

Once daily fluticasone propionate aqueous nasal spray controls symptoms of most patients with seasonal allergic rhinitis

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This multicentre, randomized, double-blind, parallel-group study was designed to compare the efficacy and tolerability of fluticasone propionate aqueous nasal spray 200 µg once daily (FPANS 200 µg od) with FPANS 200 µg twice daily (bd) in patients whose seasonal rhinitis symptoms were not completely controlled with FPANS 200 µg od. A total of 549 patients initially received FPANS 200 µg od during the open-treatment phase of the study. After 2 weeks, 65% of patients had their symptoms well controlled by FPANS 200 µg od and continued with this treatment for a further 2 weeks. The remainder received either FPANS 200 µg od or FPANS 200 µg bd for a further 2 weeks. Efficacy was evaluated by the analysis of symptom-free days. In the uncontrolled group, there was a significant increase in the percentage of symptom-free days in the FPANS 200 µg bd group over the FPANS 200 µg od group for nasal blockage on waking ($P < 0.05$) and nasal blockage during the day ($P < 0.05$). Similar trends were observed for sneezing, rhinorrhoea, nasal itching, and eye symptoms. There was a significant increase in the percentage of days with a symptom score of less than 2 in the FPANS 200 µg bd group for nasal blockage during the day ($P < 0.05$). Adverse events were similar in nature and frequency in each treatment group. It is concluded that in the majority of patients symptoms of seasonal rhinitis are well controlled by FPANS 200 µg od. In the minority of patients whose symptoms are not adequately controlled by a once daily dose, FPANS 200 µg bd provides additional relief, particularly from nasal blockage.

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Seasonal allergic rhinitis is defined as an inflammatory reaction of the nasal mucosa to pollens such as grass. The primary symptoms of the disease include nasal blockage, rhinorrhoea, and sneezing, and some patients may complain of nasal itching and eye symptoms. The disease affects approximately 10% of the population and, although rarely serious, patients require active therapy during the pollen season to minimize the unpleasant symptoms.

Intranasal corticosteroids have become the preferred treatment for seasonal allergic rhinitis, providing relief of symptoms with minimal adverse effects (9, 17). Fluticasone propionate is a topically active, fluorinated glucocorticoid with no demonstrable systemic effects when given by either the intranasal or oral routes (6, 7, 13, 19). After intranasal doses of 4 mg for 7 days or a single oral dose of

16 mg, no significant effect on the hypothalamo-pituitary-adrenal (HPA) axis was observed (6).

Several placebo-controlled studies have demonstrated that fluticasone propionate aqueous nasal spray (FPANS) at a dose of 200 µg once daily is effective in the relief of seasonal allergic rhinitis (4, 5, 14). Comparative studies with beclomethasone dipropionate (BDP) have shown no significant difference between 200 µg once daily and BDP 168 µg twice daily (15), and have shown the superiority of FPANS 100 µg twice daily and FPANS 200 µg once daily over BDP 168 µg twice daily (11). In trials conducted during the 1989 pollen season in Europe, FPANS 200 µg once daily was more effective than terfenadine (3) and disodium cromoglycate (1) and as effective as astemizole (8) and flunisolide (12) in symptom relief of seasonal allergic rhinitis. In addi-

tion, there was a lower incidence of drug-related nasal adverse events in the FPANS-treated group when compared with flunisolide aqueous nasal spray.

Therefore, it is clear that most patients with seasonal rhinitis are symptom-free when treated with FPANS 200 µg once daily, but that patients with more severe symptoms may require a more frequent dosage regimen. The present study was designed to assess the efficacy of FPANS 200 µg twice daily in those more severely affected patients whose symptoms were not adequately controlled by FPANS 200 µg once daily and to confirm the tolerability of FPANS in these patients.

