Beclomethasone dipropionate aerosol in allergic rhinitis

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Treatment with beclomethasone dipropionate aerosol (BDA), 50 μg four times daily in each nostril, was compared with placebo therapy in a double-blind non-crossover trial of 30 matched patients with allergic rhinitis induced by ragweed pollen. The trial was started at the beginning of the ragweed season and continued for 42 days. Response to treatment was assessed from information on daily diary cards, weekly objective measurements of nasal patency and measurement of total eosinophil count (TEC) before treatment and at week 4. Patients in the BDA group had significantly less ($P < 0.05$) sneezing, rhinorrhea and nasal stuffiness at 36 days, cough at 10 days and antihistamine consumption at 17 days. There was no significant difference between the groups in eye symptoms, nasal airway inspiratory resistance, maximum inspiratory nasal flow or TEC. Overall comparison with previous pollen seasons by the patients indicated moderate to great improvement in 86% of the BDA group and in 13% of the placebo group ($P < 0.01$). Minor side effects were noted by two patients in each group.

Le traitement au dipropionate de béclométhasone en aérosol (DBA), à raison de 50 μg dans chaque narine quatre fois par jour, a été comparé au traitement à un placébo dans une étude à double insu, sans chassé-croisé, chez 30 patients appariés souffrant de rhinite allergique provoquée par le pollen de jacobée. L'essai a débuté au commencement de la saison des jacobées et s'est poursuivi pendant 42 jours. La réponse au traitement a été évaluée à partir de l'information recueillie sur des agendas, les mesures objectives hebdomadaires de l'ouverture nasale et le compte des éosinophiles totaux (CET) avant le traitement et après 4 semaines. Les patients dans le groupe DBA ont eu significativement moins ($P < 0.05$) d'éternuements de rhinorrhée et de congestion nasale après 36 jours, de toux après 10 jours et de consommation d'antihistaminiques après 17 jours. On n'a constaté aucune différence significative entre les deux groupes en ce qui a trait aux symptômes oculaires, à la résistance nasale inspiratoire, au débit inspiratoire nasal maximum ou au CET. La comparaison globale par les patients avec les saisons de pollen antérieures a indiqué une amélioration moyenne à grande chez 86% des sujets du groupe DBA et chez 13% du groupe placebo ($P < 0.01$). Des effets secondaires mineurs ont été observés chez deux patients de chaque groupe.

Allergic rhinitis is a common, troublesome condition. In the past, therapy has been based on environmental control, antihistamines, α-sympathetic stimulants, sodium cromoglycate and allergen injection. In spite of these measures symptoms may occur that require therapy with corticosteroids. Attempts to avoid the systemic side effects of corticosteroids have been made by using topical hydrocortisone,[1] prednisolone[2] and dexamethasone.[3] Although these agents control the rhinitis they still result in substantial adrenal suppression.[4,5] Recently two other corticosteroids, betamethasone-17-valerate[6,7] and beclomethasone dipropionate,[8-11] which have potent local effects when used in small doses, have been introduced. Trials have shown these to be effective topically in controlling allergic rhinitis with no adrenal suppression.[6-11] However, in all these trials improvement was assessed by subjective methods (symptom scores, pill counts and observation of the nose). Objective assessment of nasal patency can be obtained by measuring nasal resistance[12,13] and maximum inspiratory nasal flow (MINF).[14,15]

We have carried out a double-blind non-crossover trial of therapy with beclomethasone dipropionate aerosol (BDA) in 30 matched subjects with ragweed-pollen-induced rhinitis. Improvement was assessed both subjectively and objectively.

Patients and methods

Patients

Thirty patients with troublesome symptoms of allergic rhinitis in the ragweed pollen season were selected from the chest-allergy clinics of St. Joseph's Hospital and McMaster University Medical Centre. All gave a positive early response on prick skin-testing with ragweed pollen extract and a negative response to extracts of *Alternaria* and *Hormodendrum*, fungal spores present in the atmosphere concurrently with ragweed pollen.[16] None had nasal polyps. Fourteen had associated mild seasonal asthma.

