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The effect of intranasal azelastine and beclomethasone on the symptoms and signs of nasal allergy in patients with perennial allergic rhinitis*

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SUMMARY

A double-blind, randomized, parallel-group, placebo-controlled study involving 130 patients was conducted at 9 centres in the U.K. to assess the effect of 6 weeks of treatment with azelastine nasal spray (azelastine) and beclomethasone dipropionate nasal spray (BDP) on the symptoms of perennial rhinitis. Efficacy was assessed by patients recording daily the severity of the symptoms of rhinitis on 10-cm visual analogue scales. Analysis of this diary data showed significant reductions in sneezing, blocked nose, running nose, and itching nose during azelastine treatment. Patients on BDP recorded a consistent reduction in rhinitis symptoms, but these reductions were significant only for sneezing on treatment day 7. When rhinitis symptoms were assessed by clinical investigators on a 4-point scale, the scores obtained following treatment with the 2 study medications showed little change from baseline or "active" treatment scores. There was no evidence of a consistent change in nasal airway resistance, measured using anterior rhinomanometry, following treatment with either BDP or azelastine. Azelastine nasal spray and BDP nasal spray were well tolerated by the patients and the relative incidence of adverse events was similar in the azelastine and placebo/azelastine treatment groups, except that taste perversion occurred more frequently during azelastine treatment than during placebo/azelastine treatment. There was no evidence of an increased incidence of somnolence or fatigue in patients who received azelastine nasal spray. Overall, the results of this study indicate that azelastine administered twice daily as an intranasal spray is a safe and efficacious treatment for the symptoms of rhinitis in patients suffering from mild to moderate perennial rhinitis.

Key words: perennial rhinitis, nasal sprays, beclomethasone, azelastine

INTRODUCTION

Azelastine is a phthalazinone compound with a selective and potent affinity for histamine H_1-receptors *in vitro* (Little et al., 1988). The drug has been shown to inhibit histamine release from mast cells *in vitro* following antigen and non-antigen stimuli and is at least 5,000 times more potent in this action than ketotifen, sodium cromoglycate, theophylline, and astemizole (Chand et al., 1983, 1985; Fields et al., 1985). Furthermore, azelastine inhibits the synthesis and release of other mediators of hypersensitivity including leukotrienes and Platelet-Activating Factor (Achterrath-Tuckermann et al., 1988), but has negligible cholinergic and $ß_2$-adrenergic action and no histamine H_2 effect (Achterrath-Tuckermann et al., 1988).

Azelastine has been shown to antagonize histamine- and leukotriene-induced bronchospasms (Albazza and Patel, 1988; Chand et al., 1987), to reduce airway response to inhaled antigen or distilled water and exercise challenge

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(Ollier et al., 1986; Carino et al., 1988; Magnussen et al., 1988), and to inhibit Platelet Activating Factor-induced rat paw oedema (Achterrath-Tuckermann et al., 1988).

Azelastine in oral doses of up to 2 mg/day has been shown to relieve symptoms in patients with perennial (Meltzer et al., 1988) and seasonal rhinitis (Weiler et al., 1988). Altered taste perception has been reported following the use of the oral formulation, but overall the drug is well tolerated (unpublished data on file, ASTA Pharma A.G.).

Perennial rhinitis is commonly associated with nasal symptoms. The delivery of azelastine by nasal spray to the nasal mucosa would be expected to produce a high local concentration and therefore prove to be an effective method of alleviating many of the symptoms of perennial rhinitis. A nasal formulation of azelastine is now available and so the following clinical study was performed to determine the efficacy of nasally administered azelastine and to study the side effect profile of the nasal formulation.

SUBJECTS AND METHODS

Subjects

One hundred and thirty male and female outpatients (17 to 63 years; mean age 32.4±10.1 years; 60 males and 70 females) were entered into the study from 9 centres in the U.K. during a 5-month period from December to the beginning of May. To enter into the study patients had to sign a written informed consent form indicating their willingness to participate in the study. Ethical approval for the study was obtained from the North-West Ethical Committee and from the ethical committees for each study centre. All patients had a history of mild or moderate perennial rhinitis and were allergic to house dust mite and/or cat or dog dander as demonstrated either by a positive skin prick test or by RAST testing.

To participate in the study, patients had to forego treatment with systemic or intranasal antihistamines, intranasal decongestants, intranasal corticosteroids, intranasal sodium cromoglycate, sodium nedocromil or ketotifen fumarate, from entry into the placebo run-in phase of the study until completion of the study. Treatment with astemizole was withdrawn 6 weeks prior to the start of the "active" treatment phase of the study.

