

The efficacy and tolerability of fluticasone propionate aqueous nasal spray in children with seasonal allergic rhinitis

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Fluticasone propionate aqueous nasal spray (FPANS) contains fluticasone propionate, which is a new topically active glucocorticoid with approximately twice the potency of beclomethasone dipropionate. In this European multicentre study, 143 children with seasonal allergic rhinitis were recruited: 47 received FPANS 100 µg once a day (od), 46 received FPANS 200 µg od, and 50 patients received placebo od, for 4 weeks. Treatment efficacy was assessed using diary card nasal symptom scores for sneezing, rhinorrhoea, blockage and itching, and eye watering/irritation. Patients receiving FPANS 100 µg or FPANS 200 µg demonstrated statistically significant improvements in median nasal symptom scores in all the symptoms recorded, when compared with placebo. There were no statistically significant differences between the FPANS 100 µg and FPANS 200 µg groups in improvement in nasal symptom scores. There was no effect on eye watering/irritation symptoms which could be attributed to either FPANS 100 µg or FPANS 200 µg when compared with placebo. Use of rescue antihistamine medication was significantly reduced in the FPANS 100 µg group when compared with placebo. The adverse events profile was similar in all three treatment groups, and the events reported were generally mild and related to the patients' rhinitis.

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On their introduction into clinical medicine in the late 1950s, topically applied corticosteroids were recognized as a possible treatment for rhinitis. However, before the early 1970s, there were few advantages to be gained from giving these drugs by the topical route as compared with the systemic route because, whatever the route of administration, they produced similar and often unacceptable systemic effects such as clinically significant suppression of the hypothalamo-pituitary-adrenal (HPA) axis (20).

In 1972, several clinical studies of a new inhaled steroid, beclomethasone dipropionate (BDP), reported a clear differentiation between systemic and local anti-inflammatory effects (4, 6), and a year later Mygind started using BDP topically for the treatment of hay fever (18). Since then, topical corticosteroids by the intranasal route have become the preferred treatment for seasonal rhinitis (1–3, 7, 11, 16, 27, 29, 31).

Topical glucocorticoids have been shown to be significantly more effective than intranasal sodium

cromoglycate (3, 11, 29) and H₁ antihistamines (1, 7, 31) in relieving nasal symptoms, particularly nasal obstruction (2, 16, 27).

Fluticasone propionate aqueous nasal spray (FPANS) contains fluticasone propionate (FP), a new topically active glucocorticoid, with approximately twice the potency of beclomethasone dipropionate as judged by the McKenzie skin vasoconstrictor score (22). It has been shown that FPANS has little or no systemic steroid activity in man, following intranasal doses of up to 4 mg for 7 days (10). Furthermore, oral dosing studies employing single doses of up to 16 mg of FP have confirmed that the compound has no clinically significant effects on the HPA axis when given by the oral route. A possible explanation for the weak HPA suppressive activity when given by the oral route is that FP undergoes first-pass metabolism in the liver, since it is rapidly metabolized by liver homogenates (from mouse, rat, or dog) to the corresponding inactive 17β-carboxylic acid, resulting in an oral systemic bioavailability

essentially equal to zero, a result which is unique for glucocorticosteroids (5).

In view of this lack of systemic activity and the finding in adults and adolescents that FPANS 200 µg given once daily is effective and well tolerated in the treatment of seasonal allergic rhinitis in a number of placebo-controlled and comparator studies (8, 14, 23), it was decided to examine the absolute efficacy and tolerability of FPANS 200 µg once daily and FPANS 100 µg once daily in children with seasonal allergic rhinitis.

