

Prevention of pollen rhinitis symptoms: comparison of fluticasone propionate aqueous nasal spray and disodium cromoglycate aqueous nasal spray

A multicenter, double-blind, double-dummy, parallel-group study

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Fluticasone propionate aqueous spray, a new intranasal corticosteroid preparation, and disodium cromoglycate 2% aqueous nasal spray, an established preventive treatment for seasonal allergic rhinitis, were compared in a double-blind, double-dummy, parallel-group, multicentric study in France. A total of 218 patients with seasonal allergic rhinitis caused by grass pollen (verified by positive skin prick test) were preventively treated before the onset of the grass pollen season with either fluticasone propionate 200 µg once daily or disodium cromoglycate 5.2 mg four times daily. Half of these doses was given in each nostril. Treatment started before the onset of the pollen season in most patients (178/218). Diary cards, including symptoms of rhinitis and usage of nasal sprays, were filled in twice daily for 6 weeks.

Terfenadine in 60-mg tablets and eye-drops could be used as rescue medications. We treated 110 patients with fluticasone propionate and 108 patients with disodium cromoglycate. Patients treated with fluticasone propionate had significantly more days free of primary efficacy symptoms of sneezing ($P < 0.001$) and nasal discharge during the day ($P = 0.002$), as well as free of all the other nasal symptoms ($P < 0.01$), and significantly lower median scores ($P < 0.05$) for all nasal symptoms except nasal discharge than patients treated with disodium cromoglycate. There was no difference in eye symptoms or in rescue medication use between the two groups. Compliance with the treatment was assessed. Eleven patients recorded incorrect use of both nasal sprays for over 25% of days, and 55 patients recorded incorrect use of four-times-daily spray only; no patient recorded incorrect use of morning spray only. Both treatments were generally well tolerated.

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Symptoms of pollen-induced rhinitis often occur after a few days of low-grade pollen exposure, causing the so-called priming effect on the nasal mucosa. This was first described by Connell in 1968 (9, 10), and although its significance was not fully appreciated for many years it is now widely accepted (5, 7, 18, 29) and better understood. Low pollen counts probably induce the accumulation of inflammatory cells in the nasal mucosa (4, 8, 20, 31) and possibly their priming by cytokines (11) with insignificant symptoms. During the pollen season, an influx of inflammatory cells, including eosinophils and metachromatic cells (24, 30) is observed in the nasal mucosa, and it is blocked by topical corticosteroids (24, 30). A similar blocking effect of topical corticosteroids is also noticed during nasal challenge with pollen allergens (1, 3). Thus, it is likely that topical corticosteroids may have a preventive effect on nasal symptoms when administered before the pollen season.

Disodium cromoglycate (DSCG) is an antiallergic drug that was found, at least in asthma, to prevent allergic symptoms (13). It was later used as a preventive treatment of allergic rhinitis (15, 17, 22) and was chosen as the comparative drug in trials assessing the preventive effect of antiallergic drugs.

Fluticasone propionate (FP) is a new topical corticosteroid with an extremely low systemic bioavailability because of a combination of poor gastrointestinal absorption and extensive first-pass metabolism (14) that was shown to be active in the treatment of seasonal allergic rhinitis when administered once daily at a dose of 200 µg (12, 23). At this dose, studies demonstrated no systemic side-effects (14).

A double-blind, double-dummy, parallel-group, multicentric study was carried out in France to compare the efficacy and safety profile of FP (200 µg, once daily) and DSCG (5.2 mg four times daily) in the preventive treatment of seasonal allergic rhinitis in 218 patients mostly allergic to grass pollens.

The treatment was intended to be started before the onset of the grass pollen season and continued for a period of 6 weeks, covering the estimated peak of the grass pollen season. The efficacy of both treatments was assessed by symptom scores.

Material and methods

Patients

A total of 218 patients were recruited in 13 clinics in France (Fig. 1). Patients ranged in age from 12 to 66 years (mean $\pm$ SD of 33 ± 12.5 years). All had a history of typical seasonal rhinitis to grass pollens for at least the 2 preceding years, a positive prick test to a grass pollen allergen extract, and eventually a positive RAST to one of the grass pollen species.

