Rhinology, 31, 169–174, 1993

A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis*

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SUMMARY

Two hundred and fifty-one patients, aged 16 years and over, with perennial rhinitis were recruited to this multicentre, randomized, double-blind, parallel group study. One hundred and fifty-nine patients received fluticasone propionate (200 μg) aqueous nasal spray (FPANS) twice daily, and 83 patients received beclomethasone dipropionate (200 μg) aqueous nasal spray (BDPANS) twice daily; treatment randomization being 2:1, respectively, in order to increase the number of patients in the FPANS group as FPANS was the drug under study. After 1 year of treatment, nasal blockage ($p=0.002$), nasal discharge ($p=0.002$) and eye watering/irritation ($p=0.048$) were significantly improved in patients treated with FPANS twice daily, compared to patients treated with BDPANS twice daily. The symptom grades for nasal itching ($p=0.052$) were improved in the FPANS group, but just failed to attain statistical significance at the 5% level. The symptom grades for sneezing tended to be better for the FPANS group, but the difference was not statistically significant. Assessment of changes in the findings during nasal examination (rhinoscopy) and in haematological, biochemical and urinary parameters, and measurements of plasma cortisol levels during the one year of treatment with the study drugs, showed that there were no clinically significant differences between the two treatment groups and that the study drugs were equally well tolerated. This study indicates that long-term use of FPANS provides better relief than BDPANS for most of the symptoms of perennial rhinitis.

Key words: perennial rhinitis, nasal sprays, beclomethasone, fluticasone

INTRODUCTION

Perennial rhinitis is a common and frequently uncomfortable condition that is characterized by nasal obstruction, sneezing, nasal itching, and rhinorrhoea. Although the condition is not serious, patients require active therapy to alleviate the unpleasant symptoms.

The pharmacotherapy of rhinitis has advanced in recent years. Since intranasal steroid sprays first appeared more than 15 years ago, numerous studies have provided evidence of their effectiveness in treating rhinitis (Beswick et al., 1985; Juniper et al.,1989, 1990). At doses needed to achieve this efficacy, the newer intranasal steroids demonstrate no evidence of systemic steroid activity and the local adverse effects have mainly been drying and crusting of the nasal mucosa.

It is thought that intranasal steroids decrease symptoms by exerting anti-inflammatory effects. These include reduction of the numbers of eosinophils and basophilic cells (Mygind,

* Accepted February 22, 1993

1982). Also, the degree of oedema and vasodilation in the nasal mucosa decreases during treatment and there is probably some decongestant effect on the normal mucous membrane (Mygind, 1982).

Several new corticosteroids have been developed in the past 15 years, for the treatment of both nasal disorders and asthma. Beclomethasone dipropionate was one of the first of these newer corticosteroids that clearly demonstrated a separation of topical activity from systemic effects.

In an attempt to provide further differentiation between the local anti-inflammatory effects and the unwanted systemic effects of corticosteroids, Glaxo Group Research Ltd. have developed a new, topically active, fluorinated glucocorticoid, fluticasone propionate (FP). This compound has been shown to have twice the potency of beclomethasone dipropionate as judged by skin vasconstrictor tests and to undergo extensive first-pass metabolism by the liver (Phillips, 1990).

The potential for fluticasone propionate aqueous nasal spray (FPANS), administered topically, to have minimal systemic effects has been verified by studies carried out in man. A dose-tolerance study involving more than 400 patients with moderate to severe symptoms of seasonal allergic rhinitis receiving up to 1,600 μg FPANS per day, indicated that no measure of hypothalamo-pituitary-adrenocortical (HPA) axis function was affected nor did routine laboratory tests reveal any treatment-related effects (Meltzer et al., 1990).

Furthermore, single oral doses of up to 16 mg FP for 7 days have confirmed that the compound has no clinically significant effect on the HPA axis, as assessed by morning plasma cortisol levels (Harding, 1989). This is an important finding since a proportion of the intranasal or inhaled steroid dose is absorbed from the airway mucosa, while the remainder is transported by the cilia to the pharynx and swallowed.

