

Original article

Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis

Background: Topical steroids are first-line medication to control nasal polyposis (NP), a disease with long-term clinical course.

Objective: The aim of this study was to evaluate the efficacy and safety of fluticasone propionate aqueous nasal spray (FPANS) 200 µg twice a day (bd) after 1 month of treatment, and to compare FPANS 200 µg bd and FPANS 200 µg once a day (od) in maintenance and long-term treatment.

Methods: Double-blind, placebo-controlled, 8-month study with three treatment periods (1-month acute period followed with 1-month maintenance period and 6-month follow-up period) was carried out. Group 1 received FPANS 200 µg bd, during acute, maintenance and follow-up periods, Group 2 received FPANS 200 µg bd during acute period and FPANS 200 µg od during maintenance and follow-up periods, and Group 3 received placebo during acute and maintenance periods and FPANS 200 µg bd during follow-up period. Endpoints were change from baseline in clinic peak nasal inspiratory flow (PNIF), domiciliary evening PNIF, intensity of symptoms and polyposis grade.

Results: After acute period and maintenance periods, FPANS 200 µg bd was significantly more effective than placebo on all endpoints and more effective than FPANS 200 µg od after 1-month maintenance period on clinic PNIF, evening PNIF, obstruction, percentage of days with no sense of smell and percentage of nights with no disturbances. The two doses were similar on other endpoints. After the 6-month follow-up period, there was no difference between the two doses of FPANS at all efficacy endpoints. The safety profile of FPANS did not highlight any new or unanticipated adverse events.

Conclusion: The study demonstrated the efficacy of FPANS 200 µg bd in acute treatment and FPANS 200 µg od as a sufficient dose to maintain a long-term efficacy in the treatment for NP.

**R. Jankowski¹, J.-M. Klossek²,
V. Attali³, A. Coste⁴, E. Serrano⁵**

¹Hôpital Central de Nancy, Service ORL, Nancy;

²Hôpital Jean Bernard, Service ORL, Poitiers;

³GlaxoSmithKline, Route de Versailles, Marly-le-Roi Cedex; ⁴Centre Hospitalier Intercommunal de Créteil, Service ORL, Créteil; ⁵Hôpital Larrey, Service ORL, Toulouse, France

Key words: clinical treatment; fluticasone propionate; glucocorticoids; nasal polyps.

Prof. Roger Jankowski
Hôpital Central de Nancy, Service ORL,
29, avenue Maréchal de Tassigny
Nancy 54000
France

Accepted for publication 23 September 2008

Nasal polyposis (NP) is the result of chronic inflammation of the nasal and paranasal sinus mucosa (1, 2). Nasal polyposis is characterized by endoscopic sign of polyps and two or more following symptoms: nasal obstruction, facial pain, rhinorrhoea or hyposmia (1, 2). These symptoms can be accompanied with sleep disturbance (1–3). Histologically defined, NP appears as oedematous bags in the upper nasal cavity, covered mostly with respiratory pseudostratified epithelium and characterized by a thickening of the basement membrane, glands that have undergone cystic degeneration, poor vascularization and lack innervation except at the base of NP (4–7).

The prevalence of NP in general population is 4% (2, 8–12). For unknown reasons, NP develops preferentially in about 7–15% of patients with asthma and in 36–96% of patients with aspirin intolerance (2, 12–15). Nasal polyposis is more frequent in men than in women and significantly increases with age with an

average onset at approximately 42 years (2, 8, 13). Nasal polyposis is not a life-threatening disorder but has high impact on the quality of life of patients (16–19).

Management of NP has been the topic of frequent controversial debates for many decades. An update of a European Position Paper on NP (EP³OS) still recommended topical steroid as the first-line medication based on the results of several randomized controlled trials with fluticasone propionate (FP), beclomethasone dipropionate, budesonide or mometasone furoate (2). While NP is a disease with a long-term clinical course, no data on long-term efficacy and tolerability of topical steroids are available (2, 19).

In this context, we evaluated efficacy and safety of FP aqueous nasal spray (FPANS) 200 µg twice a day (bd) as a starter treatment and compared long-term efficacy and tolerability of FPANS 200 µg bd or once a day (od) in maintenance treatment of NP for a 7-month period.

