Fluticasone Propionate: An Effective Alternative Treatment for Seasonal Allergic Rhinitis in Adults and Adolescents

Craig F. LaForce, MD; Robert J. Dockhorn, MD; Steven R. Findlay, MD†; Eli O. Meltzer, MD; Robert A. Nathan, MD; William Stricker, MD; Suzanne Weakley, MD; Elizabeth A. Field, PhD; and Paula R. Rogenes, PhD

Raleigh and Research Triangle Park, North Carolina; Prairie Village, Kansas; Austin and Houston, Texas; San Diego, California; Colorado Springs, Colorado; and Rolla, Missouri

Background. Topical corticosteroids are widely regarded as the reference standard in allergic rhinitis therapy because they are well tolerated and effective against all rhinitis symptoms. We evaluated the efficacy, onset of action, and safety of two dosing regimens of the new corticosteroid fluticasone propionate compared with that of beclomethasone dipropionate in patients with moderate to severe seasonal allergic rhinitis.

Methods. In this double-blind, randomized multicenter trial, 110 adolescents and 128 adults were treated for 4 weeks with one of the following regimens: fluticasone aqueous nasal spray 100 μg twice daily or 200 μg once daily, beclomethasone aqueous nasal spray 168 μg twice daily, or placebo.

Results. Patient-rated scores for nasal obstruction, rhinorrhea, and combined nasal symptoms indicated that the two fluticasone regimens were equally effective and that both were superior to beclomethasone during most of the study ($P \leq .05$) and to placebo throughout the study ($P \leq .01$). Both fluticasone regimens also demonstrated significant clinical efficacy by 24 hours after the first dose. Clinician-rated mean total nasal symptoms scores for all three active treatments were superior to placebo at most time points but were not significantly different from each other. All treatments were well tolerated, with similar incidence and type of adverse events in all treatment groups and no apparent effects on hypothalmic–pituitary–adrenal (HPA) axis function.

Conclusions. Fluticasone aqueous nasal spray was effective in relieving nasal symptoms in adolescents and adults with seasonal allergic rhinitis. Fluticasone administered once or twice daily was superior to beclomethasone administered twice daily in relieving nasal obstruction and rhinorrhea and in reducing nasal symptoms more quickly.

Key words. Fluticasone; beclomethasone; allergic rhinitis; nasal sinuses; hay fever; allergens; pollen.
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Seasonal allergic rhinitis is the 6th most common chronic condition in the United States.[1] More than 25 million individuals in this country suffer from allergic rhinitis,[2] accounting for approximately 8.4 million office visits to physicians annually.[3] Onset of allergic rhinitis is most likely to occur during childhood or adolescence,[4] with a prevalence of 20% to 30% in adolescents.[5,6]

Symptoms of allergic rhinitis arise when susceptible individuals mount an immunoglobin E antibody response to the presence of inhaled airborne allergens, in particular, pollen from grasses, weeds, and trees. With characteristic symptoms of nasal congestion and blockage, rhinorrhea, and sneezing, allergic rhinitis is not only a bothersome condition, but it may have a substantial social, economic, and medical impact on patients. It is estimated that annually allergic rhinitis is responsible for 6 million bedridden days, 2 million missed school days,

†*Deceased.*

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From Carolina Allergy & Asthma Consultants, PA, Raleigh, (C.F.L.) and Glaxo, Inc, Research Triangle Park (E.A.F., P.R.R.), North Carolina; Immuno-Allergy Technical Consultants, Inc, Prairie Village, Kansas (R.J.D.); HealthQuest Research, Austin (S.R.F.†), and Kelsey-Seybold Clinic, PA, Houston (S.W.), Texas; Allergy and Asthma Medical Group and Research Center (E.O.M.), San Diego, California; Allergy Associates, PC (R.A.N.), Colorado Springs, Colorado; and Clinical Research of the Ozarks (W.S.), Rolla, Missouri. Reprint requests should be addressed to Craig F. LaForce, MD, Carolina Allergy & Asthma Consultants, PA, 4301 Lake Boone Trail, Raleigh, NC 27607.

