

Local Immunotherapy of Seasonal Allergic Rhinitis in Children Due to *Parietaria officinalis* Pollen: A Preliminary Report

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ABSTRACT

Fifteen children presenting with a typical allergic rhinitis due to the pollens of *Parietaria officinalis* were investigated. Diagnosis was confirmed by history, physical examination, skin tests, radioallergosorbent test, and the nasal provocation test. Patients were separated into two groups: Ten received specific nasal immunotherapy and five were on placebo. Results were assessed on the following criteria: diminution of clinical symptomatology, reduction of the quantity of medication required to control symptoms, and results of provocation nasal tests, that showed an increase of the end point, which is the maximum tolerated dose. Compared to a placebo group, the ten children showed a significant improvement in all the cases without any side effects.

INTRODUCTION

IN RESPIRATORY ALLERGY, specific immunotherapy has been, until now, the most utilized specific treatment. However, besides the classical treatment by the parenteral route, new therapeutic approaches have been tried using the local nasal route. This technique, however, is not very new since it was already employed at the turn of the century by N.P. Dumbar in 1913⁽¹⁾ and later by H. Herxheimer in 1952,⁽²⁾ and by O. Swineford in 1955.⁽³⁾ Since 1975, it has been revisited by S.B. Mehta in 1975,⁽⁴⁾ H. Deuschl et al. in 1977,⁽⁵⁾ and M. Bardare et al. in 1988.⁽⁶⁾

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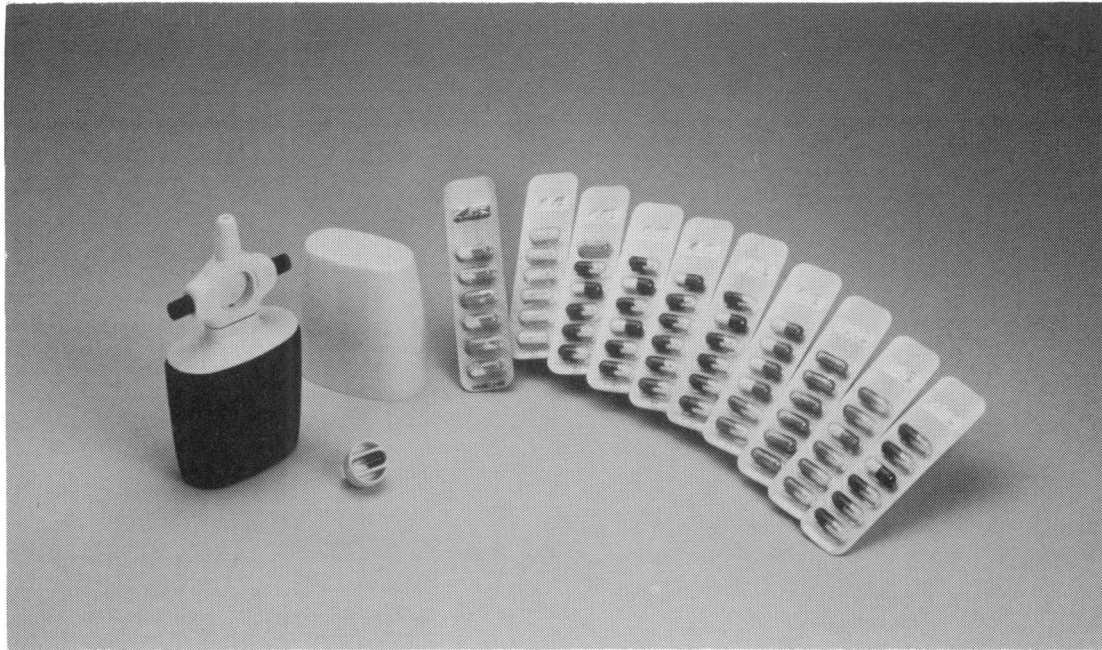


FIG. 1. Apparatus and capsule for nasal insufflation.

