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Original article

A double-blind, placebo-controlled comparison of treatment with fluticasone propionate and levocabastine in patients with seasonal allergic rhinitis

Key words: fluticasone propionate; levocabastine; seasonal allergic rhinitis.

Fluticasone propionate aqueous nasal spray (FPANS) is a topically active glucocorticoid which has been successfully used for the treatment of seasonal allergic rhinitis (SAR). Topical levocabastine is a highly selective H₁ antagonist which has been proposed as an alternative treatment of SAR. The purpose of this study was to compare the clinical efficacy of two topical nasal treatments, FPANS and levocabastine, in the treatment of SAR. Additionally, the effect of treatments on nasal inflammation was examined during natural pollen exposure. A group of 288 adolescent and adult patients with at least a 2-year history of SAR to seasonal pollens participated in a multicenter, double-blind, double-dummy, and placebo-controlled study. Patients were treated with either FPANS 200 µg, once daily ($n=97$), or topical levocabastine, 200 µg, given twice daily ($n=96$), or matched placebo ($n=95$) for a period of 6 weeks, starting from the expected beginning of the pollen season. Clinically relevant pollens included *Parietaria*, olive, and grass. Assessment of efficacy was based on scores of daily nasal symptoms and on nasal cytology of nasal lavage. Nasal lavage was performed immediately before, during, and at the end of treatment in 39 patients. FPANS significantly increased the percentage of symptom-free days for nasal obstruction on waking and during the day, rhinorrhea, sneezing, and itching. FPANS provided a better control for night and day nasal obstruction ($P<0.02$ and $P<0.01$) and rhinorrhea ($P<0.01$) than levocabas-

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tine. In addition, fewer patients treated with FPANS used rescue medication ($P < 0.025$). The percentage of eosinophils in nasal lavage was reduced only during treatment with FPANS. The results of this study indicate that FPANS 200 µg, once daily, provides a better clinical effect than levocabastine 200 µg, twice daily, in patients with SAR. Unlike levocabastine, FPANS significantly attenuates nasal eosinophilia during pollen exposure, a feature which may explain its therapeutic efficacy.

Seasonal allergic rhinitis (SAR) is a common disease characterized by nasal obstruction, rhinorrhea, sneezing, and itching (1). Treatment options for allergic rhinitis include cromolyn or nedocromil sodium, oral or topical antihistamines, and topical corticosteroids (1–3). It has been shown that topical antihistamines are as effective as oral (4), with very little difference. Topical antihistamines such as levocabastine demonstrate a rapid onset of activity, a marked effect on nasal symptoms, and fewer side-effects (5). Levocabastine is a potent and selective histamine H₁-receptor antagonist and has proved to be highly effective in controlling nasal symptoms in SAR (6, 7) and to be a valuable clinical alternative to topical cromolyn (8) or oral terfenadine (9) in the treatment of nasal symptoms in patients with allergic rhinitis.

In recent years, topical nasal corticosteroids have been established as the first-line treatment for SAR (2, 3). Among them, fluticasone propionate, as aqueous nasal spray (FPANS), has been shown to be safe and effective in the treatment of both seasonal and perennial rhinitis, even when administered as a single daily dose of 200 µg (10–13). In patients with SAR, FPANS 200 µg once daily has been shown to be more effective than terfenadine 60 mg, given twice daily (14–16); loratadine 10 mg, given once daily (17, 18); and astemizole 10 mg, given once daily (19).

In this study, we compared the clinical efficacy and safety of FPANS 200 µg given once daily and levocabastine nasal spray 200 µg given twice daily with placebo in the treatment of patients with SAR during natural pollen exposure. In addition, we examined the effect of the treatments on inflammatory cell counts in nasal lavage performed throughout the pollen season.

