Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen–induced rhinoconjunctivitis

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The clinical efficacy and side effect of (1) beclomethasone dipropionate aqueous nasal spray, 400 μg daily, (2) astemizole, 10 mg daily, and (3) beclomethasone, 400 μg, plus astemizole, 10 mg daily, were compared in a double-blind, randomized, parallel-group trial. Ninety adults were matched into groups of three according to sensitivity to ragweed pollen. One of each of the three subjects was assigned to nasal spray alone, one was assigned to astemizole alone, and one subject was assigned to both medications. Medications were started 1 week before and continued daily until 1 week after the ragweed-pollen season (6 weeks). If rhinoconjunctivitis was inadequately controlled with the trial medications, pressurized steroid nasal spray and/or antihistamine-decongestant eye drops were used in the minimum dose that would ensure relief. Nose and eye symptoms and concomitant medication use were recorded daily in a diary. Sneezing, nasal obstruction, and rhinorrhea were significantly better, and less additional nasal spray was used in subjects taking beclomethasone alone than in subjects taking astemizole alone. Beclomethasone plus astemizole provided no better control of rhinitis than beclomethasone alone. Eye symptoms and eye drop use tended to be less in subjects taking astemizole alone than in subjects taking beclomethasone alone, but the best control of eye symptoms was recorded in the subjects taking both trial medications. Side effects were mild or transient. (J ALLERGY CLIN IMMUNOL 1989;83:627-33.)

Antihistamine tablets and intranasal steroid spray have been used successfully to treat rhinoconjunctivitis induced by seasonal pollens.[1, 2] Most previous comparisons have suggested that nasal symptoms may be controlled better by steroid nasal sprays,[3-6] although the conclusions are not unanimous,[7] and that conjunctivitis is treated more effectively by antihistamines.[4-7] These results and the different pharmacologic properties of the two types of treatment suggest that a combination of nasal steroid and antihistamine may be the most effective approach of overall treatment.

In the last few years, effective, nonsedative antihistamines have become popular for the treatment of seasonal allergic rhinoconjunctivitis. More recently, aqueous steroid nasal sprays, with efficacy comparable to the original Freon-propelled delivery system, but with less nasal bleeding and drying, have been introduced.[8] The pharmacologic profile of nasal steroids suggests that the most effective approach to treatment is regular prophylactic use[9]; therefore, an aqueous delivery system should be effective in achieving this with a reduced risk of side effects. In this study, we have compared the clinical efficacy of beclomethasone dipropionate aqueous nasal spray (Aq. Beconase; Glaxo Canada, Inc., Toronto, Ontario, Canada), taken before and continued daily throughout the ragweed-pollen season, with that of astemizole (Hismanal; Janssen Pharmaceutica, Inc., Mississauga, Ontario, Canada), a nonsedative antihistamine whose pharmacologic profile also recommends prophylactic and continuous treatment for allergic rhinoconjunctivitis.[10] We have also examined whether taking the two medications together produces better symptom control than taking either medication individually.

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TABLE I. Subject characteristics

	Astemizole alone	Beclomethasone alone	Beclomethasone plus astemizole
No.	30	30	30
Sex (M/F)	16/14	15/15	15/15
Age (mean, SD)	39.8 (13.5)	41.3 (11.8)	42.2 (13.8)
Initial ragweed skin sensitivity (mean wheal diameter)			
<2.5 mm	3	3	3
2.5-3.0 mm	4	4	4
3.0-3.5 mm	8	6	7
3.5-4.0 mm	5	7	6
4.0-4.5 mm	6	5	6
>4.5 mm	4	5	4
Severity of ragweed rhinoconjunctivitis the previous year			
1*	5	5	6
2†	5	5	7
3‡	16	12	11
4§	1	6	5
5‖	3	2	1
History of asthma	5	7	6
Sensitivity to fungal spores	5	4	5
Sensitivity to grass pollen	18	15	20

*Symptoms were well controlled with antihistamine or nasal spray.
†Symptoms were well controlled with antihistamine plus nasal spray or mild symptoms when subject was treated with antihistamine or nasal spray.
‡Mild symptoms when subject was treated with antihistamine plus nasal spray or moderate symptoms when subject treated with antihistamine or nasal spray.
§Moderate symptoms when subject was treated with antihistamine plus nasal spray or severe symptoms when subject was treated with antihistamine or nasal spray.
‖Severe symptoms when subject was treated with antihistamine plus nasal spray.