Moreover, our study design allowed determination of minimal efficacy dose in long-term treatment.

Methods

Patients

Patients aged over 18 years, with diagnosis of symptomatic bilateral NP (at least two of the following symptoms: nasal obstruction, rhinorrhoea with anterior or posterior nasal drip, hypo or anosmia) were eligible. Exclusion criteria were: patients receiving systemic corticosteroids, nonsteroidal sulphur drugs, intranasal anticholinergics or intranasal sulphur containing drugs during the 4 weeks prior to inclusion, and antihistamines or nasal steroids 15 days prior to inclusion; patients with history of ethmoidectomy, severe septal deviation, history of severe epistaxis, severe or noncontrolled asthma requiring permanent or recurrent systemic corticosteroids, NP requiring systemic corticosteroids, daily use of saline solution for nostrils and inability to cease this treatment and other significant medical conditions.

Study design

This was a multi-centre, randomized, double-blind, parallel group, placebo-controlled, 8-month study. Following the run-in period, patients were randomized to one of the three groups as shown in Fig. 1.

Relief medications for NP such as analgesics (except NSAIDs and aspirin > 3g/day), antibiotics and antiasthmatics were allowed during treatment periods. Antihistamines, depot or systemic corticosteroids and saline solution for instillation were allowed only during period 3. Not allowed:

- during the whole study: nasal corticosteroids other than FPANS, local vasoconstrictors, local anticholinergics, ritonavir, topic sulphur containing drugs, NSAIDs and aspirin (> 3 g/day);
- during the run-in and the whole study: polypectomy, sinus surgery and/or ethmoidectomy.

Assessments

During periods 1 and 2, domiciliary measurements in the evening of PNIF (evening PNIF) and symptom score over the previous 24 h on a 4-point Likert scale (representing: no, mild, moderate or severe symptoms) were recorded in a Diary Record Card (DRC).

The primary efficacy endpoint was the change from baseline in PNIF measured at the visit (clinic PNIF) after period 1.

Secondary efficacy endpoints were the change from baseline after periods 2 and 3 in:

- Clinic PNIF, mean evening PNIF and intensity of rhinorrhoea, nasal blockage or sense of smell and taste measured by a 100-mm Visual Analogic Scale (VAS) (0 mm: symptom of the greatest intensity and 100 mm: no symptom).
- Nasal polypsis grade assessed by endoscopy (Grade 0: absence of NP, Grade I: NP in middle meatus, Grade II: NP beyond middle meatus but not blocking the nose completely and Grade III: NP completely obstructing the nose).

Safety assessments. At each visit, after the patient had opportunity to spontaneously report any problem, the investigator enquired about adverse events (AEs).

Withdrawals. Withdrawals because of treatment failure were defined as any study or any study drug discontinuation due to lack of efficacy (including not permitted medication for NP or nasal surgery) or drug-related AE.

Statistical analysis

The Intent-to-Treat (ITT) population, defined as primary population for analyses, consisted of all patients randomized to treatment, who received at least one dose of the study medication, with any on-treatment efficacy data.

Data concerning patients of Groups 1 and 2, both receiving FPANS 200 µg bd during period 1, were pooled for analysis, in