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3.5 million lost work days, and $154 million in lost wages.[3] Additionally, if allergic rhinitis is untreated, it may contribute to the development of other respiratory diseases such as asthma and sinusitis.[7–9]

Although several types of drugs, including antihistamines, decongestants, and anti-allergy medications such as cromolyn sodium, have been used extensively with varying degrees of success to treat seasonal allergic rhinitis, topical corticosteroids are widely regarded as the reference standard in allergic rhinitis therapy.[10–13] Intranasal corticosteroids are well tolerated and, unlike other treatments, effective against all rhinitis symptoms, including sneezing, rhinorrhea, nasal itching and congestion.[14] They are thought to alleviate rhinitis symptoms by blocking mediator release and inhibiting the influx of inflammatory cells into the nasal epithelium.[12,14]

Fluticasone aqueous nasal spray, a new corticosteroid preparation, and beclomethasone aqueous nasal spray both relieve nasal symptoms of allergic rhinitis when compared with placebo or oral antihistamines in controlled clinical trials.[15–21] Both drugs have a high ratio of topical-to-systemic activity, which reduces their potential for systemic effects.[22,23] Fluticasone is twice as potent as beclomethasone, as measured by the McKenzie vasoconstrictor assay,[23] and potentially allows less frequent dosing or lower doses to achieve maximal efficacy.

The objective of this study was to evaluate whether greater potency would translate into greater clinical efficacy or faster onset of action and permit effective treatment with once-daily dosing. We compared fluticasone aqueous nasal spray with beclomethasone aqueous nasal spray using two dosing regimens in the treatment of seasonal allergic rhinitis in a group of adolescents and adults with moderate to severe symptoms. The safety of these inhaled corticosteroids was carefully monitored.

Methods

Study Design

A double-blind, randomized, placebo-controlled, parallel-group trial was conducted during the 1989 spring allergy season at seven centers across the United States, all of which were associated with clinical practices of board-certified allergists. The study protocol was approved by an institutional review board for each center, and written informed consent was obtained from each participant or his or her guardian.

Eligible study participants included adults at least 18 years old and adolescents 12 to 17 years old who had a history of allergic rhinitis for at least two spring seasons, a positive skin test to at least one spring allergen present in the geographical area, and moderate to severe symptoms. Pollen collections at each center throughout the study period documented the levels of grass and tree pollens. To document current symptoms, patients recorded the severity of their nasal symptoms (obstruction, rhinorrhea, sneezing, itching) on daily diary cards using a visual analog scale ranging from 0 (no symptoms) to 100 (severe symptoms) during a 4- to 14-day run-in period. Patients were instructed on proper completion of the diary card at the screening visit. Patients with a total nasal symptom score of at least 200 of 400 possible points on at least 4 of the 7 days immediately preceding enrollment were selected for the study.

Patients were excluded from the study if they were being treated with corticosteroids or intranasal sodium cromolyn, required inhaled or systemic corticosteroid therapy for ongoing asthma, had an upper respiratory tract infection, or if they were scheduled to alter their immunotherapy regimen during the study, because any of these conditions could confound evaluations of study drug safety and efficacy. Women at risk of pregnancy (postmenarchal or premenopausal women and those not using oral contraceptives) and patients with any significant medical disorder or impaired adrenal function as indicated by clinical laboratory tests also were not enrolled.

After completing the screening period and satisfying the enrollment requirements, patients at each center were randomly assigned to receive one of four treatments for 28 days: fluticasone aqueous nasal spray 200 μg once daily or 100 μg twice daily, beclomethasone aqueous nasal spray 168 μg twice daily, or placebo twice daily. Patients were issued two bottles of nasal spray, one each for morning and evening use, along with a patient instruction leaflet. The first dose was administered in the clinic under supervision. To maintain the double-blind, patients in the fluticasone 200 μg once daily group applied two sprays of the drug into each nostril in the morning and two sprays of placebo in the evening; those in the other groups applied two sprays into each nostril in the morning and evening. The use of chlorpheniramine maleate 4-mg tablets was permitted to relieve unbearable symptoms, but no other medication that might affect nasal symptoms of rhinitis was permitted. Patients were instructed to record their use of study medication and rescue medication on the daily diary cards.

