

Fluticasone propionate aqueous nasal spray: a well-tolerated and effective treatment for children with perennial rhinitis

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A total of 535 children aged 4–11 years with perennial rhinitis were recruited to two double-blind studies performed at 56 centres in eight European countries, Israel, and South Africa. One study compared the efficacy and tolerability of fluticasone propionate aqueous nasal spray (FPANS), at either 100 µg once daily (od) or 100 µg twice daily (bd), with beclomethasone dipropionate (BDPANS) 200 µg bd for 12 weeks in 120 children aged 6–11 years. The second study compared FPANS 100 µg od with FPANS 200 µg od and placebo for 4 weeks in 415 children aged 4–11 years. Efficacy was determined by means of patient assessments of nasal symptoms of perennial rhinitis and by investigator assessments of symptoms and nasal condition. The symptoms of nasal blockage, on waking and during the day, sneezing, rhinorrhoea, and nasal itching were assessed by the investigator at clinic visits and by the completion of a patient daily diary card. Safety was assessed by collection of adverse event information, routine haematology and biochemistry testing, and monitoring plasma cortisol levels. FPANS demonstrated good control of symptoms at each dose regimen, which was equivalent or superior to BDPANS and superior to placebo. There was no difference between the dose regimens of FPANS. FPANS was as well tolerated as placebo and BDPANS. It is concluded that FPANS 100 µg od is an effective and well-tolerated treatment for perennial rhinitis in children aged 4–11 years.

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Perennial rhinitis is a common and frequently uncomfortable condition characterized by sneezing, rhinorrhoea, nasal blockage, itching, and postnasal drip. It is normally termed “perennial allergic rhinitis” when exposure to allergens present in the environment throughout the year is considered responsible. The most frequent provoking allergens are house-dust mite, animal dander, and fungal spores. Where no association with allergen exposure can be demonstrated, the disease is termed “perennial nonallergic rhinitis”. Perennial rhinitis occurs in a large number of children. Epidemiologic studies of seasonal/perennial rhinitis have reported incidence rates of 10–20% in the general population, with an overall incidence in children of 5–9% (1). The disorder can be very troublesome in this age group, reducing quality of life and affecting education.

Current treatment is usually with drugs, whether the rhinitis is allergic or nonallergic, although allergen avoidance may be partially effective where the

rhinitis is allergic in origin. The drug treatment of choice is an intranasal corticosteroid, since this treats the mucosal inflammation which causes the nasal symptoms, and is efficacious in most patients.

There is a body of evidence to support the efficacy of intranasal steroids in both perennial allergic and perennial nonallergic rhinitis in this age group, beclomethasone dipropionate (BDANS) (2, 3), flunisolide (4), budesonide (5, 6), triamcinolone acetonide (7), and fluticasone propionate (8, 9) all being apparently efficacious.

The use of antihistamines in perennial rhinitis in children is also well documented. Among the newer antihistamines, there are reports of treatment efficacy with terfenadine (10), astemizole (11), loratidine (10), cetirizine (12), and azelastine (13) in this population of patients. Antihistamines have not previously been the treatment of choice for perennial rhinitis in adults because of the perceived lack of effect on nasal blockage, usually regarded as the pri-