Material and methods

Patients

A total of 549 patients from 22 centres in Europe were recruited to the study. All patients were over 12 years of age with symptoms of seasonal rhinitis (nasal blockage, rhinorrhoea, sneezing, nasal itching) which had been of at least moderate severity during the previous two seasons. In addition, patients had to demonstrate a positive skin prick test to a seasonal allergen known to be relevant to the period and geographical location of the study. The following patients were excluded from the study: those who had taken intranasal, inhaled, or systemic corticosteroids or intranasal or inhaled sodium cromoglycate or nedocromil sodium within the previous month, or the long-acting antihistamine astemizole within the previous 6 weeks, or who were taking any other medication for nasal complaints; those who had undergone nasal surgery within 6 weeks of the start of the study or who had obstructing polyps, significant deviation of the nasal septum, or an infection of the paranasal sinuses; those with concurrent perennial rhinitis or with serious and unstable concurrent disease; those who had received immunotherapy within the last year; those in whom corticosteroids were contraindicated; and those female patients who were pregnant, lactating, or at risk of pregnancy.

Ethics committee approval was obtained in each of the study centres according to local regulations. Written or verbal informed consent was obtained from each patient or legal guardian prior to participation in the study. The study was conducted in accordance with the Declaration of Helsinki as revised by the 35th World Medical Assembly, Venice, Italy, 1983.

Study design

This was a multicentre, randomized, parallel-group study carried out during the 1990 pollen season.

There was a 2-week open-treatment period followed by a 2-week double-blind treatment period and a 2-week follow-up period. Suitable patients were identified at a pretrial visit which could be combined with clinic visit 1 at the start of the pollen season. During the 2-week open-treatment period, all patients received FPANS 200 µg (two 50-µg actuations to each nostril) once daily in the morning. At clinic visit 2, patients were assessed as being controlled or uncontrolled on FPANS 200 µg once daily. Those patients who were assessed as being uncontrolled by once daily treatment were randomized in a double-blind manner to receive either FPANS 200 µg or placebo in the evening in addition to FPANS 200 µg each morning. Patients whose symptoms were assessed as being adequately controlled continued treatment with FPANS 200 µg once daily each morning. All patients attended the clinic for clinic visit 3 after a further 2 weeks and for a follow-up visit 2 weeks after the end of treatment.

Patients were asked to stop taking all medication affecting nasal function from clinic visit 1 onward. All patients were provided with terfenadine 60 mg antihistamine tablets to be taken up to a maximum of two per day and sodium cromoglycate eye-drops to be used up to a maximum of four applications per day if their rhinitis symptoms were troublesome.

At the pretrial visit, a full medical history and demographic details were recorded. The presence of a positive skin prick test to a seasonal allergen known to be relevant to the period and geographical location of the study was recorded. The presence or absence of nasal polyps and deviations of the nasal septum were recorded at clinic visit 1, and a nasal assessment was carried out at clinic visits 1, 2, and 3. Clinical evidence of oral candidiasis was recorded at clinic visits 1 and 3 and, if detected, the investigator took an oropharyngeal swab to confirm the presence of *Candida albicans*.

Each patient was issued with a diary card for each 2-week treatment period at clinic visits 1 and 2. Patients were asked to classify their symptoms of nasal blockage on waking every morning and nasal blockage during the rest of the day, sneezing, nasal itching, rhinorrhoea, and eye watering/irritation every evening. Each symptom was graded according to a 4-point scale, as outlined below.

For nasal blockage on waking and during the day:

- 0 = breathing through the nose freely and easily
- 1 = slight difficulty in breathing through the nose
- 2 = moderate difficulty in breathing through the nose
- 3 = breathing through the nose very difficult/impossible.

For sneezing:

- 0 = absent
- 1 = occasionally present (<5 episodes per day)

- 2 = troublesome episodes of sneezing (5–10 episodes per day)
 3 = frequent, troublesome episodes of sneezing (> 10 episodes per day).

For nasal itching, rhinorrhoea, and eye watering/irritation:

- 0 = absent
 1 = present, mostly unaware of it
 2 = present, but not a persistent distraction
 3 = present, a persistent distraction.

The daily use of study medication, rescue medication, and any other medication was also recorded. At clinic visits 2 and 3, patients assessed the treatment as very effective, effective, partially effective, or ineffective.

All untoward events reported spontaneously by the patient at any stage during the study were recorded. At every visit after the pretrial visit, patients were asked whether they had experienced any medical problems since the last clinic visit and events elicited were recorded.