Material and methods

Study design

The study plan is summarized in Table 1. This double-blind, placebo-controlled, parallel-group study was conducted at 18 research centres in Europe by the same protocol. The study protocol was approved by ethics review committees for each centre. Children were included in the study only after the informed consent of their parents/guardians was obtained. All patients recruited had a positive skin prick test to a known seasonal allergen relevant to the geographic area in which the patient lived, and the study was conducted during the relevant allergy season. Furthermore, to qualify for enrolment in the study, patients were required to have symptoms of seasonal rhinitis (nasal blockage, sneezing, nasal

itching, rhinorrhoea, and eye watering/irritation) at the time of presentation and to have had symptoms of at least moderate severity for at least one previous season. No patient who had perennial rhinitis or who had undergone a course of immunotherapy was admitted to the study. Other exclusion criteria were the use of intranasal, inhaled, or systemic corticosteroids or intranasal or inhaled sodium cromoglycate or nedocromil sodium within 1 month of the start of the trial medication, and/or use of astemizole within 6 weeks of the start of the trial medication.

Patients were randomized such that equal numbers were to receive FPANS 100 µg taken once daily in the morning (administered as two 50-µg actuations, one in each nostril), FPANS 200 µg taken once daily in the morning (administered as two 100-µg actuations, one in each nostril), or placebo aqueous nasal spray also taken once daily in the morning.

Patients were also provided with antihistamine syrup or tablets and sodium cromoglycate (2% w/v) eye-drops to use as rescue medications for troublesome symptoms.

Evaluations

There was a 4-week treatment period followed by a 2-week follow-up period. Patients attended the research centres every 2 weeks. Patients (or parents,

Table 1. Study plan

FP aqueous nasal spray 100 µg/actuation; one actuation to each nostril each morning			
FP aqueous nasal spray 50 µg/actuation; one actuation to each nostril each morning			
Placebo aqueous nasal spray; one actuation to each nostril each morning			
◀ Daily diary card ▶	◀ Daily diary card ▶		
Week 0 (Visit 1)	2 (Visit 2)	4 (Visit 3)	6 (Visit 4)
Patient selection Skin prick test ENT history Physical examination Nasal assessment Symptom assessment Haematology Biochemistry Urinalysis	Nasal assessment Symptom assessment Adverse events	Physical examination Nasal assessment Symptom assessment Adverse events Haematology Biochemistry Urinalysis	Adverse events * Haematology * Biochemistry * Urinalysis

* Only if abnormal at previous visit.

for the youngest children) kept a daily record of their symptoms of sneezing, rhinorrhoea, nasal blockage on waking and during the day, nasal itching, and eye watering/irritation, using a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Patients also recorded the daily use of the study and rescue medications.

At each clinic visit, the investigator was asked to judge the severity of the patient's rhinitis symptoms (nasal blockage, rhinorrhoea, sneezing, nasal itching, and eye watering/irritation), using the same four-point scale. The colour of the nasal mucosa was recorded, and an overall assessment of nasal secretions was made.

The primary measurements of treatment efficacy were based upon the analysis of the percentage of symptom-free days for sneezing and rhinorrhoea. The percentage of symptom-free days for the remaining diary card symptoms, analysis of median symptom scores for all symptoms, use of rescue medication, and the physician's assessment of rhinitis symptoms were all used as secondary measurements of treatment efficacy.

Safety was evaluated by monitoring adverse events at each evaluation visit. Haematologic, biochemical, and urinary analysis was performed before the start of study treatment (clinic visit 1), at the end of study treatment (clinic visit 3), and, if necessary, at the follow-up visit (clinic visit 4). An overall assessment of clinical chemistry, renal function, hepatic function, haematology, and urinalysis was made by the physician at the end of the trial.

Statistical analysis

Hypothesis testing to detect treatment differences was performed on clinician-rated symptom scores, patient-rated symptom scores, use of rescue medication, and overall clinical evaluation. In each case, testing was performed on data from all centres combined, adjusting for centre effect as appropriate for a multicentre study.

All patients entered into the study were analysed initially, provided sufficient data were available. The efficacy analysis was repeated after the removal of patients who violated the protocol. All safety analyses were performed on the total sample of patients.

Each symptom recorded on the diary card during the 4-week treatment period was summarized separately by the percentage of symptom-free days and the median symptom score. If a median fell midway between two points of the scale, then the more severe of the two scores was taken as the median. A patient was included in the analysis if data on the variable were available from at least 10 days following treatment. The analysis of percentage of symptom-free days was completed using the Wilcoxon rank-sum

test. An adjustment for centres was made if appropriate, using the van Elteren method (13). Analyses of the median symptom scores were performed by the use of proportional odds models for ordinal data (12), provided the assumptions necessary for such an analysis were justified.

