

# Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis

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**Background:** Comparative studies with topical corticosteroids and antihistamines for treatment of allergic rhinitis have not always demonstrated clear distinctions between the two on the basis of therapeutic efficacy.

**Objective:** This study was designed to compare the efficacy and tolerability of fluticasone propionate aqueous nasal spray with those of terfenadine in the treatment of seasonal allergic rhinitis.

**Methods:** Three hundred forty-eight patients with allergic rhinitis were given fluticasone propionate aqueous nasal spray (200 µg once daily), terfenadine tablets (60 mg twice daily), or placebo for 4 weeks in a multicenter, randomized, double-blind, double-dummy, parallel-group study.

**Results:** Clinician-rated total nasal symptom scores after 1, 2, 3, and 4 weeks of therapy and patient-rated total nasal symptom scores throughout treatment were significantly ( $p < 0.05$ ) lower in the fluticasone propionate group compared with the terfenadine group or the placebo group. Terfenadine was not statistically different from placebo on the basis of clinician-rated nasal symptom scores, except for sneezing. Total nasal airflow, measured by rhinomanometry, significantly ( $p < 0.05$ ) improved in the fluticasone propionate group compared with the terfenadine group or the placebo group. More fluticasone propionate-treated patients compared with placebo-treated patients had reduced nasal mucosal eosinophil counts after 4 weeks of therapy ( $p < 0.05$ ). No serious or unusual drug-related adverse events were reported. Morning plasma cortisol concentrations after 4 weeks of therapy did not differ among groups.

**Conclusion:** Fluticasone propionate aqueous nasal spray is more effective than terfenadine tablets for treatment of seasonal allergic rhinitis. (*J ALLERGY CLIN IMMUNOL* 1996;97:915-21.)

**Key words:** Fluticasone propionate, terfenadine, seasonal allergic rhinitis, antihistamine, glucocorticosteroid, comparative study

The efficacy and tolerability of pharmacotherapy for seasonal allergic rhinitis have improved sub-

stantially in recent years with the introduction of low-dose topical corticosteroids and second-generation antihistamines, now the most widely recom-

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mended and prescribed classes of medication for allergic rhinitis.<sup>1-3</sup> Both topical corticosteroids and antihistamines have been shown to alleviate the nasal itching, rhinorrhea, and sneezing characteristic of allergic rhinitis.<sup>2,4</sup> Topical corticosteroids are also highly effective at relieving nasal obstruction.<sup>2,4</sup> The selection of one of these classes of medication for the treatment of patients with seasonal allergic rhinitis is guided by the goals of maximizing therapeutic efficacy and minimizing the occurrence of side effects.

Fluticasone propionate, a corticosteroid formulated as an aqueous nasal spray, has been shown to be more effective than the second-generation antihistamine terfenadine.<sup>5</sup> This study was conducted to confirm and extend these results. This study was conducted for 4 weeks rather than 2 weeks and during the spring allergy season (February to May) at sites across the United States as opposed to the winter mountain cedar (*Juniperus ashei*) season<sup>6</sup> in central Texas. In addition, this was the first study in which fluticasone propionate aqueous nasal spray and terfenadine tablets were compared with respect to the objective measure, anterior rhinomanometry, in addition to subjective measures, such as nasal symptom scores.

## METHODS

### Patients

Male and female patients, aged 12 years or older, were eligible for the study if they or a parent or guardian gave written informed consent. Each patient was required to have moderate-to-severe seasonal allergic rhinitis diagnosed according to four criteria: (1) positive (>2+) skin test reaction to at least one spring (February to May) allergen, (2) appearance of the nasal mucosa consistent with a diagnosis of seasonal allergic rhinitis, (3) at least a 1-year history of symptoms, and (4) moderate to severe symptoms of rhinitis evidenced by patient diary card ratings during a run-in period (see Procedure section below). Patients were required to have a morning plasma cortisol concentration equal to or greater than 7 µg/dl. Patients must not have received oral antihistamines or cromolyn sodium for at least 2 weeks before screening, and they must not have received astemizole or inhaled, intranasal, or systemic corticosteroids for at least 1 month before screening.