Preliminary assessment included determination of the level of allergy by duplicate prick skin-testing with serial 10-fold dilutions of ragweed pollen extract (1/10 to $1/10^5$) and determination of serum concentration of ragweed-specific IgE by the radioallergosorbent test (RAST) with whole-pollen extract of common ragweed (Pharmacia). Total blood eosinophil count (TEC), history of remote or recent ragweed allergen injection therapy, estimation of daily pollen exposure, age and sex of the patients were also recorded. From these data an independent observer formed two matched groups; group 1 received BDA and group 2 received placebo aerosol (Table I).

Methods

The trial began at the start of the ragweed pollen season and continued for 42 days. At the start nasal airway inspiratory resistance at a standard flow of 0.4 *l*/s ($NAIR_{0.4}$), MINF and TEC were determined. The patients

Table I—Pretrial data for patients with allergic rhinitis induced by ragweed pollen

Variable	Group 1, n = 15 (beclomethasone dipropionate therapy)	Group 2, n = 15 (placebo therapy)
Age, mean (yr)	34.2	34.1
Male (n)	8	9
Mild asthma (n)	7	7
Recent allergen injection treatment (n)	5	5
Remote allergen injection treatment (n)	4	4
Exposure, mean (h/d without air-conditioner)	15.7	15.3
Skin test end-point, mean (negative power of 10)	2.87	2.87
RAST result, mean (0 to 4)*	1.47	2.13
Total eosinophil count, mean ($\times 10^6/l$)	200	204

*Results of radioallergosorbent test: 0 = negative; 1 = borderline; 2 = clearly positive; 3 = strongly positive; 4 = very strongly positive.

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were given double-blind a nasal inhaler containing either BDA, 50 μg per spray, or an inert Freon propellant (Freon 11, trichlorofluoromethane, and Freon 12, dichlorodifluoromethane) and were instructed to use it in each nostril four times daily. They were carefully instructed to direct the spray posteriorly in the line of the nasal cavity while gently inhaling. They were permitted to use antihistamine tablets if needed but no topical decongestants. Symptoms and number of antihistamine tablets required were recorded each day and night on a diary card. $NAIR_{0.4}$ and MINF determinations were repeated weekly on the same day of the week at the same time. The nasal mucosa was examined each week. TEC determination was repeated during the week of the peak pollen count (week 4). At the end of the study the patients were asked whether they thought their symptoms were improved (greatly, moderately or slightly) or unimproved as compared with previous years.

The diary card was similar to the one used by Norman and colleagues.[3] Daily and nightly sneezing, stuffy, runny nose, red itchy eyes and cough were each recorded as 0 if they had not occurred, 1 if they had lasted less than 30 minutes, 2 if they had lasted 30 minutes to 2 hours and 3 if they had lasted more than 2 hours. The cards were reviewed with the patient every week.

$NAIR_{0.4}$ was measured by the method of Taylor and Shivalkar.[13] A tight-fitting skin diver's mask applied over the nose and eyes was connected to a pneumotachograph for measuring flow and to a pressure transducer for measuring the transnasal pressure between the mask and the mouthpiece held tightly between the teeth and lips. Flow and pressure were recorded on the y and x axes of an x–y recorder, and the $NAIR_{0.4}$ in cm $H_2O/l \cdot s$ was calculated from the slope of the tangent to the pressure–flow curve at a flow of 0.4 l/s. The mean of four measurements during tidal nasal breathing was determined. Measurement of $NAIR_{0.4}$ was not possible in two subjects who gagged on the mouthpiece and in one who could not keep the posterior pharynx in communication with the mouthpiece. MINF was measured during forced nasal inspiration with the patients wearing only the mask. Patients who could flare their nostrils were requested not to do so. The best of four tracings was recorded. Measurement of MINF was possible in all patients. Antihistamines were not taken for 8 hours prior to any measurement.

Statistical analysis was done with the unpaired *t*-test and the chi-square test.

Ragweed pollen counts were measured by a Hirst automatic volumetric spore trap located on the roof of McMaster University Medical Centre at a height of 11.7 m.[16]

Results

Patient attrition

Twenty-two patients completed the study. Of the eight dropouts three were in the BDA group and five in the placebo group. In the BDA group one patient withdrew after 3 days because of headache and was excluded from further analyses, one withdrew at week 4 because of troublesome symptoms of rhinitis and one withdrew at week 5 for reasons unrelated to the trial. All five patients who withdrew from the placebo group did so because of troublesome symptoms of rhinitis, three at week 4 and two at week 5.