MATERIAL AND METHODS

Subjects

Ninety ragweed pollen–sensitive adults, aged 18 to 70 years, who were either attending the Firestone Regional Chest and Allergy Clinic or who responded to a newspaper article, participated in the study. All subjects gave a history of rhinoconjunctivitis that required treatment during the previous two ragweed-pollen seasons, and all subjects had a positive response to skin prick test with ragweed-pollen extract. None of the subjects had perennial rhinitis, and none were more than mildly sensitive to the fungal spores that are in the air at the same time as ragweed pollen. None of the subjects had serious illness other than seasonal rhinitis or asthma. Pregnant and nursing mothers were excluded, and women of childbearing potential were advised to use an effective method of birth control throughout the study and for 2 months thereafter. None of the subjects had taken astemizole, steroid nasal spray, or oral steroid within 6 weeks of enrollment. All subjects signed an informed consent, which, with the study protocol, had been approved by the St. Joseph's Hospital Research Committee.

Study design

The study was designed as a double-blind, randomized, parallel-group comparison of (1) beclomethasone dipropionate aqueous nasal spray, 50 μg per nostril four times daily, (2) astemizole, 10 mg once daily, and (3) beclomethasone dipropionate aqueous nasal spray, 50 μg per nostril four times daily plus astemizole, 10 mg daily. A double-dummy technique was used to achieve blinding.

Three weeks before the anticipated start of the ragweed-pollen season, subjects had duplicate skin prick tests with tenfold serial dilutions of ragweed-pollen extract (25 to 25,000 Noon units, Bencard Allergy Service, Weston, Ontario), with single dilutions of *Alternaria tenuis* and *Cladosporium (Hormodendrum)* (Hollister Steir Laboratories of Canada, Rexdale, Ontario), and mixed grass-pollen extract (Bencard Allergy Service). An allergy history was obtained by questionnaire. Severity of rhinoconjunctivitis during the previous ragweed season was estimated from symptoms and medication requirements (Table I). Subjects were matched into groups of three according to skin sensitivity to the ragweed extract, the severity of ragweed

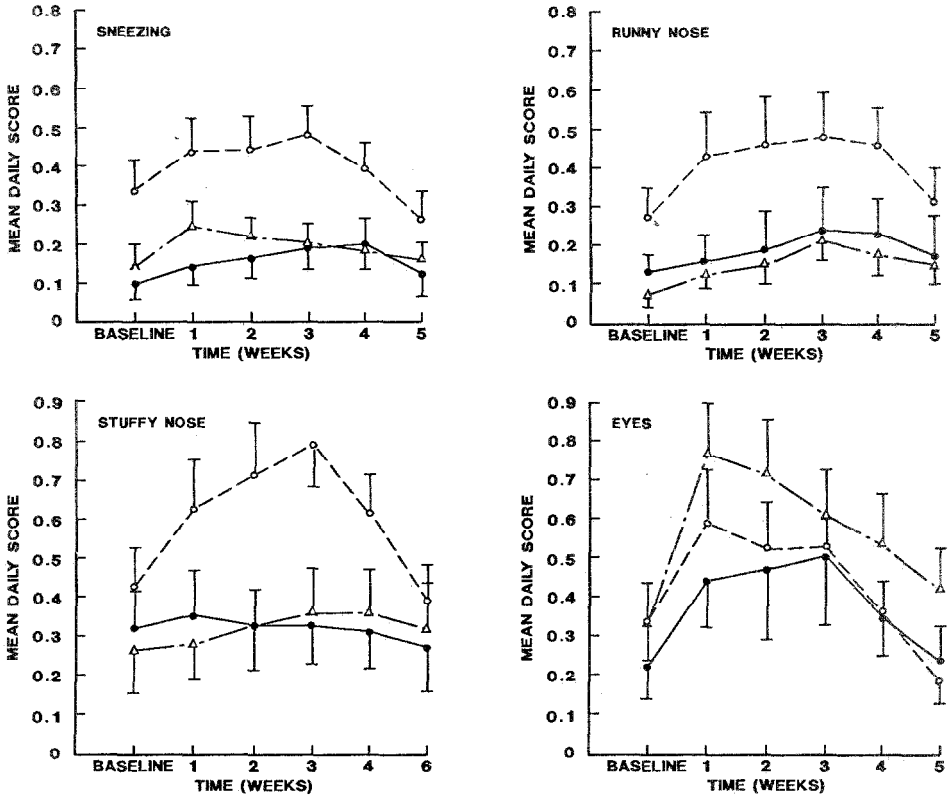

FIG. 1. Mean daily nose and eye symptom scores (SEM) before and throughout the ragweed-pollen season; astemizole alone (○); aqueous beclomethasone nasal spray alone (△); astemizole plus aqueous beclomethasone nasal spray (●).

pollen–induced rhinoconjunctivitis, sensitivity to *Alternaria* and *Cladosporium (Hormodendrum)*, history of asthma, grass-pollen sensitivity, and gender. One of each of the three subjects was assigned randomly to beclomethasone alone, one was assigned to astemizole alone, and one subject was assigned to the combination of beclomethasone and astemizole.