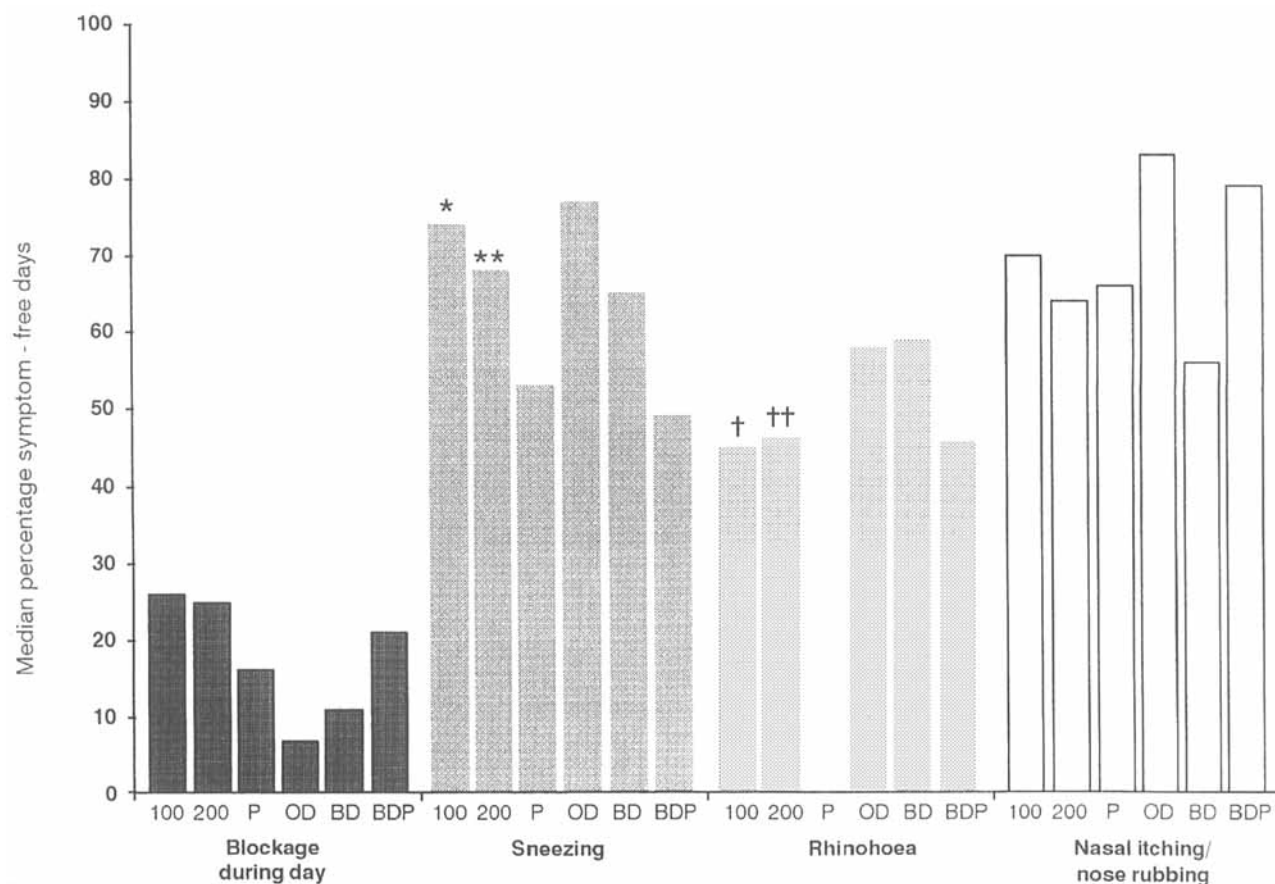


Fig. 1. Intent-to-treat population: percentage of symptom-free days for daytime symptoms. 100 and OD = FPANS 100 µg od; 200 = FPANS 200 µg od; P = placebo; BD = FPANS 100 µg bd; BDP = BDPANS 200 µg bd.

* = FPANS 100 µg od with placebo ($P = 0.050$).

** = FPANS 200 µg od with placebo ($P = 0.030$).

† = FPANS 100 µg od with placebo ($P = 0.14$).

†† = FPANS 200 µg od with placebo ($P = 0.005$).

mary symptom. The demonstrable efficacy of these drugs may reflect the fact that nasal blockage may not be perceived to be the most important symptom in this age group.

Sodium cromoglycate is also used; however, the frequent-dosing regimen recommended reduces patient compliance (14). Other therapies tend to treat only a proportion of the symptoms. For example, anticholinergics such as ipratropium bromide are effective only against the symptom of rhinorrhoea (15).