Efficacy Evaluations

Patients rated their nasal symptoms (obstruction on awakening and during the entire day, rhinorrhea, sneezing, and itching) daily on diary cards using a visual

analog scale. At weekly clinic visits, nasal examinations were conducted, and clinicians rated the severity of patients' nasal symptoms using the visual analog scale. Clinicians also evaluated turbinate enlargement, mucosal color, and the quantity, consistency, and color of secretions on 3- or 4-point scales. At the end of the study, they evaluated each patient's overall clinical response to therapy (ie, significant, moderate, or mild improvement; no change; or mildly, moderately, or significantly worse).

Safety Evaluations

The hypothalamic–pituitary–adrenal (HPA) axis function was monitored by comparing pretreatment morning plasma cortisol concentrations and response to adrenocorticotropic hormone (ACTH) stimulation with those on the final study day. In adolescents, pretreatment and posttreatment urinary excretion of free cortisol (cortisol, creatinine, and 17-ketogenic steroid concentrations) also were evaluated by means of 24-hour urine collections. All adverse events were recorded and followed to resolution.

Statistical Analyses

Clinician-rated nasal symptoms scores at each visit were compared between groups using the nonparametric van Elteren statistic[24,25] (a stratified Wilcoxon test controlling for investigator), as it was assumed that these symptoms scores were not necessarily normally distributed. Patient-rated symptoms scores, however, were assumed to be normally distributed since they were first averaged over 1-week intervals for each patient and then averaged over the treatment group. To assess differences in patient-rated symptoms scores between treatment groups at one-week intervals, the analysis of variance F test,[25] using contrasts and controlling for investigator, was used. The Cochran-Mantel-Haenszel test,[25] controlling for investigator, was used to assess differences in overall clinical evaluations. Fisher's exact test was used to detect statistically significant differences in the number of patients in each group with an adverse event. Treatment group comparisons of morning plasma cortisol and urine steroid concentrations were made using an F test. Results were considered statistically significant at $P < .05$.

Results

Patients

A total of 238 patients were enrolled in the study, nearly half of whom were under 18 years of age. Three patients were withdrawn from the study—two from the fluticasone 100-μg group because of protocol violations and one from the beclomethasone group because of an adverse event (asthma exacerbation). Treatment groups were balanced with respect to demographic characteristics except for sex, with the placebo-treated group having fewer women (Table 1). Diary card data indicated that over 98% of patients in each treatment group followed dosing instructions, with more than 80% of the morning and evening doses administered.

Efficacy of Therapy

Fluticasone 100 μg twice a day was significantly more effective than beclomethasone 168 μg twice a day in reducing nasal obstruction and rhinorrhea throughout the 4 weeks of treatment, according to patient ratings (Figure 1). Patients treated with fluticasone 200 μg once a day also experienced greater reductions in nasal symptoms than did patients treated with beclomethasone, although differences between the two treatments were not statistically significant at all time points. Throughout treatment, individual nasal symptoms (ie, obstruction, rhinorrhea, sneezing, and itching) were significantly improved in patients receiving fluticasone compared with those receiving placebo, while patients treated with beclomethasone experienced statistically significant reductions only in sneezing and nasal itching and not at every time point when compared with placebo.

Patient-rated symptoms of rhinorrhea and obstruction, including obstruction on awakening, were reduced more quickly following treatment with fluticasone than with either placebo or beclomethasone (Figure 2). Within 12 hours of the first dose, the 100-μg group had less nasal obstruction than did the beclomethasone group. Within 24 hours after the first dose and before the morning dose on day 2, both fluticasone groups had significantly less nasal obstruction on awakening than did the placebo group. Within 36 hours (evening of day 2), both fluticasone groups had significantly less rhinorrhea than did the placebo group.