Recently, a new technique has been developed incorporating allergens in granulometrically controlled powder form, suitable for naso-bronchial insufflation.⁽⁷⁻⁸⁾ Using this technique, problems, such as the decomposition of allergens in solution, the lack of precision in the quantity administered, and possible consequence of the use of preservatives (which affect the ciliated cells motility), were all overcome.

TABLE 1. CLINICAL AND IMMUNOLOGICAL DATA

Cases	Age	Gender	Skin tests to P. officinalis	Other skin tests positive	RAST	Nasal provocation test ^a
1	10	M	2+	GR2 OL2	2	10
2	12	M	4+	GR2	3	40
3	13	F	2+	0	2	20
4	12	M	4+	GR2	3	10
5	11	M	4+	DP2	4	40
6	10	F	3+	DP3	2	10
7	14	M	3+	0	4	40
8	11	M	2+	GR1	2	20
9	12	F	2+	0	3	20
10	13	F	3+	0	4	20
11	10	M	2+	GR2	2	10
12	14	M	2+	0	2	10
13	12	F	3+	DP2	3	20
14	10	M	3+	0	4	40
15	13	F	4+	0	4	40

Mean age: 11, 8; D.S. = 1, 42. GR, grasses pollen; OL, *O. europea*; DP; *D. pteronyssinus*.

^aThreshold of sensitivity in AU.

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Only grass pollens and mites were used and then primarily with adults.⁽⁹⁻²⁰⁾ No attempts were made with *Parietaria officinalis* pollens among children. We performed this study of local intranasal immunotherapy (LII) only in children presenting with an allergic rhinitis due to the pollens of *P. officinalis*.

PATIENTS AND METHODS

Methods

We used a powdered allergic extract standardized in U.A. (Allerkin-Parietaria [Lofarma, Milan, Italy]). AU (Allergenic Units) were based on the radioallergosorbent test (RAST) inhibition technique in comparison with an internal standard, the potency of which was determined by skin tests on allergic volunteers. Polystyrene beads were used as solid supports and the 125-anti-IgE for the RAST-inhibition were from a commercial source (Sferikit-specific-IgE [Laboratorio Farmaceutico Lofarma, Milan, Italy]). Technical procedures and statistical analysis of experimental data were done according to H.C. Anderson and H. Baer.⁽²¹⁾

Allerkin-specific desensitizing insufflation therapy consists of capsules designed for use with an insufflator (Fig. 1). The allergens are extracted from pollens of the highest grade of purity and subjected to purification processes necessary to obtain the fraction 5KD.

Increasing antigen amounts are incorporated in 25 mg of lactose. The insufflator generates a powder with a mean particle size of 35 μ m.

Skin testing. Prick testing was performed with the Dome Hollister lancet (Via Certosa, Milan, Italy). Extracts were kindly provided by Lofarma Laboratories (Milan, Italy) and were used in a 1/20 solution (wt/vol). We adopted the following scores: A 3+ reaction corresponds to the wheal and erythema of the