Intranasal corticosteroids are effective within a few days, probably within 24 h (16), and are well tolerated, with a low incidence of adverse events. However, there is a special need in children for the corticosteroid to have a very low potential for suppression of the hypothalamic-pituitary-adrenal (HPA) axis, since drugs which affect adrenal function in children are generally associated with decreased growth rate.

Wolthers & Pedersen (17) have demonstrated short-term reduction in lower leg growth rate with the recommended dose of budesonide nasal spray in children aged 7–15 years. While the long-term significance of these changes is not clear, such findings may explain a certain reluctance among paediatricians to use topical steroids to treat perennial rhinitis.

Fluticasone propionate is a highly topically active fluorinated glucocorticoid with a high receptor affinity and selectivity for the glucocorticoid receptor (18, 19). It has a very low gastrointestinal absorption, and the small proportion which is absorbed is rapidly metabolized in the liver, by a nonspecific route, to an inactive metabolite.

As a result of this, the bioavailability of fluticasone propionate after an intranasal dose is low and has been reported to be no more than 1.8% (20). This compares favourably with the bioavailability of some of the other steroids after intranasal dosing such as budesonide, which is reported to be 102%

Table 1. Intent-to-treat population: patient demography and classification of rhinitis

	Study 1			Study 2		
	FP100 <i>n</i> = 138 (%)	FP200 <i>n</i> = 136 (%)	Placebo <i>n</i> = 141 (%)	FPod <i>n</i> = 30 (%)	FPbd <i>n</i> = 35 (%)	BDPANS <i>n</i> = 30 (%)
Sex						
Male	85 (62)	86 (63)	86 (61)	19 (63)	24 (69)	21 (70)
Female	53 (38)	50 (37)	55 (39)	11 (37)	11 (31)	9 (30)
Age (years)						
Mean	8.0	8.0	8.0	9.3	8.5	8.7
SD	2.5	2.4	2.3	1.5	1.7	1.7
Weight (kg)						
Mean	31.0	30.9	31.7	34.9	31.5	32.1
SD	9.6	10.2	11.0	9.1	9.6	9.5
Ethnic origin						
Caucasian	123 (89)	125 (92)	128 (91)	25 (83)	32 (91)	27 (90)
Asian	13 (9)	9 (7)	9 (6)	2 (7)	3 (9)	1 (3)
Other	2 (2)	2 (1)	4 (3)	3 (10)	0 (0)	2 (7)
Perennial allergic rhinitis	87 (63)	92 (68)	92 (65)	19 (63)	23 (66)	21 (70)
Perennial nonallergic rhinitis	46 (33)	43 (32)	5 (32)	9 (30)	10 (29)	8 (27)
Not recorded	5 (4)	1 (<1)	4 (3)	2 (7)	2 (6)	1 (3)

bioavailable after intranasal dosing (21). Repeated intranasal dosing of 2 mg twice daily (bd) for 7 days in normal volunteers demonstrated no significant effect on plasma cortisol measurements at 9 am, despite being 40 times the recommended dose for children with rhinitis (22).

Since children with perennial rhinitis may receive topical steroids for asthma and eczema, as well as to treat their perennial rhinitis, both the efficacy and bioavailability, and therefore potential to cause systemic side-effects, must be considered together (23).

Wide experience has already been gained with fluticasone propionate aqueous nasal spray (FPANS). The many studies performed in adult patients with seasonal and perennial rhinitis have established its efficacy and good tolerability (16, 24, 25). The long-term use of FPANS has been assessed, and it has been shown to provide better relief than beclomethasone dipropionate aqueous nasal spray (BDPANS) for most of the symptoms of perennial rhinitis (26, 27). In studies in adults with perennial rhinitis, FPANS has demonstrated equivalent efficacy at half the dose of BDPANS and superiority at equal doses. Therefore, it may be useful to treat children with perennial rhinitis. In recent studies, FPANS has been shown to be effective and safe in children as young as 4 years with seasonal allergic rhinitis when used at doses of 100 or 200 µg once daily (od) (28–30).