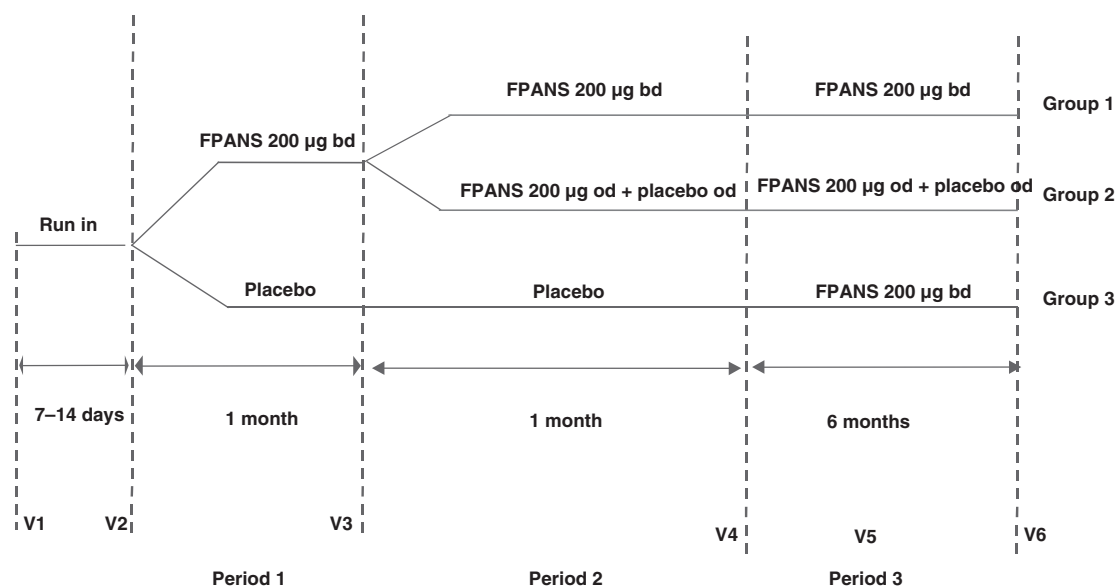


Figure 1. Study design.

order to evaluate efficacy of FPANS 200 µg bd vs placebo at 1 month.

Change from baseline in PNIF was analysed using an analysis of covariance (ANCOVA). The model included adjustment for the effects of sex, age and baseline value.

Change from baseline in mean evening PNIF, symptom intensity assessed using VAS and mean symptom scores were analysed the same way as PNIF. Distribution of NP grade was analysed using Cochran-Mantel-Haenszel test adjusted for NP grade at baseline. Change from baseline in percentage of symptom-free days was analysed using Wilcoxon rank sum test.

Finally, the proportion of patients withdrawn because of treatment failure was analysed for the overall treatment period using the chi-squared test. Treatment failure was defined as a lack of efficacy or drug-related AEs. Safety analysis was based on AEs reported during pretreatment period (V1–V2), periods 1 and 2 (V2–V4) and period 3 (V4–V6) (Fig. 1).

Results

Study population

Of the 261 recruited patients, 246 (94%) were randomized to treatment, 245 were included in safety population and 242 in ITT population. A total of 199 patients completed the study (Group 1: 85%, Group 2: 83%, Group 3: 77%). The baseline characteristics of ITT population are summarized in Table 1. In average, NP grading was similar in all groups (around 40% grades I and II and 18% grade III).

Proportion of patients with a low baseline PNIF was more important in Group 1 (28%) than in Group 2 (22%), while mean baseline PNIF was not significantly different in Groups 1 and 2.

The reasons for the 46 withdrawals are presented in Table 2. The median time to withdrawal was 100 days in Group 1, 110 days in Group 2 and 78 days in Group 3.

During the whole treatment period, there was no difference between groups in the use of rescue medication for NP, oral steroid courses and change or daily dose in inhaled corticotherapy for concurrent asthma. Twenty-two patients were administered antihistamines: most of them ($n = 16$) during period 3 ($n = 4$ in Group 1, $n = 10$ in Group 2 and $n = 2$ in Group 3), and six during period 1 ($n = 1$ in Group 2 and $n = 5$ in Group 3, including two patients treated for only 1 day).

Period 1: efficacy of FPANS 200 µg bd (Groups 1 + 2) vs placebo (Group 3)

As shown in Table 3, after 1 month, FPANS 200 µg bd was more effective than placebo at all endpoints. Peak nasal inspiratory flow increased significantly ($P = 0.0001$) in patients receiving FPANS (108.6 ± 53.8 vs 141.4 ± 52.9 l/min) and remained unchanged in patients receiving placebo (106.4 ± 43.4 vs 112.3 ± 48 l/min). The adjusted mean change in PNIF was significantly higher ($P = 0.0001$) in Groups 1 + 2 (32.9 l/min) than in Group 3 (5.9 l/min). Similar trend was observed in evening PNIF ($P = 0.0001$).