The present study was designed to evaluate the long-term efficacy and safety of FPANS compared with beclomethasone dipropionate aqueous nasal spray (BDPANS) in patients with perennial rhinitis.

MATERIALS AND METHODS

Patients

Two hundred and fifty-one patients, aged 16 years and over, who had at least a two-year history of perennial rhinitis were included. Perennial rhinitis was defined as a condition experienced by patients with one or more of the following symptoms at the time of entry: (1) nasal blockage; (2) nasal discharge; (3) nasal itching; and (4) sneezing. Patients should have experienced the symptom(s) throughout the year and were only entered if their symptom(s) were severe enough to warrant regular treatment. Patients were not entered if they had serious or unstable concurrent disease, infection of the paranasal sinuses, upper or lower respiratory tract infections, structural abnormalities (such as large polyps) or had undergone nasal surgery less than six weeks prior to the study. Patients were also excluded if they were taking concurrent medication such as oral or inhaled corticosteroids, astemizole, intranasal sodium cromoglycate or intranasal sympathomimetic therapy. Female patients were excluded if they were pregnant or lactating.

Study design

Patients were given a placebo aqueous nasal spray to use, two actuations to each nostril twice daily during the two week run-in period. Following this, the patients were randomized to receive treatment with either FPANS (200 μg) twice daily or BDPANS (200 μg) twice daily for up to one year in a double-blind manner. Randomization was such that twice as many patients would receive treatment with FPANS compared with BDPANS. This maximized the number of patients in the FPANS group, as FPANS was the drug being studied. Patients were provided with terfenadine (60-mg tablets) to use as rescue medication if their symptoms were not adequately controlled by the study nasal sprays.

The treatment response was assessed on five occasions; after the first four weeks following the start of treatment, then at 12 weekly intervals until the first anniversary of commencing the active treatment. A final assessment was scheduled for two weeks after stopping treatment. At each of these five visits, patients were asked to classify their symptoms of sneezing, nasal itching, nasal discharge, nasal blockage and eye watering/irritation as experienced over the past seven days, according to a scale of 0–3 (0: none; 1: mild; 2: moderate; and 3: severe). Anterior rhinoscopy was performed at every visit by the investigator who examined the nostril for the presence of swelling of the mucosa, polyps, crusting, bleeding and patency. Any other nasal pathology identified by the investigator was also recorded.

At each clinic visit, patient's compliance was ascertained by asking the patients to record the daily use of their nasal spray.

Safety evaluations were conducted during the study. This included documenting and monitoring all adverse events, reported both spontaneously by the patient at any stage during the study and those invoked by the investigator at each clinic visit. Blood and urine samples were obtained both pre- and post-treatment, for routine haematology and urine analysis. Pre- and post-treatment plasma cortisol levels following stimulation with synthetic adrenocorticotrophic hormone (ACTH) were also measured in 70 patients from three centres.

Statistical analysis

Each symptom assessed after one year of treatment was analysed separately using the proportional odds model for ordinal data. Symptom scores of 2 and 3 were combined into a single score since few patients recorded severe symptoms following either treatment. Centres were grouped into country and the model allowed for effects due to treatment and country. The relative odds of a lower rather than higher

symptom score for FPANS against BDPANS were estimated and tested for significance.

RESULTS

Nasal symptoms

A total of 251 patients were recruited, of which 159 patients were randomized to receive FPANS (200 µg) twice daily and 83 patients to receive BDPANS (200 µg) twice daily. Nine patients did not receive any treatment.

One hundred and sixteen patients in the FPANS treatment group and 63 patients in the BDPANS treatment group completed the study. Only patients who adhered closely to the protocol were included in the efficacy analysis. Demographic details of the patients are shown in Table 1. Sex, age, weight and height distribution were similar for both treatment groups.