Separate comparisons of FP 100 µg with placebo and of FP 200 µg with placebo were made. A comparison of FP 100 µg with FP 200 µg was also made.

Results

A total of 143 patients were recruited: 47 received treatment with FPANS 100 µg once daily, 46 received treatment with FPANS 200 µg once daily, and 50 received placebo. The demographic characteristics of the study population are presented in Table 2. Age was similar among treatment groups, whereas sex was not equally distributed, since males were significantly more numerous than females in all the groups studied (Table 2), although there was no difference in the male/female ratio among the three groups.

Two populations of patients were identified; these were the total population, which included all patients randomized to study treatment, and the efficacy population, which included only those patients from the total population who adhered closely to the requirements of the protocol (42 patients in the placebo group, 42 patients in the FPANS 200 µg group).

Efficacy

Similar results were obtained for the efficacy and total populations. The efficacy population formed 88% of the total population.

The analysis of percentage of symptom-free days (days 1–28) is shown in Fig. 1. For the efficacy

Table 2. Patient demography

		No. of patients (%)		
		FPANS 100 <i>n</i> =47	FPANS 200 <i>n</i> =46	Placebo <i>n</i> =50
Sex	Male	33 (70)	34 (74)	37 (74)
	Female	14 (30)	12 (26)	13 (26)
Age (years)	Mean	8.3	8.2	8.5
	SD	2.1	2.3	2.1
	Minimum	4	4	4
	Maximum	12	11	11
Height (cm)	Mean	133	133	137
	SD	14	15	16
Weight (kg)	Mean	30.2	29.9	32.6
	SD	9.8	9.7	8.9

FPANS 100=fluticasone propionate aqueous nasal spray 100 µg once daily.
FPANS 200=fluticasone propionate aqueous nasal spray 200 µg once daily.

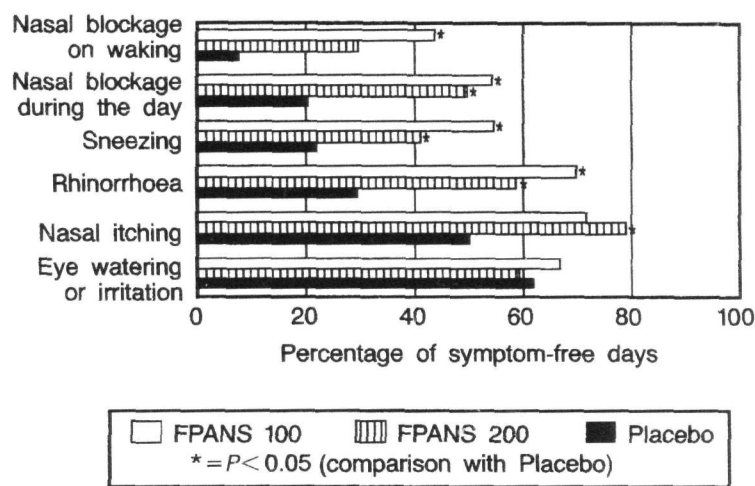


Fig. 1. Analysis of symptom-free days.

population, the median percentage of symptom-free days for sneezing ($P=0.016$), rhinorrhoea ($P=0.011$), and nasal blockage on waking ($P=0.011$) and during the day ($P=0.031$) was significantly greater in patients treated with FPANS 100 μg once daily as compared with those treated with placebo. Similarly, the median percentage of symptom-free days for sneezing ($P=0.018$), rhinorrhoea ($P=0.042$), nasal blockage during the day ($P=$

0.032), nasal blockage on waking ($P=0.018$), and nasal itching ($P=0.014$) was significantly greater in patients treated with FPANS 200 μg once daily as compared with placebo. There was no significant difference in the median percentage of symptom-free days for sneezing, rhinorrhoea, nasal blockage, and nasal itching between patients treated with FPANS 100 μg and those treated with FPANS 200 μg . There was no evidence of a difference in the percentage of days free from eye symptoms among the three measurements.