Table 1. Baseline characteristics of ITT population (242 patients)

	Group 1 ($n = 79$)	Group 2 ($n = 82$)	Groups 1 + 2 ($n = 161$)	Group 3 ($n = 81$)
Age (mean in years)	50	50	50	53
Male/female (% of patients)	68/32	60/40	64/36	60/40
Patients with rhinorrhoea (% of patients)	86	82	84	77
Patients with sense of smell disorders (% of patients)	90	90	90	85
Patients with sense of taste disorders (% of patients)	47	43	45	43
Symptoms ≥ 5 years (% of patients)	58	56	57	58
Diagnosis of NP ≥ 5 years (% of patients)	37	28	32	31
NP stage total score (mean)	3.46	3.71	3.59	3.44
PNIF (mean in l/min)	108.0	109.3	108.7	109.1
Nasal obstruction using VAS (mean in mm)	43.2	40.1	41.6	42.9
Rhinorrhoea using VAS (mean in mm)	53.2	62.5	57.9	64.9
Sense of smell disorders using VAS (mean in mm)	37.5	32.6	35.0	34.1
Sense of taste disorders using VAS (mean in mm)	60.3	57.0	58.6	57.0
Nasal obstruction score (mean)	1.39	1.47	1.43	1.39
Rhinorrhoea score (mean)	1.10	0.92	1.01	0.89
Sense of smell disorders score (mean)	1.75	1.85	1.80	1.72
Nasal obstruction-free days (mean in %)	8.8	3.5	6.1	8.3
Rhinorrhoea free days (mean in %)	20.7	29.8	25.2	37.9
Sense of smell disorder-free days (mean in %)	9.0	10.4	9.7	12.3
Concomitant asthma (% of patients)	11	26	19	26
Allergy (% of patients)	13	18	15.5	23

ITT population, intention-to-treat population; VAS, Visual Analogic Scale.

At baseline, the distribution of NP grades was similar in all groups in right or left nostrils (grade 0: 1–0%, grade I: 43–40%, grade II: 42–41% and grade III: 14–19%). After 1 month of treatment, it was significantly in favour of Groups 1 + 2 for right ($P < 0.01$) and left ($P < 0.001$) nostrils.

Intensity of all symptoms assessed using VAS or recorded by DRC, was significantly lower in Groups 1 + 2 compared with Group 3. After 1 month of treatment, percentage of symptom-free days increased significantly ($P = 0.0001$) in Groups 1 + 2 but remained unchanged in Group 3. Percentage of nasal obstruction-free days increased significantly ($P = 0.0001$) from 6.1% to 25.6% in Groups 1 + 2 while remained unchanged in Group 3 (8.3–12.1%). Similar results were observed in percentage of days with no rhinorrhoea (25.2–43.4% in Groups 1 + 2 vs 37.9–36.8% in Group 3, $P = 0.0001$) and no sense of smell disorders (9.7–16.3% in Groups 1 + 2 vs 12.3–10.0% in Group 3, $P = 0.0001$).

Regarding parameters recorded using DRC, analyses on a week-by-week basis showed that FPANS 200 µg bd exhibited a very rapid onset of action on objective evening PNIF and nasal obstruction score as shown in Fig. 2. The difference vs placebo was statistically significant as early as week 1 ($P = 0.0001$).

Period 2: comparison of two dosing regimen of FPANS

Comparison of Group 1 vs Group 2. Group 1 showed an additional increase in PNIF (Baseline: 107.6; Period 1: 145.3; Period 2: 150.3 l/min) and Group 2 showed a plateau effect (Baseline: 108.6, Period 1: 139.5, Period 2: 135.5 l/min). There was a significant difference between the two groups in adjusted mean change from baseline of clinic PNIF (40.1 l/min in Group 1 vs 26.7 l/min in Group 2, $P < 0.05$) and evening PNIF (39.1 l/min in

Group 1 vs 24.8 l/min in Group 2, $P < 0.05$) as shown in Fig. 3. Regarding symptoms, there was a significant difference between the two groups on adjusted mean change of nasal obstruction score (-0.73 in Group 1 vs -0.54 in Group 2, $P < 0.05$) and on percentage of days with no sense of smell disorders (35.07 in Group 1 vs 22.29 in Group 2, $P < 0.05$). Difference in nasal obstruction assessed using VAS, percentage of nasal obstruction-free days and mean sense of smell disorders score failed to reach the 5% significance level.