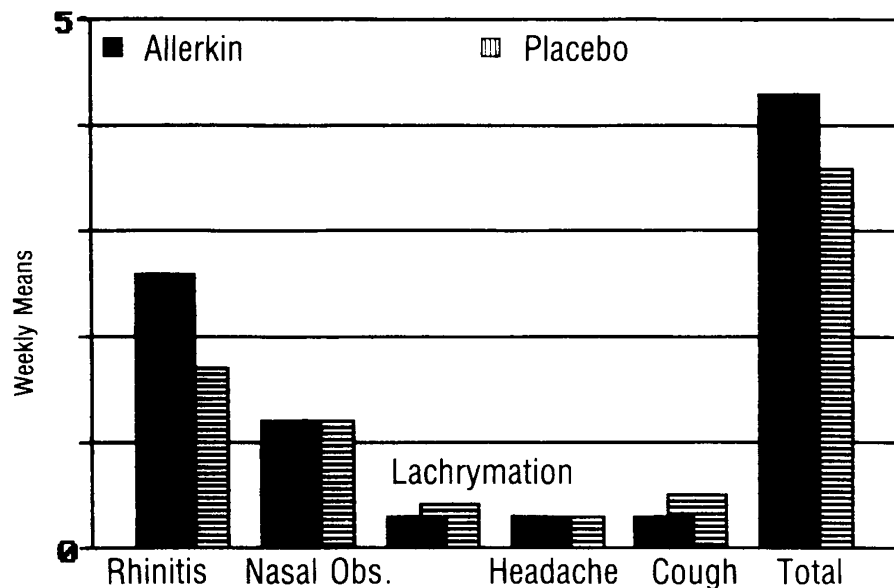


FIG. 2. Pre-seasonal symptoms score. No statistically significant difference between allerkin and placebo.

histamine prick test. A 4+ reaction corresponds to a greater reaction than that to histamine. A 2+ reaction is 75%, and a 1+ reaction is half the size of the histamine reaction.

Rast. The RAST was performed as described by L. Wide et al.⁽²²⁾ The following commercial reagents, purchased from Lofarma, Milan, Italy (Sferikit®) were used:

- 1) solid phases: commercial polystyrene balls 6.4 mm in diameter covalently coated with allergens
- 2) a reference system: *Poa pratensis* solid phases and human grass-positive serum pool
- 3) a tracer: ¹²⁵I-labelled antihuman antibody raised in goats. The bound radioactivity was measured by a γ counter (Packard 800 [Cammerra Packard, Milan, Italy]) and the percent of bound radioactivity calculated.

We used the same extracts as the ones used for the prick test. We followed the Phadebas RAST Units System (PRU)

Detection of IgG antibodies in serum and nasal secretions. The test was performed following the common ELISA technique, with some modifications that are briefly described.

Reagents. The antigens of grass pollen, *Parietaria* pollen and *Dermatophagoïdes pteronyssinus* were extracted at the concentration of 5% w/vol in PBS, dialyzed and covalently bound to glutaraldehyde-activated polystyrene eight-well strips (Titertek™ [Daltec Instrument, Milan, Italy], Eflab) according to the procedure described in Italian Patent Number 1218348.

The serum samples were diluted 1:100 with ELISA-diluent (phosphate buffer saline [PBS] 0.15 M, pH 7.2, Tween 20 R 0.05%) containing BSA 5%.

Goat antihuman-IgG antibodies peroxidase-conjugated (Sigma, Milan, Italy) were diluted before use in 1/1000 with ELISA-diluent.

The substrate was orthophenylendiamine (OPD, Kem-en-tec [DK-2100, Copenhagen, Denmark]): 4.0 mg (2 tablets) were dissolved before use in 15 ml of phosphate-citrate buffer 0.15 M, pH 5.0 and 5 μ l of H₂O₂ 30% were added to the solution.

Test procedure. 1) 100 μ l of the sample were incubated in each well for 1 h.

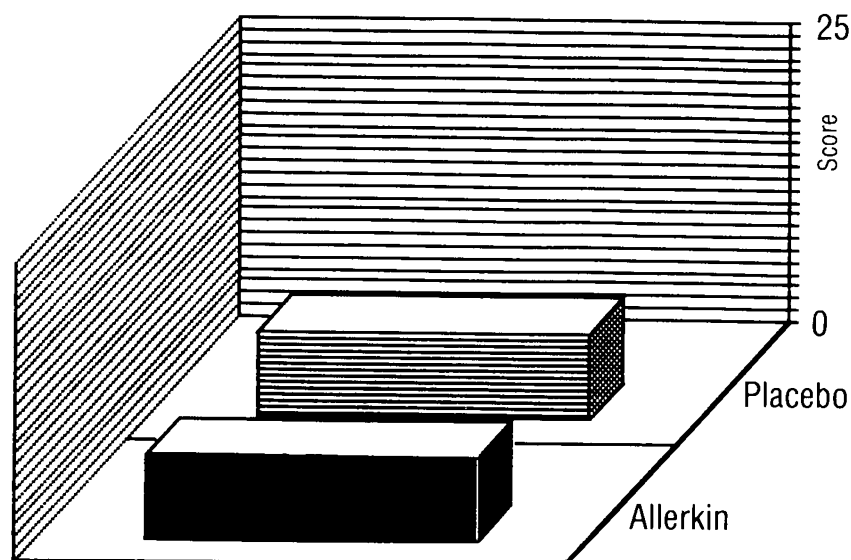


FIG. 3. Pre-seasonal medication score. No statistically significant difference between allerkin and placebo.

