# Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis

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**Background: Intranasal corticosteroids, such as budesonide and fluticasone propionate, are widely prescribed in the treatment of perennial allergic rhinitis. Once daily budesonide dry powder and fluticasone propionate aqueous suspension have been found to provide similar efficacy in controlling symptoms of perennial allergic rhinitis.**
**Objective: The purpose of this study was to assess the efficacy and safety of treatment with once daily budesonide aqueous nasal spray.**
**Methods: This study involved a multicenter, blinded, randomized, parallel-group, placebo-controlled trial of adults with perrenial allergic rhinitis. Patients (n = 273) recorded daily nasal symptoms for 8 to 14 days (baseline) and 6 weeks (treatment).**
**Results: Budesonide decreased combined symptoms to a significantly greater extent than did fluticasone (*P* = .03); both treatments significantly decreased mean combined nasal symptoms scores compared with placebo. Of the 3 nasal symptoms assessed (ie, nasal blockage, runny nose, and sneezing), nasal blockage was significantly (*P* = .009) more decreased with budesonide compared with fluticasone. Both treatments also significantly improved runny nose and sneezing compared with placebo. Improvement in combined nasal symptom scores of the budesonide-treated group reached statistical significance within 36 hours compared with placebo (*P* = .01); in those patients treated with fluticasone, significant improvement compared with placebo was first observed within 60 hours. Adverse events were mild and transient.**
**Conclusions: Once daily budesonide aqueous nasal spray, 256 μg, was significantly better in controlling the symptoms of perrenial allergic rhinitis than once daily fluticasone propionate, 200 μg, especially nasal blockage. Both treatments were superior to placebo. Budesonide may have a faster onset of action than fluticasone. (J Allergy Clin Immunol 1998;102:902-8.)**

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This study was performed in cooperation with the Perennial Allergic Rhinitis Study Group: J. Hebert, Ste-Foy, Canada; F.I. Warrington, Winnipeg, Canada; C. Leavitt, Calgary, Canada; D. Thomson, Montreal, Canada; K. Tse, Vancouver, Canada; J. Garcia, Mátlaga, Spain; J. Code, Seville, Spain; J. Garrets, Santander, Spain; F. Gozalo, León, Spain; M. Tejedor, Albacete, Spain; F. Feo, Ciudad Real, Spain; P. Garcia, Tarragona, Spain; and with Astra Pharma Inc (Mississauga, Ontario, Canada) and Astra Draco AB (Lund, Sweden).

Supported by a grant from Astra Draco AB, Lund, Sweden.
Received for publication April 28, 1998; revised July 8, 1998; accepted July 8, 1998.

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0091-6749/98 $5.00 + 0 **1/1/93396**

***Key words:*** *Budesonide, glucocorticoids, intranasal administration, birch pollen, aqueous spray, fluticasone propionate, onset of action, placebo-controlled, randomized, double-blind*

Allergic rhinitis is an inflammatory condition of the nasal mucous membranes. Hypersensitivity to allergen causes infiltration of the nasal epithelium by mast cells, T lymphocytes, and eosinophils. Release of histamine, leukotrienes, tachykinins, prostaglandins, and other inflammatory mediators results in the characteristic symptoms of rhinitis: nasal blockage, rhinorrhea, itching, and sneezing. It is estimated that allergic rhinitis affects between 10% to 30% of the population of the United States and at least 16% of the population of the United Kingdom,[1,2] and its prevalence seems to be increasing.[3,4]

Pharmacotherapy for perennial allergic rhinitis includes antihistamines, decongestants, anticholinergics, cromolyn, and corticosteroids. Intranasal corticosteroids combat the inflammation of rhinitis by decreasing mast cell and eosinophil infiltration of the nasal epithelium,[5,6] modifying arachidonic acid metabolism, decreasing mediator production[7] and release,[8,9] and inhibiting the effects of cytokines.[10] The efficacy of intranasal corticosteroids with the ability to affect multiple steps of the inflammatory process while maintaining a large margin of safety has prompted their increased use in the treatment of perennial allergic rhinitis over the last 20 years.[11]

The corticosteroid budesonide is available for intranasal use as an aqueous suspension in a pump spray applicator (Rhinocort Aqua; Astra Draco AB, Sweden). To harmonize the delivered doses with the dry powder and pressurized metered dose inhaler formulations, budesonide aqueous nasal spray has recently been reformulated to deliver 32 μg and 64 μg per actuation. Fluticasone propionate (Flonase/Flixonase; Glaxo Wellcome, UK) is another corticosteroid also available as an aqueous pump spray (50 μg/actuation) for topical intranasal use.