The two large, multicentre studies reported here were carried out to provide additional efficacy and safety data on the use of FPANS in children with perennial rhinitis. Together these studies represent a substantial population and provide data on probably the largest clinical study of paediatric patients with perennial rhinitis hitherto reported.

Material and methods

Subjects

A total of 535 children aged 4–11 years were recruited to two multicentre, multinational, double-blind, parallel-group studies to investigate the efficacy and tolerability of FPANS in the treatment of perennial rhinitis. One study, conducted at 38 centres in seven European countries, Israel, and South Africa, was a 4-week comparison of two dose levels of FPANS, 100 or 200 µg od, with placebo. This study recruited 415 children aged 4–11 years. The second study was conducted at 18 centres in Denmark, France, Iceland, and the UK and recruited 120 children aged 6–11 years. This study compared the efficacy and safety of FPANS 100 µg od, FPANS 100 µg bd, and BDPANS 200 µg bd over a 12-week treatment period. All patients were treated as outpatients at hospital or general practice centres. In total, 339 patients received FPANS, 30 received BDPANS, and 141 received placebo. Both studies were conducted outside any relevant pollen season to exclude effects of seasonal allergic rhinitis.

Children with a history of moderate to severe perennial rhinitis and current symptoms of rhinitis were eligible for inclusion in both studies. Cutaneous allergy testing was performed with a skin prick test to a positive (histamine) and negative control and to common inhaled perennial allergens such as house dust, house-dust mite (*Dermatophagoides pteronyssinus*), animal dander, and moulds. The use of antihistamines was not permitted for 48 h before testing. Rescue antihistamine medication was provided during both studies, but no other medication for nasal conditions was allowed. Written informed

parental consent and (where the patient was old enough to understand) patient consent were obtained before participation. Patients requiring inhaled or systemic steroids for the treatment of concurrent asthma were ineligible to enter the study.

Efficacy assessments

Both studies used standard assessment criteria. Efficacy evaluations included symptom assessments recorded daily by patients and at clinic visits by the investigators. For the placebo-controlled study, patients were assessed by the investigator at 2-week intervals during the 4-week treatment period, and for the comparator study, patients returned to the clinic at 4-week intervals during the 12-week treatment period.

Each patient made a self-assessment of rhinitis symptoms recorded in a daily record card. For those patients who were too young to record their symptoms, parents completed the record of symptoms. These included nasal blockage on waking, nasal blockage during the rest of the day, sneezing, rhinorrhoea, nasal itching, and overall assessment of symptoms by a four-point rating scale from 0 = no symptoms to 3 = severe symptoms. The use of rescue medication was also recorded.

At each clinic visit, the investigator assessed the patient's symptoms of nasal blockage, rhinorrhoea, sneezing, nasal itching, postnasal drip, and eye watering/irritation on the same rating scale. A rhinoscopic examination was performed by the investigator for evidence of oedema (mucosal and turbinate swelling), bleeding, or crusting. The colour of the nasal mucosa and any nasal abnormality were recorded.

Safety assessments

A physical examination was carried out on each patient at the start and end of both studies. This included measurements of blood pressure, heart rate, respiratory rate, and body temperature, as well as anatomical examination of the eyes, ears, mouth,

throat, neck, chest, heart, abdomen, the extremities, nervous system, skin, and cervical lymph nodes.

Adverse events were monitored throughout the studies. Any untoward medical event either reported spontaneously by the patient or elicited after questioning by the investigator was documented. Patients returned to the clinic for a follow-up visit 2 weeks after the end of treatment, when any adverse events were noted.

Comprehensive tests of clinical chemistry, renal and hepatic function, haematology, and urinalysis were carried out at baseline and at the end of the study. An assessment of HPA function was made at the beginning and end of both studies by measurement of morning plasma cortisol levels.

