

A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis

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The clinical potency of budesonide, a new glucocorticosteroid, was compared in a randomized double-blind study with beclomethasone dipropionate in the treatment of seasonal allergic rhinitis during the ragweed-pollen season. Sixty-one subjects were matched according to their skin sensitivity to ragweed-pollen extract and the severity of ragweed-induced rhinitis during the previous season. Thirty subjects received budesonide, and 31 received beclomethasone dipropionate, 50 µg per actuation. A double-dummy technique was used to achieve blinding, since the aerosol canisters and adaptors were dissimilar. Subjects were instructed to keep rhinitis well controlled by starting intranasal trial medication as soon as symptoms became troublesome, two puffs into each nostril, when it was needed, up to four times per day. If this became inadequate, subjects received supplementary chlorpheniramine maleate, 4 mg. Nasal symptoms (none = 0, mild = 1, moderate = 2, and severe = 3) and all medication use were recorded daily in a diary. Budesonide demonstrated better clinical potency than beclomethasone in that less was needed to maintain good control of nasal symptoms. Side effects were mild and transient for both groups. (J ALLERGY CLIN IMMUNOL 1987;79:887-92.)

Nearly two decades ago, intranasal corticosteroids were demonstrated to be effective in the treatment of seasonal allergic rhinitis.¹ Possible mechanisms of action of these corticosteroids include reduction of inflammation and edema,^{2,3} modification of chemotaxis of mediator cells,⁴ and reduction of eosinophils⁵ and basophilic⁶ cells in the nasal mucosa.

Budesonide is a nonhalogenated glucocorticosteroid with high lipid and negligible water solubility. It has an increased ratio between local anti-inflammatory and systemic potencies⁷ and is highly metabolized in the liver with negligible local metabolism in the lung.⁸ The two major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, are not clinically active.

Most clinical trials of budesonide have been carried out in asthma in which it has been demonstrated to be at least as potent as beclomethasone dipropionate

as a topical glucocorticoid but with a lower systemic potency.^{9,10} As an intranasal aerosol, it is more effective than placebo in the treatment of seasonal allergic rhinitis.^{11,12} One study has suggested that, when it is taken in a fixed daily intranasal dose of 400 µg, budesonide is more effective than beclomethasone dipropionate.¹³

The aim of the present study was to compare the efficacy of intranasal budesonide and beclomethasone dipropionate in controlling symptoms of ragweed pollen-induced rhinitis during the ragweed-pollen season. Both medications were taken on an as needed basis, since this avoided unnecessary use of trial medication, and previous studies have demonstrated that this can be an effective approach to the treatment of pollen-induced rhinitis.^{14,15}

MATERIAL AND METHODS

Subjects

Sixty-one subjects, attending the Firestone Regional Chest and Allergy Clinic, participated in the study. All gave a history of rhinitis during the two previous ragweed-pollen seasons and had a positive skin prick test for ragweed-pollen extract. There were 30 male and 31 female subjects with a mean age of 43.5 ± 11.4 (SD) years (Table I). Each subject's history was taken by questionnaire, a physical examination was performed, and blood and urine were sampled for routine laboratory screening. Subjects were ex-

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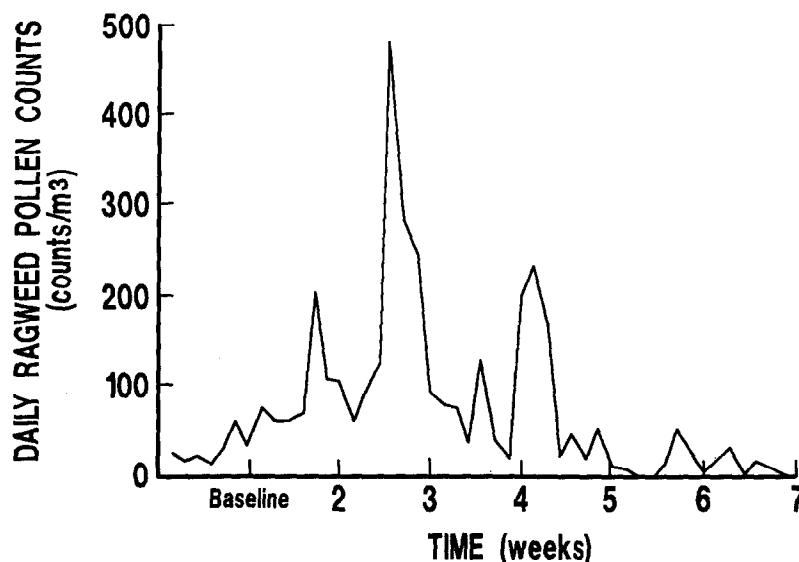


FIG. 1. Daily ragweed-pollen counts during the 7-week study period.