A study comparing budesonide dry powder with a delivered once daily dose of 280 μg with fluticasone propionate aqueous suspension with a once daily delivered dose of 200 μg found that both preparations provided similar efficacy in controlling symptoms of perennial allergic rhinitis.[14] However, the comparative efficacy of the aqueous formulations of budesonide and fluticasone propionate in perennial allergic rhinitis has not been studied.

**TABLE I.** Demographic baseline characteristics of patients

| | Patients (no) | Mean age in years (range) | Sex (M/F) | Mean disease duration in years (range) |
|---|---|---|---|---|
| Budesonide | 111 | 30.1 (18-74) | 47/64 | 10.8 (1-40) |
| Fluticasone propionate | 109 | 31.2 (17-70) | 49/60 | 11.3 (1-34) |
| Placebo | 53 | 31.0 (18-58) | 27/26 | 12.5 (1-36) |
| All | 273 | 30.8 (17-74) | 123/150 | 11.4 (1-40) |

**TABLE II.** Prevalence of allergies for randomized patients

| | Patients (no) | | |
|---|---|---|---|
| | All (%) | Canada (%) | Spain (%) |
| Allergen | 314 (100) | 161 (51.3) | 153 (48.7) |
| *D farinae* and/or *D pteronyssinus* | 286 (91.1) | 143 (45.5) | 143 (45.5) |
| Dog/cat | 132 (42.0) | 102 (32.5) | 30 (9.6) |
| Mold | 65 (20.7) | 55 (17.5) | 10 (3.2) |

The primary objective of this study was to compare the efficacy of budesonide aqueous nasal spray, 256 μg given once daily for the treatment of perennial allergic rhinitis, with the efficacy of fluticasone propionate nasal spray, 200 μg once daily. A secondary objective was to compare the incidence of adverse events associated with both treatments.

## METHODS

### Subjects

Three hundred seventy-five patients with perennial allergic rhinitis were recruited in Canada and in Spain between November 1994 and July 1995.

Patients aged 18 years and older with at least a 1-year history of allergic perennial rhinitis were considered for entry into the study. Diagnosis was verified by a positive skin prick test response to 1 or more perennial allergens performed within 1 year of the start of study. Participants were required to exhibit at least 2 of 3 symptoms of rhinitis (blocked nose, runny nose, or sneezing) with severity rated 1 or more on a 0 to 3 symptom severity scale during at least 8 of the 8- to 14-day baseline period.

Patients were not eligible for participation in the study if they had received systemic or topical intranasal corticosteroid treatment within 2 months before enrollment, if they required high doses (≥1000 μg/day) of inhaled topical steroids for asthma, or if they had other nasal abnormalities possibly interfering with efficacy assessments.

Medications other than the supplied rescue antihistamine possibly interfering with the evaluation of the symptoms of allergic rhinitis were not allowed during the study. Pregnant and nursing women and those of childbearing age not using effective contraception were also denied participation in the study. Patients undergoing immunotherapy for perennial allergy were allowed to participate if the maintenance dose administered remained constant throughout the entire study.

Patients were withdrawn from the study if they were noncompliant with the treatment protocol, if they required treatment with a prohibited medication, or if they experienced a serious adverse event.

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of each institution participating in the study.

### Study design

The study was done in double-blind fashion for budesonide and placebo (the bottles being identical) and single-blind fashion (to the investigator) for fluticasone propionate. Patients were assigned to parallel treatment groups according to a computer-generated block randomization list. For every 2 patients randomized to treatment with budesonide, 2 were randomized to treatment with fluticasone and 1 to treatment with placebo.