Material and methods

Population

A total of 288 patients were enrolled in 16 centers located in different parts of Italy. They ranged in age from 13 to 64

years. Patients were recruited on the basis of a clinical history of allergic rhinitis only during the pollen seasons of at least 2 years' duration and the presence of positive skin prick test response to seasonal pollens. Patients were excluded if they had taken the following drugs: long-acting antihistamine antagonists, within the previous 6 weeks; inhaled, intranasal, or systemic corticosteroids and cromolyn or nedocromil sodium within the previous 4 weeks. The exclusion criteria were presence of concurrent perennial rhinitis, infection of the paranasal sinuses and of the respiratory tract, nasal polyps, nasal surgery within the past year, and structural abnormalities of nasal cavities. Pregnant or lactating women were also excluded. The protocol was approved by the ethics committee of each hospital, and patients gave informed consent to participate in the study.

Study design

A randomized, double-blind, double-dummy, placebo-controlled, parallel-group study design was used. Patients received the following treatments:

- 1) FPANS 200 mg daily (50 mg per puff; two puffs in each nostril only in the morning) and placebo (nasal spray; two puffs in each nostril in the morning and evening)
- 2) levocabastine 200 mg twice daily (50 mg per puff; two puffs in each nostril in the morning and evening) and placebo (aqueous nasal spray; two puffs in each nostril only in the morning)
- 3) placebo (aqueous nasal spray; two puffs in each nostril only in the morning and nasal spray, two puffs in each nostril in the morning and evening).

The treatments were not distinguishable from each other. The treatment period started at least 1 week before the anticipated start of the pollen season without any run-in. Patients were treated for 6 weeks. Each patient attended the clinics on four different occasions: at the start of treatment (visit 1), after 3 (visit 2) and 6 weeks of treatment (visit 3), and 2 weeks after the end of the treatment period (visit 4). This follow-up visit was planned for all patients, including withdrawals.

At visit 1, the clinical history was obtained by means of a questionnaire, and skin prick testing with a standard battery of 12 common aeroallergens was performed if not done within the previous 12 months. At visits 1, 2, and 3, nasal symptoms were assessed by patients by means of a visual analog scale, and nasal lavage was performed (at selected centers only). At visit 1, a blood sample was taken to assess

blood eosinophilia and serum cortisol. Serum cortisol levels were assessed also at visit 3. Enrolled patients received a daily record diary for nasal and eye symptoms. The study was conducted during spring 1995. All centers documented local daily pollen counts throughout the study period.

Assessment of symptoms

Patients were instructed to record their daily symptoms on diary cards. Nasal symptoms included blockage on waking and during the day, rhinorrhea, sneezing, and itching. Eye symptoms included watering and/or irritation. Nasal obstruction was scored as follows: 0) not present; 1) slightly difficult breathing through the nose; 2) moderately difficult breathing through the nose; 3) very difficult or impossible breathing through the nose. Any other recorded symptom was scored as follows: 0) none; 1) mild (occasionally present); 2) moderate (rather frequent); 3) severe (persistent). Rescue medications included terfenadine (oral tablet, 60 mg) and sodium cromoglycate eye-drops (4% w/v). No other medication for rhinitis was permitted during the trial.

Nasal lavage

Nasal lavage was always performed between 8 and 10 AM by a previously described method (13, 20). Nasal lavage was done in only two centers (located in northern Italy). This entailed instilling 5 ml of 0.9% sterile saline solution, warmed to 37°C, in each nostril, with the patient's head tilted 45° forward. After 5 min, lavage fluid was recovered in a plastic graduate tube. The fluid was shaken for mucus dispersion and filtered through a nylon gauze (100 µm) to remove the mucus and the broken cells. Then, the cellular suspension was centrifuged at 300 g at 4°C for 10 min. The cell pellet was resuspended in 1 ml of sterile saline solution, and the total cell count was done with a Neubauer hemocytometer. An aliquot of the cellular suspension (about 25×10^3 cells) was cytocentrifuged (Cytospin 3; Shandon, Inc., Pittsburgh, PA, USA) at 700 rpm for 5 min. The slides were air-dried for 4–6 h and stained with Diff Quik (Baxter Healthcare Corp., Scientific Div., McGaw Park, IL, USA). Differential cell count was performed on 300 cells by light microscope (Diaplan; Leitz, Hamburg, Germany) at a magnification of $\times 100$. Cells were identified by their structure as neutrophils, eosinophils, monocytes, and epithelial cells.