TABLE I. Subject characteristics

	Budesonide	Beclomethasone dipropionate
No.	30	31
Age (yr)	42.1 $\pm$ 12.0	44.7 $\pm$ 10.8
Gender (M/F)	13/17	19/12
Ragweed sensitivity*		
250	6	3
2500	15	16
25000	7	8
>25000	2	4
Severity of ragweed- induced rhinitis for the previous year (history)†		
Mild	21	17
Moderate	7	12
Severe	2	2
Presence of asthma	9	10
Sensitivity to fungal spores	9	3

*Concentration of ragweed extract needed to produce a wheal of 4 mm diameter or greater (Noon units per milliliter).

†Mild, symptoms well controlled with antihistamines or nasal spray; moderate, symptoms well controlled with antihistamines and nasal spray; severe, symptoms inadequately controlled with antihistamines and nasal spray.

cluded if they had perennial rhinitis or illnesses other than seasonal rhinitis and asthma, were using oral steroids, or had received hyposensitization therapy during the previous 12 months. Pregnant and nursing mothers and patients who were more than mildly sensitive to fungal spores, in the air

before and concurrent with ragweed pollen, were excluded. All subjects gave informed written consent to participate.

Study design

Each subject had duplicate skin prick tests with tenfold serial dilutions of ragweed extract (2.5 to 25,000 Noon units, Bencard Allergy Service, Weston, Ontario) and single dose extracts of *Alternaria tenuis* and *Cladosporium* (Hollister Stier Laboratories, Rexdale, Ontario). The diluent for the extracts and 1 mg/ml of histamine solution were used as negative and positive controls, respectively.

Subjects were matched on the basis of skin sensitivity to ragweed-pollen extract, severity of ragweed-induced rhinoconjunctivitis during the previous 2 years, presence of asthma, sensitivity to fungal spores, and gender. One of each pair was randomly allocated to budesonide and the other to beclomethasone dipropionate treatment. Both medications were delivered as an aerosol from a metered-dose inhaler, in a dose of 50 μ g per canister actuation. The canisters and adaptors containing the two trial medications were not identical. Therefore, a double-dummy technique was used to achieve blinding. Each subject received a budesonide-type canister and a beclomethasone-type canister, but only one contained active medication; the other canister contained placebo. Each time medication was required, one puff was applied to each nostril from both canisters. The aerosols were delivered in a standardized way. First, the nose was cleared of secretions, and the canister was shaken vigorously. After the applicator had been positioned correctly in one nostril and the other nostril had been closed by pressing a finger against it, the canister was activated once during a slow inspiration. A second puff was immediately applied to the other nostril without reclearing.

At enrollment, rhinitis symptoms were minimal, as expected for July in southern Ontario. The objective of the

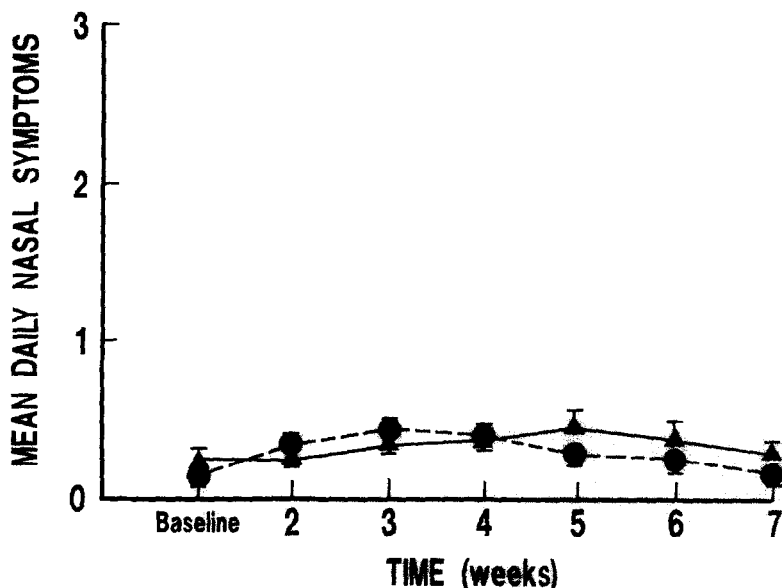


FIG. 2. Mean ($\pm$ SEM) daily nasal symptom scores global for subjects receiving budesonide (▲) and beclomethasone (■) (1 = mild, 2 = moderate, and 3 = severe).