Patients were excluded if they had concurrent pe-

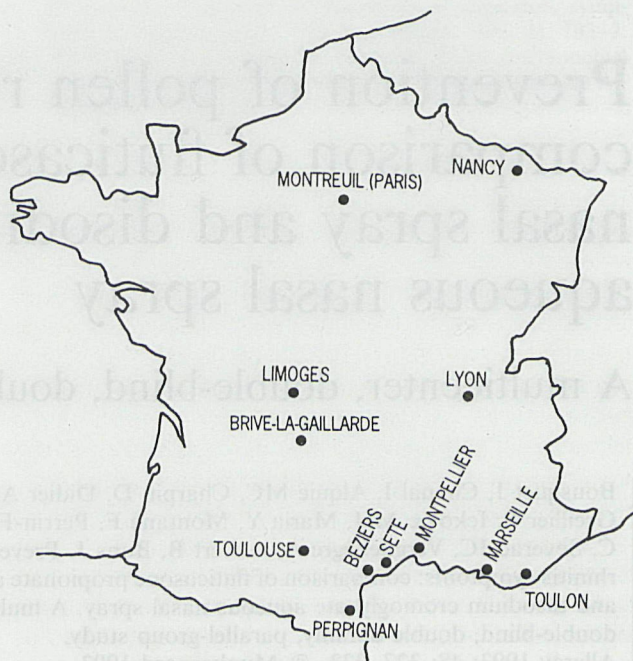


Fig. 1. Geographic distribution of centers in France.

rennial rhinitis or had taken the following drugs: astemizole within the previous 6 weeks; intranasal, inhaled, or systemic corticosteroids within the previous month; intranasal or inhaled DSCG or nedocromil sodium, intranasal vasoconstrictors, or other treatment for rhinitis within the previous week (6). Other exclusion criteria included a course of grass pollen immunotherapy within the last year, recent nasal or sinus infection, and pregnancy.

The study was approved by the ethics committee of the Marseille Teaching Hospital. Written informed consent was obtained from all patients.

Treatments

Patients were randomly allocated to one of the two following treatments. 1) Fluticasone propionate aqueous nasal spray 200 µg (two puffs of 0.09 ml in each nostril) was taken once a day in the morning, and placebo aqueous spray (one puff of 0.13 ml in each nostril) was taken four times daily. 2) Disodium cromoglycate 5.2 mg was taken four times daily (one puff of 0.13 ml in each nostril), and placebo aqueous nasal spray (two puffs of 0.09 ml in each nostril) was taken once daily in the morning. The patients were instructed to use in the morning the once-daily spray first and to use the first dose of the four-times-daily spray at least 30 min after the once-daily spray.

Patients were also given a supply of 60-mg tablets of terfenadine and phenylephrine-brompheniramine eyedrops to be taken if required as rescue medications for nasal symptoms.

Investigations

When patients attended the clinic for the initial visit and at the three subsequent visits, a rhinoscopy was performed, and they were asked by the investigator to give an overall assessment of symptoms on a visual analog scale of 10 cm. Adverse reactions were monitored by the physician. The investigator registered any adverse reactions spontaneously reported by patients and asked them whether they had experienced any medical problems since their last visit, and any reactions elicited were recorded. The investigator also evaluated compliance with the treatment. Patients were assessed as showing poor compliance if they recorded incorrect use of one or both study nasal sprays on more than 25% of days covered by each diary card.

Patients recorded their symptoms on a diary card, evaluating on a 0–3 scale nasal blockage on waking and during the rest of the day, rhinorrhea on waking and during the rest of the day, sneezing, nasal itching, and eye watering and irritation. Rescue medications that were taken were also recorded on the diary card. The patients' symptoms of nasal blockage, nasal discharge, sneezing, nasal itching, and eye watering/irritation were assessed by the investigator during each visit by a four-point scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe symptoms. A venous blood sample was taken and a urine specimen collected at the beginning and at the end of the treatment for determination of routine blood biochemistry, hematology, and urinalysis values.

Pollen counts

By means of a Burkard's trap, we obtained pollen counts for 11 centers (Fig. 2) using the French National Pollen Survey of the Institut Pasteur (Paris) (16).