A baseline period of 8 to 14 days was ended when the patients started the randomized treatment. The patients returned to the clinic after 3 weeks of treatment and at the end of the next 3-week period (ie, the conclusion of the 6-week treatment period), when the final visit was made.

### Study therapy

During the treatment period, the patients were instructed to administer 2 actuations of the study medication to each nostril every morning for the next 6 weeks. The study medication consisted of either budesonide aqueous nasal spray, 64 μg/spray (256 μg once daily), or fluticasone propionate aqueous nasal spray, 50 μg/spray (200 μg once daily), or placebo with the vehicle for budesonide aqueous nasal spray. Compliance was estimated by having patients note in the diaries the number of doses of study medication taken. Rescue medication was local market versions of loratadine, 10-mg tablets (Claritin/Clarityne; Schering Plough, USA). Throughout the baseline and active treatment periods, patients had access to the rescue medication for use if symptoms became intolerable. The number of loratadine tablets used by patients was recorded in the diaries and confirmed by counting the unused tablets returned to the clinic.

### Clinical and laboratory assessments

*Skin prick test.* Patients were given a skin prick test with a panel of dog, cat, *Dermatophagoides farinae, D pteronyssinus, Alternaria, Penicillium, Hormodendron, Aspergillus,* grass pollen mix, tree pollen mix, and ragweed allergen extracts (100,000 Allergen Unit/mL). Histamine, 10 mg/mL, was used as a positive control, and the diluent was used as the negative control. A positive reaction was defined as a wheal diameter at least 3 mm greater than the diluent control and/or at least a 50-mm flare (ie, erythema measured as the sum of the greatest diameter and the perpendicular diameter through the midpoint of the greatest diameter).

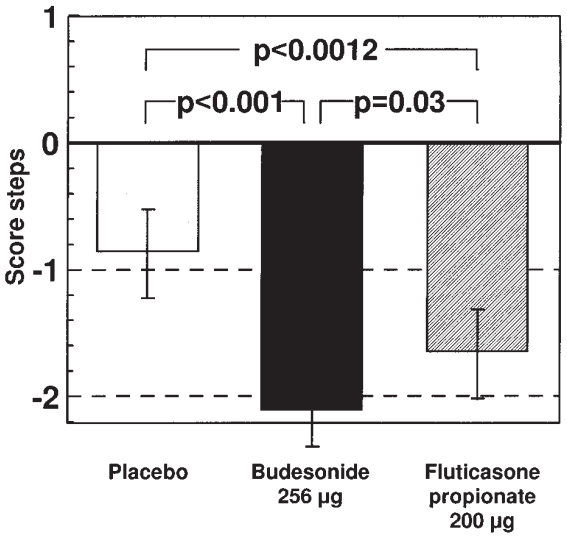


**FIG 1.** Mean reduction from baseline in the combined nasal symptom scores (sum of blocked nose, runny nose, and sneezing) over the 6-week treatment period.

*Nasal examination.* Rhinoscopy was performed at all visits and signs of hypertrophy of the conchae, edema, secretion, pus, nasal polyps, septum deviation, and physical signs of Candida infection were recorded.

*Symptom assessment and patient diary.* Every evening, each patient evaluated nasal and eye symptoms (blocked nose, runny nose, sneezing, and eye irritation) over the preceding 24-hour period and entered that information in a diary. Symptoms were scored according to a 4-point scale: 0, no symptoms; 1, mild symptoms (present but not troublesome); 2, moderate symptoms (frequently troublesome but not sufficient to interfere with normal daily activity or night-time sleep); and 3, severe symptoms (sufficiently troublesome to interfere with normal daily activity or night-time sleep).

The primary efficacy variables that were measured were the scores of 3 individual nasal symptoms (blocked nose, runny nose, and sneezing). Mean values of the symptom scores for the 3 individual symptoms and mean combined nasal symptoms scores (sum of the 3 individual symptom scores) over the 2-week baseline period and the 6-week treatment period (divided into two 3-week periods) were calculated.

Onset of action was assessed by a comparison of the change from baseline in combined nasal symptom scores for each active treatment with that of placebo for the first 4 consecutive scoring intervals (ie, within 12, 36, 60, and 84 hours).