### Procedure

The protocol for this double-blind, double-dummy, parallel-group study was approved by an institutional review board for each of the 10 study sites. During screening for the study, the clinician rated individual nasal symptoms (sneezing, nasal obstruction, rhinorrhea, and nasal itching) on a visual analog scale, ranging from 0 (absent) to 100 (severe).<sup>7</sup> Patients who

had symptoms began the 4- to 14-day run-in period immediately after screening, and patients who were free of symptoms were instructed to return to the clinic when they began to have symptoms so that the run-in period could be initiated. During the run-in period and throughout the study, patients used the visual analog scale to rate their nasal symptoms daily on diary cards. Nasal obstruction was evaluated on awakening and in the evening; all other symptoms were rated only in the evening to represent symptoms throughout the day.

To qualify for enrollment, the total nasal symptom score (derived by adding individual symptom scores for sneezing, nasal obstruction, rhinorrhea, and nasal itching) when all rhinitis medications were withheld was required to be at least 200 of a possible 400 on 4 of the 7 days immediately preceding enrollment.

Patients who met this criterion were randomly assigned on day 1 to receive one of three regimens for 28 days (days 1 to 29): fluticasone propionate aqueous nasal spray (two 50 µg sprays per nostril at 8 AM plus a placebo tablet at 8 AM and 8 PM); terfenadine tablets (Marion Merrell Dow, Inc.; one 60 mg tablet at 8 AM and 8 PM plus a placebo spray at 8 AM); or placebo (two sprays per nostril at 8 AM and a tablet at 8 AM and 8 PM). Patients recorded their nasal symptoms daily on diary cards throughout the treatment phase and during the 1-week follow-up period (days 29 to 36). Daily use of study medication on days 1 to 28 was also recorded on the diary cards. On days 1, 8, 15, 22, and 29, nasal symptoms were assessed (before the first dose of drug was administered on day 1) by the clinician, and diary cards were reviewed. During the treatment period, patients were not permitted to use any medication that might affect rhinitis symptoms. The occurrence of adverse events, defined as any untoward medical occurrence (drug-related or not), was recorded at each visit by the clinician. On day 29, measurements of morning plasma cortisol concentrations were repeated.

Nasal mucosal specimens were obtained with a Rhinoprobe (Synbiotics Corp., San Diego, Calif.) on days 1 and 29. Specimens were fixed at each site and sent to one laboratory for staining and interpretation. Numbers of eosinophils and basophils were rated on a 5-point scale: 0 = none; 1 = few, scattered; 2 = moderate number, small clumps; 3 = large clumps, not covering entire field; 4 = clumps covering entire field.

At four of the 10 study sites, bilateral nasal airflow was measured with the single-nostril anterior rhinomanometry technique<sup>8</sup> on days 1, 8, 15, 22, 29, and the follow-up visit on day 36. At each of these visits, inspiratory flow (milliliters per second at -1.5 cm H<sub>2</sub>O) was measured three times per nostril with a Connell rhinometer (Nasal Disease Study Center, Englewood, N.J.). The highest of the three values for the right and left nostrils, respectively, were combined

to yield the total nasal airflow (in milliliters per second).

### Statistical analysis

Efficacy measures were changes in mean clinician- and patient-rated nasal symptoms (both total and individual symptom scores), frequency of patient- and clinician-scored ratings of overall response to treatment, changes in total nasal airflow recorded by anterior rhinomanometry, and changes in nasal cytology scores. The Cochran-Mantel-Haenszel test was performed on pairs of treatments for overall response to treatment and nasal cytology ratings. The van Elteren statistic was performed on pairs of treatments for clinician-rated nasal symptom scores, and analysis of variance *F* tests, based on contrasts, were performed on patient-rated nasal symptom scores and total nasal airflow rates to detect mean treatment differences in changes from baseline by week of study.

Safety measures included the incidence of potentially drug-related adverse events and mean morning plasma cortisol concentrations. Fisher's exact test was performed on pairs of treatments to detect differences in the number of patients with potentially drug-related adverse events overall and by body system. Analysis of variance *F* tests on mean morning plasma cortisol concentrations were performed to detect treatment differences.

## RESULTS

### Patient characteristics

Three hundred forty-eight patients were enrolled, and 319 completed the study. Six patients discontinued the study because of adverse events, six patients withdrew because of lack of efficacy, and 17 patients withdrew for other reasons (Table I). Demographic characteristics were similar among groups (Table I).