Statistical analysis

The statistical analysis was performed on the uncontrolled group. The primary efficacy analysis was based on the analysis of the percentage of symptom-free days for symptoms of nasal blockage on waking, sneezing, and rhinorrhoea. This was supplemented by the analysis of the percentage of days with a symptom score of less than 2. The remaining symptoms were analysed as secondary analyses. Analyses were carried out using differences from baseline and these differences were analysed using the Wilcoxon rank sum test (12). Wilcoxon rank sum tests were also used to analyse the use of rescue medication. The assessment of treatment efficacy at visit 3 was analysed using the proportional odds model for ordinal data (10).

Of patients recruited to the study, 35% were from one centre. This represented 55% of the uncontrolled group in the efficacy population. All the patients included in the efficacy population were recruited from four of the total 22 centres; therefore, for the purposes of statistical analysis, no adjustment was made for centre.

Results

Patient populations

A total of 549 patients were recruited to the study. Fourteen patients withdrew before clinic visit 2 and a further two patients did not attend for clinic visit 2. Of the 533 patients who were assessed at clinic visit 2, 348 were assessed as being controlled on FPANS 200 µg once daily and so continued with this treatment for a further 2 weeks. These patients

constituted the controlled group. By skin tests, 282 of 398 patients were positive to grass pollen, 212/348 were positive to birch, and 95/348 were positive to at least one other seasonal allergen. One hundred and eighty-five patients were assessed as uncontrolled on FPANS 200 µg once daily (the uncontrolled group). Of these, 96 patients were randomized to receive placebo in the evening and 89 patients were randomized to receive FPANS in the evening in addition to receiving FPANS 200 µg every morning for a further 2 weeks. In the uncontrolled group, 167 patients were positive to grass pollen, 102 were positive to birch, and 37 were positive to at least one other seasonal allergen.

Statistical analysis was performed on the uncontrolled group only and the efficacy population was defined only for the uncontrolled group. One hundred and fifty-nine of the 185 randomized patients were included in the efficacy population, which comprised those patients who were compliant with the protocol. Results for the total and efficacy populations were very similar; therefore, results for the total population have been considered throughout.

Twenty-five patients were withdrawn from the study. Fourteen of these were withdrawn at or before clinic visit 2. Eleven patients withdrew after assessment as being controlled or uncontrolled at clinic visit 2. Of these, seven withdrew from the controlled group, two withdrew from the uncontrolled FPANS 200 µg od group, and two withdrew from the uncontrolled FPANS 200 µg bd group.

Demographic data for the total population are given in Table 1. The controlled group and both the

Table 1. Demographic data

	Controlled FPod n=348	Uncontrolled	
		FPod n=96	FPbd n=89
Sex			
M	196 (56)	56 (58)	45 (51)
F	152 (44)	40 (42)	44 (49)
Age			
Mean (years)	29.6	27.0	27.6
Ethnic origin			
Caucasian	345 (99)	96 (100)	87 (98)
Asian	1 (0)	0	2 (2)
Oriental	1 (0)	0	0
Not recorded	1 (0)	0	0
Number of patients reporting			
ENT abnormalities	140 (40)	60 (63)	52 (58)
Duration of rhinitis			
2–5 years	105 (30)	20 (21)	15 (17)
6–10 years	67 (19)	20 (21)	19 (21)
> 10 years	176 (51)	56 (58)	55 (62)

FPod = fluticasone propionate aqueous nasal spray 200 µg once daily; FPbd = fluticasone propionate aqueous nasal spray 200 µg twice daily; ENT = ear, nose, and throat. Figures in parentheses are percentages.

uncontrolled groups were well matched. There were approximately equal numbers of males and females in each group. Over 98% of patients in all groups were Caucasian and the majority of patients were under 30 years of age. Forty per cent of patients in the controlled group and over 58% of patients in the two uncontrolled groups reported ear, nose, and throat abnormalities. Over half the patients in all groups had a rhinitis history of more than 10 years.

Efficacy

At clinic visit 2, 348 of the total of 533 patients (65%) were assessed as being well controlled by FPANS 200 µg once daily.