*Patients' overall evaluation of efficacy.* At the clinic visits after 3 and 6 weeks of treatment, patients were asked to evaluate the ability of the study medication to control their nasal symptoms during the previous 3 weeks. The following 5-point scale was used for each evaluation: 0, symptoms were aggravated; 1, no control of symptoms; 2, minor control of symptoms; 3, substantial control of symptoms; and 4, total control of symptoms.

### Adverse events

At randomization and after 3 and 6 weeks of treatment, patients were asked whether they had experienced any adverse events. Records of these and any other symptoms observed by the investigator were made along with information about the date of onset, duration, maximum intensity (rated as mild, moderate, or severe), outcome, seriousness, and action taken.

### Data management and statistical analysis

In all tests of significance, 2-tailed alternatives were used, and *P* values of less than .05 were considered statistically significant. Calculations of the main analysis of efficacy were based on data available from all patients who did not deviate from the protocol.

Changes from baseline in the mean symptom scores were compared with ANOVA with treatment, center, treatment-by-center interaction, and baseline score as factors in the covariate model, followed by pairwise comparisons. The same model was used for eye symptoms, weekly consumption of antihistamine, and the patients' overall evaluation of treatment efficacy (after 3 and 6 weeks of treatment).

## RESULTS

### Patient population

A total of 273 patients (Canada, n = 150; Spain, n = 123) of 314 randomized patients fulfilled the study as stipulated in the protocol. The 3 treatment groups were comparable with respect to age and duration of disease. There was a similar preponderance for males in the actively treated groups (Table I). Most patients were allergic to more than 1 antigen. Approximately 90% of the randomized patients were allergic to house dust mites, and 40% were allergic to dogs or cats, with a higher frequency of allergy to dog/cat and mold allergen observed in Canada (Table II).

### Clinical efficacy

A total of 273 patients were evaluable and included in the efficacy analysis. The mean baseline period was approximately 12 days, and the mean treatment period was approximately 40 days. Treatment compliance was calculated to be 3.9 of the prescribed 4 sprays per day per patient in each of the 3 groups.

*Combined nasal symptoms.* Baseline mean scores were 4.28 in the placebo-treated group and 4.31 and 4.07 in the budesonide- and fluticasone-treated groups, respectively. The reduction from baseline in combined nasal symptom scores was 2.11 for budesonide and 1.65 for fluticasone, both statistically significant compared with placebo ($P < .0001$ and $P = .0012$, respectively). When comparing the 2 active treatment groups, a significantly greater improvement in the budesonide-treated patients ($P = .031$) was revealed (Fig 1).

*Individual nasal symptoms.* Budesonide successfully reduced mean symptom scores of nasal blockage by 0.75 compared with 0.31 for placebo, whereas 0.5 score-steps reduction for fluticasone was not a statistically significant decrease in mean symptom scores compared with placebo (Fig 2, *A*). Both budesonide and fluticasone were significantly more effective than placebo in reducing symptoms of runny nose (0.73 and 0.59 score steps, respectively) and sneezing (0.66 and 0.55 score steps, respectively; Fig 2, *B* and *C*).

No significant change from baseline in eye symptoms was observed for either drug compared with placebo.