study was to prevent deterioration from this state by the use of the trial medications taken in a standardized manner. Throughout the 7-week study period, subjects were instructed not to use the trial nasal sprays when they were asymptomatic, but to start using them immediately when rhinitis became noticeable. At this time, they applied one puff from both canisters into each nostril every 4 hours until symptoms were controlled. If they required more than four puffs per nostril per day, they increased the dose to two puffs into each nostril, from both canisters, every 4 hours, up to a maximum of four times per day. If this maximum daily dose was inadequate, they added chlorpheniramine maleate, 4 mg, as needed, up to six tablets per day. Once nasal symptoms were controlled, subjects were instructed to stop antihistamines and to use the trial nasal sprays only when symptoms recurred and then in the minimum dose that would maintain good control.

Eye symptoms were controlled with a naphazoline hydrochloride-antazoline ophthalmic drop preparation as needed up to four times per day and, if it was necessary, medrysone eye drops, four times per day. Chlorpheniramine was not permitted for the control of eye symptoms. Subjects with asthma used salbutamol aerosol, 200 μ g, when it was needed, up to four times per day.

Diary cards were completed twice daily for the 7 weeks that encompassed the ragweed-pollen season. This included 1 week before and 1 week after the season when counts were minimal (Fig. 1). Subjects recorded both trial and concomitant medication use and symptoms. Scores were recorded for runny nose, stuffy nose, sneezing, ocular symptoms, and cough. They were based on an interval scale of 0 to 3 for both severity and frequency: 0 = none; 1 = mild/a few short episodes; 2 = moderate/many episodes; 3 = severe/continuous.¹⁴

Subjects attended the clinic on five occasions during the

7-week study period. At these times, diary cards were checked for accuracy, the technique for application of the nasal sprays was observed, symptoms were discussed to ensure optimal control was being achieved, and the study canisters were weighed.

Daily mean ragweed-pollen counts (number per cubic meter) were measured throughout the pollen season with a Hirst volumetric spore trap (Burkard Manufacturing Co., Ltd., Rickmansworth, Hertfordshire, England).¹⁶ The trap was located on the roof of the Regional Laboratory in Hamilton, Ontario, at a height of 6 m above the ground.

The study protocol was approved by the Research Committee at St. Joseph's Hospital, Hamilton, Ontario.

Analysis

Daily symptom scores were obtained by meaning the nocturnal and daytime severity and frequency scores. Sneezing, runny nose, and stuffy nose values were averaged into one nasal index. The mean daily symptom scores and medication use were calculated for each of the 7 study weeks. The use of trial medication and symptom scores during the 7 weeks were evaluated by repeated measures analysis of variance in MANOVA in SPSS-X.¹⁷ The association between nasal stinging and canister type was tested with a chi-squared statistic. Results were considered significant at $p < 0.05$ (two-tailed).

RESULTS

Sixty-one subjects were enrolled in the study, but only 56 subjects, 28 in each of the two treatment groups, were included in the overall efficacy analysis for the 7-week study period. The remaining subjects had incomplete data; one developed an upper respiratory tract infection, two were out of the ragweed-