Design of the study

The study was a randomized, double-blind, double-dummy, multicentre, parallel-group study of nasal sprays of FP 200 µg once daily and DSCG 5.2 mg four times daily. There was no run-in period, as, if possible, patients had to be symptom-free. The patients were to be treated for 6 weeks, with treatment beginning at least 1 week before the anticipated start of the grass pollen season. To detect a difference of 15% in the mean percentage of symptom-free days, with SD = 35.5%, $\alpha = 5\%$, $\beta = 20\%$, we needed at least 185 patients to provide data, assuming the use of a nonparametric test with asymptotic relative efficacy of 95%.

Patients attended the clinic for assessment at the start of treatment (visit 1), after 3 and 6 weeks of treatment, respectively (visits 2 and 3), and 2 weeks

after the end of the treatment period for a follow-up (visit 4).

Statistical analysis

The analyses were conducted on two populations: a total intent-to-treat population consisting of all patients randomized and the efficacy population including only patients without any major protocol violation. Some patients showed evidence of serious noncompliance with the protocol. If this occurred between visits 1 and 2, the patient was excluded from the efficacy population. Demographic data have been analyzed on the two populations. The results were similar, and the two treatments groups were generally well matched. Results of the efficacy population analyses were similar to those of the total population. For each seven symptoms studied, scores recorded were summarized in two ways: 1) by the percentage of symptom-free days compared by stratification for center by the van Elteren procedure (21) for combining Wilcoxon's rank sum test over strata, and 2) by median symptom scores analyzed by an extended Mantel-Haenszel test for standardized mid-rank scores (19). The rescue medications taken by patients were analyzed by Wilcoxon's rank sum test, stratified for center as above. All statistical analyses were performed by SAS programs and procedures.

Results

Patients

A total of 218 patients were recruited; 110 received FP and 108 DSCG. From five to 25 patients were recruited by each center. Treatment started before the onset of the pollen season in most patients (178/218). Forty patients presented nasal symptoms caused by tree pollens when they were included. These symptoms were mild. The mean daily clinical scores at the start of the treatment for each nasal symptom were between 0.120 and 0.166 for the FP group and between 0.130 and 0.252 for the DSCG group. Only one patient missed visit 2, and 94% of the patients were seen on visits 3 and 4. Fifty-eight patients were excluded from the efficacy population for one or more reasons given in Table 1, but the most important reason was poor compliance before the first assessment visit (visit 2). Seventy-eight patients (mean age: 33 years; SD: 12 years) were treated by FP, and 87 (mean age: 32 years; SD: 12 years) by DSCG.

Grass pollen counts

Fig. 2 shows grass pollen counts throughout France. Pollen counts for Montpellier are similar to those of