The distribution of symptom grades for the patients with data obtained both at baseline and after one year of treatment is shown in Figures 1–5. The baseline distribution of symptom grades (none, mild, moderate/severe) was similar for both the treatment groups for all symptoms, except that nasal blockage tended to be worse in the FPANS group.

The symptom grades for nasal discharge and nasal blockage were significantly better for the FPANS group than for the BDPANS group at one year of treatment (p=0.002 for both symptoms). The symptom grades for eye watering and irri-

Table 1. Demographic characteristics of patients.

characteristics	FP	BDP
number of patients (%)	159 (66)	83 (34)
sex		
male	70 (44)	35 (42)
female	89 (56)	48 (58)
age (years)		
mean ± SD	37.7±13.2	37.5±13.6
range	16–73	17–69
weight (years)		
mean ± SD	67.9±11.7	67.1±12.5
height (years)		
mean ± SD	169.3±8.9	167.9±8.4

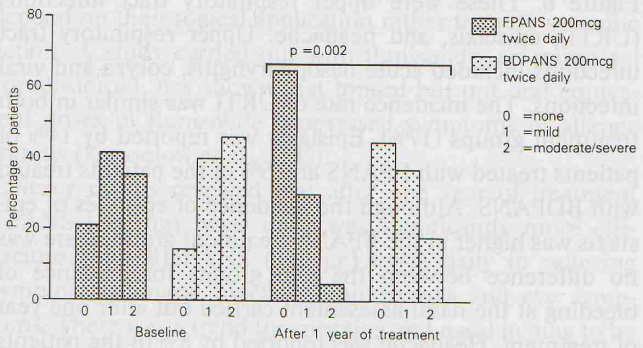

Figure 1. Nasal discharge (baseline data were obtained by averaging the symptom scores for the last 7 days of the run-in period).

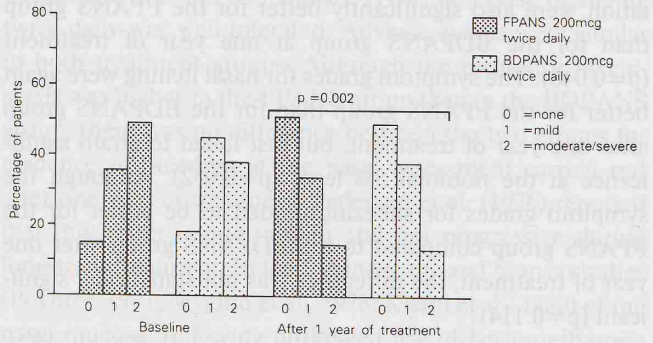

Figure 2. Nasal blockage (baseline data were obtained by averaging the symptom scores for the last 7 days of the run-in period).

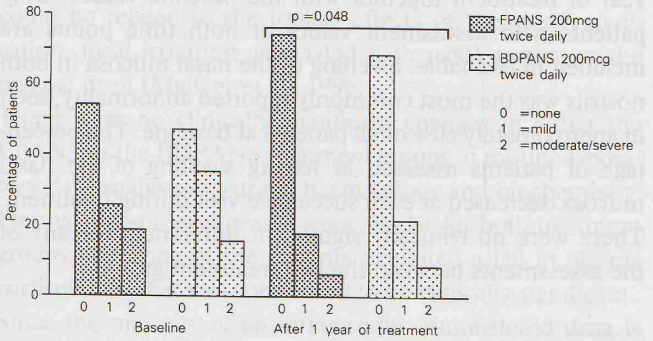

Figure 3. Eye watering/irritation (baseline data were obtained by averaging the symptom scores for the last 7 days of the run-in period).