Subjects started taking the trial medication 1 week before ragweed pollen was expected in the air (Monday, August 10) and continued daily until 1 week after the pollen season (Monday, September 21), that is, for a total of 6 weeks. Subjects were instructed to take the tablet in the morning either 1 hour before or 2 hours after food and to use the nasal spray four times per day. If they had difficulty remembering to use the spray at regular intervals, they were allowed to take two doses in the morning and two in the evening. If, during the season, symptoms were not adequately controlled by the trial medications, subjects were instructed to take additional medications in the minimum dose that would keep them well controlled. For nasal symptoms they used Freon-propelled beclomethasone dipropionate nasal spray, one puff (50 μg) into each nostril, when it was needed, up to four times a day. Even for subjects taking the trial beclomethasone, this additional dose provided a total daily amount that was lower than the recommended maximum dose. For eye symptoms, subjects used naphazoline HCl and anatazoline ophthalmic drops, one drop into each eye, when it was needed, up to four times per day. If this treatment was insufficient, sodium cromoglycate eye drops, up to four times per day, were added. Subjects were instructed not to use other medication for rhinoconjunctivitis. Nasal spray and eye drops were selected over an antihistamine tablet as the concomitant medication so that nose and eye symptoms could be evaluated separately. Subjects with asthma used salbutamol aerosol, 200 μg, when it was needed, up to four times per day and those with more severe asthma took beclomethasone dipropionate, 100 μg, up to four times per day. No oral steroids were used. The provision and use of standardized concomitant medications allowed the efficacy of the trial medications to be estimated from the amount of additional medication used, prevented subjects dropping out of the study because of inadequate symptom control, and reduced the risk of subjects using unauthorized hay fever medications.

Subjects made entries in a diary each morning and each evening throughout the study.[11] They recorded the severity (0, absent; 1, mild; 2, moderate; and 3, severe) and duration (0, absent; 1, a few short episodes; 2, many episodes; and 3, continuous) of sneezing, stuffy nose, runny nose, eye symptoms, and asthma. At the end of each day, they recorded the amount of concomitant medication needed in the previous 24 hours.

Subjects attended the clinic after 1, 3, and 6 weeks of treatment. At each visit, symptoms were reviewed to ensure

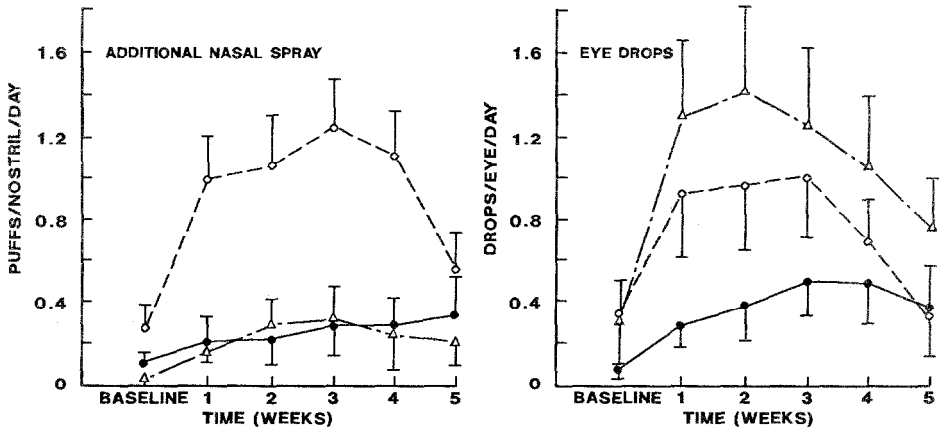

FIG. 2. Mean daily additional medication use (SEM) before and throughout the ragweed-pollen season; astemizole alone (○); aqueous beclomethasone nasal spray alone (△); astemizole plus aqueous beclomethasone nasal spray (●).

TABLE II. Efficacy results (mean daily score)

	Astemizole alone	Beclomethasone alone	Beclomethasone plus astemizole
Overall (mean of 6 weeks)			
Sneezing	0.395	0.193	0.155
Stuffy nose	0.594	0.319	0.322
Runny nose	0.406	0.152	0.192
Eye symptoms	0.424	0.563	0.355
Asthma	0.030	0.015	0.048
Beclomethasone use	0.871	0.206	0.241
Eye drop use	0.707	1.016	0.354
Asthama aerosol use	0.195	0.049	0.113

that they were adequately controlled and diaries were examined for accuracy and completeness. Subjects reported all nonrhinoconjunctivitis symptoms that they had experienced since the previous visit, irrespective of whether they perceived them as trial-medication related. The nasal spray bottles were weighed and tablets were counted for compliance. At all visits except the last, each subject gave a demonstration of the technique of nasal spray application to confirm correct use.