Statistical analysis

For both studies, the primary efficacy evaluations were based on the percentage of symptom-free days for the patient assessments of nasal blockage on waking, nasal blockage during the rest of the day, and rhinorrhoea, as recorded in the daily diary cards. This was supplemented by analysis of the percentage of days on which patients recorded their symptoms as none or mild. The patient assessments of sneezing, nasal itching, and overall symptoms; the use of rescue medication; and the investigator assessments of rhinitis symptoms were analysed as secondary efficacy variables.

Two populations were defined for analysis. The intent-to-treat population consisted of all patients randomized to treatment. This population was in turn subdivided into patients suffering from perennial allergic rhinitis, as defined by positive skin prick test to at least one common inhaled perennial allergen, and patients with perennial nonallergic rhinitis who were negative to these tests. The safety population consisted of all patients recruited to both studies.

Since only small numbers of patients were recruited in some of the centres, it was necessary to amalgamate centres in some countries for the purpose of the statistical analysis. Consequently, analyses were adjusted for country rather than for centre. Data was pooled within each study for those countries where the number of patients recruited was small.

For the patient assessments of efficacy, the analyses of percentage of symptom-free days and percentage of days with a symptom score of less than two were carried out by the Wilcoxon rank sum test, the van Elteren extension being used to adjust for country and rhinitis category for each study. A patient's data were excluded from the analysis if that patient could not be categorized as having either allergic or nonallergic rhinitis.

Table 2. Adverse events reported

	Number of patients (%)		
	FPANS	BDPANS	Placebo
Number of patients	339	30	141
Patients with any event	162 (48)	20 (67)	57 (40)
Upper respiratory tract infection	10 (12)	6 (20)	11 (8)
Headache	19 (6)	4 (13)	16 (4)
Cough	19 (6)	4 (13)	6 (4)
Asthma and related events	18 (5)	5 (17)	14 (10)
Epistaxis	18 (5)	2 (7)	2 (1)
Influenza	12 (4)	3 (10)	2 (1)

For the placebo-controlled study, separate comparisons were made of FPANS 100 µg od with placebo, FPANS 200 µg od with placebo, and FPANS 100 µg od with FPANS 200 µg od. An analysis of variance was performed, allowing for effects due to centre groupings, rhinitis category, and treatment, in order to address consistency of treatment differences.

The percentage of days on which no rescue medication was required and the standardized number of unit doses were analysed in the same way as the symptom scores.

Results

Study population

Both studies had a balanced distribution between the treatment groups for all of the demographic parameters reported (Table 1). In each study, approximately two-thirds of patients were classified as suffering from perennial allergic rhinitis (Table 2). In the placebo-controlled study, the mean age of children was 8 years, most patients recruited being in the 4–8 years range. The ratio of boys to girls was approximately 3:2. In the comparator study, most patients were aged 9–11 years, with a ratio of approximately 2:1 of boys to girls.

Efficacy

Of the 535 patients recruited to the two studies, a total of 510 were randomized to receive study treatment, and 487 patients provided sufficient daily record card data to be included in the analysis of efficacy. Overall, 168 patients were randomized to receive FPANS 100 µg od, 171 to receive FPANS 200 µg od, 30 to receive BDPANS 200 µg bd, and 141 to receive placebo.

FPANS consistently reduced rhinorrhoea, in the placebo-controlled study, to either mild or no symptoms, although over 60% of the children had symptoms scored as moderate or severe at baseline. Children receiving FPANS recorded a higher median percentage of days free of rhinorrhoea with both FPANS 100 µg od ($P = 0.014$) and FPANS 200 µg

od ($P = 0.005$) than with placebo. Both FPANS 100 µg od and FPANS 200 µg od showed statistically significant improvement compared to placebo for the first investigator assessment of rhinorrhoea, $P = 0.008$ and $P = 0.006$, respectively, but only FPANS 200 µg od achieved statistical significance at the final investigator assessment ($P = 0.012$). In the BDPANS comparator study, FPANS 100 µg od was as effective as FPANS 100 µg bd and BDPANS 200 µg bd in increasing the proportion of rhinorrhoea-free days recorded by patients and in reducing rhinorrhoea as assessed by the investigator.