In the uncontrolled group, there was a significant increase in the percentage of symptom-free days in the FPANS 200 µg bd group over the FPANS 200 µg od group for nasal blockage on waking ($P=0.043$) and nasal blockage during the day ($P=0.049$) (Table 2). A trend in favour of FPANS 200 µg bd was seen for sneezing (11%), rhinorrhoea (7%), nasal itching (8%), and eye symptoms (3%), but the differences were not statistically significant. There was an increase of 7% in the percentage of days with a symptom score of less than 2 in the FPANS 200 µg bd group over the FPANS 200 µg od group for nasal blockage during the day ($P=0.049$). There was no evidence of a treatment difference for the remaining symptoms.

The effectiveness of the study medication is shown for both the controlled and uncontrolled groups in Table 3. In patients whose symptoms were adequately controlled by FPANS 200 µg od at visit 2, over 90% still thought that the once daily regimen was either very effective or effective at clinic visit 3. In patients whose symptoms were uncontrolled at visit 2, 33 (57%) and 51 (58%) patients in the FPANS 200 µg od and FPANS 200 µg bd groups, respectively, considered the study medication very

Table 3. Patients' assessment of effectiveness of study medication

	Controlled FPod n=342	Uncontrolled	
		FPod n=94	FPbd n=87
Visit 2 (baseline)			
Very effective	150 (44)	11 (12)	15 (17)
Effective	166 (49)	42 (45)	36 (41)
Partially effective	25 (7)	39 (41)	35 (40)
Ineffective	1 (0)	2 (2)	1 (1)
Visit 3			
Very effective	181 (53)	27 (29)	32 (37)
Effective	144 (42)	45 (48)	41 (47)
Partially effective	15 (4)	20 (21)	14 (16)
Ineffective	2 (1)	2 (2)	0

FPod=fluticasone propionate aqueous nasal spray 200 µg once daily; FPbd=fluticasone propionate aqueous nasal spray 200 µg twice daily.

Figures in parentheses are percentages.

effective or effective at visit 2; by visit 3, the respective numbers were 72 (77%) and 73 (84%).

Analysis of the percentage of rescue-free days and the number of occasions that rescue medication was used showed no significant difference in the usage of either terfenadine tablets or eye-drops in the FPANS 200 µg od and the FPANS 200 µg bd groups.

At clinic visit 1, the majority of patients showed no evidence of crusting, bleeding, deviated nasal septum, the presence of nasal polyps, or the presence of any other nasal pathology. Fewer patients reported nasal oedema, crusting, bleeding, abnormal colour of the nasal mucosa, or secretions at clinic visits 2 and 3 compared with clinic visit 1 in both the controlled and uncontrolled groups. No formal statistical comparisons were performed on the nasal assessment data.

Safety and tolerability

The incidence of adverse events was low and was similar in each treatment group. In particular, there was no apparent side-effect penalty associated with doubling the dose of FPANS. During the open treatment period, 117 patients (21%) reported adverse events. During the randomized phase, 53 patients (15%) in the controlled group reported adverse events. In the uncontrolled group, 15 patients (16%) in the FPANS od group and 13 patients (15%) in the FPANS bd group reported adverse events. Most of the adverse events reported were mild, the most common being headache and upper respiratory tract infection (Table 4). There were no deaths during the study. During the open-treatment period, one patient reported a serious adverse event; this was a leg abscess which was considered by the investigator to be unrelated to treatment. During the randomized

Table 2. Percentage of symptom-free days (uncontrolled group)

	Mean difference from baseline		Median difference (FPbd-FPod)	P value
	FPod n=94*	FPbd n=88*		
Nasal blockage on waking	8	15	7	0.043
Nasal blockage during day	8	17	8	0.049
Sneezing	17	24	11	0.096
Rhinorrhoea	16	21	7	0.270
Nasal itching	16	21	8	0.191
Eye watering/irritation	10	15	3	0.619

FPod=fluticasone propionate aqueous nasal spray 200 µg once daily; FPbd=fluticasone propionate aqueous nasal spray 200 µg twice daily.

* Patients with at least 7 days' data during baseline period and at least 7 days' data between visit 2 and visit 3.