### Efficacy data

Clinician-rated total nasal symptom scores were significantly lower in the fluticasone propionate group than in either the terfenadine group or the placebo group at each clinic visit, but terfenadine did not statistically differ from placebo at any of these time points (Table II). After 2 weeks of therapy, reductions from baseline clinician-rated total nasal symptom scores of 49%, 35%, and 23% were observed for the fluticasone propionate, terfenadine, and placebo groups, respectively ( $p < 0.001$  fluticasone propionate vs terfenadine or placebo). After 4 weeks of therapy, reductions from baseline of 52%, 33%, and 22% were observed for the fluticasone propionate, terfenadine, and placebo groups, respectively ( $p < 0.001$  fluticasone propionate vs terfenadine or placebo). A similar

**TABLE I.** Patient characteristics

|                    | Fluticasone<br>propionate | Terfenadine | Placebo  |
|--------------------|---------------------------|-------------|----------|
| Number of patients | 117                       | 116         | 115      |
| Mean age (yr)      | 30.4                      | 29.7        | 30.1     |
| Sex, no. (%)       |                           |             |          |
| Male               | 68 (58%)                  | 62 (53%)    | 73 (63%) |
| Female             | 49 (42%)                  | 54 (47%)    | 42 (37%) |
| Mean weight (lb)   | 162.1                     | 164.1       | 164.6    |
| Withdrawn, no. (%) |                           |             |          |
| Adverse events     | 1 (1%)                    | 2 (2%)      | 3 (3%)   |
| Lack of efficacy   | 0 (0%)                    | 3 (3%)      | 3 (3%)   |
| Other*             | 5 (4%)                    | 8 (7%)      | 4 (3%)   |

\*"Other" includes noncompliance, lost to follow-up, protocol violation, and withdrawn consent.

pattern of improvement was observed with patient-rated total nasal symptom scores (Table II). After 2 weeks of therapy, reductions from baseline of 50%, 32%, and 26% were observed for the fluticasone propionate, terfenadine, and placebo groups, respectively ( $p < 0.001$  fluticasone propionate vs terfenadine or placebo). After 4 weeks of therapy, reductions from baseline of 57%, 38%, and 32% were observed in the fluticasone propionate, terfenadine, and placebo groups, respectively ( $p < 0.001$  fluticasone propionate vs terfenadine or placebo).

The data for clinician-rated individual nasal symptoms were similar to the total nasal symptom data (Table II). Scores in the fluticasone propionate group were significantly ( $p < 0.05$ ) lower than terfenadine group scores for nasal obstruction, rhinorrhea, and nasal itching at most weekly assessments. Clinician-rated scores in the terfenadine group were significantly ( $p < 0.05$ ) lower than placebo group scores only for sneezing on days 8 and 15.

Patient-rated individual nasal symptom score data conformed to a similar pattern (Table II). For nasal obstruction on awakening, fluticasone propionate scores were significantly lower than placebo scores, beginning on days 8 to 10, and terfenadine scores, beginning on days 4 to 7. Terfenadine scores for nasal obstruction (morning and evening) were not significantly different from placebo scores.

Mean total nasal airflow rates did not differ among groups on day 1 (Fig. 1). On Days 8, 15, 22, and 29, mean total nasal airflow was increased relative to the day 1 baseline value in the fluticasone propionate group and decreased relative to