For the symptom of sneezing, both FPANS treatment groups were superior to placebo in terms of symptom-free days recorded by the patient (FPANS 100 µg od, $P = 0.05$; FPANS 200 µg od, $P = 0.03$). Over 60% of patients receiving FPANS reported no sneezing, when assessed by the investigator, compared with 20% or less at baseline, but this was not statistically significant, as compared to placebo, due to a strong placebo effect. In the BDPANS comparator study, FPANS 100 µg od was as effective as FPANS 100 µg bd and BDPANS 200 µg bd in increasing the percentage of days free of sneezing and the percentage of days scored by patients as “none” or “mild”.

Patients receiving FPANS recorded a higher median percentage of days free of nasal blockage on waking and during the day, compared with placebo, but the differences did not reach statistical significance. Similarly, although a large number of patients receiving FPANS reported an improvement in nasal blockage, with 61–79% scored as “none” or “mild”, this was not statistically significant compared with placebo, due to a strong placebo effect. In the comparator study, FPANS 100 µg od was as effective as FPANS 100 µg bd or BDPANS 200 µg bd, with a median of 68–76% days scored as “none” or “mild” for nasal blockage on waking, compared to 8–26% at baseline.

A gradual improvement in the control of nasal itching was demonstrated in the analysis of patients’ symptoms, but this could not be attributed to FPANS. Investigator assessments showed that im-

Table 3. Shifts in plasma-cortisol to below or above the normal range

	Study 1			Study 2		
	FP100 n = 99 (%)	FP200 n = 93 (%)	Placebo n = 100 (%)	FPod n = 13 (%)	FPbd n = 12 (%)	BDPANS n = 13 (%)
High or normal to low	3 (3)	7 (8)	7 (7)	2 (15)	1 (8)	1 (8)
Low to normal or high	0 (0)	5 (5)	1 (1)	1 (8)	0 (0)	0 (0)

FP100/FPod = Fluticasone propionate aqueous nasal spray 100 µg once daily.

FP200 = Fluticasone propionate aqueous nasal spray 200 µg once daily.

FPbd = Fluticasone propionate aqueous nasal spray 100 µg twice daily.

BDPANS = Beclomethasone propionate aqueous nasal spray 200 µg twice daily.

provement in nasal itching was statistically significant compared with placebo after 2 weeks ($P = 0.028$) and 4 weeks ($P = 0.006$) only in the group receiving FPANS 200 µg od. In the comparator study, FPANS 100 µg od was as effective as FPANS 100 µg bd and BDPANS 200 µg bd in increasing from baseline the median percentage of days free of nasal itching and increasing from baseline the percentage of days when this symptom was scored by patients as "none" or "mild".

In the placebo-controlled study, there was no statistical significance between the three treatment groups in the use of rescue medication, which was very low throughout. In the comparator study, both FPANS 100 µg od and FPANS 100 µg bd significantly increased over baseline the percentage of days during which no rescue medication was required, compared with BDPANS 200 µg bd, but there was no difference between the two FPANS treatment groups.

Nasal assessments revealed a reduction in turbinate swelling, crusting, and secretions and a tendency toward a change to normal in the colour of the nasal mucosa during both studies. No differences were observed between the two FPANS treatment groups.

Patients' overall assessments showed a statistically significant increase ($P = 0.024$) in the percentage of symptom-free days compared to placebo, in patients receiving FPANS 200 µg od. In the comparator study, FPANS 100 µg od was as efficacious as FPANS 100 µg bd and BDPANS 200 µg bd.

When considered separately, there were similar changes attributable to treatment with either FPANS or BDPANS in both the allergic and nonallergic groups of patients, although, clearly, since the sample size of the individual groups was reduced, statistical significance could not always be demonstrated. Since the changes were similar in the perennial allergic and nonallergic groups, the data for the whole population are shown.