Methods

The study was of a randomized, double-blind, parallel group, placebo-controlled design comparing azelastine.HCl nasal spray (azelastine) with placebo/azelastine, and BDP with placebo/BDP. Azelastine nasal sprays, placebo/azelastine nasal sprays and placebo solution were provided by ASTA Medica A.G., Germany. BDP was obtained as Beconase inhalers from a local pharmacy.

Double-blinding was achieved by repackaging or relabelling the study materials (Pharmaserve Ltd., U.K.). It was not possible to package placebo/BDP and placebo/azelastine in the same form. Azelastine and placebo/azelastine were administered using nasal sprays fitted with pumps rated to deliver 0.14 ml (i.e., 0.14 mg of azelastine) per activation. BDP and placebo/BDP were administered as nasal sprays with pumps rated to deliver 0.1 ml (i.e., 0.05 mg of BDP per activation).

On entry into the study subjects were treated for 2–4 weeks with either placebo/azelastine (one spray per nostril b.i.d.) or placebo/BDP (two sprays per nostril b.i.d.).

Eligible subjects on placebo/azelastine during this run-in subsequently underwent 6 weeks of "active" treatment with either azelastine or azelastine/placebo (1 spray per nostril b.i.d.). Eligible subjects who received placebo/BDP during the run-in were subsequently treated with either BDP or placebo/BDP (2 sprays per nostril b.i.d.) during the "active" treatment phase. The treatment administered to each patient during the study was defined prior to the study by the randomization number allocated to each patient at entry to the study.

On each day of the study, patients recorded adverse events, use of non-study medication, and severity of the symptoms of rhinitis (sneezing, running nose, nasal itch and nasal blockage) in diaries. The severity of rhinitis symptoms were assessed by patients using 10-cm visual analogue scales.

Clinical assessment of rhinitis symptoms and anterior rhinomanometry were performed by the clinical investigators immediately prior to entry into the study, at the end of the placebo run-in, and 2 and 6 weeks after starting "active" treatment.

Clinical assessment of the symptoms of rhinitis (sneezing, nasal blockage, nasal itch, and rhinorrhoea) was performed by the clinical investigators using the following 4-point rating scale: (0) absent; (1) mild (occurs infrequently and not troublesome); (2) moderate (occurs frequently but not incapacitating); and (3) severe (frequent and distressing).

Anterior rhinomanometry measurements were made using an NR8 rhinomanometer (Mercury Electronics, U.K.). At each assessment the nasal airway resistance (NAR) for the left and right nostril were recorded twice over 4 separate breathing cycles. For each set of NAR recording total nasal airway resistance (total NAR) was calculated using the following formula:

$$\frac{1}{\text{total NAR}} = \frac{1}{\text{left NAR}} \quad \frac{1}{\text{right NAR}}$$

The total NAR calculated from the first set of recordings at each assessment was designated total NAR1 and the total NAR calculated from the second set of recording was designated total NAR2.

Laboratory variables (haematology and serum biochemistry) were assessed at entry into the study and at the end of treatment with the study medication.

Statistical analysis

For the demographic data, all statistical comparisons were made between all 4 treatment groups. The ratio of male to

female patients in each treatment group was analysed using the Chi-squared test whilst the ages of patients in each treatment group were compared using t-tests.

For the efficacy and safety data, all statistical comparisons were made between azelastine and placebo/azelastine-treated patients, and between BDP and placebo/BDP-treated patients. A direct comparison of efficacy and safety data from azelastine- and BDP-treated patients was not possible because of differences in appearance and method of usage of the BDP and azelastine inhalers.

Since the placebo run-in varied in duration, the diary scores for 2 days prior to the start of "active" treatment (days -3 and -2) were averaged to give a baseline pre-treatment score for each symptom for each patient. Adjusted "active" treatment scores were then calculated for each patient by subtracting the baseline scores from the "active" treatment scores obtained on days 3, 7, 14, 21, 28, 35, and 42.

At each time point, the means of the adjusted scores for azelastine- and BDP-treated patients were compared to those obtained from their respective controls using analysis of variance.

Clinical assessment scores obtained after 2 and 6 weeks of "active" treatment were adjusted to a -3 to +3 scale by deduction of the appropriate baseline clinical assessment score obtained at the end of the placebo run-in. Analysis was performed on combined negative (-3 and -2) adjusted scores and combined positive (+3 and +2) scores using the Chi-squared test.