When individual symptoms of daily obstruction, rhinorrhea, sneezing, and itching were totaled, fluticasone 100 μg twice daily was significantly more effective than beclomethasone 168 μg twice daily in reducing overall patient-rated nasal symptoms during the entire treatment period, and fluticasone 200 μg once daily was significantly more effective than beclomethasone during the second and third weeks of treatment ($P < .05$) (Figure 3A). In contrast to both regimens of fluticasone, which reduced mean total nasal symptoms scores compared with placebo throughout treatment, mean scores

Table 1. Demographic Characteristics of 238 Adults and Adolescents with Seasonal Allergic Rhinitis Who Participated in a Study Comparing 3 Treatment Regimens and Placebo

Characteristic	Placebo (n = 58)	FP ANS 100 μg bid (n = 64)	FP ANS 200 μg qd (n = 55)	BDP ANS 168 μg bid (n = 61)
Sex, %				
Male	84	70	62	67
Female	16	30	38	33
Age, y				
Mean	23.0	24.4	24.6	24.6
Range	12–63	12–67	12–63	12–58
Age group, n				
Adolescents				
Male	25	27	21	26
Female	3	3	3	2
Adults				
Male	24	18	13	15
Female	6	16	18	18
Allergen sensitivities, n				
Grass	48	50	44	55
Trees	40	36	36	30
Concurrent medical conditions, n				
Asthma	22	28	29	21
Perennial rhinitis	41	46	46	46
Concurrent immunotherapy	12	20	19	16

*P < .05
FP ANS denotes fluticasone propionate aqueous nasal spray; BDP ANS, beclomethasone dipropionate aqueous nasal spray.

were reduced by beclomethasone only during the first half of the treatment period ($P < .05$) (Figure 3A).

Clinician-rated mean total nasal symptom scores were similar to those rated by patients (Figure 3B). Improvements were significantly greater for the fluticasone 100 μg twice daily group as compared with the placebo group ($P \leq .01$) at all clinic visits during the treatment phase. Improvements in the mean total nasal