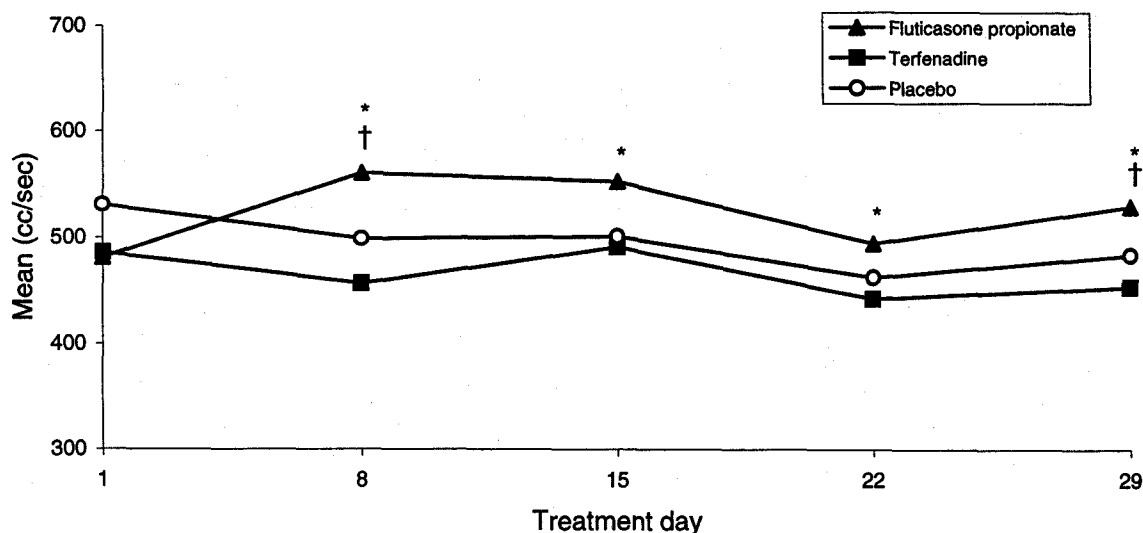


**FIG. 1.** Total nasal airflow (milliliters per second) measured by anterior rhinomanometry during treatment with fluticasone propionate aqueous nasal spray ( $n = 60$ ), terfenadine tablets ( $n = 62$ ), or placebo ( $n = 59$ ). \* $p < 0.05$ , fluticasone propionate versus placebo, based on change from day 1. † $p < 0.05$ , fluticasone propionate versus terfenadine, based on change from day 1.

**TABLE II.** Clinician- and patient-rated mean nasal symptom scores

|                          | Fluticasone propionate |       |        |        |        | Terfenadine |       |        |        |        | Placebo |       |        |        |        |
|--------------------------|------------------------|-------|--------|--------|--------|-------------|-------|--------|--------|--------|---------|-------|--------|--------|--------|
|                          | Day 1                  | Day 8 | Day 15 | Day 22 | Day 29 | Day 1       | Day 8 | Day 15 | Day 22 | Day 29 | Day 1   | Day 8 | Day 15 | Day 22 | Day 29 |
| Total nasal symptoms     |                        |       |        |        |        |             |       |        |        |        |         |       |        |        |        |
| Clinician                | 257                    | 144*† | 127*†  | 108*†  | 115*†  | 252         | 173   | 160    | 163    | 163    | 258     | 194   | 190    | 174    | 174    |
| Patient                  | 271                    | 155*† | 134*†  | 122*†  | 113*†  | 279         | 198   | 187    | 172    | 171    | 283     | 215   | 206    | 196    | 191    |
| Obstruction              |                        |       |        |        |        |             |       |        |        |        |         |       |        |        |        |
| Clinician                | 72                     | 45*†  | 44*†   | 39*†   | 39*†   | 68          | 55    | 53     | 53     | 54     | 71      | 56    | 56     | 53     | 53     |
| Patient                  | 71                     | 44*†  | 40*†   | 38*†   | 35*†   | 74          | 57    | 53     | 50     | 50     | 75      | 57    | 54     | 53     | 51     |
| Rhinorrhea               |                        |       |        |        |        |             |       |        |        |        |         |       |        |        |        |
| Clinician                | 69                     | 39*   | 32*†   | 25*†   | 31*†   | 64          | 42    | 39     | 38     | 40     | 67      | 46    | 45     | 42     | 43     |
| Patient                  | 71                     | 42*†  | 34*†   | 31*†   | 29*†   | 71          | 51    | 48     | 43     | 42     | 72      | 53    | 51     | 48     | 47     |
| Sneezing                 |                        |       |        |        |        |             |       |        |        |        |         |       |        |        |        |
| Clinician                | 52                     | 24*   | 21*    | 18*†   | 21*    | 56          | 35*   | 30*    | 32     | 33     | 55      | 44    | 41     | 37     | 36     |
| Patient                  | 62                     | 32*†  | 28*†   | 25*†   | 23*†   | 65          | 43*   | 41*    | 38*    | 39     | 66      | 52    | 49     | 47     | 45     |
| Itching                  |                        |       |        |        |        |             |       |        |        |        |         |       |        |        |        |
| Clinician                | 65                     | 36*   | 30*†   | 26*†   | 25*†   | 64          | 41    | 38     | 40     | 37     | 65      | 49    | 48     | 43     | 42     |
| Patient                  | 67                     | 38*†  | 32*†   | 28*†   | 26*†   | 69          | 48    | 45     | 41     | 40     | 71      | 53    | 51     | 48     | 48     |
| Obstruction on awakening |                        |       |        |        |        |             |       |        |        |        |         |       |        |        |        |
| Patient                  | 71                     | 53†   | 46*†   | 44*†   | 41*†   | 74          | 65    | 61     | 59     | 57     | 74      | 61    | 60     | 59     | 56     |

Note: Symptoms were scored on a scale from 0 (absent) to 100 (severe). Patient-rated scores represent the mean diary card scores for the 4-day periods preceding days 1, 8, 15, 22, and 29.