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2) After a cycle of 5 washings with PBS containing Tween 20 R 0.05%, 100 μ l of anti-IgG conjugate were added and incubated for 1 h.

3) After a washing cycle as above, 100 μ l of OPD substrate were added and incubated for 30 min in the dark.

4) The reaction was blocked by adding 50 μ l of H_2SO_4 1M, and OD read at 492 nm.

Calculation of results. The ratio between optical density (OD) of sample and of human normal serum is calculated to determine the P/N value: $P/N < 2.5$: not detectable or low; $2.5 < P/N < 6$: medium; $6 < P/N < 9$: high; $P/N > 9$: very high.

Nasal provocation test. We utilized the Youlten (Lansona, Bologna, Italy) peak inspiratory flow meter (PIFRn meter).⁽²³⁾ It offers some advantage over the expiratory flow rate meter, especially when used in provocation tests and it is easier to handle compared with standard rhinomanometry. The results are expressed as the mean values of three consecutive registrations. A test was considered as positive when we observed a drop in the basic value of 20% or more after instillation of at least 20 allergenic units AU of a solution of the allergen.

Protocol of treatment. A premedication with dichromoglycate 20 min before the testing was used to prevent untoward reactions. Capsules containing an increasing dose of extract of pollens (*P. officinalis*) from 2.5 to 320 AU in the following order 2.5, 5, 10, 20, 40, 60, 80, 160, 320 were used.

The allergen was autoadministrated with a one-way rhino-sprayer every two days alternatively in one nostril. In order to avoid the insufflation of the allergen to the bronchi, patients were told to vocalize during each administration. The total dose ranged from 3225 to 4132 AU. The starting dose was based on the nasal provocation test. The maximal tolerated dose was repeated. The duration of the treatment was for 12 wks.

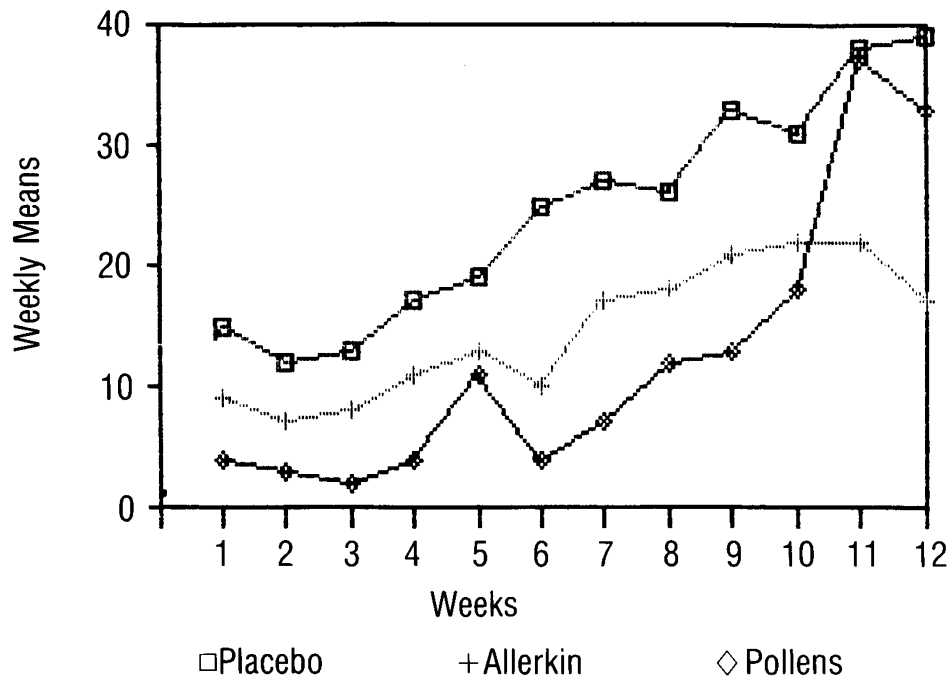


FIG. 4. Seasonal symptoms. Correlation between allerkin, placebo and pollen count.