For symptoms of sneezing ($P=0.016$), rhinorrhoea ($P=0.016$), nasal blockage on waking ($P=0.002$) and during the day ($P=0.033$), and nasal itching ($P=0.011$), patients treated with FPANS 100 μg once daily had significantly lower median symptom scores than placebo-treated patients (Fig. 2). Similarly, patients treated with FPANS 200 μg once daily recorded significantly lower median symptom scores for sneezing ($P=0.048$), nasal blockage on waking ($P=0.015$), and nasal itching ($P=0.038$) than the placebo-treated patients. There was no significant difference in median symptom scores between patients treated with FPANS 100 μg

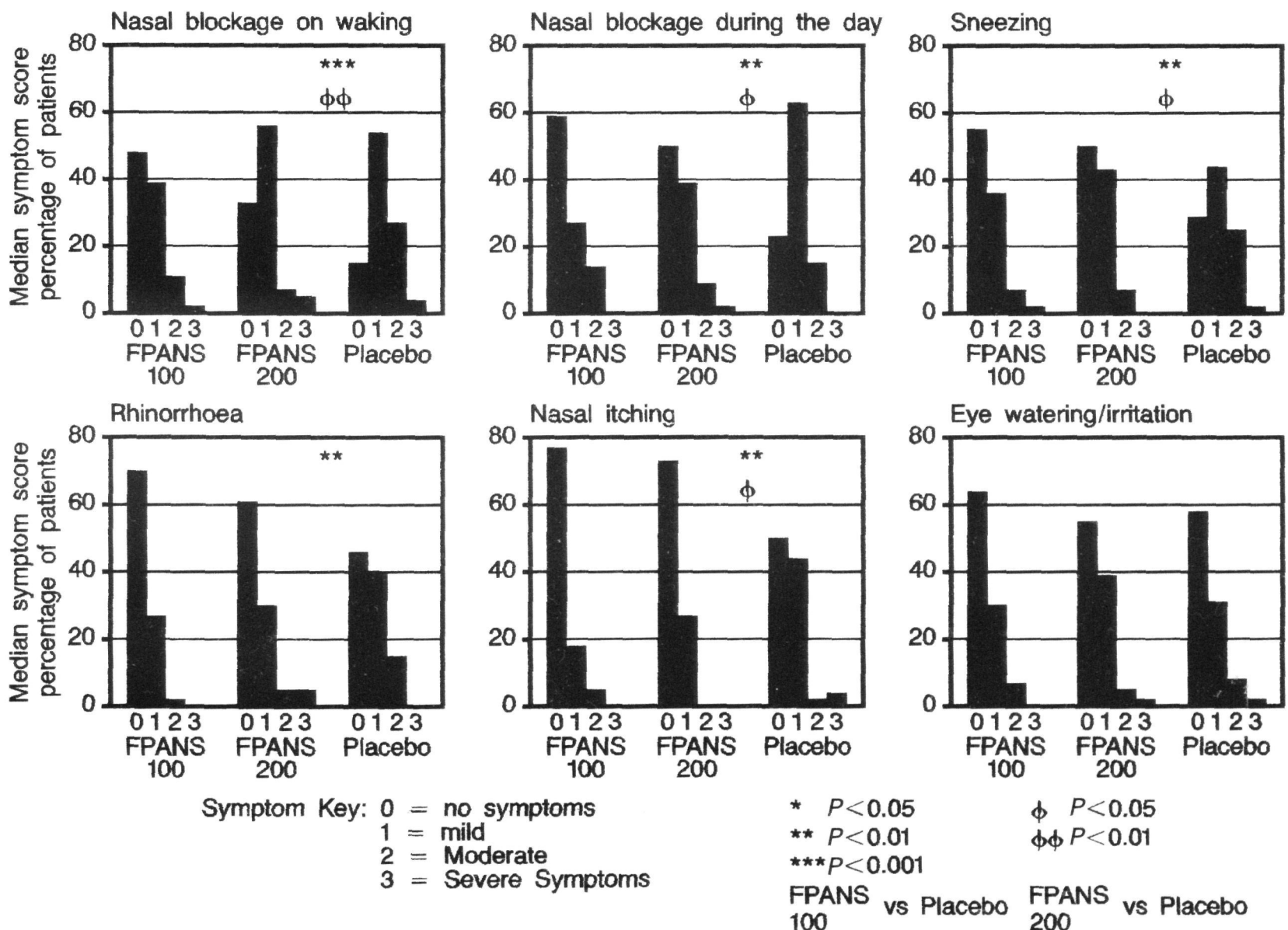


Fig. 2. Analysis of median symptom scores.

once daily and those treated with 200 µg once daily for any of the symptoms assessed (Fig. 2). There was no significant difference between FPANS and placebo in the control of eye symptoms. For antihistamine (tablets or syrup) use as rescue medication, the percentage of rescue-free days was significantly greater ($P = 0.009$) and the median number of times antihistamine rescue medication was used was significantly lower ($P = 0.005$) in patients treated with FPANS 100 µg once daily (median 0 days, lower quartile 0.0 and upper quartile 10.6) as compared with placebo (median 4.5 days, lower quartile 0.0 and upper quartile 21.1). There was no such difference when comparing patients treated