Comparison of Group 1 or Group 2 vs Group 3. Fluticasone propionate aqueous nasal spray 200 µg bd was more effective than placebo at all endpoints as shown in Table 3. Adjusted mean change from baseline for clinic PNIF and evening PNIF was significantly ($P < 0.001$) higher in Group 1 (40.1 and 39.1 l/min) than in Group 3 (17.2 and 13 l/min). Differences between Group 2 and Group 3 were statistically significant for the majority of endpoints. The difference in PNIF, even if it was not significant, was in favour of Group 2 (change from baseline: 26.7 l/min in Group 2 vs 17.2 l/min in Group 3). Figure 3 illustrated the comparison of three treatments, week after week for evening PNIF and nasal obstruction score during periods 1 and 2. Change from baseline in mean evening PNIF was significantly ($P < 0.05$) higher in Group 2 (24.8 l/min) than in Group 3 (13.0 l/min). Regarding symptoms, differences were statistically significant for rhinorrhoea ($P < 0.05$) assessed using VAS or DRC and for nasal obstruction ($P < 0.001$) and sense of smell disorders ($P < 0.05$) as recorded in DRC. In an additional analysis, it has been shown that baseline value of clinic PNIF has an impact on 8-week response in treated groups and not in placebo group. Indeed, patients with a low baseline value (PNIF < 70 l/min) had higher amelioration after 8 weeks of treatment than those with a high baseline value.

Table 2. Summary of withdrawals after the start of the treatment period (safety population)

	Group 1 (n = 81)	Group 2 (n = 83)	Group 3 (n = 81)	Total (n = 245)
Total number of withdrawals n (%)	12 (15)	15 (18)	19 (23)	46 (19)
Reason for withdrawal				
Adverse event	1 (1)	2 (2)	5 (6)	8 (3)
Consent withdrawn	1 (1)	4 (5)	0	5 (2)
Lack of efficacy†	4 (5)	4 (5)	10 (12)	18 (7)
Lost to follow-up	3 (4)	2 (2)	0	5 (2)
Noncompliance	1 (1)	2 (2)	2 (2)	5 (2)
Protocol violation	1 (1)	0	0	1 (<1)
Not permitted medication‡	0	0	2 (2)	2 (<1)
Other	1 (1)	1 (1)	0	2 (<1)

NP, nasal polyposis.

†Including not permitted medication for NP or nasal surgery.

‡Other disease than NP.

Table 3. Treatment differences after acute period (period 1) and maintenance treatment period (period 2) with regard to primary and secondary endpoints

Periods	Period 1	Period 2
Treatments	FPANS 200 µg bd (1 month) vs placebo (1 month)	FPANS 200 µg bd (2 months) vs placebo (2 months)
Groups of treatments	Groups 1 + 2 (n = 161) vs Group 3 (n = 81)	Group 1 (n = 79) vs Group 3 (n = 81)
Clinic PNIF (l/min)	+27.0 ($P = 0.0001$)	+22.9 ($P < 0.001$)
Mean evening PNIF (l/min)	+19.1 ($P = 0.0001$)	+26.1 ($P = 0.0001$)
Mean nasal obstruction score	-0.42 ($P = 0.0001$)	-0.48 ($P < 0.01$)
Mean rhinorrhoea score	-0.26 ($P = 0.0001$)	-0.25 ($P < 0.01$)
Mean sense of smell disorders score	-0.27 ($P < 0.001$)	-0.37 ($P < 0.001$)
Nasal obstruction using VAS (mm)	+17.6 ($P = 0.0001$)	+13.1 ($P < 0.01$)
Rhinorrhoea using VAS (mm)	+14.8 ($P = 0.0001$)	+8.2 ($P < 0.05$)
Sense of smell disorders using VAS (mm)	+10.8 ($P < 0.001$)	+3.3 (NS)
Sense of taste disorders using VAS (mm)	+8.3 ($P < 0.05$)	+4.8 (NS)
		FPANS 200 µg bd (1 month) + FPANS 200 µg od (1 month) vs placebo (2 months)
		Group 2 (n = 82) vs Group 3 (n = 81)
		+9.4 (NS)
		+11.8 ($P < 0.05$)
		-0.30 ($P < 0.001$)
		-0.16 (NS)
		-0.20 ($P < 0.05$)
		+5.9 (NS)
		+10.0 ($P < 0.05$)
		+0.4 (NS)
		+2.9 (NS)