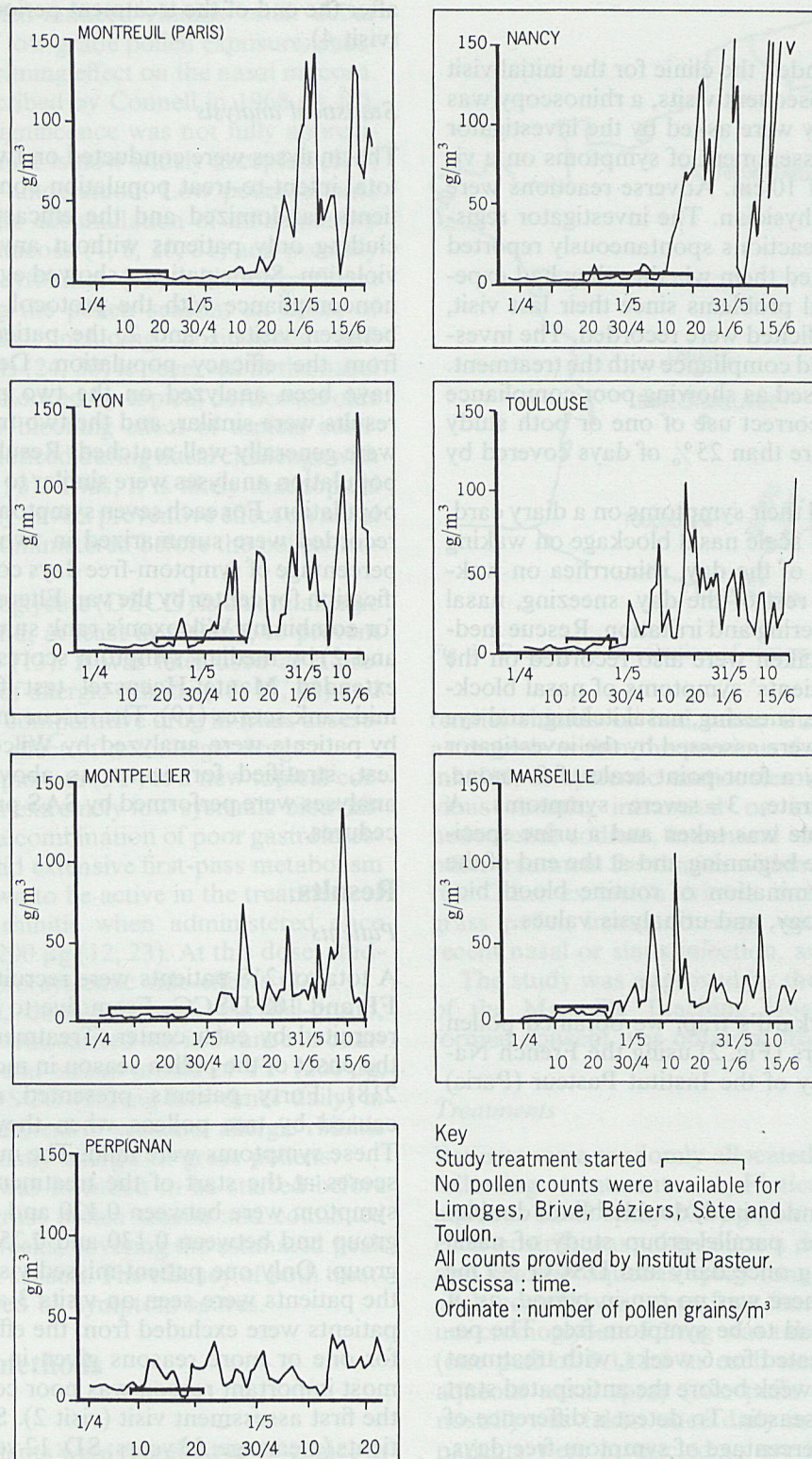


Fig. 2. Grass pollen counts during study period.

Sète and Béziers since these cities are, respectively, located 35 and 70 km from the pollen trap and their climate is identical to that of Montpellier. It can be seen that most patients were included before the

Key

Study treatment started ———
 No pollen counts were available for
 Limoges, Brive, Béziers, Sète and
 Toulon.
 All counts provided by Institut Pasteur.
 Abscissa : time.
 Ordinate : number of pollen grains/ m^3

onset of the grass pollen season, but, in Perpignan, grass pollen counts were very low during the whole study.

Table 1. Summary of reasons for complete exclusion from the efficacy population

Reasons for exclusion	FP	DSCG
Fewer than 10 d of diary card data	2	2
Concomitant use of inhaled DSCG	1	
Poor compliance	29	16
Disallowed drug used in first 10 d of treatment	5	3
Total number of patients excluded	37	21

Efficacy

The percentage of symptom-free days is presented in Table 2. Fluticasone propionate showed significant improvement over DSCG for the primary efficacy symptom of sneezing ($P < 0.001$) and for rhinorrhea during the day ($P = 0.002$), nasal blockage on waking ($P < 0.001$) or during the day ($P = 0.009$), rhinorrhea on waking ($P < 0.001$), and nasal itching ($P = 0.001$). On the other hand, there was no difference in the percentage of days free of eye symptoms.

When the median symptom scores were examined (Fig. 3), FP showed a significant improvement over DSCG for nasal blockage on waking ($P = 0.036$) or during the day ($P = 0.005$), sneezing ($P = 0.002$), nasal itching ($P = 0.031$), and nasal discharge during the day ($P = 0.007$). The improvement of nasal discharge on waking approached significance ($P = 0.050$). There was no significant difference between treatments for eye symptoms.

Table 2. Efficacy: mean percentage of symptom-free days (days 1–42), total population, and record card symptom scores

	FP <i>n</i> = 108	DSCG <i>n</i> = 106	<i>P</i> *
Nasal blockage on waking	65.10	50.90	$P = 0.001$
Nasal discharge on waking	82.40	71.60	$P < 0.001$
Nasal blockage during day	72.50	62.10	$P = 0.009$
Sneezing during day	67.10	51.60	$P < 0.001$
Nasal itching during day	79.10	67.60	$P = 0.001$
Nasal discharge during day	74.90	64.20	$P = 0.002$
Eye watering/irritation during day	69.70	71.10	$P = 0.825$

* Wilcoxon test stratified for center.