with FPANS 200 µg, who showed a median rescue medication use of 0.5 days, with a lower quartile of 0.0 and an upper quartile of 19.3, with those treated with placebo, or when comparing patients treated with FPANS 200 µg with those treated with FPANS 100 µg.

For sodium cromoglycate eye-drop use, the percentage of rescue-free days was similar among the three treatment groups, as was the median number of times eye-drops were used, which was 2 days (lower quartile 0.0 and upper quartile 21.8) for children treated with FPANS 100 µg, 1.6 days (lower quartile 0.0 and upper quartile 24.2) for children treated with FPANS 200 µg, and 4.5 days (lower quartile 0.0 and upper quartile 23.8) for the placebo group. The investigator's assessment of symptoms at the end of the treatment period and the nasal assessment at clinic visits 1 and 3 are reported in Figs. 3 and 4, respectively. These clinical assessments demonstrate the efficacy of FPANS in alleviating both the signs and symptoms of rhinitis. A large number of patients in the FPANS groups were recorded as having no symptoms at the end of the treatment period, and in spite of a large placebo response this effect was statistically superior to placebo in the case of nasal blockage, rhinorrhoea, and nasal itching (Fig. 3). The appearance of the nose

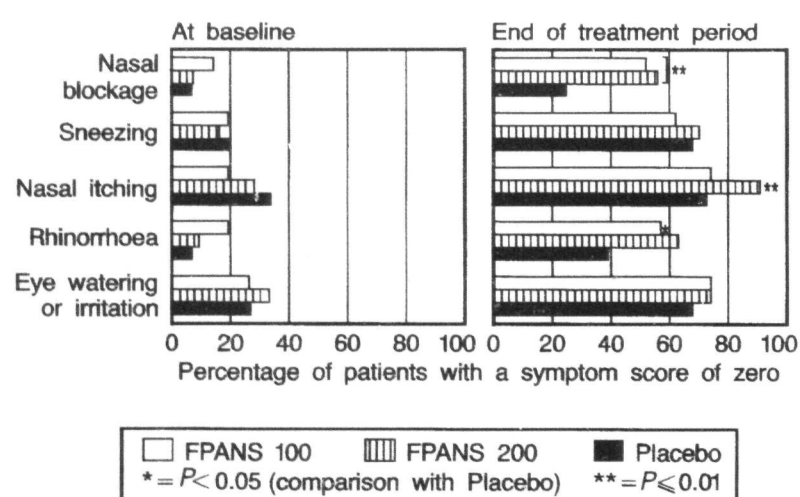


Fig. 3. Analysis of investigator's assessment of symptoms.