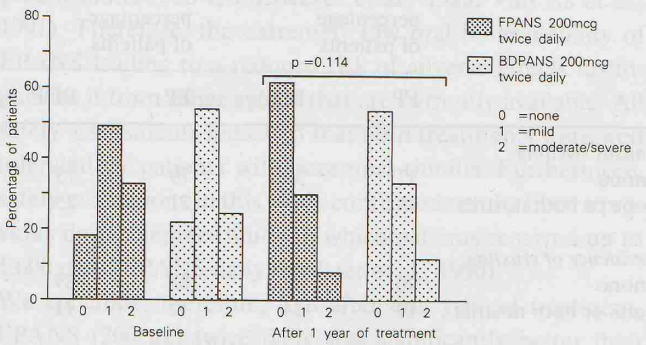

Figure 4. Sneezing (baseline data were obtained by averaging the symptom scores for the last 7 days of the run-in period).

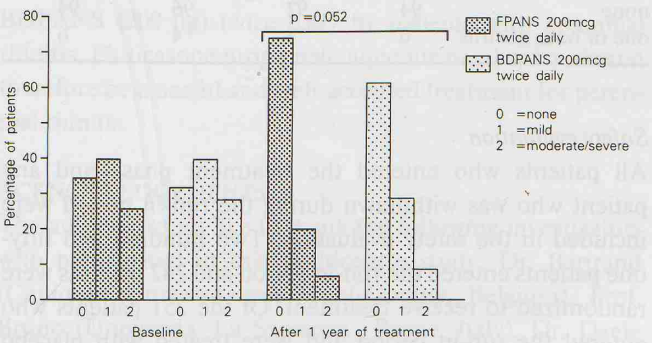

Figure 5. Nasal itching (baseline data were obtained by averaging the symptom scores for the last 7 days of the run-in period).

tation were also significantly better for the FPANS group than for the BDPANS group at one year of treatment (p=0.048). The symptom grades for nasal itching were again better for the FPANS group than for the BDPANS group after one year of treatment, but just failed to attain significance at the nominal 5% level (p=0.052). Although the symptom grades for sneezing tended to be better for the FPANS group compared to the BDPANS group after one year of treatment, the difference was not statistically significant (p=0.114).

Nasal assessments

Nasal assessments (rhinoscopy) were carried out at each visit. Table 2 shows the assessments for all patients after one year of treatment together with the baseline values. Only patients with assessment values at both time points are included in this table. Swelling of the nasal mucosa in both nostrils was the most commonly reported abnormality, seen in approximately 60% of all patients at baseline. The percentage of patients assessed as having swelling of the nasal mucosa decreased at each successive visit during treatment. There were no clinically significant differences for any of the assessments between the two treatment groups.

Table 2. Nasal assessment at baseline (visit 2) and after one year of treatment.

	baseline		after 52 weeks of treatment	
	percentage of patients		percentage of patients	
	FP	BDP	FP	BDP
nasal swelling				
none	37	35	79	75
one or both nostrils	63	65	21	25
evidence of crusting				
none	90	86	88	89
one or both nostrils	10	14	12	11
evidence of bleeding				
none	97	94	96	92
one or both nostrils	3	6	4	8
nasal polyps				
none	94	92	96	94
one or both nostrils	6	8	4	6

Safety evaluation

All patients who entered the treatment phase and any patient who was withdrawn during the run-in period were included in the safety evaluation. Two hundred and fifty-one patients entered the run-in period and 242 patients were randomized to receive treatment. Of the 251 patients who entered the run-in period and were treated with placebo aqueous nasal spray, 40 patients were recorded as having reported a total of 44 adverse events.

In this study, serious adverse events were defined as: (1) all deaths; (2) life-threatening events; (3) events which were disabling or incapacitating; (4) events which required prolonged hospitalization; (5) clinical or laboratory events which led to withdrawal of the drug; and (6) any congenital abnormality or cancer or drug overdose. All other events were considered to be minor adverse events.

One patient reported a serious adverse event prior to receiving active treatment and was withdrawn. During the one-year-long treatment, a total of 11 serious adverse events were reported by 7 patients in the FPANS group and 3 patients in the BDPANS group, however, the percentage of patients reporting serious adverse events were the same in both treatment groups (4%). Of the seven events reported by the FPANS treatment group, one event (i.e., severe bronchial asthma) was considered to be probably related to the study drug, the remainder were considered unrelated to the study drug. The opinion of the investigator that this episode of severe bronchial asthma was related to treatment is purely from the point of view that the patient was in the study and not that the intranasal steroid had caused the asthma per se. All four events reported by the BDPANS group were considered unrelated to the study drug.