Laboratory data

Blood samples were taken from each patient at visit 1 to assess blood eosinophil count and morning serum cortisol and at visit 3 to assess changes in morning serum cortisol. Blood eosinophil counts were expressed as percentage of white blood cells. The serum cortisol samples were collected and analyzed locally at each participating center. The normal range of serum cortisol, according to the assay used in each center, was considered the reference value for assessment of the systemic effect of intranasal FPANS. Serum cortisol was given in nmol/l.

Pollen count

Pollen was collected and measured daily throughout the study period. Pollen amounts were expressed as grains per cubic meter. Pollen profiles recorded during the season at two representative sites are shown in Fig. 1.

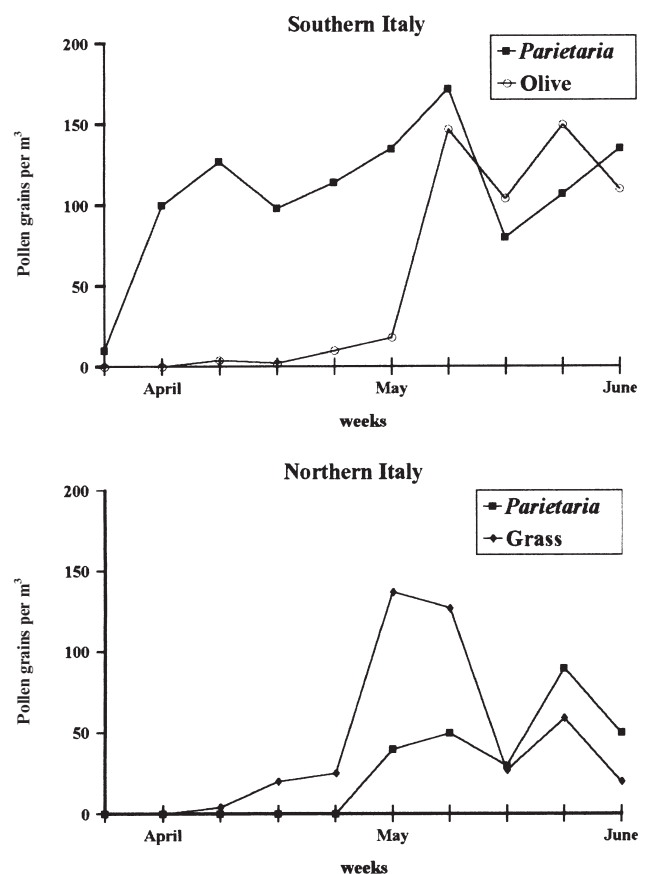


Figure 1. Weekly pollen counts for *Parietaria*, olive, and grass pollens during spring 1995 in southern and northern Italy at two representative sites where study was conducted.

Table 1. Patient characteristics

	FPANS (n = 97)	Levocabastine (n = 96)	Placebo (n = 95)
Male to female ratio	55/42	56/40	58/37
Mean age (years)	31.3	29.0	30.3
Age range (years)	15–64	13–61	13–60
Duration of rhinitis			
1–3 years	24	24	27
4–6 years	27	34	22
> 7 years	46	38	46
Grass +	68	72	66
<i>Parietaria</i> +	56	53	60
Olive +	23	28	19
Mean blood eosinophils (%)	4.5	4.7	4.7
No. of withdrawals	9	11	12
Adverse event	3	0	1
Lack of efficacy	1	5	4
Lost	5	6	7

Statistical analysis

Three population samples were analyzed:

- 1) the intent-to-treat population, which included all patients with diary data for at least 10 days or at least one efficacy evaluation during a scheduled visit
- 2) the per-protocol population (or efficacy population), which included all patients who completed the study without major protocol violation
- 3) the safety population, comprising all patients who were randomized and who received at least one dose of study treatment.