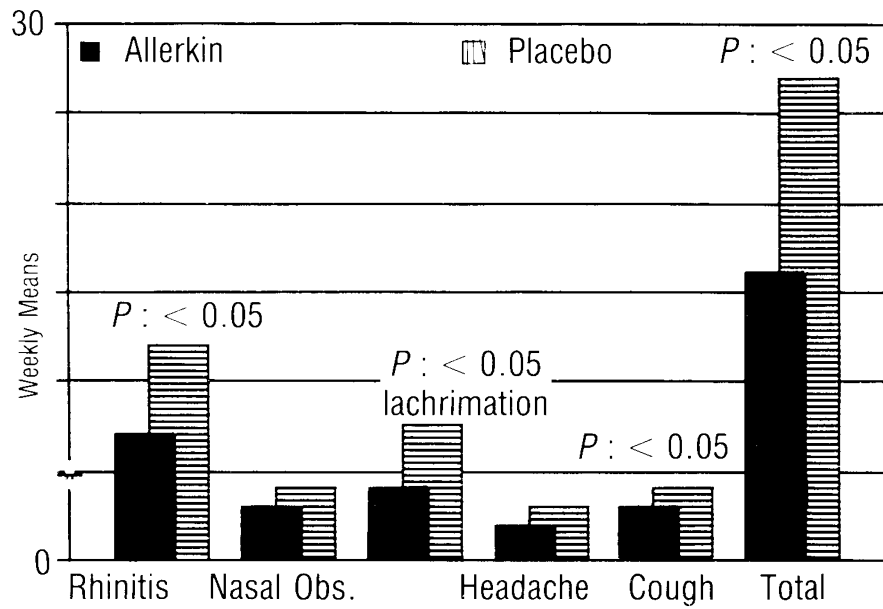


FIG. 5. Seasonal symptoms score. Statistically significant difference between allerkin and placebo.

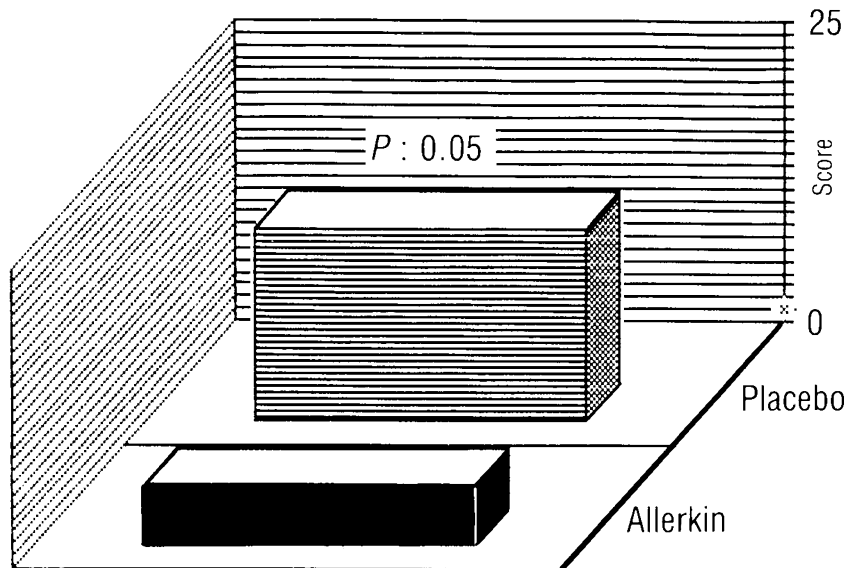


FIG. 6. Seasonal medication score. Statistically significant difference between allerkin and placebo.