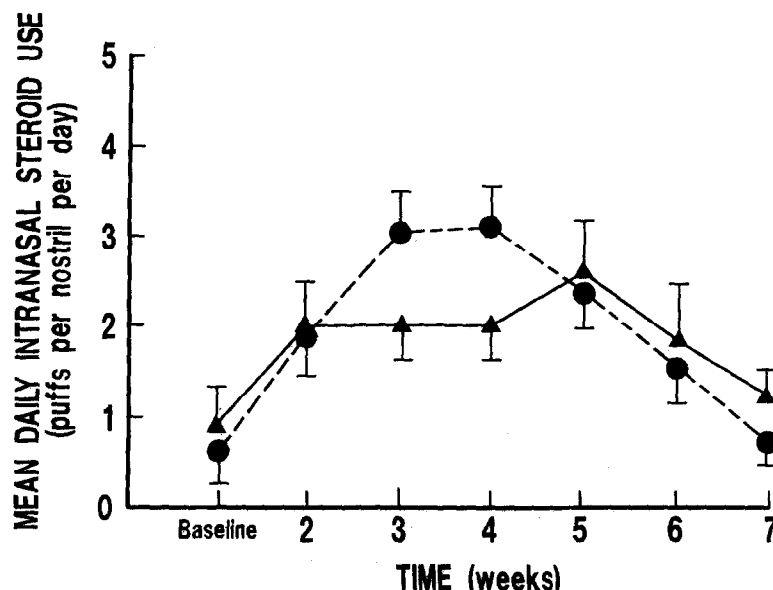


FIG. 3. Mean ($\pm$ SEM) daily use of budesonide (▲) and beclomethasone dipropionate (■) throughout the ragweed-pollen season ($p = 0.016$).

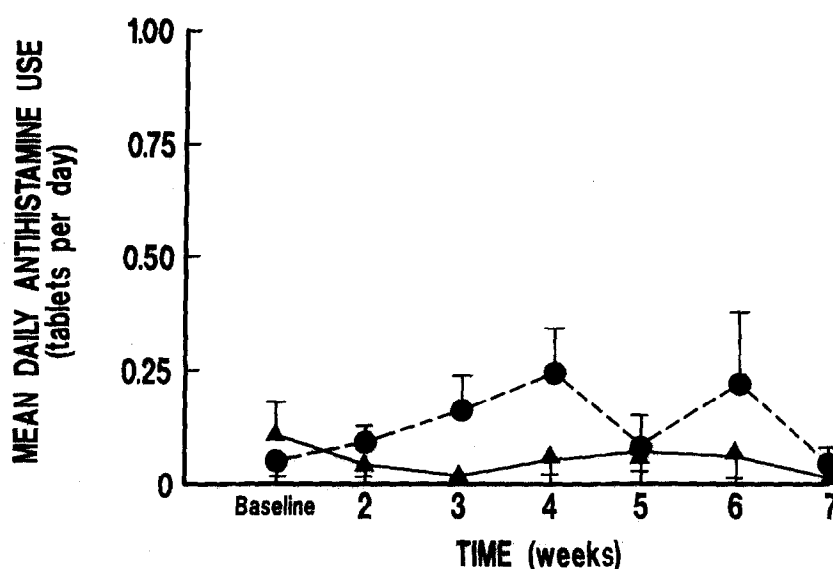


FIG. 4. Mean ($\pm$ SEM) daily antihistamine use, required in addition to trial medication to control nasal symptoms; budesonide group (▲) and beclomethasone dipropionate (■).

pollen area for more than 1 week, and two subjects developed severe headaches. The two treatment groups were homogenous with respect to the matching criteria ($p > 0.05$).

Subjects started recording symptoms and medication use 1 week before airborne ragweed pollen was expected. During this baseline week, the mean daily pollen count was negligible at $20/m^3$ (Fig. 1). Since subjects were required not to have perennial rhinitis or be sensitive to other common pollen allergens,

which were in the air at that time, symptoms were minimal and can be considered as baseline (Fig. 2).

During the 7-week study period, budesonide demonstrated greater clinical potency than beclomethasone in that fewer applications of budesonide were needed to keep rhinitis well controlled ($p = 0.016$; Fig. 3). Differences were greatest during the third and fourth weeks of the study when the ragweed-pollen counts were at their highest (Fig. 1). In 13 subjects receiving budesonide and 14 subjects receiving bec-

TABLE II. Conjunctivitis and cough: symptoms and medications

	Budesonide	Beclomethasone dipropionate	<i>p</i>
Eye symptom score (mean daily) (range 0-3)	0.43	0.36	0.86
Naphazoline hydrochloride-antazoline eye drops (applications/day)	0.66	0.64	0.91
Medrysone eye drops (applications/day)	0.12	0.11	0.81
Cough score (mean daily) (range 0-3)	0.14	0.07	0.42
Salbutamol aerosol (actuations/day)	0.17	0.36	0.94

lomethasone, nasal spray alone, in the maximum daily dose, was inadequate to maintain good symptom control. Therefore, these subjects took oral chlorpheniramine on an as needed basis. Fewer tablets per subjects were required by the budesonide-treated group (2.4 versus 5.9 for budesonide and beclomethasone, respectively) (Fig. 4), but with only 27 of the 56 subjects requiring this treatment, this difference did not reach statistical significance.