FPANS, fluticasone propionate aqueous nasal spray; PNIF, peak nasal inspiratory flow; VAS, Visual Analogic Scale; NS, not significant.

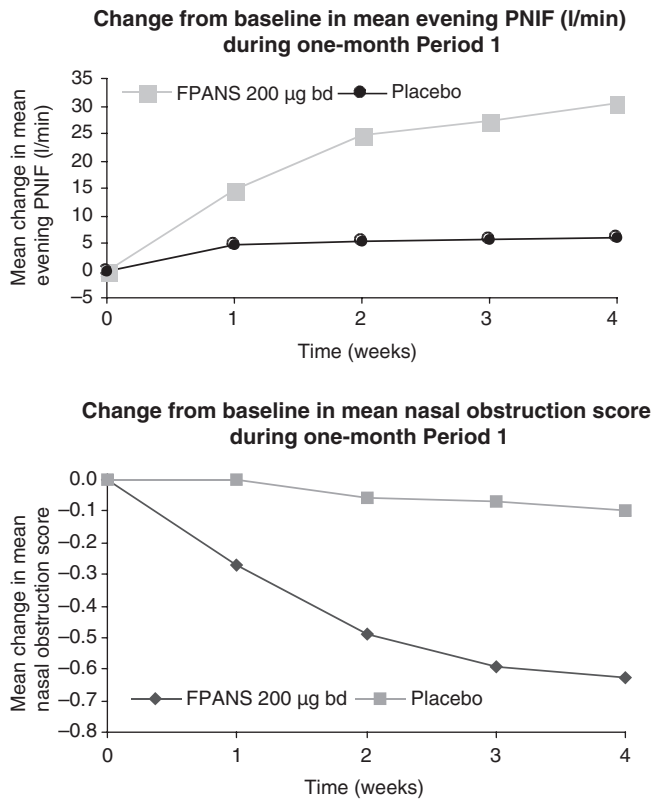


Figure 2. Change from baseline with regard to mean evening peak nasal inspiratory flow (PNIF) and nasal obstruction score during acute period (period 1).

Period 3: long-term efficacy of FPANS

Both doses of FPANS allowed a maintenance efficacy. At end of study, compared with maintenance period (2 months), PNIF was stable in Group 1 (41.8–42.8 l/min) but increased slightly but steadily in Group 2 (26.6–34.9 l/min) as shown in Fig. 4. At end of study, no significant difference was observed between Groups 1 and 2 on PNIF, NP grades and symptoms.

Safety

A total of 281 AEs occurred during the study. Their overall distribution was not statistically different between the three groups during periods 1 and 2 (31% in Group 1, 33% in Group 2 and 36% in Group 3). During period 3, 36% of patients in Group 1 and Group 2 and 20% in Group 3 experienced a total of 120 AEs with mild to moderate intensity (45 in Group 1, 52 in Group 2 and 23 in Group 3).

The incidence of drug-related AEs (sinusitis, rhinitis, headaches and bronchitis) was similar in three groups (around 4–6%). Epistaxis occurred during periods 1 and 2 in 4% in Group 1, 1% in Group 2 and none in Group 3 and during period 3, respectively, in 7%, 5% and 5%.