Table 4. Most commonly occurring adverse events

Adverse events	Open treatment All groups FPod n=549	Randomized phase		
		Controlled FPod n=342	Uncontrolled	
			FPod n=94	FPbd n=87
Headache	33 (6)	14 (4)	4 (4)	5 (6)
Asthma and related events	14 (3)	3 (1)	1 (1)	0
URTI	11 (2)	5 (1)	3 (3)	2 (2)
Epistaxis	10 (2)	1 (0)	1 (1)	0
No overall diagnosis	1 (0)	1 (0)	3 (3)	1 (1)

FPod=fluticasone propionate aqueous nasal spray 200 µg once daily; FPbd=fluticasone propionate aqueous nasal spray 200 µg twice daily; URTI=upper respiratory tract infection. Figures in parentheses are percentages.

phase, one patient in the uncontrolled FPANS bd group was withdrawn because of a rash which was considered unrelated to treatment. Most of the adverse events were considered unrelated or unlikely to be related to the study medication.

Discussion

This study was designed to compare fluticasone propionate aqueous nasal spray 200 µg once daily with fluticasone propionate aqueous nasal spray 200 µg twice daily in patients with seasonal rhinitis whose symptoms were not completely controlled by fluticasone propionate aqueous nasal spray 200 µg once daily. There was no evidence that blinding was broken and therefore no evidence of any bias toward a particular treatment group.

The study provides strong evidence that the majority of patients (65%) with seasonal rhinitis have their symptoms well controlled by fluticasone propionate aqueous nasal spray 200 µg once daily. Of the remaining uncontrolled patients, 77% of those that remained on FPANS 200 µg once daily and 84% of patients who then received FPANS 200 µg twice daily thought their medication was effective or very effective at the end of the study. Thus, 90% of patients who received FPANS 200 µg once daily assessed their medication as effective or very effective. A once daily dosage regimen is likely to increase patient acceptance and ease of administration and encourage better patient compliance (2). In addition, as rhinitis symptoms are most evident in the morning (16), administration of FPANS at this time of day could be important therapeutically (18).

In the minority of patients whose symptoms were not adequately controlled by fluticasone propionate aqueous nasal spray 200 µg once daily, there was evidence that fluticasone propionate aqueous nasal spray 200 µg twice daily was more effective than a once daily dosage regimen. Fluticasone propionate aqueous nasal spray 200 µg twice daily significantly

increased the percentage of symptom-free days for nasal blockage on waking and nasal blockage during the day compared with fluticasone propionate aqueous nasal spray 200 µg once daily. In addition, the percentage of days with a symptom score of less than 2 for nasal blockage during the day was significantly higher in the FPANS 200 µg bd group. There was a trend in favour of FPANS 200 µg bd for all the other analyses of diary card data, but the differences were not statistically significant. It is clear that in those patients whose symptoms are not adequately controlled by FPANS 200 µg once daily, FPANS 200 µg twice daily may provide additional relief of symptoms, particularly nasal blockage.

Patient assessment of the effectiveness of the medication confirmed the findings of the diary card analyses. In the controlled group, over 90% of patients assessed the study medication as being effective or very effective at both clinic visits 2 and 3. In the uncontrolled groups, approximately 57% of patients assessed the study medication as being effective or very effective at clinic visit 2; this figure increased to 77% at clinic visit 3 in the FPANS 200 µg od group and to 84% in the FPANS 200 µg bd group.

Fluticasone propionate was well tolerated at both doses. One patient had a serious adverse event and one patient was withdrawn because of an adverse event. Neither of these was assessed by the investigator as being drug-related. Most adverse events reported were mild and resolved over the course of the study. Many of these events could be related to local irritation associated with nasal sprays, topical effects of the study medication, or seasonal allergic rhinitis itself. The most commonly occurring adverse event in all groups was headache. The incidence of adverse events was not significantly different between treatment groups.

Conclusion

The results of this study demonstrate that fluticasone propionate aqueous nasal spray, administered as a once daily 200 µg dose, is an effective and well-tolerated treatment for seasonal allergic rhinitis in most patients. In those patients whose symptoms are not completely controlled by a once daily dose, fluticasone propionate 200 µg twice daily may provide additional therapeutic benefit, particularly in the relief of nasal blockage.