Nasal symptoms were well controlled, as demonstrated by very low mean daily nasal symptom scores during the 7-week study period for both treatments (budesonide = 0.34; beclomethasone dipropionate = 0.30) (Fig. 2). Mean daily eye and cough symptom scores were similar in both groups, as were the use of eye drops and inhaled bronchodilator (Table II).

Side effects from the nasal sprays were few, the most common being stinging of the nasal mucosa on application. This was spontaneously reported more frequently after use of the beclomethasone canister and adaptor than for the budesonide unit (11 subjects versus one; $p = 0.002$). Headaches occurred in four subjects receiving budesonide and seven receiving beclomethasone dipropionate and were sufficiently severe in two, one from each treatment group, that they were withdrawn from the study. One subject, in the budesonide-treated group, recorded nasal bleeding that did not necessitate study withdrawal.

The accuracy of total diary recordings of nasal spray use was checked against canister weight changes for the entire study period. Subjects in the active budesonide-treated group recorded using 81.8 puffs per subject in their daily diaries compared to 70.2 determined by canister weight measurements. In the beclomethasone dipropionate-treated group, this discrepancy was not evident (diary = 91.6; weight = 9.04). In the analysis, efficacy was determined from recorded use. If it had been evaluated from canister weight, the difference in intranasal steroid use between the two treatment groups would be greater than presently being reported.

DISCUSSION

The results of this study demonstrate that budesonide nasal spray is more effective than beclomethasone dipropionate in controlling symptoms of rhinitis during the ragweed-pollen season. These findings are in agreement with those of Pipkorn and Rundcrantz¹³ who, in another direct comparison of budesonide and beclomethasone dipropionate but using a fixed-dose study design, demonstrated that a higher frequency of subjects had a "very good" effect with budesonide.

Side effects were relatively few, although the incidence of stinging of the nasal mucosa immediately after application of the spray was higher with the beclomethasone dipropionate canister. This was likely due to the delivery of more than twice the amount of propellant per actuation from both the active and placebo beclomethasone canisters than from the budesonide active and placebo units. Headaches were reported by four subjects taking active budesonide and by seven subjects taking beclomethasone dipropionate. This incidence is similar to that reported by Pipkorn and Geterud¹⁸ and in keeping with a recent review of beclomethasone dipropionate.¹⁹

The design for this investigation was somewhat different from most previous comparative studies in seasonal allergic rhinitis. Rather than measuring differences in symptom scores between the treatment groups at fixed drug doses, subjects were requested to maintain optimal control of their symptoms with a hierarchy of study medications. First, they used the intranasal corticosteroid spray when it was needed, and if this was inadequate at a maximum recommended dose, antihistamine tablets were added. By ensuring that optimal levels of rhinitis symptom control were achieved and that the two groups were similar for demographic and clinical characteristics, efficacy of the budesonide and beclomethasone dipropionate could be compared on the basis of the quantity of medication used. Thus, the potential problems of overtreatment with fixed doses and compliance were overcome.

Double-dummy techniques have been criticized be-

cause of the potential for acute drying of the nasal mucosa from excessive intranasal fluorocarbon flashing, particularly in fixed-dose study designs. In the present study, although the beclomethasone dipropionate-treated group used more aerosolized nasal steroid (and placebo) and, consequently, were exposed to a greater "drying effect," nasal symptoms were controlled to equivalent clinical levels with smaller quantities of budesonide (and placebo). This would indicate that the effect being measured was not excessively confounded by the mucosal drying properties of the aerosol propellants. The higher frequency of subjects complaining of nasal stinging with the beclomethasone aerosol was probably a propellant-related problem.

The objective of this study was to compare two intranasal steroids by their potency in preventing deterioration of rhinitis. Subjects only initiated use of the nasal spray when rhinitis became noticeable and then continued to use it in the minimum dose that would maintain good symptom control. By the use of this approach to treatment, unnecessary medication use in asymptomatic subjects was avoided, and symptoms were successfully kept very mild. Manufacturers have recommended that nasal steroid sprays should be used in fixed daily doses, and there is evidence that they can require several days to effect an improvement.²⁰ This study suggests that a less rigorous approach to the treatment of pollen-induced rhinitis may be successful. The main difference between this study and other studies is that we were aiming to prevent deterioration, not to ameliorate already established rhinitis. The approach described in this study has been used previously,^{14, 15} and we believe that it can be successful in situations where the severity of allergen exposure fluctuates, such as during pollen seasons. However, a formal comparison of fixed and "as needed" dosing schedules is required before any conclusions can be made on their relative effectiveness.

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