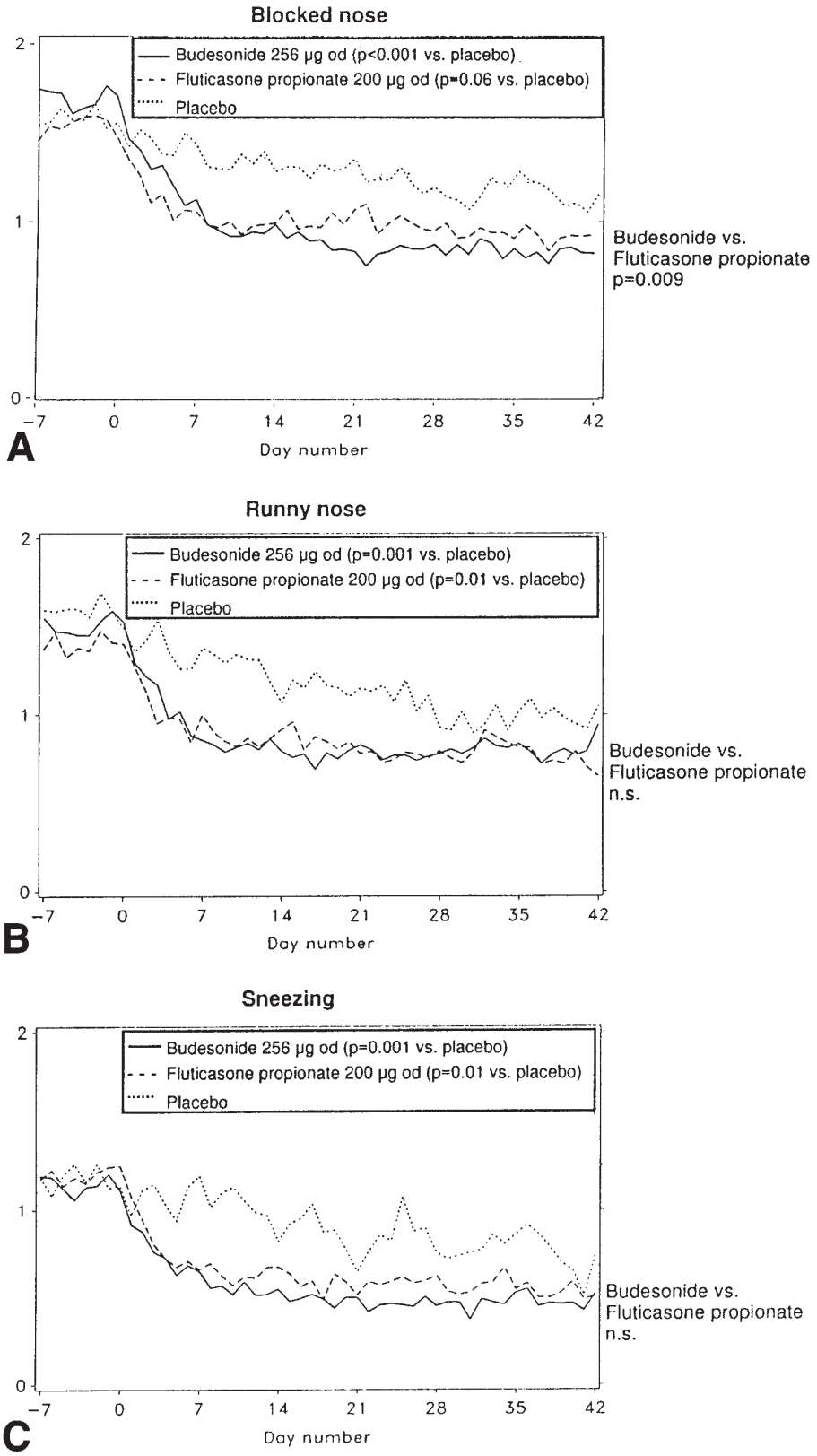


**FIG 2.** Mean symptom scores for individual nasal symptoms: **A**, blocked nose; **B**, runny nose; and **C**, sneezing. Treatment started at day 0. Statistical comparison vs placebo and between budesonide and fluticasone during 6 weeks of treatment (change from baseline).

