen tablets in grass pollen-allergic patients. The safety study included 12 hay fever patients and the efficacy study included 56 hay fever patients.

The safety study will be described here. The efficacy study will be described elsewhere.

METHOD AND MATERIAL

The safety study was carried out from March to September 1981. Twelve young adults (9 males and 3 females) with a history of grass pollen hay fever were admitted to the study. All had a positive skin prick test and positive nasal

provocation test with extracts of timothy grass (*Phleum pratense*) pollen. None had received immunotherapy with grass pollen extract during the preceding 3 years. All gave informed consent to participate. The 12 patients were randomly allocated to one of three treatment groups with four patients in each group taking:

- A. Enteric-coated Conjuvac Timothy (*Phleum pratense*) tablets.
- B. Enteric-coated Whole Timothy pollen (*Phleum pratense*) tablets.
- C. Enteric-coated placebo (lactose) tablets.

The pigmented enteric coat consisted of polyvinyl acetate phthallate applied in methanolic solution. The pigments were non-allergenic iron oxides or titanium dioxide giving colours of red, yellow and white for top (10,000 PNU), middle (1,000 PNU) and bottom (100 PNU) tablet strengths respectively. A film thickness equivalent to an approximate tablet weight gain of 6–7% ensured they withstood 2 h immersion in 0.1 M HCl at 37°C in a tablet disintegration apparatus. When 0.1 M HCl was replaced by mixed phosphate buffer at pH 6.8, tablet disintegration occurred in 3 to 7 min (European Pharmacopoeia). The tablets were manufactured and provided by Dome/Hollister-Stier. The trial was double blind.

The patients took the tablets on an empty stomach, early in the morning together with 100 ml cold water. The dosage schedule was as shown in Table 1.

When no adverse effects had been reported after 10 weeks on this dose it was decided to increase the dose 10 times to determine whether this dose was also tolerated. The dosage schedule was as shown in Table 2.

Preseasonally, the patients received 342,500 PNU and in total they received 4,500,000 PNU during the study. Skin prick using a positive reference of histamine chloride 1 mg/ml and negative control according to the Nordic guidelines (5) and nasal provocation testing with timothy (from Allergologisk Lab.®) were carried out before and after the grass pollen season. The following immunological investigations were carried out before the investigation, after 7 days, 14 days, 1 month, 2 months, 3 months,

and 5 months: histamine liberation from basophils, total IgE, allergen specified IgE (RAST), allergen-specific IgG, crossed radioimmuno-electrophoresis (CRIE), IgA, and IgM. All 12 patients completed diary cards during the study. Analyses were restricted to week numbers 13–31 inclusive. This period represented 19 weeks between March and August 2, 1981, which was the longest continuous period for which all patients' diary card results were available. Nose, eye, lung, and gastrointestinal tract symptoms were recorded daily. The medication of seasonal symptoms was standardized and recorded in the diary. As the first drug of choice the patients were asked to use Antistin-Privine® nose and eye drops. If this was not sufficient to

Table 1

The first 10 doses were administered in the allergy clinic and the patients remained there for the following hour. Subsequent doses were self-administered by the patient at home, 10,000 PNU on alternate days before breakfast

Day	PNU
1	100
2	200
3	400
4	800
5	1000
6	2000
7	4000
8	6000
9	8000
10	10000

Table 2

Dose increases were made in the allergy clinic, after which patients continued on a dose of 100,000 PNU on alternate days self-administered at home before breakfast

Dose schedule	PNU
Next dose	20,000
2 days later	30,000
2 days later	40,000
2 days later	60,000
2 days later	80,000
2 days later	100,000

treat symptoms the patients were allowed to take prednisone tablets, 5–10 mg in the morning.

RESULTS

The investigation showed that grass pollen allergic patients did not have any side effects when grass pollen was administered orally in enteric-coated tablets during a period of 6 months. In the last 3½ months of the trial the patients received 100,000 PNU on alternate days. No significant changes were shown in the skin and nasal reactivity to grass pollen during the study. Neither were there any changes in timothy-specific IgE, specific IgG, total IgE nor histamine liberation from basophils. We found no significant changes in medication score, or symptoms scores from nose, eye, and lung, between the placebo group and the two active groups.