Because the difference between the intent-to-treat and the per-protocol populations was only one patient, the results were based on the intent-to-treat population, stratified by centers. The primary assessment of efficacy was based on the analysis of the percentages of symptom-free days during the 6 weeks of treatment. Moreover, a median score was obtained in each patient for each symptom. Treatments were compared with the Kruskal-Wallis test. A separate comparison of FPANS with placebo and with levocabastine was carried out with the Wilcoxon rank-sum test (stratified for groups of centers based on three geographic regions). No statistical comparison was done between levocabastine and placebo, since the power of the statistical tests was based on the expected difference between FPANS and other topical treatments.

The percentage of the different cells in nasal lavage was expressed as mean $\pm$ SEM. Differences among treatment

groups were examined by analysis of variance, and comparison between groups by the Newman-Keuls multiple comparison test. Serum cortisol values were logarithmically transformed and treated by analysis of covariance, taking pretreatment values as covariate. All statistical tests were two-sided and used a 5% level of significance.

Results

A group of 288 patients were randomized to treatments (97 patients in the FPANS group, 96 patients in the levocabastine group, and 95 patients in the placebo group). Thirty-two patients withdrew during the treatment period (nine patients in the FPANS group, 11 patients in the levocabastine group, and 12 patients in the placebo group). Sixteen patients were excluded from the intention-to-treat population due to insufficient data (four patients in the FPANS group, six patients in the levocabastine group, and six patients in the placebo group). The characteristics of patients and reasons for withdrawals are shown in Table 1. The three groups did not differ in demographics, allergic status, duration of disease, and blood eosinophil counts.

Assessment of efficacy

During treatment with FPANS, the median percentage of symptom-free days for obstruction, rhinorrhea, sneezing, and itching was always significantly higher than in the

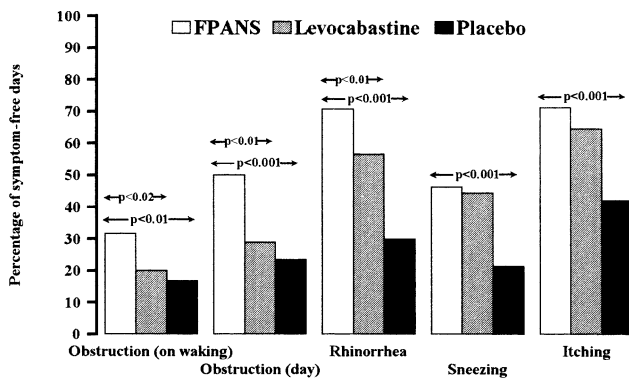


Figure 2. Median number of symptom-free days during treatment with fluticasone propionate aqueous nasal spray (FPANS) 200 µg, once daily; levocabastine 200 µg, given twice daily; or placebo.

placebo group (Fig. 2). In addition, FPANS provided a significantly better protection than levocabastine in terms of the percentage of days without obstruction and rhinorrhea (Fig. 2). Analysis of frequency distribution of nasal scores for each symptom gave similar results (Fig. 3). However, the median percentage of days without eye symptoms in the three treatment groups was not statistically different (FPANS group, 58.5 days; levocabastine group, 71.4 days;