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Patients

We selected fifteen patients from ten to fourteen years old (average age 11.6 SD = 1.65); the group consisted of nine boys and six girls presenting with an allergic rhinitis due to the pollens of *P. officinalis*. The pollen season of *P. officinalis* starts in Italy, depending upon specific areas, between January and March and

TABLE 2. SKIN TESTS, IGE AND IGG LEVELS BEFORE AND AFTER TREATMENT IN THE TREATED GROUP AND THE PLACEBO GROUP: STATISTICAL ANALYSIS OF VARIANCE

<i>Skin tests</i>			
	<i>Area before</i>	<i>Area after</i>	<i>Analysis of variance</i>
Treated group	Mean: 131.3 SD: 76.79	Mean: 130.50 SD: 78.06	<i>t</i> : 0.85 <i>P</i> : 0.417 NS
Control	Mean: 92.8 SD: 6.72 <i>t</i> : 1.24 <i>P</i> : 0.086 NS	Mean: 91.80 SD: 7.22 <i>t</i> : 0.37 <i>P</i> : 1.22 NS	<i>t</i> : 1.12 <i>P</i> : 0.326 NS
<i>Serum IgE</i>			
	<i>Area before</i>	<i>Area after</i>	<i>Analysis of variance</i>
Treated group	Mean: 20.13 SD: 5.18	Mean: 23.09 SD: 6.96	<i>t</i> : 2.01 <i>P</i> : 0.07 NS
Control	Mean: 3.26 SD: 1.47 <i>t</i> : 1.6 <i>P</i> : 0.95 NS	Mean: 2.96 SD: 1.11 <i>t</i> : 1.42 <i>P</i> : 0.66 N.S.	<i>t</i> : 0.37 <i>P</i> : 0.38 NS
<i>IgE in nasal secretions</i>			
	<i>Area before</i>	<i>Area after</i>	<i>Analysis of variance</i>
Treated group	Mean: 16.6 SD: 9.5	Mean: 17.92 SD: 9.4	<i>t</i> : 0.66 <i>P</i> : 0.52 NS
Control	Mean: 17.14 SD: 0.93 <i>t</i> : 0.79 <i>P</i> : 0.42 NS	Mean: 18.38 SD: 4.6 <i>t</i> : 0.16 <i>P</i> : 0.95 NS	<i>t</i> : 0.71 <i>P</i> : 0.51 NS
<i>Serum IgG</i>			
	<i>Area before</i>	<i>Area after</i>	<i>Analysis of variance</i>
Treated group	Mean: 3.26 SD: 1.47	Mean: 2.96 SD: 9.4	<i>t</i> : 1.29 <i>P</i> : 0.23 NS
Control	Mean: 3.48 SD: 1.16 <i>t</i> : 1.18 <i>P</i> : 0.85 NS	Mean: 2.88 SD: 0.54 <i>t</i> : 1.24 <i>P</i> : 0.80 NS	<i>t</i> : 1.82 <i>P</i> : 0.14 NS
<i>IgG4 nasal secretion</i>			
	<i>Area before</i>	<i>Area after</i>	<i>Analysis of variance</i>
Treated group	Mean: 1.75 SD: 1.83	Mean: 1.45 SD: 1.35	<i>t</i> : 0.45 <i>P</i> : 0.65 NS
Control	Mean: 3.48 SD: 1.16 <i>t</i> : 0.42 <i>P</i> : 0.157 NS	Mean: 2.88 SD: 0.54 <i>t</i> : 0.71 <i>P</i> : 0.42 NS	<i>t</i> : 0.76 <i>P</i> : 0.49 NS

SD, standard deviation; NS, not significant.

ends between September and December. These patients had not received any hyposensitization treatment during the last three years. We also exclude patients with a history of recent respiratory infection, nasal polyps, or recent use of nasal steroids.