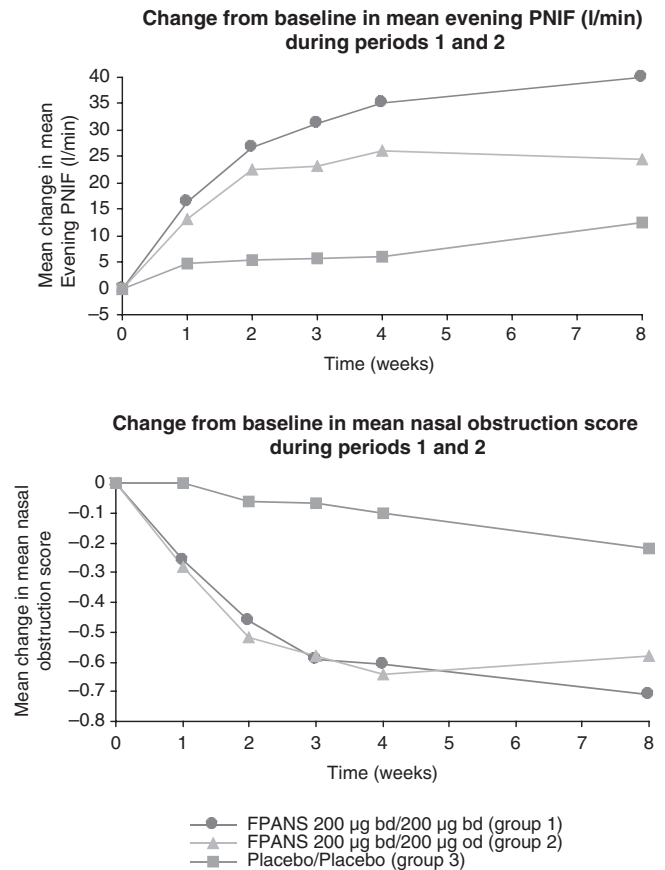


Figure 3. Change from baseline with regard to mean daily PNIF and nasal obstruction score during periods 1 and 2 (2 months).

Discussion

Besides being the first large study to compare FPANS with placebo, this study is the first to assess long-term efficacy and tolerability of topical steroids and to determine a minimal efficacy dose in NP maintenance treatment. The low level of withdrawals (19%) illustrated the quality of monitoring during the follow-up.

The PNIF was chosen as the primary efficacy endpoint, as it objectively reflects nasal obstruction, the major complaint of NP patients (20). Indeed, PNIF is also a simple, cost-effective, reliable and readily available tool for determining the extent of nasal patency, which can be obtained easily at home or in community. Peak nasal inspiratory flow provides information that is qualitatively different to that provided by symptom scores. Data have shown the sensitivity of this test and the close correlation with symptoms of nasal blockage (21). It is the most reproducible method of assessing nasal patency, closely related to the signs of rhinitis, as determined by clinical examination (22, 23). In our study, PNIF was measured at each clinic visit and was also daily recorded by patients. By measuring PNIF at home, patients could

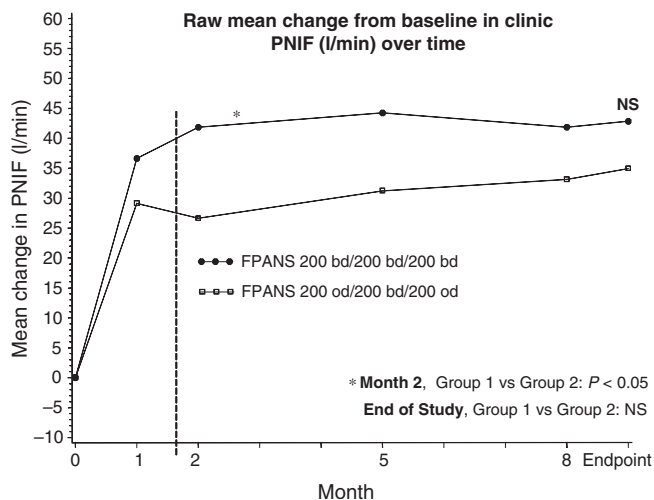


Figure 4. Change in PNIF measured at different visits (V4, V5 and V6) from baseline over follow-up in Group 1 (FPANS 200 µg bd during 8 months) and in Group 2 (FPANS 200 µg bd during 1 month and 200 µg od during 7 months). FPANS, fluticasone propionate aqueous nasal spray.

objectively assess daily improvement of nasal obstruction that could increase the adherence to NP medication. However, there are questions regarding PNIF repeatability when used to assess the degree of nasal obstruction in large populations. It has been shown to be sufficiently good to be used in epidemiological studies (24).