For analysis of the anterior rhinomanometry data, the total NAR1 and total NAR2 for assessments made after 2 and 6 weeks of "active" treatment were expressed as percentages of the total NAR1 and total NAR2 values obtained immediately prior to the start of "active" treatment. Percentage changes in total NAR1 and total NAR2 were compared between treatment groups using the non-parametric Mann-Whitney (Wilcoxon) test.

Adverse events reported during the study were coded using a modified version of the World Health Organisation "preferred term" coding system. Statistical analysis of the adverse events data was not feasible because of the low incidence of reported adverse events.

RESULTS

Of the 130 patients entered into the study, 45 were treated with azelastine, 22 were treated with placebo/azelastine, 45 were treated with BDP, and 18 were treated with placebo/BDP. There was no evidence of a bias in the ratio of male to female patients in any treatment group. Similarly, there were no significant differences in mean ages or age ranges for the 4 treatment groups (Table 1).

There was no statistically significant difference in baseline diary VAS scores for the 4 treatment groups. Mean adjusted diary VAS scores for sneezing, blocked nose, running nose and itching nose on days 3, 7, 14, 21, 28, 35 and 42 of "active" treatment are shown in Figures 1-4, respectively. Azelastine treatment was associated with a significant reduction in

Table 1. Age (in years) and sex at entry.

	TREATMENT GROUP A	PA	B	PB	all
male n	17	12	21	10	60
mean	31.3	30.8	33.9	32.3	32.3
sd	6.7	7.4	9.1	10.4	8.3
female n	28	10	24	8	70
mean	31.9	35.6	31.1	35.1	32.5
sd	10.1	14.1	10.8	15.3	11.5
all n	45	22	45	18	130
mean	31.7	33.0	32.4	33.6	32.4
sd	8.9	11.0	10.0	12.5	10.1
age range					
min	17.0	21.0	19.0	20.0	17.0
max	59.0	61.0	63.0	58.0	63.0

(A: azelastine; PA: placebo/azelastine; B: beclomethasone; PB: placebo/beclomethasone)

sneezing ($p<0.01$; $p<0.05$; $p<0.05$ on treatment days 3, 7 and 14, respectively), blocked nose ($p=0.05$, on treatment days 3 and 14), running nose ($p<0.01$, $p=0.05$; $p<0.01$; $p=0.05$ on treatment days 3, 7, 14 and 35, respectively) and itching nose ($p=0.01$ on day 42).

Patients on BDP showed consistent reductions in sneezing, blocked nose, running nose and itching nose but, with one exception (sneezing on treatment day 7; $p<0.05$), none of these reductions achieved statistical significance.

Following analysis of the data obtained from clinical assessment of rhinitis symptoms by the clinical investigators after 2 and 6 weeks of treatment, there was no evidence of a significant effect of either BDP or azelastine on any of the symptoms assessed.

Comparison of changes in rhinomanometrical measurements of nasal airways resistances after 2 and 6 weeks of treatment showed only one significant difference, patients on BDP treatment showed a significant difference ($p<0.05$) in total NAR2 following 2 weeks of BDP treatment compared to placebo/BDP-treated patients. However, NAR2 values for these two groups were higher than baseline values after 2 weeks of treatment and, overall, the BDP-treated group showed an increase in NAR2, that is a worsening of the clinical significance.

Tolerance of all 4 study treatments was good with few patients permanently discontinuing study medication before the end of the specified treatment period (Table 2).

A total of 282 adverse events were reported during the 2- to 4-week placebo run-in and 420 adverse events were reported during the 6 week "active" treatment phase. Table 3 contains a summary of all adverse events reported by more than three patients in any of the treatment groups during either the placebo run-in or the "active" treatment phase. Except for taste perversion, which occurred at a relatively high incidence during azelastine treatment, there was no evidence of a treatment relationship in the occurrence of adverse events.

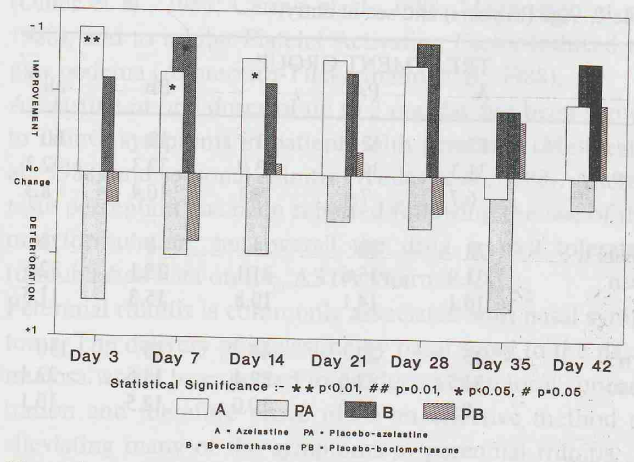

Figure 1. VAS sneezing scores from diary data.