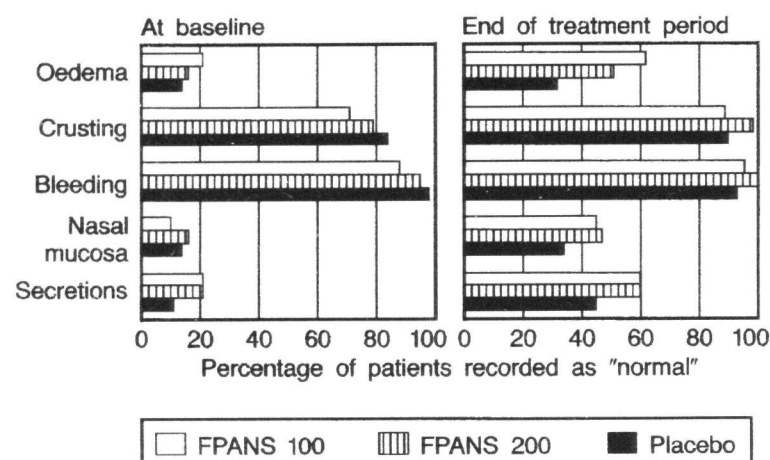


Fig. 4. Analysis of investigator's nasal examinations.

had reverted to "normal" in a large number of patients on examination by the investigator at the end of the treatment period (Fig. 4), with the reduction in oedema and nasal secretions being most associated with treatment with FPANS.

Safety

All 143 patients randomized to receive study treatment were included in the analysis of safety. The numbers of adverse events reported are summarized in Table 3. There was only one serious adverse event; an 8-year-old male patient was admitted to hospital for observation following a fall, 12 days after the start of treatment with FPANS 100 µg once daily. The patient was discharged after 2 days, and the event was considered unrelated to the study drug.

Only two patients were withdrawn from the study due to adverse events; an 11-year-old male patient developed jaundice 4 days after starting treatment with FPANS 100 µg once daily, and another 11-year-old male patient had a severe asthma exacerbation 10 days after starting treatment with placebo aqueous nasal spray. Both of the above adverse events were considered by the investigator to be unrelated to the study treatment.

Table 3. Summary of adverse events

Adverse events	During treatment		
	FPANS 100	FPANS 200	Placebo
No. of patients	47	46	50
No. of adverse events	30	16	40
No. of patients with adverse event (%)	20 (40)	13 (28)	23 (46)
No. of patients with serious adverse event (%)	1 (2)	0	0
No. of patients withdrawn due to adverse event (%)	1 (2)	0	1 (2)

FPANS 100=fluticasone propionate aqueous nasal spray 100 µg once daily.
FPANS 200=fluticasone propionate aqueous nasal spray 200 µg once daily.

The adverse events reported in each of the three treatment groups were generally mild and of the type to be expected. In the FPANS 100 µg-treated patients, upper respiratory tract infection, asthma and related events, and cough, reported by 13%, 11%, and 6% of patients, respectively, were the most commonly reported adverse events. In the FPANS 200 µg-treated group of patients, cough and sore throat, each reported by 7% of patients, were the most commonly reported adverse events. In the placebo-treated group of patients, the most commonly reported adverse events during treatment included asthma and related events reported by 14% of patients and upper respiratory tract infection, cough, and rhinitis, each reported by 6% of patients. The great majority of adverse events reported in all three treatment groups were considered to be either unlikely to be related or unrelated to study treatment. Changes in laboratory parameters including haematology, biochemistry, or urinalysis during treatment were small and similar among the three treatment groups.

The incidence of headache was very low, with no reports of headache in either of the FPANS-treated groups and 4% incidence in the placebo-treated group. There were no reports of nasal dryness or irritation, and the incidence of sore throat was 2% in the FPANS group and 4% in the placebo group.

The incidence of reports of epistaxis was also low with this complaint being reported by 2% of patients in the FPANS 100 µg-treated group and 4% in the placebo-treated group, and no report being recorded in the FPANS 200 µg-treated group.

Discussion

This is the largest European study of seasonal allergic rhinitis involving administration once a day of intranasal FP in children. Overall, the results demonstrated that both doses of FPANS were significantly superior to placebo in relieving the symptoms of seasonal allergic rhinitis. This was evident despite the large placebo response, which is usually observed in studies of rhinitis pharmacotherapy (16).