\* $p < 0.05$  versus placebo.

† $p < 0.05$  versus terfenadine.

the day 1 baseline value in the terfenadine and placebo groups.

Only patients with paired pretreatment and posttreatment nasal mucosal samples that could be

evaluated were included in the analyses. The pattern of change over the course of treatment in ratings for nasal inflammatory cell counts also reflected the high degree of efficacy of fluticasone

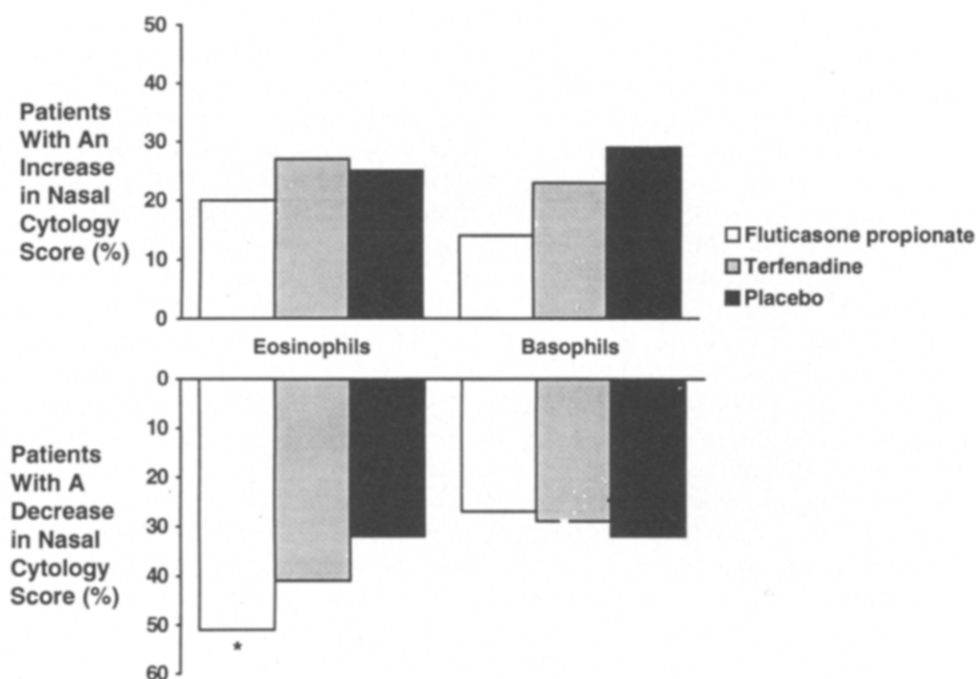


**FIG. 2.** Percent of patients showing increases or decreases in eosinophils or basophils after 4 weeks of therapy with fluticasone propionate aqueous nasal spray ( $n = 106$ ), terfenadine tablets ( $n = 99$ ), or placebo ( $n = 94$ ). Numbers of inflammatory cells were rated on a 5-point scale: 0 = none; 1 = few, scattered; 2 = moderate number, small clumps; 3 = large clumps, not covering entire field; 4 = clumps covering entire field. \* $p < 0.05$ , fluticasone propionate versus placebo, for overall pattern of change within three categories (increase, decrease, no change).

propionate (Fig 2). More patients treated with fluticasone propionate compared with those treated with placebo exhibited decreases, and fewer patients exhibited increases in eosinophils over the course of treatment ( $p < 0.05$ ). The change in ratings for numbers of basophils was not significantly different among groups.

### Safety data

The number of patients who reported potentially drug-related adverse events was not statistically different between groups. The most commonly reported adverse event was headache (three patients in the fluticasone propionate group, three in the terfenadine group, and five in the placebo group). Six patients discontinued the study because of adverse events. In only two of these patients were the events considered to be potentially related to study medication (one in the fluticasone group and one in the placebo group).

Morning plasma cortisol concentrations did not differ among the three groups at the time of screening, when mean morning plasma cortisol concentrations were 16.2  $\mu\text{g/dl}$ , 15.3  $\mu\text{g/dl}$ , and

15.9  $\mu\text{g/dl}$  for the fluticasone propionate, terfenadine, and placebo groups, respectively. On day 29, mean morning plasma cortisol concentrations were 16.5  $\mu\text{g/dl}$ , 17.0  $\mu\text{g/dl}$ , and 15.8  $\mu\text{g/dl}$  in the fluticasone propionate, terfenadine, and placebo groups, respectively ( $p < 0.05$  placebo vs terfenadine).