Regular daily ragweed-pollen counts were not available throughout this study. However, intermittent counts were made with a Hirst volumetric spore trap (Burkard Manufacturing Co., Ltd., Richmansworth, Hertfordshire, England). These counts suggested that the duration and severity of the local ragweed-pollen season of the year 1987 was very similar to duration and severity of each of the previous 10 years when regular daily counts were made.[11, 12]

Analysis

Mean daily symptoms and medication scores were calculated for each subject for each of the 6 weeks of the study. These data were analyzed for treatment effect with a repeated measures analysis of variance. Differences between the three treatments were examined with Student's-Newman-Keuls method for multiple comparisons.[13] These data demonstrated instability of variance across the time periods, and therefore, a square root transformation was used to improve their statistical properties. Percent compliance was estimated from the observed and expected bottle-weight loss and tablet use. Differences were considered significant at $p < 0.05$ (two-tailed).

RESULTS

Ninety subjects were enrolled, and eighty-nine completed the study. One subject withdrew because he could not remember to take the trial medication. Demographic and allergy characteristics were well balanced across the three treatment groups (Table I).

In all three treatment groups, nose and eye symptoms were well controlled, as indicated by the highest mean weekly score for any symptom <0.8 (maximum, 3.0) (Figs. 1 and 2). Nevertheless, aqueous beclomethasone was more effective in controlling

TABLE III. Statistical comparison of trial medications (with Student's-Newman-Keuls method for multiple comparisons)

	Astemizole vs beclomethasone	Astemizole vs astemizole plus beclomethasone	Beclomethasone vs astemizole plus beclomethasone
Symptoms			
Sneezing	$p < 0.05$*	$p < 0.05$†	NS
Stuffy nose	$p < 0.05$*	$p < 0.05$†	NS
Runny nose	$p < 0.05$*	$p < 0.05$†	NS
Eye symptoms	NS	NS	NS
Asthma	NS	NS	NS
Concomitant medication use			
Nasal spray	$p < 0.05$*	$p < 0.05$†	NS
Eye drops	NS	NS	NS
Asthma aerosols	NS	NS	NS

NS, Not significant.
*Beclomethasone alone was better than astemizole alone.
†Astemizole plus beclomethasone was better than astemizole alone.

TABLE IV. Compliance (% observed/expected)

	Astemizole alone	Beclomethasone alone	Beclomethasone plus astemizole
Pills (mean, SD)	99.3 (2.8)	100.2 (4.1)	99.2 (4.7)
Nasal spray (mean, SD)	91.8 (14.0)	94.1 (7.6)	91.3 (12.6)

sneezing, stuffy nose, and runny nose than astemizole ($p < 0.05$), as demonstrated both by lower symptom scores and less need for additional nasal spray (Figs. 1 and 2; Tables II and III). For nasal symptoms, the subjects who took both aqueous beclomethasone and astemizole were better protected than subjects taking astemizole alone but no different from subjects taking nasal spray alone. For each of the 6 weeks of the study, sneezing, stuffy nose, and runny nose demonstrated similar treatment differences, suggesting the treatments had similar time courses on each of these symptoms (Fig. 1). As might have been expected, subjects taking astemizole alone had lower eye symptom scores than subjects taking beclomethasone alone, but the lowest eye scores and the least need for additional eye drops was demonstrated by the subjects taking both astemizole and beclomethasone. However, these differences for eye symptoms and eye drops did not reach statistical significance, possibly as a result of poor statistical power, since not all subjects gave a history of allergic conjunctivitis. Asthma symptoms and medication requirements were similar in the three groups.

Compliance with taking the trial medications was very good (Table IV) with no differences between the three treatment groups. The most common side effect was drowsiness, which was reported on one or more occasions by nine subjects taking astemizole alone, four subjects taking beclomethasone alone, and four subjects taking the combined medications (Table V). In most cases the drowsiness was mild and transient. However, it was troublesome in one subject taking astemizole alone, but he elected to continue taking the medication because his rhinoconjunctivitis was well controlled. The subjects who reported drowsiness experienced a wide range of rhinoconjunctivitis severity; therefore, it was not possible to evaluate whether the drowsiness was caused by persistent symptoms, the trial medications, the direct effect of the ragweed,[14] or factors unrelated to the study. Although some subjects reported hunger during the study, none experienced inappropriate weight gain.

DISCUSSION

The results of this study have demonstrated that seasonal allergic rhinitis is more effectively controlled by the regular use of beclomethasone dipropionate aqueous nasal spray (400 μg daily) than by the regular use of astemizole (10 mg daily). Results have also demonstrated that there is no further improvement in

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