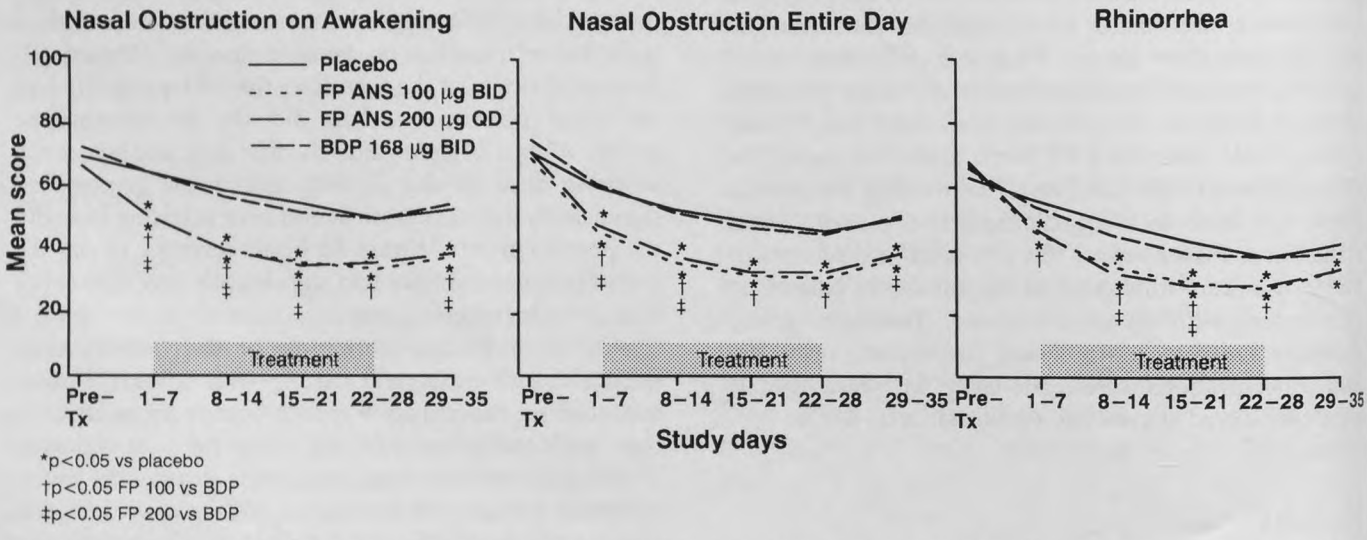

Figure 1. Patient-rated individual symptoms scores. Each symptom was rated on a visual analog scale ranging from 0 (no symptoms) to 100 (severe symptoms). Patients rated symptoms on diary cards at the end of the day, except for nasal obstruction on awakening, which was evaluated before the morning dose of study medication. *P* values are based on treatment group differences in mean scores at pretreatment and change from pretreatment, using an analysis of variance *F* test, controlling for investigator. FP ANS denotes fluticasone propionate aqueous nasal spray; BDP ANS, beclomethasone dipropionate aqueous nasal spray.

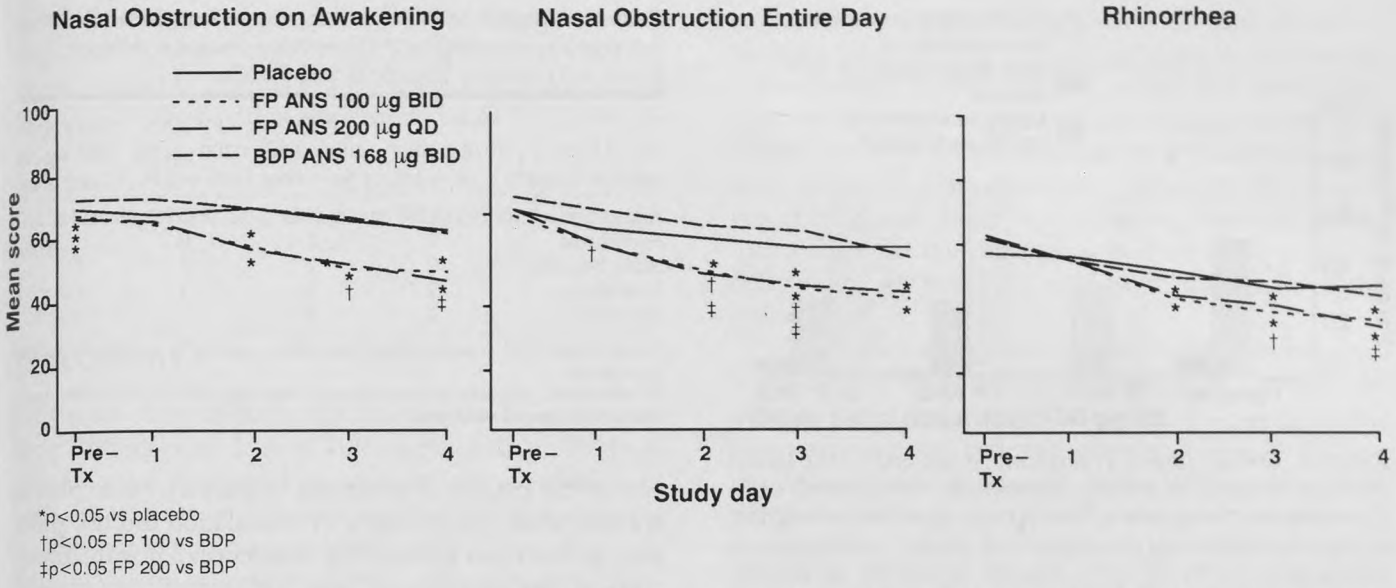

Figure 2. Patient-rated onset of action. Each symptom was rated on a visual analog scale ranging from 0 (no symptoms) to 100 (severe symptoms). Patients rated symptoms on diary cards at the end of the day, except for nasal obstruction on awakening, which was evaluated before the morning dose of study medication. *P* values are based on treatment group differences in mean scores at pretreatment and change from pretreatment, using an analysis of variance *F* test, controlling for investigator. FP ANS denotes fluticasone propionate aqueous nasal spray; BDP ANS, beclomethasone dipropionate aqueous nasal spray.

symptoms scores were also significantly greater for the fluticasone 200 μg once daily group as compared with placebo on days 8 and 15 of treatment and approached significance ($P \leq .059$) on days 22 and 29. Improvements in the beclomethasone group as compared with placebo were significantly greater on days 15, 22, and 29 ($P < .05$).