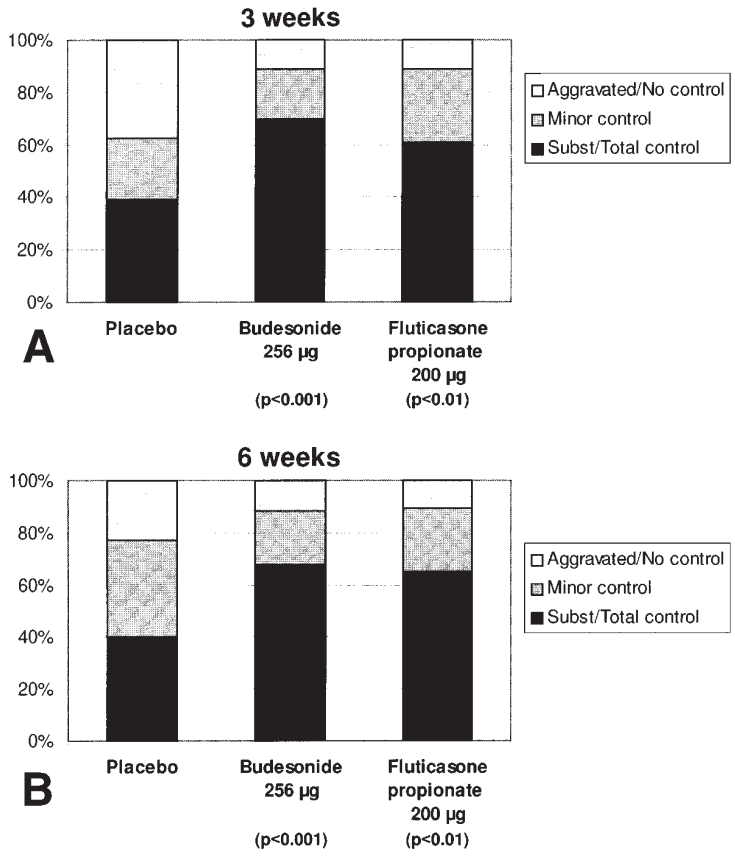


**FIG 3.** Patients' overall evaluation of efficacy after 3 **(A)** and 6 weeks **(B)** of treatment (*P* values for each active treatment compared with placebo).

*Onset of action.* At the first assessment, within 12 hours of the first dose, no difference in the efficacy of either of the 2 drugs, compared with placebo, was shown. Within 36 hours, patients using budesonide showed a 1.02 score-step reduction significantly greater than the 0.21 in placebo for the combined nasal symptom score ($P = .012$). The symptom reduction grew progressively at 60 hours to reach a 1.32 score-step reduction within 84 hours. For fluticasone, significant relief compared with placebo was first experienced within 60 hours (reduction of 1.28 score steps; $P < .001$) but not at 36 hours. Both active treatments continued to provide significant relief of nasal symptoms throughout the study when compared with placebo.

*Patients' overall evaluation of treatment efficacy.* No statistically significant difference was found between the 70.1% budesonide-treated patients who reported substantial or total control over symptoms at 3 weeks compared with the 61.0% in the fluticasone-treated group ($P = .31$). After 6 weeks, a likewise nonsignificant difference was found between the 67.5% in the budesonide-treated group and the 65.3% in the fluticasone propionate–treated group ($P = .44$). Both active treatment groups were better compared with the 39.4% in the placebo group after 3 weeks (Fig 3, *A*) and the 40.4% after 6 weeks of treatment (Fig 3, *B*).

*Rescue medication.* Weekly use of antihistamines by patients in the budesonide-treated group was reduced from 1.14 to 0.40 tablets/week and from 1.16 to 0.42 tablets/week in the fluticasone propionate–treated group. In the placebo group, consumption was reduced from 1.05 to 0.83 tablets/week. These reductions from baseline reached statistical significance in the active treatment groups only; again, there was no statistically significant difference between the active-treatment groups.

## Safety

*Adverse events.* Of the 303 patients eligible for the safety analysis, adverse events were reported by 46% of patients who were treated with budesonide, 37% of patients treated with fluticasone propionate, and 36% of patients treated with placebo. The most frequently reported adverse events were respiratory infection, blood-tinged nasal secretions, and headache (Table III). Blood-tinged nasal secretions were reported more often in the budesonide group compared with the fluticasone propionate group. Regarding adverse events, no statistically significant differences between active treatments and placebo were found ($P = .256$, chi-squared test).

Four serious adverse events occurred during the study, all in the budesonide group, and none of which was con-

**TABLE III.** Most frequently reported adverse events and number of patients affected

| Adverse event | Budesonide (%) | Fluticasone propionate (%) | Placebo (%) |
|---|---|---|---|
| Bloody nasal discharge | 22 (18) | 8 (7) | 1 (2) |
| Respiratory infection | 12 (10) | 8 (7) | 10 (16) |
| Headache | 11 (9) | 12 (10) | 5 (8) |
| Pharyngitis | 5 (4) | 3 (2) | 2 (3) |

sidered likely to be related to intake of the drug. Two patients in each of the budesonide and the fluticasone treatment groups withdrew because of adverse events. Two patients in the budesonide-treated group and 1 patient in each of the fluticasone- and placebo-treated groups withdrew because of deterioration of disease.