### DISCUSSION

The results of this study demonstrate that fluticasone propionate aqueous nasal spray (200  $\mu\text{g}$  once daily) is significantly more effective than terfenadine tablets (60 mg twice daily) in the treatment of seasonal allergic rhinitis. Both clinician- and patient-rated total nasal symptom scores and individual nasal symptom scores for obstruction, rhinorrhea, sneezing, and itching demonstrate that fluticasone propionate, compared with either terfenadine tablets or placebo, decreases the symptoms of seasonal allergic rhinitis.

Unlike fluticasone propionate, terfenadine did not differ from placebo in its ability to consistently decrease morning nasal obstruction. Terfenadine's lack of effect on nasal obstruction in this study was

not unexpected. Terfenadine also failed to relieve nasal itching and rhinorrhea compared with placebo. Daily flushing of the nasal mucosa with the placebo nasal spray may have accounted for the lack of difference observed between terfenadine- and placebo-treated patients. Additionally, placebo response rates may exceed 30% in nasal pharmacotherapy studies.<sup>9</sup> Data from the study by van Bavel et al.<sup>5</sup> also failed to reveal a consistent effect of terfenadine on nasal itching and rhinorrhea. In the study by van Bavel et al.,<sup>5</sup> intranasal fluticasone propionate (200 µg once daily) administered for 2 weeks during the mountain cedar season in Texas decreased the symptoms of seasonal allergic rhinitis significantly more than either terfenadine tablets (60 mg twice daily) or placebo. The data reported here, which were obtained during the spring allergy season at 10 sites throughout the United States, extend the findings of van Bavel et al.<sup>5</sup> to other geographic locations and to allergy seasons other than the mountain cedar season.

Rhinometrically measured total nasal airflow rate, previously shown to be inversely related to degree of nasal obstruction,<sup>10</sup> provided an objective correlate of the symptomatic improvement in fluticasone propionate-treated patients. The increase in total nasal airflow in fluticasone propionate-treated patients and the decrease in terfenadine- and placebo-treated patients are consistent with the decrease in both clinician- and patient-rated (morning and evening) nasal obstruction in the fluticasone propionate group, but not in the terfenadine or placebo groups.

Data reflecting the clinical efficacy of fluticasone propionate are corroborated by cytologic and rhinometric data. Nasal mucosal eosinophil counts after 4 weeks of therapy were reduced in a substantially greater percentage of patients treated with fluticasone propionate than patients treated with placebo. Similar results were reported in several other studies, which also demonstrated that more patients treated with fluticasone propionate, compared with those treated with placebo<sup>11-13</sup> and terfenadine,<sup>5</sup> had reductions in nasal mucosal eosinophil counts after therapy, ranging in duration from 2 weeks to 6 months. During the pollen season, the amount of influx of eosinophils into the nasal mucosa is directly related to the severity of allergic rhinitis symptoms.<sup>14</sup> Possibly, the reduction in nasal inflammatory cell counts that occurs with fluticasone propionate treatment not only reflects but also contributes to the amelioration of the inflammatory disease process.

The beneficial cytologic changes and the de-

crease in rhinitis symptoms associated with fluticasone propionate treatment in this study occurred in the absence of untoward side effects. Fluticasone propionate, administered for 4 weeks, did not affect hypothalamic-pituitary-adrenal axis function, as indicated by mean morning plasma cortisol concentrations. A similar lack of effect of fluticasone propionate on hypothalamic-pituitary-adrenal axis function has been documented in other studies, including one in which patients with perennial allergic rhinitis were given fluticasone propionate for 6 months.<sup>11, 12, 15</sup> Furthermore, the incidence of potentially drug-related adverse events occurring after administration of fluticasone propionate did not differ from the incidence after administration of placebo. Terfenadine's adverse event profile did not significantly differ from the adverse event profile of placebo.

The results of this study demonstrate that fluticasone propionate aqueous nasal spray (200 µg), administered once daily for 4 weeks to patients with seasonal allergic rhinitis, is well-tolerated and more effective than the second-generation antihistamine terfenadine in alleviating allergic rhinitis symptoms. These data complement and extend earlier findings indicating that intranasal fluticasone propionate, administered for 2 weeks, is more effective than terfenadine in the treatment of seasonal allergic rhinitis.<sup>5</sup>

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