Diagnosis was made on the following basis: Anamnesis, history, a physical examination, positive skin tests (prick), positive RASTs (at least class II), and a positive nasal provocation test to the allergen also standardized in AU (Lofarma, Milan, Italy). Patients were also tested with a panel of allergens that included grass pollens, *Olea europea* pollen, *D. pteronyssinus*, and *Alternaria tenuis*. In a few cases, there was also a skin positivity to some of these allergens but the main clinical sensitization was to *P. officinalis* pollen (Table I).

In every case, at the beginning and at the end of the treatment, the following data were gathered:

- 1) threshold of skin reactivity by prick test, using progressively greater concentrations of the allergen
- 2) specific IgE and IgG in sera and in nasal secretions
- 3) nasal provocation test with *P. officinalis* allergen in macronized powder

For each patient, the symptoms (nasal blockage, sneezing, nasal itching, rhinorrhea, and lacrimation) and the use of drugs were maintained in a diary. The patients were only allowed to take antihistamines. The physician who controlled the patients did not know which patient had received real treatment or a placebo.

In conjunction with our investigation, a monitoring of the pollens in the atmosphere was made and correlated statistically with the symptoms.

Our study was conducted before the start of the pollen season of *P. officinalis*, i.e., between January and March.

The fifteen patients were divided into two groups: ten received the active allergens, five received a placebo.

Statistical analysis. An analysis of variation allowed us to compare the mean values of the two groups.⁽²⁴⁾ Separation of total variation into partial variations was arrived at by using Student's *t* test (null hypothesis).

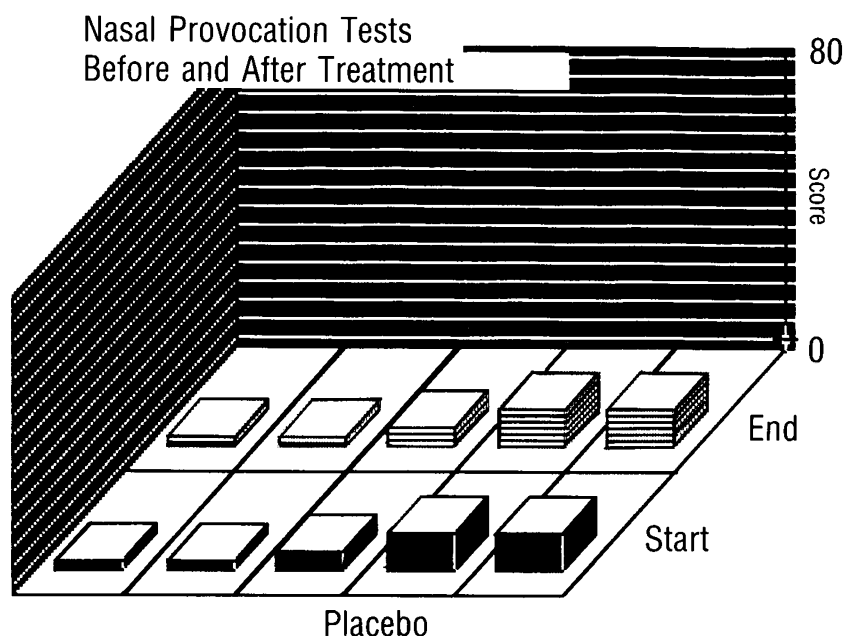


FIG. 7. No statistically significant difference between the beginning and the end of the treatment.

When the probability in favor of the null hypothesis is not superior to 5% ($P = 0.05$) it is assumed that there is a significant difference between the two groups. When the probability is inferior to 1% ($P = 0.01$) there is a highly significant difference.

RESULTS

During that part of treatment that was conducted before the pollen season, we observed no difference between the group that received the therapy and the group that received a placebo, as far as symptomatology and the use of drugs were concerned. ($P > 0.05$) (Fig. 2 and Fig. 3).

Conversely, during the pollen season and at the end of the treatment, we found statistically significant differences between the group treated with Allergen-Parietaria and the placebo group ($P < 0.05$). Results of symptomatology are recorded in Figure 4 and Figure 5, and results concerning consumption of drugs are recorded in Figure 6. In Figure 4, it is easy to see the correlation between a placebo or Allergen-Parietaria and the pollen counts.