There was no significant difference in rescue medication use between the two treatment groups.

For investigator symptom assessment (four-point rating scale), FP was significantly superior to DSCG at visit 2 for nasal blockage (mean value: 0.462 for FP vs 0.682 for DSCG, $P = 0.022$), sneezing (mean value: 0.342 for FP vs 0.570 for DSCG, $P = 0.009$), nasal itching (mean value: 0.287 for FP vs 0.476 for DSCG, $P = 0.016$), and nasal discharge (mean value: 0.351 for FP vs 0.644 for DSCG, $P = 0.006$). At visit 3, FP was significantly superior to DSCG for nasal blockage (mean value: 0.457 for FP vs 0.772 for DSCG, $P = 0.002$) and nasal discharge (mean value: 0.419 for FP vs 0.752 for DSCG, $P = 0.003$).

For patients (visual analog score assessment of symptoms), FP was significantly superior to DSCG

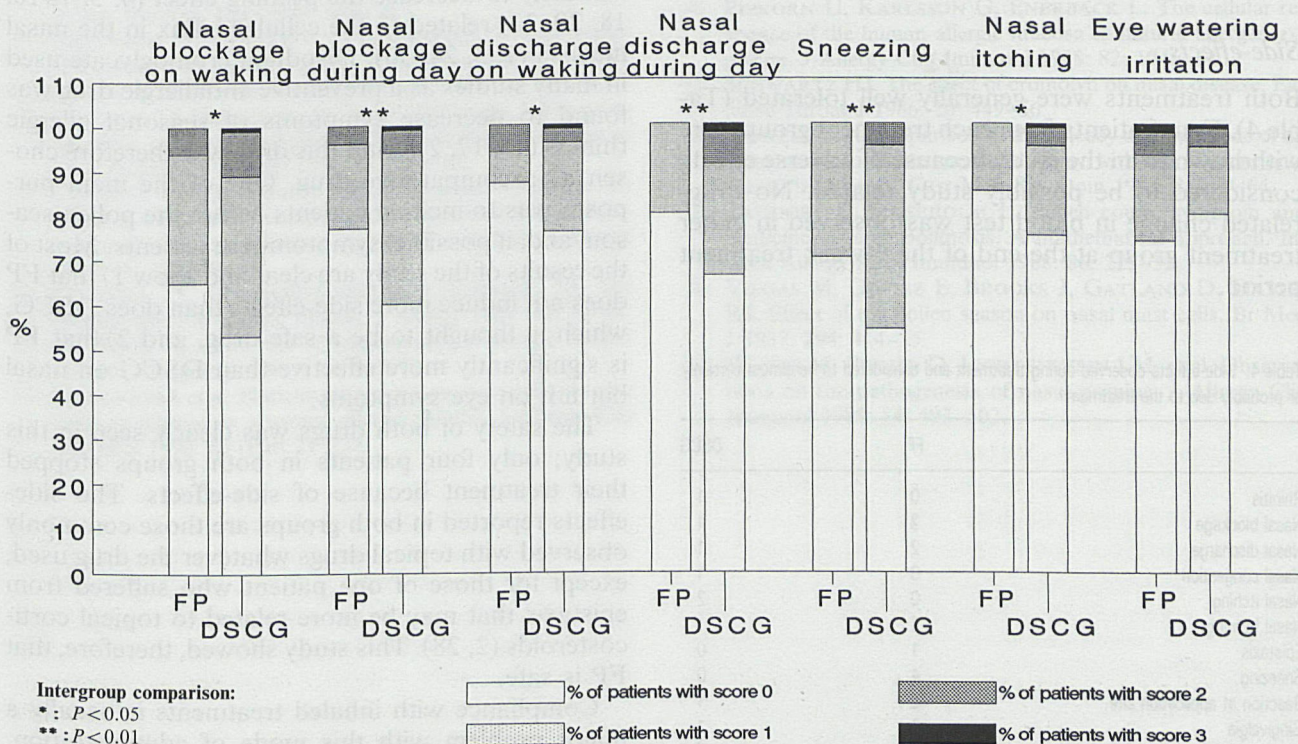


Fig. 3. Record card symptom scores. Median symptom score (days 1–42) FP: $n = 108$; DSCG: $n = 106$.