While the majority of patients had a mild or moderate disease after endoscopic evaluation, 20% of them had NP grade III. No patient had a previous surgical treatment. Nasal obstruction and sense of smell disorders were observed in almost all patients. At inclusion, PNIF was low (around 110 l/min) when compared with values observed in healthy subjects, which are generally around 134 l/min (25).

Results at 1 and 2 months demonstrated efficacy of FPANS 200 µg bd as starter NP treatment, which was significantly superior to placebo at all endpoints. The size of NP decreased in treated groups but more than that, the significant increase of PNIF (25% of baseline value) shows in an objective way the ability of FPANS to reduce the size of polyps. Moreover, FPANS 200 µg bd exhibited a very rapid onset of action and was significantly superior to placebo as early as week 1 on PNIF and nasal obstruction. Furthermore, published studies, which assessed efficacy of intranasal corticosteroids in NP patients, showed a significant increase in PNIF, which was accompanied by subjective improvement of nasal blockage (2). Pentilla et al. have previously demonstrated in 142 patients the efficacy and tolerability of nasal drops presentation of FP 400 µg od or bd over a 12-week randomized treatment period followed by a 12-week open period with FP 400 µg od (26). Holmberg et al. in a 26-week comparative study

with 400 µg of budesonide or FPANS, showed a significant improvement in symptoms and PNIF for treated groups compared with placebo and no statistically difference between the two treated groups (27). In a 12-week study, Lund et al. found a similar trend with a quicker improvement of morning PNIF in favour of FPANS group (2). In some studies, a significant reduction in NP size was also observed (2, 26).

During period 2, doses of FPANS (200 or 400 µg) were both more effective than placebo, but patients who received FPANS 200 µg od (Group 2) showed a plateau effect in PNIF whereas those patients who continued on FPANS 200 µg bd (Group 1) showed an additional increase. However, the difference in PNIF observed after 4 weeks of treatment between Groups 1 and 2 while patients received a same dosage of FPANS (200 µg bd) could be explained by a difference in baseline PNIF between the groups. Indeed, proportion of patients with a low baseline PNIF was more important in Group 1 (28%) than in Group 2 (22%), while mean baseline PNIF was not significantly different in Groups 1 and 2. Moreover, an additional analysis has shown that treated patients with a low baseline value (PNIF < 70 l/min) had higher amelioration after 8 weeks of treatment than those with a high baseline value.

Difference between Groups 1 and 2 at 2 months seems to support higher dosing regimen as primary therapy in order to provide a rapid and maximal control of polyp size and symptoms and positively impact on adherence to treatment. Continuing on FPANS 200 µg bd during the second month of treatment may provide some further increase in nasal patency. However, a dose regimen reduction to FPANS 200 µg od may appear sufficient to maintain improvement in some patients after 1 month on FPANS 200 µg bd depending on individual response on symptoms to therapy. In some patients, extension of the primary dosing regimen for one additional month may well be recommended.

During period 3, both doses of FPANS showed a persistent efficacy. At end of study, difference observed between these groups is no longer statistically significant indicating that FPANS 200 µg od is as effective as FPANS 200 µg bd for long-term maintenance treatment. Fluticasone propionate aqueous nasal spray 200 µg od is therefore an effective dose regimen, once the disease has been controlled with higher dose. However, as an 8-month treatment with placebo was objectionable in this very symptomatic disease, patients of Group 3 switched to FPANS 200 µg bd during the period 3.

Our study confirmed good safety profile of FPANS during 8 months. It is interesting to notice that the incidence of nasal bleeding, which is a common AE well known with nasal steroids, remained very low (1–7%) during the study, even in patients treated with the highest dosage of FPANS. Those results are similar to those reported in comparable studies with other steroids (28, 29).

Conclusion

In conclusion, FPANS 200 µg bd was effective and well tolerated in the acute treatment of NP where it reduced

significantly the symptoms and polyp size. Once the symptoms of the disease were controlled, reduction of the FPANS dose to 200 µg od allowed to maintain long-term efficacy with a good safety profile.

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