Although the clinician-rated total symptoms scores

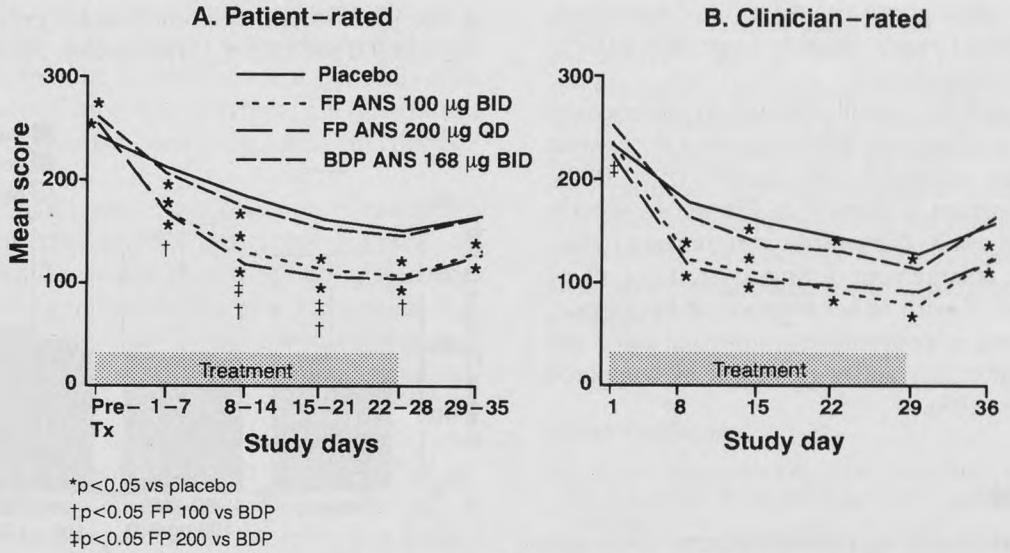

Figure 3. Patient- and clinician-rated mean total nasal symptoms scores (a sum of scores for obstruction, rhinorrhea, sneezing and itching). Each symptom was rated on a visual analog scale ranging from 0 (no symptoms) to 100 (severe symptoms). Patients rated symptoms on diary cards at the end of the day. *P* values are based on treatment group differences in mean scores at pretreatment and change from pretreatment, adjusting for investigator. FP ANS denotes fluticasone propionate aqueous nasal spray; BDP ANS, beclomethasone dipropionate aqueous nasal spray.

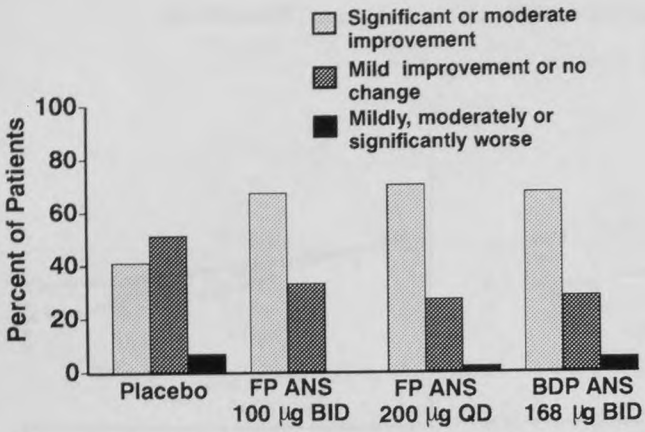

Figure 4. Overall clinical evaluation. At the end of the study, clinicians reviewed all efficacy data and rated the patient's overall response to therapy on a 7-point scale: significant, moderate, or mild improvement; no change; or mildly, moderately, or significantly worse. FP ANS denotes fluticasone propionate aqueous nasal spray; BDP ANS, beclomethasone dipropionate aqueous nasal spray.

were not significantly different among the active treatment groups, fluticasone was rated as significantly better than beclomethasone for some individual symptoms (ie, rhinorrhea and itching) at a few time points. At the end of 1 week of treatment, clinician-rated mean total nasal symptoms scores decreased by 48% in both fluticasone groups and to 35% in the beclomethasone group compared with pretreatment values. Symptoms scores continued to decline throughout the 4 weeks of treatment, with a decrease from baseline ranging from 55% to 67% in the active treatment groups.