DISCUSSION

A large number of recent studies have shown that it is possible to induce tolerance by oral administration of the allergen (14). The principal function of the gastrointestinal tract is that of digestion and absorption of nutrients. Until recently it was presumed that intraluminal protein antigens are completely digested and are thus not transported in an appreciable quantity across the epithelium into the lamina propria or systemic circulation. However, there is increasing experimental and clinical evidence to suggest that large antigenic molecules can penetrate the intestinal epithelial surface in quantities of no nutritional importance but possible immunological significance (17).

The classical studies of Chase in 1946 first demonstrated that the administration of simple chemicals such as picryl chloride would lead to hypo-responsiveness to systemic contact hypersensitivity to the specific antigen (3). Studies in the early 1960's suggest that the liver may play a critical role, since injection of picryl chloride into the mesenteric vein produces solid tolerance while jugular vein or intraperitoneal injection of

the same agents was not as tolerogenic (1). Several studies have suggested that particular portions (fragments) of certain proteins such as β -galactosidase, bovine serum albumin and lysozyme appear to be tolerogenic, perhaps through their ability to induce suppressor cells. Recent studies in mice indicate that oral tolerance can be produced not only in classical soluble proteins, such as ovalbumin and human gammaglobulin, but also in ragweed antigen (both short ragweed and purified antigen E) (14). The systemic tolerance resulting from oral immunisation with ragweed includes the formation of antibodies of the type IgA in saliva, while such antibodies are apparently absent from serum (14).

In earlier clinical trials concerning the efficacy of oral hyposensitization it was most common to use aqueous allergen solution or allergen administered as powder. Only in two trials in 1927 (12) and 1942 (13) have enteric-coated tablets been used in the oral treatment of ragweed hay fever.

All previous studies concerning the efficacy of oral hyposensitization are uncontrolled except for one trial in 1982 (15). In the uncontrolled studies most investigators found a treatment effect, particularly when using house dust mite and various grass pollens. In the controlled trial placebo and an aqueous solution of house dust mite with a cumulative dose of 36,000 PNU administered during a period of 42 weeks was used. This is the normal recommended dose for oral hyposensitization with house dust mite allergens in Germany and Austria. The treatment showed no effect. This cumulative dose of house dust mite allergens is remarkably low. Using subcutaneous hyposensitization with house dust mite the recommended maintenance dose is 10,000 PNU every 4 to 6 weeks (Allpyral®). Normally, it takes 11–12 weeks to reach the maintenance dose of 10,000 PNU. During the initial house dust mite hyposensitization, for a period of 42 weeks the cumulative dose would be 100,000 PNU, three times as much as normally given by oral hyposensitization. Due to protein digestion in the stomach and intestine it is almost a certainty that only a small percentage of orally administered aller-

gens will reach the intestinal wall completely intact and be available for absorption/persorption. When one compares the cumulative doses in the two different hyposensitization regimens it is not surprising that no treatment effect was found.

For pollen hay fever patients the recommended oral hyposensitization dose is a total of 160,000 PNU (19) (pollen from Purex® given preseasonally for 20 weeks). Comparing the same required cumulative dose by subcutaneous hyposensitization the dose would be 50,000 PNU (Allpyral).

In two previous uncontrolled studies enteric-coated tablets have been used in oral grass pollen hyposensitization (12, 13). In the literature concerning oral hyposensitization some investigators suggest that variable denaturation of allergen proteins may occur in the stomach due to the acid and in the intestine due to enzymatic activity. This, however, has not been systematically investigated. In order to avoid grass pollen inactivation in the stomach we used enteric-coated tablets.

In this pilot study the patients received a cumulative dose of 4.5 million PNU of grass pollen, 30 times as much as used in previously published reports on grass pollen allergic patients. We did not find any systemic side effects, and the gastrointestinal side effects were the same in the placebo group and the treatment groups. In many clinical trials it has been claimed that during oral hyposensitization it is possible to induce asthma, rhinoconjunctivitis and urticaria, but that gastrointestinal side effects are commonest. Gastrointestinal symptoms are most often diarrhoea and stomach-ache. In the literature it appears that anaphylactic reactions have not been described.

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