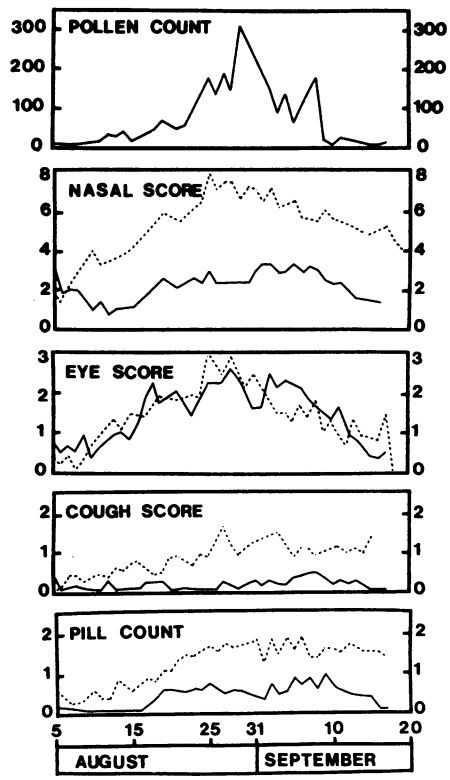

FIG. 1—Mean daily values for ragweed pollen count (grains/m³), nasal symptoms (sum of day and night scores for stuffy, runny nose and sneezing; maximum, 12), eye symptoms and cough (sum of day and night scores; maximum, 6) and antihistamine consumption (no. of tablets per day). Solid curve represents mean values for beclomethasone dipropionate aerosol (BDA) group; dotted curve, those for placebo group.

Diary cards

Results of study of the diary cards are summarized in Fig. 1. Patients receiving BDA had significantly lower mean scores than those receiving placebo ($P < 0.05$) for sneezing and stuffy, runny nose at 36 days. The difference was highly significant ($P < 0.001$) on 7 consecutive days during week 4. The BDA group also had significantly less ($P < 0.05$) cough at 10 days and antihistamine tablet consumption at 17 days. There was no significant difference in eye symptoms ($P > 0.2$) between the two groups.

Self-assessment of symptoms by the patients (Table II) showed that 12 of 14 who received BDA (86%) and 2 of 15 who received placebo (13%) had a moderate to great improvement over previous ragweed pollen seasons (X^2 test; $P < 0.01$).

Objective measurements

Mean baseline values for $NAIR_{0.4}$ were 3.30 ± 2.64 ($n = 13$) for group 1 and 5.37 ± 4.77 ($n = 13$) for group 2 (not significantly different; $P > 0.1$). Values for MINF were 1.45 ± 0.44 ($n = 14$) for group 1 and 1.27 ± 0.37 ($n = 15$) for group 2 (not significantly different; $P > 0.1$). The mean percent changes from baseline values for $NAIR_{0.4}$, MINF and TEC are shown in Fig. 2. Although $NAIR_{0.4}$ increased 113% and TEC 56% in the placebo group, compared with 5 and 6%, respectively, in the BDA group, these differences were not significant ($P > 0.05$).

Side effects

Minor side effects were reported by two patients in each group — headache in one and postaerosol sneezing in three. Weekly examination of the nasal mucosa revealed only changes consistent with allergic rhinitis. There was no evidence of thrush-like plaques in any patient.

Discussion

This study demonstrated that BDA sprayed into the nose in a dose of 400 μg daily effectively controlled the symptoms (particularly sneezing, rhinorrhea and nasal stuffiness) of 86% of a group of patients with allergic rhinitis. Other studies show similar improvement with BDA therapy at the same daily dose (73 to 86%),[8,9,11] be-

Table II—Patient self-assessment of symptoms after trial of aerosol therapy

Symptomatic improvement	Group 1, n = 14 (beclomethasone dipropionate therapy)	Group 2, n = 15 (placebo therapy)
Great	10	1
Moderate	2	1
Slight	1	4
None	1	9

tamethasone-17-valerate at 400 μg daily (77 to 82%),[6,7] hydrocortisone (84%)[1] and dexamethasone (75%).[3]