Safety

The adverse event profile in the two studies was as expected in this population; the most commonly reported events are shown in Table 3.

Overall, there were no treatment differences in the numbers of patients reporting events or the numbers of adverse events considered by the investigator to be treatment related. Within each study, the numbers of individual events and the numbers of events considered by the investigator to be treatment related were similar, except for epistaxis.

In the placebo-controlled study, epistaxis was the most frequently reported drug-related event in all three groups and was more commonly reported in

the FPANS 100 µg od group (nine patients; 7%) than with FPANS 200 µg od or placebo (two patients; 1% in each group). In the comparator study, epistaxis was reported more commonly in the FPANS 100 µg bd treatment group, with five patients (14%) compared with two patients (7%) in each of the other two groups, but none were thought to be treatment related, and the numbers involved were too small to extrapolate any clinical significance to this finding. The severity of epistaxis was variable, and the classification term included minor episodes such as streaking of blood in the mucus after nose blowing, or slight nose bleeds. Rhinoscopy showed no evidence of thinning of the nasal tissues or atrophy of the nasal mucosa and no increase in epistaxis.

There were few withdrawals due to adverse events: 7/339 patients (2%) receiving FPANS, 0/30 receiving BDPANS, and 2/141 (1%) receiving placebo. For the placebo-controlled study, the withdrawal rate due to adverse events was comparable in all treatment groups and was related to intercurrent infection or underlying atopy. For the BDPANS comparator study, three patients in the FPANS treatment groups (two receiving FPANS 100 µg od and one 100 µg bd) withdrew from the study due to an adverse event, two of whom reported lack of efficacy of the treatment. Overall, two serious adverse events were reported, both by two patients who had received placebo, and they were not considered by the investigator to be drug-related. One was a fractured arm after a car accident and the other, surgery after an "accidental injury".

There were no significant or unexpected drug-related effects on vital signs or in the results of the laboratory data. The number of patients with changes in laboratory data to outside the normal range was generally low and evenly distributed between the groups.

A large number of plasma cortisol determinations were made in each of the studies, and samples were taken in the early morning both before and at the end of treatment.

Examination of the patients' results showed that any changes were small, and there was no detectable trend of a fall in cortisol levels. Examination of the shifts from the normal range to outside the normal range (either above or below) during the study revealed no changes different from either placebo or BDPANS (Table 4).

Discussion

The results of these two large studies have demonstrated that FPANS is well tolerated in perennial rhinitis in children. FPANS dosage regimens of 100 µg od, 200 µg od, and 100 µg bd were tested, provid-

ing convincing evidence that FPANS 100 µg od (preferably given in the morning) is effective in the treatment of perennial rhinitis in most children and is consistent with findings in children with seasonal rhinitis (28). There was no difference between the two dosing regimens of FPANS in either efficacy or safety.

The absolute efficacy of FPANS 100 µg od was established in the placebo-controlled study. FPANS demonstrated superior efficacy to placebo, when administered at doses of 100 µg od and 100 µg bd, in terms of symptom control and improvement in the condition of the nasal mucosa. Surprisingly, although clinically improved, the results of nasal blockage for patients receiving FPANS did not achieve statistical significance. This may have been influenced by the difficulty some parents may have had in describing adequately these symptoms on behalf of young children. In this study, the absolute degree of symptomatology of nasal blockage was low, and there was a noticeable placebo effect.

Although the primary efficacy variable was determined to be nasal blockage, the disease of perennial rhinitis is a composite of at least four major symptoms. Patients were eligible for entry with any two symptoms of at least moderate severity; thus, symptoms of nasal blockage were not specifically an entry criterion. As a result, the overall severity of nasal blockage was relatively mild, and while the treatments improved nasal blockage, it proved impossible to demonstrate statistical significance. It may be that, unlike the adult situation in perennial rhinitis, nasal blockage in children with perennial rhinitis is not the most important symptom. The degree of nasal blockage reported by patients on entry to the study would appear to support this view. This would seem to be supported also by the reported efficacy of antihistamines in the treatment of perennial rhinitis in children, when their efficacy in adults is generally considered poor because of the lack of effect on nasal blockage (31).