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References

- BOUSQUET J, CHANEZ P, MICHEL FB. Pathophysiology and treatment of seasonal allergic rhinitis. *Respir Med* 1990; 84 (Suppl. A): 11–17.
- CRAMER JA, MATTSON RH, PREVEY ML, et al. How often is medication taken as prescribed? A novel assessment technique. *JAMA* 1989; 261: 3273–7.
- DARNELL R, PECOUD A, RICHARDS DH. A double-blind comparison of fluticasone propionate aqueous nasal spray, terfenadine tablets and placebo in the treatment of patients with seasonal allergic rhinitis to grass pollen. *Clin Exp Allergy* 1994; 24: 1144–50.
- DOCKHORN R, MELTZER EO, PAULL BD, et al. Fluticasone propionate aqueous nasal spray given once a day safely controls the symptoms of seasonal allergic rhinitis. *Ann Allergy* 1990; 64: 77.
- DOLOVICH J, WONG AG, CHODIRKER WB, et al. Multi-center trial of fluticasone propionate aqueous nasal spray in ragweed allergic rhinitis. *Ann Allergy* 1994; 73: 147–53.
- HARDING SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990; 84 (Suppl. A): 25–9.
- HARDING SM, FELSTEAD S. A comparison of the tolerance and systemic effects of fluticasone propionate (FP) and beclomethasone dipropionate (BDP) in healthy volunteers. *Eur Respir J* 1988; 1 (Suppl. 2): 196s.
- JOHANNESSEN TA. A comparison of fluticasone propionate, flunisolide and placebo in patients with seasonal allergic rhinitis to birch pollen – a multicentre trial. *Clin Exp Allergy* 1990; 20 (Suppl. A): 102.
- KAPP JF. Use of topical corticosteroids in the management of rhinitis. In: SELTIPANE GA, ed. *Rhinitis*. Providence, RI: New England and Regional Allergy Proceedings, 1984: 108–15.
- KOCH GG, EDWARDS S. Clinical efficacy trials with categorical data. In: PEARCE KE, ed. *Biopharmaceutical statistics for drug development*. New York: Marcel Dekker, 1988: 403–58.
- LE FORCE CF, DOCKHORN RJ, FINDLAY SR, et al. Fluticasone propionate: an effective alternative treatment for seasonal allergic rhinitis in adults and adolescents. *J Fam Pract* 1994; 38: 145–52.
- LEHMANN EL. In: *Non-parametrics: statistical methods based on ranks*. San Francisco, CA: Holden-Day, 1975: 132–41.
- MELTZER EO, ORGEL HA, BRONSKY EA, et al. A dose-ranging study of fluticasone propionate aqueous nasal spray for seasonal allergic rhinitis assessed by symptoms, rhinomanometry and nasal cytology. *J Allergy Clin Immunol* 1990; 86: 221–30.
- NATHAN RA, BRONSKY EA, FIREMAN P, et al. Once daily fluticasone propionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis. *Ann Allergy* 1991; 67: 332–8.
- RATNER PH, PAULL BR, FINDLAY SR, et al. Fluticasone propionate given once daily is as effective for seasonal allergic rhinitis as beclomethasone dipropionate given twice daily. *J Allergy Clin Immunol* 1992; 90: 285–91.
- REINBERG A, GERVAIS P, LEVI F, SMOLENSKY M, DEL CERRO L, UGOLINI C. Circadian and circannual rhythms of allergic rhinitis: an epidemiologic study involving chronobiologic methods. *J Allergy Clin Immunol* 1988; 81: 51–62.
- SIEGEL SC. Topical intranasal therapy in rhinitis. *J Allergy Clin Immunol* 1988; 81: 984–91.
- STERN MA, BENINCASA C. Once daily fluticasone propionate aqueous nasal spray in the prophylactic treatment of seasonal allergic rhinitis: is time of dosing important? *Br J Clin Res* 1994; 5: 111–22.
- VAN AS A, BRONSKY EA, GROSSMAN J, MELTZER EO, RATNER PH, REED C. Dose tolerance study of fluticasone propionate aqueous nasal spray in patients with seasonal allergic rhinitis. *Ann Allergy* 1991; 67: 156–62.