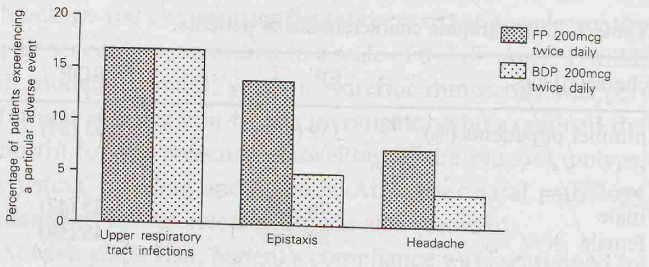

Figure 6. Most commonly occurring adverse events during the one-year treatment period (visit 2 to visit 7).

The overall percentage of patients who reported adverse events during treatment were similar in both treatment groups, with 55% in the FPANS group and 58% in the BDPANS group. The most commonly reported adverse events during the year long treatment period are shown in Figure 6. These were upper respiratory tract infections (URTI), epistaxis, and headache. Upper respiratory tract infections included acute nasopharyngitis, coryza and viral infections. The incidence rate of URTI was similar in both treatment groups (17%). Epistaxis was reported by 14% of patients treated with FPANS and 5% of the patients treated with BDPANS. Although the incidence of episodes of epistaxis was higher in the FPANS treatment group, there was no difference between the two groups for evidence of bleeding at the nasal assessment carried out after one year of treatment. Headache was reported by 8% of the patients treated with FPANS and by 4% of the patients treated with BDPANS.

Laboratory evaluations

Routine laboratory analyses on urine, and blood samples were carried out on four occasions: (1) at the start of the run-in period; (2) at the start of the treatment period; (3) after 16 weeks of treatment; and (4) at the end of the treatment period.

The values for each parameter were compared with the normal range of the laboratory that had analysed the sample. The result was then classed as within the normal range (normal), above the upper limit of normal (high) or below the lower limit of normal (low).

Few patients showed any major shifts in laboratory parameters from baseline values. Nine patients had abnormal laboratory values which were, in the investigator's opinion, considered to be possibly related to the study treatment; of these, six patients (three patients from the FPANS group and three patients from the BDPANS group) had abnormal renal function values, and three patients (one from the FPANS nasal group and two from the BDPANS group) had abnormal hepatic function values. An overall review of these cases showed no consistent trend of any clinical significance.

Plasma cortisol levels

Results for plasma cortisol levels were obtained for 47 patients in the FPANS group and 23 patients in the BDPANS group. Eleven patients in the FPANS group and 4 patients in the BDPANS group exhibited a fall in baseline plasma cortisol levels but these changes were considered to be clinically insignificant, as these values were still within the normal range. Five patients (3 from the FPANS group and 2 from the BDPANS group) demonstrated a subnormal response to a stimulation test using synthetic ACTH. Of these, one patient (FPANS-treated group) demonstrated a post-stimulation plasma cortisol level which was below the lower limit of normal, but this change was considered to be clinically insignificant by the investigator.

DISCUSSION

This study was designed to compare the efficacy and safety of FPANS (200 μg) twice daily with that of BDPANS (200 μg) twice daily when used for periods of up to one year in the treatment of perennial rhinitis.

The clinical efficacy of intranasal steroids does appear to depend on their topical application rather than on systemic action. A study carried out with flunisolide, an intranasal corticosteroid, has shown that topical but not oral equivalent doses of flunisolide suppressed symptoms of allergic rhinitis (Kwaselow et al., 1985).

Efficacy results revealed that after one year of treatment FPANS (200 μg) twice daily was significantly more efficacious than BDPANS (200 μg) twice daily in relieving symptoms of nasal blockage, rhinorrhoea and eye symptoms. There was a trend for sneezing and nasal itching to be better in the FPANS group compared to the BDPANS group, but the difference was not statistically significant.