In the comparator study, FPANS was shown to be at least as effective as BDPANS 200 µg bd, at a dose of 100 µg either od or bd, in alleviating the symptoms and signs of perennial rhinitis. This confirms the findings in adults with perennial allergic rhinitis (16). None of the comparisons between FPANS 100 µg od and either FPANS 100 µg bd or BDPANS 200 µg bd, or between FPANS 100 µg bd and BDPANS 200 µg bd, reached statistical significance, except that patients receiving BDPANS required rescue medication on significantly more days and required significantly more doses of rescue medication per day. It is generally accepted that the dose-response curve for intranasal steroids is shallow and the methods for assessing treatment response – symptom scores – are rather imprecise. Therefore, the

lack of discrimination between the different doses of FPANS may not be surprising.

FPANS was well tolerated when administered to the group of children aged 4–11 years. Individual adverse events reported in all three treatment groups (FPANS, BDPANS, and placebo) were generally minor in nature, of the type expected in the population studied, and similar to those previously observed in adults with FPANS. Upper respiratory tract infection, headache, cough, asthma and related events, and influenza were commonly reported, but were likely to be due to intercurrent infection or related underlying atopy.

Epistaxis was the only other event with a frequency of ≥5% that was possibly associated with FPANS. However, this event was also reported in patients receiving placebo and BDPANS with a frequency which was not significantly different from that of those receiving FPANS. No serious events were reported with FPANS. The incidence of individual events showed little difference between treatments, FPANS being as well tolerated as placebo and BDPANS.

Increasing the dose of FPANS to 100 µg bd or 200 µg od did not appear to confer an additional advantage in terms of efficacy in the patients studied; FPANS 100 µg od is the optimum dose for most children. There was little evidence of any dose-related effect for any individual adverse event. FPANS 200 µg od or FPANS 100 µg bd was not associated with a significantly higher incidence of adverse events than the 100-µg od dose. Epistaxis was reported more commonly in the group receiving FPANS 100 µg bd, but the number of patients in the treatment group was too small to extrapolate any clinical significance of this finding.

Analysis of laboratory data showed no evidence of a treatment effect for any laboratory parameter. As expected in a drug with a low systemic absorption, there was no evidence of systemic corticosteroid effect in relation to plasma cortisol levels or adverse event profile.

Only one patient withdrew from these studies owing to rhinitis, and only six of the 510 patients (1%) withdrew due to ineffectiveness of the medication. Rhinitis was reported as an adverse event during treatment in only six patients (1%). The numbers of patients were too small to suggest any clinical significance from the findings.

Thus, these studies have consistently shown in a large population of children that a once daily dose regimen of FPANS 100 µg is more effective than placebo and at least as effective as BDPANS given twice daily (200 µg bd), confirming the situation in adults with seasonal and perennial allergic rhinitis (16, 32) and in children with seasonal allergic rhinitis (28). There was no clear advantage in increasing

the dose of FPANS to 200 µg od or giving it more frequently (100 µg bd) in the population studied. However, in a small number of patients with severe symptoms, twice-daily doses of FPANS 100 µg might be beneficial, as has been shown in adults with both perennial and seasonal rhinitis (32, 33). Overall, the safety profile was typical of the population studied, and there were no notable differences or unexpected findings between the adverse event profile for FPANS or placebo, and for FPANS and BDPANS. In particular, there were no systemic side-effects which could be attributed to dosing with a glucocorticoid.

These data are important because the combination of good efficacy with low bioavailability and thus the propensity to cause systemic side-effects means that treatment of children with FPANS may result in a higher therapeutic ratio and a lower steroid body load, an important factor if many of these children may also be receiving topical steroids for other allergic diseases.

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