There were no statistically significant differences between the FPANS 100 µg and FPANS 200 µg groups in improvement in nasal symptoms scores, although, in the more severe cases studied, there did appear to be a benefit in using a dose of 200 µg od without any concomitant decrease in tolerability. This phenomenon was also observed in adults (8). As can be seen in Fig. 2, despite statistical results, some of the subjects appear to have been resistant to treatment, and some patients developed severe symptoms, especially for nasal blockage and rhinorrhoea, on both doses of FPANS. A possible explanation of this phenomenon is that the study took

place during the pollen season, and naturally some patients were exposed to very high quantities of pollen, which no medication would be expected to control.

There was no effect on eye watering/irritation symptoms which could be attributed to either FPANS 100 µg or FPANS 200 µg when compared with placebo. These observations are similar to those previously reported by Mygind (18) and Siegel et al. (26), who showed no significant effect of intranasal BDP on eye symptoms. An effect on eye symptoms would not be expected from treatment with a poorly bioavailable topical steroid (25).

FPANS administered once a day appeared to be effective for a full day, confirming previous observations both in adults (5, 8, 19, 23) and in children (9, 14, 21). Compared with the recommended use of BDP four times daily, the administration once a day of FPANS offers the obvious advantage that parents can supervise the correct use of the spray more easily and consistently throughout the treatment period, with an expected improvement in compliance (16). This is particularly true when the efficacy and safety of treatment are comparable to those of more frequent doses (23).

The extended duration of action of FPANS might be due both to the high topical potency of this steroid and to the insolubility of the drug, which might lead to a prolonged absorption phase from the nose (10). Effectively, 4 mg intranasal FP had no demonstrable effect on the HPA axis, suggesting insignificant systemic absorption of the drug from the nose, as a 2-mg dose administered intravenously caused marked depression of plasma cortisol levels (5, 10). We did not perform any evaluation in our patients of HPA function associated with the use of intranasal fluticasone, since HPA effects with intranasal glucocorticosteroids do not appear to be present even with topical steroids with less favourable topical/systemic activity (15, 24, 25, 28). Furthermore, the lack of effects of FPANS, at the doses of 100 µg and 200 µg once a day, on the HPA axis was demonstrated in children both with the evaluation of morning plasma cortisol concentration (9, 17) and with the more sensitive method of 24-h urinary excretion of cortisol and 17-ketogenic steroids (14).

The oral bioavailability of FPANS is <1% (5, 10, 22), a significant factor when up to 80% of the intranasal dose of a topical steroid is ultimately swallowed. Additionally, the effective dose of FPANS in this study has been shown to be 100 µg od. This dose is one-quarter of that recommended for children in the cases of BDP or budesonide, two other steroids indicated for this condition in children.

The low potential for systemic steroid-related side-effects of FPANS, combined with the very low effective dose, produces a very well-tolerated drug,

which in these studies has demonstrated excellent control of symptoms of rhinitis when compared with placebo.

The adverse event profile of FPANS 100 µg/day or 200 µg/day was similar to that of placebo. The local side-effects, spray-induced sneezing, nose dryness, and nose bleeding, were carefully recorded in our study, and we did not find any difference between active and placebo treatment. These results confirm those of other placebo-controlled studies in which the tolerability of FP was evaluated both in adults (8, 15, 19, 24, 28, 30) and children (9, 14, 17, 21).

In conclusion, FPANS at either 100 µg once daily or 200 µg once daily was significantly superior to placebo in relieving all symptoms of seasonal allergic rhinitis in this paediatric population. There were no significant tolerability penalties associated with either FPANS dosage regimen.

Our study is the first European study to be performed in children with allergic rhinitis. It confirms the efficacy and safety profile of FPANS in children with hay fever reported in studies performed in the USA (9, 14, 21). FPANS given as a 100-µg once daily dose should be a useful and well-accepted treatment of allergic rhinitis in children as young as 4 years of age.

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