### Rhinoscopy

Results of rhinoscopy were reassuring in all treatment groups because no clinical signs of fungal infection were seen, and purulent secretions were seen only occasionally in the fluticasone- and placebo-treated groups.

## DISCUSSION

The efficacy of both budesonide and fluticasone propionate as pharmacotherapy for perennial allergic rhinitis has been demonstrated previously.[15-17] In this study, the significant decreases observed in nasal symptoms and rescue medication use in the budesonide and fluticasone propionate treatment groups confirm the superiority of both drugs over placebo in controlling the symptoms of perennial allergic rhinitis. Results of the patients' overall evaluation of treatment efficacy further support these findings.

Control of the combined nasal symptoms of perennial rhinitis was better achieved among patients who received budesonide therapy than fluticasone propionate therapy. This difference in efficacy is consistent with findings in a seasonal allergic rhinitis study comparing budesonide and fluticasone, where budesonide at similar doses was more effective than fluticasone propionate in achieving control of symptoms.[19]

Nasal blockage is considered the most pronounced symptom of perennial rhinitis.[18] In this respect, budesonide demonstrated greater efficacy compared with fluticasone propionate and placebo. The effect of fluticasone propionate in relieving the symptom of blocked nose did not differ significantly from that of placebo. The symptoms of runny nose and sneezing, however, were improved by both treatments. The differences in efficacy observed between the 2 intranasal corticosteroids may be explained by the difference in water solubility and lipophilicity of the 2 compounds. Furthermore, it can be speculated that conjugates to fatty acids constitute an intracellular depot of budesonide as has been shown in animal airway models, which might contribute to a prolonged duration of antiinflammatory action and hence superior efficacy.[23,24]

The onset of action of intranasal corticosteroids is of interest because early benefit has already been identified, thus presenting a new dimension for this medicine.[25] This study does suggest that budesonide acts earlier on symptoms than fluticasone propionate, but it should be recognized that the study was not specifically designed to determine brief time intervals. Furthermore, the evaluation of onset of action of the 2 intranasal corticosteroids and placebo represent time intervals of 24 hours rather than data collected at discrete time points. A study specifically evaluating the onset of action of budesonide that uses shorter time limits in a controlled environment and that is associated with objective measurements should follow.

The improvements of approximately 20% in the placebo-treated group is of a magnitude consistent with previous corticosteroid studies on perennial rhinitis. The benefits accompanying the use of placebo may be explained, in part, by the wetting effect of the placebo solution on the nasal mucosa, which may in itself provide limited relief of nasal symptoms.

The study design was not ideal because, for practical reasons, double blinding of fluticasone propionate was not possible (whereas an aqueous solution was available for use as a placebo for budesonide). Because of this, a risk of bias in favor of fluticasone propionate on the part of the patients existed. Efficacy expectations would be greater in patients who receive the active drug. Any such bias has no impact, however, on the validity of the conclusion.

Lack of compliance with treatment regimens can hamper clinical studies, but all treatment groups in this study showed high compliance in the use of study medications.

Local effects on the nose are relatively common with intranasal corticosteroids. Mild adverse events were reported among all 3 treatment groups in this study. Among them, the report of blood-tinged nasal secretions was more often in the budesonide-treated group. The reason for this is unclear. However, the frequency of these findings vary in clinical trials with nasal steroids and is reported to be in a range from approximately 5% to 20%.[12,20] The variations could be attributed to differences in the activity of the disease because most chronic diseases are characterized by a disease severity that fluctuates over time. Other short-term studies have reported no increased incidence in local adverse effects with the use of intranasal budesonide.[12,16,19] In a long-term study involving at least 4 years of budesonide treatment, few adverse effects were observed.[21]

In conclusion, budesonide aqueous nasal spray, 256 μg once daily, provided better symptom relief than fluticasone propionate aqueous nasal spray, 200 μg once daily. Both treatments were superior to placebo in controlling the symptoms of perennial allergic rhinitis. Budesonide may have a faster onset of action.

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