We found no significant difference between the two groups before and after treatment as far as skin tests, levels of IgE and IgG in blood, and nasal secretions were concerned (Table 2).

However, in contrast to these findings, the threshold of nasal reactivity measured by the nasal provocation test, before and after treatment, remained the same in the placebo group but was significantly increased in the treated group ($P < 0.005$) (Fig. 7 and Fig. 8).

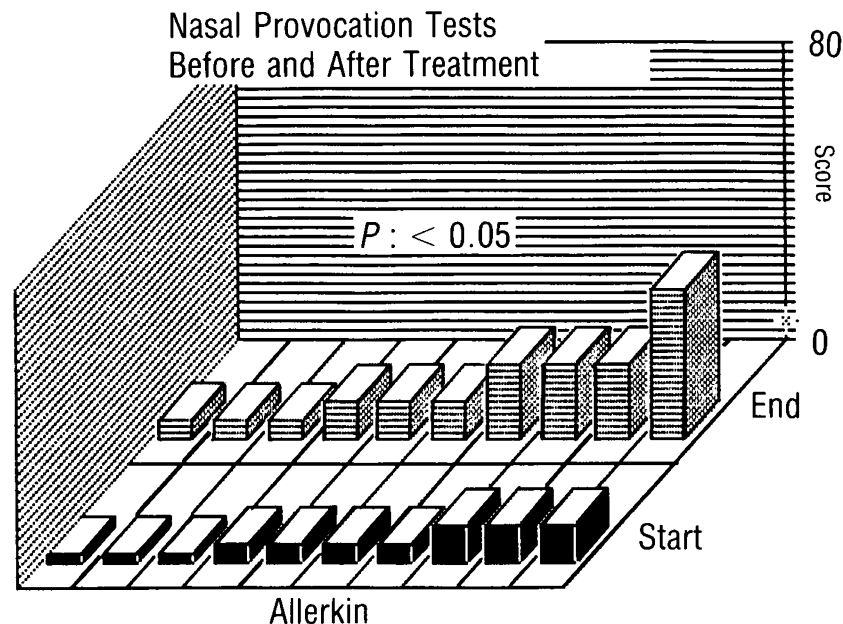


FIG. 8. Statistically significant difference between the beginning and the end of treatment.

DISCUSSION

According to clinical data (the decrease in symptoms, the diminished use of drugs, and the lowering of the threshold of sensitivity assessed by a nasal provocation test), it seems that local immunotherapy is a safe and effective treatment of the allergic rhinitis due to the pollens of *P. officinalis*, when compared to the use of a placebo.

However, it has not been possible to compare these data with those obtained by the classical parenteral route of immunotherapy. In addition, this study was not conducted using a double-blind technique.

Local nasal immunotherapy was performed very recently in two studies, as we did, with lyophilized allergens in macronized powder form. The first one⁽²⁵⁾ dealt with a group of twelve adult patients presenting with a *Dermatophagoides*-induced rhinitis; in the second one, *P. officinalis* pollen were used on 24 adult subjects suffering from allergic oculo-rhinitis.⁽²⁶⁾ In both cases, the results were good with a double-blind controlled study. No significant reactions were observed. As far as we know, no similar studies were conducted on children. The mechanism underlying the clinical benefits of this form of immunotherapy is not clear although three possibilities can be suggested: A local immunological response, a systemic immunological response, and induction of a specific tolerance. The absence of difference in IgE and IgG levels in blood and in nasal secretions between the two groups of patients before and after treatment and the increase of the threshold of nasal reactivity in the treated group suggest that more likely the third mechanism is involved.

It is interesting to note that the patients had no side effects (headache, cough, or aggravation of nasal symptoms); and that all 15 were able to complete their treatment. No one complained of a late-phase reaction. Clinical parenteral immunotherapy is not always well accepted by children; therefore, local immunotherapy may be a good substitute in children presenting with allergic rhinitis due to pollens or to other airborne allergens.

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