Treatment with FPANS and BDPANS at a dose of 200 μg twice daily was well tolerated. Adverse events were similar in both treatment groups. Although the incidence of epistaxis was higher in the FPANS group than in the BDPANS group, there was no difference between the two groups for evidence of bleeding at the nasal assessment carried out after one year of treatment. Pedersen et al. (1976) reported that this effect is intermittent and not progressive during long-term treatment. Indeed, rhinoscopy and biopsy studies (Poynter, 1977; Mygind et al., 1978; Klemi et al., 1980) of the nasal mucosa, following prolonged use of beclomethasone dipropionate, have revealed no atrophy of the nasal mucosa or histological damage. Other common local effects include irritation in the form of stinging or burning, transient episodes of sneezing and dryness. Most of these symptoms could be related to the topical effects of the study medication, local irritation associated with nasal sprays, or the disease itself (Meltzer et al., 1990).

There were no clinically significant changes in either the FPANS or the BDPANS treatment groups in routine laboratory data analyses on urine, haematology and biochemistry. Plasma cortisol level results were similar for both treatment groups and none of the patients exhibited a fall in plasma cortisol level that was considered to be clinically significant.

Since the majority of an intranasally administered drug is actually swallowed, low oral bioavailability minimizes possible systemic adverse effects. The low drug bioavailability of FPANS (<1%) compares favourably with values for budesonide (11%), flunisolide (20%), dexamethasone (>80%), and prednisolone (>80%; Edsbacker et al., 1985; Van As et al., 1991). Therefore, the extremely low oral bioavailability of FPANS leading to a reduced risk of adverse effects distinguishes it from other agents that are currently available. All safety assessments indicated that both treatments were well tolerated by patients with perennial rhinitis. Furthermore, safety evaluations in this study confirmed results from a previous dose-tolerance study in which patients received up to 1,600 μg of FPANS daily (Meltzer et al., 1990).

We conclude, therefore, that after one year of treatment, FPANS (200 μg) twice daily was significantly better than BDPANS (200 μg) twice daily in providing relief for symptoms of nasal blockage, rhinorrhoea and eye symptoms, and tended to be better for symptoms of sneezing and nasal itching. FPANS (200 μg) twice daily was as well tolerated as BDPANS (200 μg) twice daily by patients with perennial rhinitis. Fluticasone propionate aqueous nasal spray should therefore be a useful and well-accepted treatment for perennial rhinitis.

ACKNOWLEDGEMENTS

The authors would like to thank the following investigators who participated in this multicentre study: Dr. Bertrand (Cliniques Universitaires, Mont-Godine, Belgium), Prof. Bruno (Università La Sapienza , Rome, Italy), Dr. Daele (Hôpital De La Citadelle, Liège, Belgium), Dr. Felding (Aarhus Kommune Hospital, Aarhus, Denmark), Dr. Freng

(Ulleval Sykenus, Oslo, Norway), Dr. Fell (The Health Centre, Deddington, Oxford, England), Dr. Lorentzen (Aarhus, Denmark), Prof. Melillo (Ospedale Gardarelli, Naples, Italy), Dr. O Loughran (St. James Hospital, Dublin, Ireland), Prof. Patriarca (Università Catholica, Rome, Italy), Dr. Ruoppi (Kyks/Knk-Klinikka, Kuopio, Finland), Dr. Sipila (Laakarikeskus Porus, Oulu, Finland), Dr. Stefansson (Borgarspitalinn, Reykjavik, Iceland), Dr. Stokes (Memorial Hospital, Greenwich, U.K.), Dr. Svendsen (Lungemedicinsk Afdeling P, Copenhagen, Denmark), Dr. Virtanen (Etela-Saimaa Keskussairaala, Lappeenrania, Finland), and Dr. Warland (Haukeland Hospital, Bergen, Norway).

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