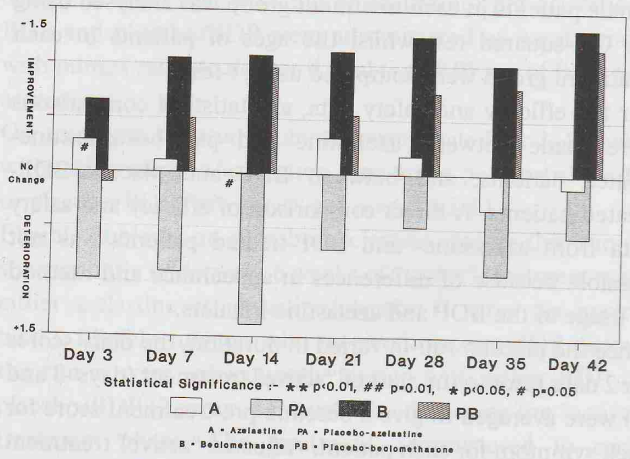

Figure 2. VAS blocked nose scores from diary data.

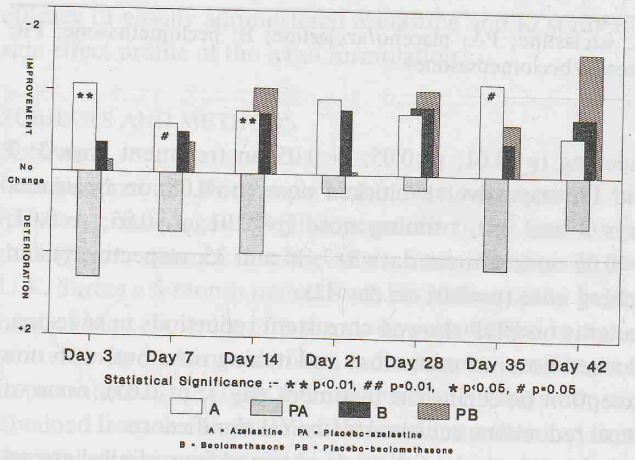

Figure 3. VAS running nose scores from diary data.

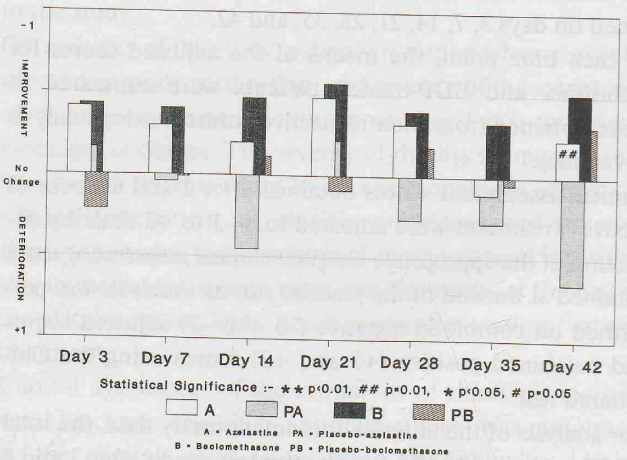

Figure 4. VAS itching nose scores from diary data.

Table 2. Completion status.

status	TREATMENT GROUP A	PA	B	PB	total
completed	33	18	38	13	102
did not complete:					
withdrew consent	1	0	1	0	2
did not attend	5	2	2	3	12
adverse event(s)	3	1	2	1	7
lack of efficacy	1	1	2	0	4
other reason(s)	2	0	0	1	3
total	45	22	45	18	130

(A: azelastine; PA: placebo/azelastine; B: beclomethasone; PB: placebo/beclomethasone)

Somnolence and fatigue were reported by azelastine-treated patients once during the placebo treatment and once during "active" therapy.

The incidence of adverse events judged by the investigator to be "probably" or "highly probably" related to treatment is shown in Table 4. The most common adverse drug reactions from this group were taste perversion and intolerance to nasal spray, both of which occurred most often in the azelastine-treated group. Only one serious adverse event, exacerbation of hand pain and parasthesiae (Carpel Tunnel Syndrome), occurred during azelastine treatment and this event was judged by the clinical investigator to be unrelated to the study treatment.