Table 3. Compliance with treatment

	Low compliance with treatment		
	FP n=110*	DSCG n=108	Total n=218
Once-daily spray only	0	0	0
Four-times-daily spray only	32	23	55 (25%)
Both nasal sprays	7	4	11 (5%)

* Numbers indicate the number of patients with low treatment compliance, as described in the section methods.

(mean value: 16 for FP vs 19 for DSCG, $P=0.02$) at visit 2, and not significantly superior to DSCG at visit 3 (mean value: 20 for FP vs 24 for DSCG).

Compliance with treatment

Compliance with treatment was examined at each assessment visit. A total of 66 patients were classified as showing poor compliance, as they recorded incorrect use of one or both study nasal sprays on more than 25% of days covered by each diary card. Compliance between the two treatment groups was not significantly different (Fisher's exact test, $P=0.230$), but 25% of patients showed poor compliance, with only the four-times-daily spray, and 5% (Table 3) did not comply with either type of spray (MacNemar test, $P<0.0001$). None of the patients reported incorrect use exclusively of the once-daily spray.

Side-effects

Both treatments were generally well tolerated (Table 4). Four patients from each treatment group were withdrawn from the study because of adverse effects considered to be possibly study related. No drug-related change in blood test was observed in either treatment group at the end of the 6-week treatment period.

Table 4. Side-effects observed during treatment and considered to be almost certainly or probably due to the treatment

	FP	DSCG
Rhinitis	0	1
Nasal blockage	2	1
Nasal discharge	2	1
Nasal congestion	0	1
Nasal itching	0	2
Nasal burning	1	1
Epistaxis	1	0
Sneezing	4	0
Reaction at application site	2	1
Gingivalgia	0	1
Nausea and vomiting	1	0

Discussion

This study shows that FP 200 µg administered once daily is significantly more effective than, and as well tolerated as, DSCG 5.2 mg administered four times daily in the preventive treatment of seasonal allergic rhinitis. Moreover, compliance with the treatment was found to be greater when topical drugs were administered once daily than four times daily.

The present study lacked a placebo group, but it was double blind and double dummy. We did not use placebo because 1) DSCG (15, 17, 22, 27) and FP (12, 23) were known to be effective in the treatment of allergic rhinitis, at least during short-term therapy, and we wanted to compare their efficacy in the prevention of pollen-induced symptoms, and 2) the number of patients to be recruited would have been too large for a similar pollen environment, making the study impossible.

One of the difficulties with such a study is related to the administration of drugs before the onset of the pollen season. All patients were recruited before the grass pollen season, and most were symptom-free. However, because of the occurrence of the tree pollen season, 40 patients had symptoms at entry, but they were not excluded from the analysis.

We intended to start the study before the pollen season for several reasons. First, preventive treatments of pollen rhinitis appear to be more efficient than (25) and we wanted to test the possibility of corticosteroids being used before the season, as they are likely to decrease the priming effect (4, 5, 7–10, 18, 29, 31) related to the cellular influx in the nasal mucosa (1, 3, 24, 30). Disodium cromoglycate used in many studies as a preventive antiallergic drug was found to decrease symptoms of seasonal allergic rhinitis (15, 17, 21), and this drug was therefore chosen as a comparative drug. One of the main purposes was to include patients before the pollen season, and, if possible, symptom-free patients. Most of the results of the study are clear and show 1) that FP does not induce more side-effects than does DSCG, which is thought to be a safe drug, and 2) that FP is significantly more effective than DSCG on nasal but not on eye symptoms.

The safety of both drugs was clearly seen in this study; only four patients in both groups stopped their treatment because of side-effects. The side-effects reported in both groups are those commonly observed with topical drugs whatever the drug used, except for those of one patient who suffered from epistaxis that may be more related to topical corticosteroids (2, 28). This study showed, therefore, that FP is safe.

Compliance with inhaled treatments is usually a major problem with this mode of administration. Even with effective intranasal drugs, many patients

do not use their inhalers or sprays properly. This fact was observed in the present study, but new information on compliance with sprays came to light. It was seen that most uncompliant patients did not follow the prescription of spray four times daily, whereas they did comply with the once-daily administration. The lack of compliance was observed in both treatment groups, suggesting that, whatever the effectiveness of a treatment, the once-daily administration is favored.

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