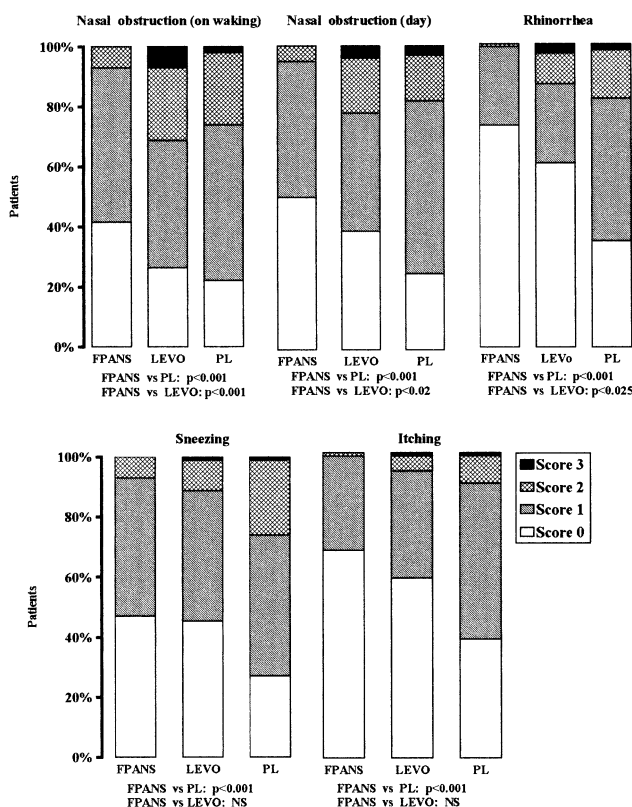


Figure 3. Frequency distribution of median symptom scores recorded by patients receiving fluticasone propionate aqueous nasal spray (FPANS) 200 µg, once daily; levocabastine 200 µg, given twice daily (LEVO); or placebo (PL). NS: not significant.

placebo group, 56.1 days). In addition, the use of rescue medication, expressed as the median number of days without the use of terfenadine tablets, was significantly lower in the FPANS group (97.5 days) than either the levocabastine or placebo group (92.5 days, $P < 0.025$ and 67.6 days, $P < 0.001$; respectively).

Nasal lavage

Nasal lavage was performed in 39 patients from two centers located in northern Italy (13 patients in each treatment group). At visit 1, the mean total cell counts obtained in nasal lavage in the three groups were not statistically different (1.1×10^5 in FPANS group, 1.4×10^5 in levocabastine group, and 1.6×10^5 in placebo group).

It appears that nasal lavage was performed when pollens were already present, as shown by the high percentage of eosinophils in some patients. At the beginning of the season, mean eosinophil counts in the three groups were not statistically different (Table 2). During the pollen season, the mean eosinophil count in the FPANS group was significantly lower than that found in the levocabastine and placebo groups ($P < 0.05$ and $P < 0.01$, respectively; Table 2). Similarly, the mean eosinophil count at the end of the pollen season in the FPANS group was lower than in the levocabastine ($P < 0.05$) and placebo groups ($P < 0.01$; Table 2). The number of neutrophils was not different in the three groups of treatment and did not change significantly during pollen exposure.

Serum cortisol

At visit 1, mean serum cortisol levels measured in the three groups were not different (FPANS group, 372 nmol/l; levocabastine group, 364 nmol/l; and placebo group, 373 nmol/l). No significant changes were found at visit 3 (FPANS group, 404 nmol/l; levocabastine group, 352 nmol/l; and placebo group, 390 nmol/l).

Safety

A low incidence of adverse events was observed in this study. Most adverse events were rated as mild or moderate. Respiratory symptoms were reported by five patients in the FPANS group, five patients in the levocabastine group, and eight patients in the placebo group. Exacerbations of nasal symptoms after treatment were reported by only two patients from the levocabastine group and one patient in the placebo group.

Table 2. Mean eosinophil counts ($\pm$ SEM), expressed as percentage, obtained from nasal lavage in three treatment groups

	FPANS group (n = 13)	Levocabastine group (n = 13)	Placebo group (n = 13)
At beginning of season	8.8 $\pm$ 4.6	8.8 $\pm$ 2.9	12.8 $\pm$ 3.8
During season	3.7 $\pm$ 1.7*#	18.7 $\pm$ 4.9	27.1 $\pm$ 6.6
At end of season	2.3 $\pm$ 1.0*#	15.2 $\pm$ 4.7	22.7 $\pm$ 5.2

* $P < 0.05$ compared to levocabastine; # $P < 0.01$ compared to placebo.

Discussion

The results of this comparative study demonstrate that FPANS administered once daily is more effective for the treatment of nasal symptoms in patients with SAR than levocabastine given twice daily. In addition, it appears that only FPANS treatment produced a significant reduction in the number of eosinophils recovered in nasal lavage during natural pollen exposure. Finally, safety evaluation further confirmed that both FPANS and levocabastine are well tolerated.