Following treatment with the study medications there was no evidence of a relationship between incidence of out-of-range haematology and biochemistry results and any of the four treatments administered to the study subjects.

DISCUSSION

The results of this study indicate that intranasally administered azelastine had a beneficial effect compared to placebo on the symptoms of sneezing, blocked nose, running nose and itching nose when assessed by patients using visual analogue scales.

There was no evidence of a significant improvement in rhinitis symptoms in patients treated with BDP compared to those treated with placebo/BDP. However, the placebo/BDP-treated patients reported a consistent improvement in rhinitis symptoms which may have masked any beneficial effects of BDP.

The improvement shown in placebo/BDP patients, compared with the deterioration shown in patients receiving placebo/azelastine may have resulted from the different

Table 3. Percentage of patients reporting the most commonly occurring adverse events (URTI: upper respiratory tract infections).

adverse events (reported by >3 patients)	percentage of patients reporting event for each treatment group				
preferred term	A	AP	B	BP	all groups
headache					
"wash-out"	44	18	40	22	35
"active" treatment	33	32	33	17	31
vomiting					
"wash-out"	0	0	0	0	0
"active' treatment	9	0	2	0	4
taste perversion					
"wash-out"	0	5	0	6	2
"active" treatment	22	0	4	0	9
nausea					
"wash-out"	2	0	2	0	2
"active" treatment	9	0	0	0	3
coughing					
"wash-out"	0	9	16	6	8
"active" treatment	7	5	4	17	7
epistaxis					
"wash-out"	13	5	11	11	11
"active" treatment	11	14	16	17	14
URTI					
"wash-out"	11	5	18	22	14
"active" treatment	20	18	18	17	18
back pain					
"wash-out"	2	0	2	0	2
"active" treatment	9	5	2	0	5
sore throat					
"wash-out"	18	18	24	6	18
"active" treatment	20	0	18	11	15
intolerance to nasal spray					
"wash-out"	7	0	2	0	3
"active" treatment	16	0	7	0	8

Table 4. Percentage of patients reporting adverse drug reactions (events regarded as "probably" or "highly probably" related to treatment).

	percentage of patients reporting events for each treatment group				
preferred term	A	AP	B	BP	all groups
headache					
"wash-out"	0	0	0	0	0
"active" treatment	2	0	0	0	1
sore throat					
"wash-out"	2	0	0	0	1
"active" treatment	2	0	0	0	1
nose pain					
"wash-out"	0	0	0	0	0
"active" treatment	2	5	2	6	3
taste perversion					
"wash-out"	0	5	0	0	1
"active" treatment	18	0	4	0	8
nausea					
"wash-out"	0	0	0	0	0
"active" treatment	2	0	0	0	1
intolerance to nasal spray					
"wash-out"	7	0	2	0	3
"active" treatment	16	0	7	0	8
epistaxis					
"wash-out"	2	0	0	0	1
"active" treatment	4	5	9	11	7
halitosis					
"wash-out"	0	0	0	0	0
"active" treatment	2	0	0	0	1
asthma					
"wash-out"	0	0	0	0	0
"active" treatment	0	5	0	0	1

appearance of the nasal sprays in these two treatment groups, with a strong placebo response in those patients who recognized the nasal spray. Additionally, the greater volume of spray given to those patients receiving BDP (0.6 ml/dosage) and its placebo treatment may have resulted in an increased wetting action on the nasal mucosa.

In contrast to the findings from the patients' diaries, assessment by the clinicians of the symptoms of rhinitis did not show a consistent effect on perennial rhinitis of either azelastine or BDP compared to their respective placebos. Since the scores obtained from clinical assessments showed little change from baseline values, it is possible that the assessment system was too insensitive to detect changes in symptoms, or that the symptoms of rhinitis were too subjective to permit accurate assessment by an observer.

Anterior rhinomanometry was used in order to obtain an objective measurement of the degree of nasal obstruction. Unfortunately, the results obtained were too variable to define any treatment effect.

The incidence of reported adverse events was high during both the placebo run-in and during the "active" treatment phase. This high rate is likely to reflect the frequent (daily) opportunity for recording adverse events offered by the patient's diaries.

The relatively high incidence of taste perversion reported during azelastine treatment is consistent with previous studies on this drug. Somnolence or fatigue was reported on one occasion only during azelastine treatment, the same incidence as reports from patients on placebo/azelastine.

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