Physicians rated the overall response to treatment as significantly better in patients receiving either fluticasone or beclomethasone compared with placebo ($P \leq .002$). This overall evaluation is shown in Figure 4. Weekly nasal examination results demonstrated significant reductions in turbinate enlargement during most, if not all, of the treatment period with either regimen of fluticasone, as well as occasional improvements in mucosal color and nasal secretions after any active treatment as compared with placebo ($P < .05$).

Safety of Therapy

There were no statistically significant differences between treatment groups for any category of drug-related adverse event (Table 2). The majority of adverse events were mild to moderate in severity, and all but one, a sore throat reported by a placebo group patient, were resolved by the completion of the study.

HPA axis function was evaluated by morning plasma cortisol levels and ACTH stimulation at screening

Table 2. Number of Patients Reporting Drug-Related Adverse Events in a Study Comparing Seasonal Allergic Rhinitis Treatment Regimens and Placebo

Adverse Event*	Placebo (n = 58)	FP ANS 100 µg bid (n = 64)	FP ANS 200 µg qd (n = 55)	BDP ANS 168 µg bid (n = 61)
Any event, n (%)	11 (19)	8 (13)	7 (13)	13 (21)
Sore throat	1	2	0	2
Nasal burning	2	1	1	4
Nosebleed	2	0	1	3
Headache	2	3	2	3

**Adverse events refer to potential drug relationship occurring in more than 3 patients across groups.*
FP ANS denotes fluticasone propionate aqueous nasal spray; BDP ANS, beclomethasone dipropionate aqueous nasal spray.

and on the last day of treatment (Figure 5). Mean plasma cortisol levels before and after stimulation did not differ among treatment groups. The incidence of posttreatment cortisol abnormalities (<7 or >25 mg/dL pre-stimulation; change of <7 mg/dL poststimulation or poststimulation peak of <18 mg/dL) did not differ significantly among treatment groups.

Analyses of 24-hour urinary steroid excretion in the adolescent patients showed no pretreatment differences among treatment groups. Following 4 weeks of treatment, there were no treatment group differences in free cortisol (corrected for creatinine excretion). Statistically significant differences in urinary 17-ketogenic steroid levels were observed as a result of an increase in the fluticasone 100-µg group (9.6 to 11.7 mg) and decreases in the placebo and beclomethasone groups (9.4 to 8.6 mg and 9.0 to 7.3 mg, respectively). Mean 17-ketogenic

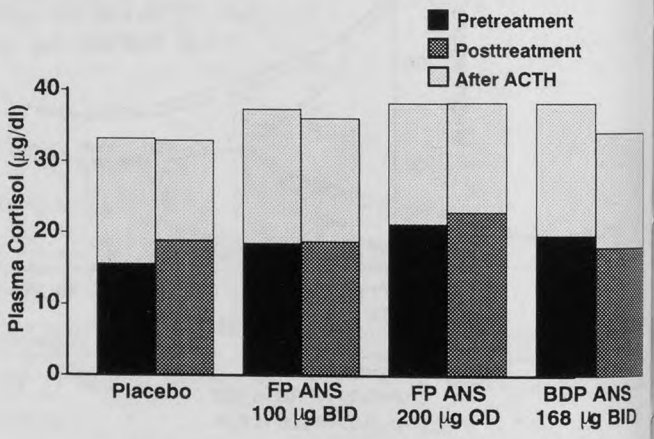

Figure 5. Mean morning plasma cortisol concentrations before and after synthetic ACTH (Cortrosyn, Organon, Inc, West Orange, NJ) stimulation. Short ACTH stimulation tests were conducted between 7:30 and 9:30 AM at screening and again at the final treatment visit prior to the last dose. ACTH denotes adrenocorticotropic hormone; FP ANS, fluticasone propionate aqueous nasal spray; BDP ANS, beclomethasone dipropionate aqueous nasal spray.