Several studies have demonstrated that FPANS has a high index of topical activity with excellent relief of nasal symptoms in patients with SAR, even when administered once daily (10–19). Our study further showed that FPANS treatment remarkably reduces obstruction on waking and during the day, rhinorrhea, sneezing, and itching, and that its clinical efficacy as regards the first two symptoms was greater than that produced by levocabastine. It is noteworthy that patients who received FPANS were free from nasal obstruction in approximately 50% of days of the scheduled period. Moreover, nasal obstruction on waking was significantly reduced only by FPANS, suggesting that the effect of this topical corticosteroid is more persistent.

This is the first study comparing the clinical effects of FPANS and a topical antihistamine, levocabastine. It has previously been shown that FPANS 200 μ g, once daily, is more effective than terfenadine 60 mg, given twice daily (14–16), loratadine 10 mg, given once daily (17), or astemizole 10 mg, given once daily (18), in patients with SAR. When compared to oral ones, topical antihistamines showed a faster onset of action, a better or equal clinical efficacy, and better safety (4). These data support the preferential use of this form of therapy in SAR.

In addition to the consistent control of the allergic nasal symptoms, FPANS had a better effect on decreasing the use of rescue medication than levocabastine. However, it should be noted that most patients included in the placebo group refrained from taking terfenadine tablets. This

phenomenon has been previously noted in other clinical studies (13).

In addition to improving nasal symptoms, FPANS also had a significant effect on decreasing nasal eosinophilia, whereas levocabastine failed to produce any change in the cytology of nasal lavage. Indeed, mean eosinophil counts in nasal lavage at the beginning of treatment were unexpectedly high. This strongly suggests that in some patients the allergic inflammatory process was already taking place in the nasal cavities. It is likely that this phenomenon was linked to the presence of a low amount of aeroallergen at the time of evaluation. It has been demonstrated in a laboratory setting that low repeated doses of inhaled allergen can remarkably activate the inflammatory process (21). Although we cannot entirely rule out the hypothesis that the study started in some patients when the season for the relevant allergen had already begun, this is unlikely since nasal lavage was performed in only two centers and in patients with single sensitization to grass. However, we are aware of the difficulties in predicting the true onset of pollen season even in selected and monitored areas (12).

This study confirms that FPANS significantly controls nasal eosinophilia throughout natural pollen exposure (10, 13, 19). It is noteworthy that at the end of treatment, the eosinophil count in seven (50%) out of 14 patients from the FPANS group was lower than 2. Mean eosinophil count in the placebo group did not significantly increase during season. In addition, no significant changes were found in nasal eosinophilia in patients treated with levocabastine. Similar results have been reported in patients with SAR treated with topical azelastine (20). This is the first study to examine the effect of levocabastine on nasal inflammation during natural pollen exposure. Several double-blind, placebo-controlled trials have previously demonstrated that topical levocabastine reduces symptoms after conjunctival (22) or nasal allergen challenge (23–25). Moreover, a small but significant difference in the number of eosinophils and ICAM-1-positive cells was detectable only in patients treated with levocabastine during the conjunctival allergic

response (22). However, albumin influx (23, 25) and tryptase release (23) after nasal allergen challenge were not blocked by topical levocabastine. Whether topical antihistamines possess a clinically relevant anti-inflammatory activity still needs further confirmation.

The serum cortisol levels over the 6-week period of treatment remained within the normal range. These results confirm that FPANS 200 µg, once daily, has no significant effect on the hypothalamic pituitary axis (13, 26). Although the measurement of morning serum cortisol is not the ideal method for assessing the adrenal function, due to its diurnal variation, it is generally agreed that it is a practical method in multicenter trials. Indeed, the measurement of cortisol

excretion in the 24-h urine is a more accurate but less practical method.

In conclusion, the results of our study demonstrate that FPANS 200 µg, once daily, provides better nasal symptom and overall disease control than levocabastine 200 µg, given twice daily, in patients with SAR caused by different pollens during natural exposure. It appears likely that this superior clinical effect is due to the decrease in the nasal eosinophilic inflammation that is seen during FPANS treatment, but not during levocabastine treatment.

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