To be effective when administered intranasally hydrocortisone and dexamethasone must be given in doses that cause systemic effects. Doses of dexamethasone intranasal aerosol of 960 μg[5] and 1600 μg[4] produced partial or complete adrenal suppression in 71 and 65% of patients, respectively. No adrenal suppression was demonstrated in other studies in which BDA, 200 to 1000 μg daily, was given by nasal,[8,10] inhalation[17-19] or oral[19] routes. Similar results were shown with nasal administration of betamethasone valerate, 400 μg daily.[6] In the present study there was no examination for systemic effects of corticosteroids. However, the failure of BDA to suppress the eye symptoms of allergic conjunctivitis is consistent with a lack of systemic effects. This contrasts with the striking relief of eye symptoms following treatment with hydrocortisone snuff.[1]

Cough developed only in the patients giving histories of mild seasonal asthma. The lower cough score in the BDA group, which contained the same number of patients with asthma as the placebo group (Table I), is most likely

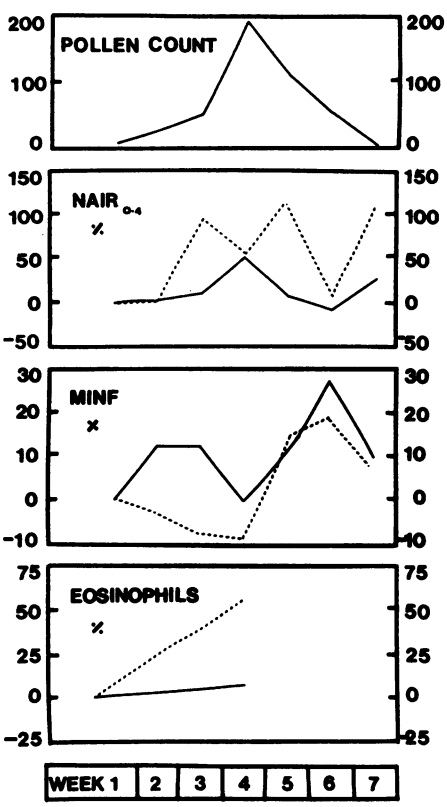

FIG. 2—Mean weekly values for ragweed pollen count (grains/m³) and mean percent change from baseline values for nasal airway inspiratory resistance at a flow of 0.4 l/s ($NAIR_{0.4}$), maximum inspiratory nasal flow (MINF) and total blood eosinophil count (TEC). Solid and dotted curves as in Fig. 1.

explained by small amounts of nasally inhaled BDA reaching the lung. The median diameter of the aerosol particles is said to vary between 1 and 10 μm, which supports this possibility. Particles of less than 4.5 μm enter the lung when inhaled through the nose.[20] Alternatively, the lower incidence of cough could be due to suppression of nasobronchial neurologic reflexes by BDA. Such reflexes elicited by cold air in the nose have been demonstrated in animals[21] and suggested in man.[22] They have, however, not been observed following challenge with nasal allergens.[23]

A beneficial effect of BDA could not be demonstrated from measurements of nasal patency, and subjective measures appeared to be more sensitive indicators of improvement. However, there are several possible explanations why the objective measurements were less sensitive. First, the wide range of values for $NAIR_{0.4}$ and the small number of patients in each group contributed to the lack of statistical significance. Similar reasons were incriminated in a trial comparing betamethasone valerate and sodium cromoglycate[24] in which symptoms clearly demonstrated greater improvement with betamethasone valerate but objective measures of nasal flow failed to support this. Since nasal resistance has been shown to have a normal day-to-day variation of up to 110%,[25] it may be necessary in similar trials to assess the variation in baseline values for $NAIR_{0.4}$ and to perform more measurements during the trials. Second, the complaints of sneezing and rhinorrhea are not necessarily paralleled by changes in measurements of nasal patency. Third, the ragweed pollen count was 40% lower in 1975 than in 1974 and this could account in part for the failure of $NAIR_{0.4}$ to increase more in the placebo group. Finally, the greater use of antihistamine tablets by the placebo group may have reduced nasal obstruction.

Aerosol-induced sneezing was the main side effect. This was as common in placebo as in BDA patients and has been observed in other short-term studies.[8,10] Nasal administration of BDA or betamethasone valerate appears not to give rise to the lesions of local candidiasis,[7,24,26] which occur frequently in the mouth following bronchial inhalation of BDA.[27] There are no data on the efficacy or complications of long-term nasal administration of BDA.

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