steroid levels in the fluticasone 200-μg group remained at pretreatment levels (8.5 mg). The differences between groups were not considered clinically significant, as the mean values were within the normal range (<12 for 11- to 14-year-olds, 5 to 23 mg for male adults, 3 to 15 mg for female adults).[26] Only one patient had a value below the normal range, and the value was normal on repeat testing.

Discussion

This study demonstrates that fluticasone aqueous nasal spray 200 μg once daily or 100 μg twice daily effectively relieves nasal symptoms of seasonal allergic rhinitis in both adolescents and adults, and that the two regimens provide comparable symptomatic relief. These data confirm previously published reports of the efficacy of fluticasone in adults treated with either dosage compared with placebo.[17,19]

In this study, fluticasone at either dosage was superior to beclomethasone given twice daily in relieving nasal obstruction and rhinorrhea, as rated by the patients themselves, and in providing faster relief of symptoms. The increased clinical effectiveness of fluticasone over beclomethasone in the current study may reflect the greater antiinflammatory potency and enhanced therapeutic ratio of this new-generation glucocorticoid, an androstone-derived carbothioate.[23] These findings conflict with those of two previous studies that compared the once-daily regimen of fluticasone with a twice-daily regimen of beclomethasone in the treatment of adults with moderate to severe seasonal or perennial allergic rhinitis and found the two preparations to be similar in effectiveness.[19,21]

Fluticasone has a rapid onset of action,[27] and in this study, significant relief of nasal symptoms was achieved more rapidly with fluticasone than with beclomethasone. The higher potency of fluticasone may account for this difference. By the second day of treatment, both dosage regimens of fluticasone significantly reduced nasal obstruction, compared with either beclomethasone or placebo, and rhinorrhea, compared with placebo. Nasal obstruction was significantly reduced 24 hours after the first dose of fluticasone 200 μg once daily. In the past, it had been suggested that patients be informed that it takes up to 10 days before full beneficial results of topical corticosteroids can be expected.[28] A more rapid response to therapy, combined with the advantage of a single daily treatment, may improve patient compliance.

Previous studies of seasonal allergic rhinitis have focused on the use of fluticasone for adults only.[15,17–20,29] Our study specifically included adolescents to allow for additional evaluation of the safety of fluticasone for younger patients. The population sample was divided approximately evenly between adults and adolescents. Most of the adolescents were male because of the strict enrollment criteria by which women at risk of pregnancy were excluded from the study. Although the placebo group by chance had proportionately more male participants than did the other groups, there is no reason to believe that sex would be a factor in the results of this rhinitis trial.

As in the earlier adult studies, fluticasone was well tolerated and demonstrated a good safety profile. Although fluticasone is highly potent following topical administration, its systemic activity is low.[23] Because fluticasone is extracted totally during its "first pass" from the gut through the liver, there is virtually no systemic absorption of the swallowed portion of an intranasal dose.[22] In this study, the absence of HPA-axis suppression in patients, as evidenced by morning plasma cortisol concentrations and urine steroid concentrations in adolescents, confirms the lack of systemic effects of fluticasone. The incidence of adverse events following treatment with either regimen of fluticasone was similar to that of placebo, further substantiating the safety of this new agent.

Conclusions

Fluticasone aqueous nasal spray administered 100 μg twice daily or 200 μg once daily provided rapid relief of symptoms in patients with seasonal allergic rhinitis. It was also more effective and provided relief more quickly than beclomethasone 168 μg administered twice daily. All treatments were equally well tolerated in adolescents and adults. These findings suggest that fluticasone, which offers the convenience of once-daily dosing, is an effective alternative to beclomethasone for treatment of allergy symptoms.

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