Eur Arch Otorhinolaryngol (1997) 254:236–241


ORIGINAL PAPER

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# A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis

Received: 24 August 1995 / Accepted: 24 September 1996

**Abstract** This study compared a new intranasal anti-allergic drug, azelastine (0.56 mg bid) with intranasal beclomethasone (0.2 mg bid) and placebo in the treatment of symptoms associated with seasonal rhinitis. After administering placebo for 3–5 days as a "run-in" period, eligible patients were randomized to treatment for 2 weeks: 83 patients received azelastine, 83 beclomethasone and 77 placebo. Each of six symptoms was assessed daily using a four-point scale. Total symptom scores showed that azelastine-treated patients experienced a more rapid onset of overall symptom relief than beclomethasone-treated patients. This was significant on day 1 ($P < 0.003$) and continued until day 5. By the end of the 2-week study period, the beclomethasone-treated group showed greater improvement than both the azelastine and placebo groups ($P = 0.002$ and $P = 0.0001$, respectively). In contrast, visual analogue scales at this time showed no significant differences between the azelastine and beclomethasone treatment groups, with both groups demonstrating significant reductions in total symptom scores compared to placebo ($P = 0.0004$ and $P = 0.0001$, respectively). Differing sensitivities were found in the four-point scales reported by the patients and the investigators and the patients' visual analogue scales in the measurement of symptom severity. However, all three techniques confirmed that both azelastine nasal spray and beclomethasone nasal spray were effective treatments for seasonal rhinitis. While a greater improvement in overall symptoms was found for the beclamethasone-treated patients compared to azelastine-treated patients, diary card data confirmed the more immediate onset of symptom relief provided by azelastine. No serious adverse events were found in the present study and included no complaints of drowsiness.

**Key words** Seasonal allergic rhinitis · Intranasal medications · Azelastine · Beclomethasone · Clinical studies

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## Introduction

Azelastine, a phthalazinone derivative, is a potent anti-allergic compound. Studies in animals and in vitro have shown that it is a selective histamine H1 receptor antagonist which also inhibits histamine release from mast cells. The effects of chemical mediators of hypersensitivity, such as leukotrienes and platelet activating factor, are also antagonized by azelastine [1]. The oral form of azelastine has proved an effective and well-tolerated treatment for patients with both perennial and seasonal allergic rhinitis [8, 9]. In controlled clinical studies azelastine as a nasal spray at a dose of 0.56 mg/day has been shown to be as effective as oral terfenadine 120 mg/day [5] and intranasal budesonide 0.4 mg/day [4]. The azelastine nasal spray was well tolerated in these studies with no sedative effect. High local levels and low circulating levels of azelastine also confirmed that systemic effects did not occur after intranasal administration of azelastine nasal spray [3].

The present investigation was performed as a double-blind placebo-controlled study in order to compare the efficacy and tolerability of the nasal formulation of azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. In so doing, a group of 291 patients were treated by general practitioners in the United Kingdom.

## Patients and methods

The study was a randomized, double-blind, double-dummy parallel group comparing azelastine hydrochloride nasal spray (azelastine) with beclomethasone dipropionate (beclomethasone) and placebo. During the 1991 hay fever season (April to July), 31 general practitioners in the United Kingdom each undertook to recruit 9 patients between 18 and 65 years of age into the study . Each patient had to have at least a 3-year history of seasonal allergic rhinitis.

Patients excluded from the study were those treated with astemizole during the previous 6 weeks or corticosteroids during the previous 4 weeks, those with perennial rhinitis or nasal polyposis, females who were pregnant or lactating, those undergoing hyposensitization or desensitization therapy, those suffering significant concurrent disease or having a known intolerance to antihistamines or corticosteroids. The following concomitant medications were not permitted during the trial period: systemic or intranasal histamine H1 antagonists, intranasal decongestants, any local or systemic corticosteroids, sodium cromoglycate, inhaled nedocromil sodium, inhaled ipratropium bromide, ketotifen or any ophthalmic anti-inflammatory or vasoconstrictor eye preparations. A written explanation of the study was provided to each patient and informed written consent was obtained. Ethical approval was granted by the ethical committee of the East Berkshire Health Authority and the study was conducted within the guidelines of the Declaration of Helsinki.

Azelastine was administered by using a nasal spray delivering 0.14 mg/activation. Beclomethasone was administered using a nasal spray delivering 0.05 mg/activation. Active medication was taken twice daily with two sprays to each nostril morning and evening giving a total daily dose for azelastine of 1.12 mg and a total daily dose for beclomethasone of 0.4 mg. Because the drugs were not available in identical bottles, the double-dummy technique was used, which meant that active medication was always accompanied by placebo. To avoid dilution and washing out of the active drug by placebo, the four administrations of each preparation were spread out during the day: i.e., 8 a.m., 10 a.m., 8 p.m., and 10 p.m. Supplies were packaged so that the active preparations were always taken at 8 a.m. and 10 p.m., as these were the times least likely to be missed. Use of the nasal spray was demonstrated at the beginning of the study and each patient's administration technique was reviewed at weekly clinic visits. In addition, patients were provided with a detailed instruction leaflet. Patients were asked to record the times of drug administration on daily diary cards.

On entry to the study, subjects were withdrawn from current treatment for seasonal rhinitis and underwent a run-in period of between 3 and 5 days. During this initial period patients received both placebo for azelastine and placebo for beclomethasone. At the end of the run-in period the severity of patients' symptoms was documented by each clinician by using a rating scale ("Total Symptom Score Investigator", or TSSI). This assessed each of the following symptoms: sneezing, rhinorrhea, nasal itching, nasal stuffiness, eye itching and eye watering (Table 1). Patients with an aggregate score of 4 or more were eligible to continue into the treatment phase of the study. Study patients were allocated in accordance with a computer-generated random code to receive treatment with either azelastine and beclomethasone placebo, beclomethasone and azelastine placebo or azelastine placebo and beclomethasone placebo. Patients were issued a diary card on which to record the severity of each of the six symptoms daily using both the four-point scale (0–3) and a 10 cm visual analogue scale (VAS). VAS were marked with "Not present" at the left of the line and "As bad as it has ever been" at the right end of the line.

Patients were seen after 7 days and again after 14 days. On each occasion the symptoms over the previous 24 h were assessed by the TSSI and a global evaluation rating scale consisting of "worse," "unchanged," "a little better," "quite a lot better" or "considerably better." The occurrence of any adverse events was determined by open questioning.

**Table 1** Symptom assessment rating scale

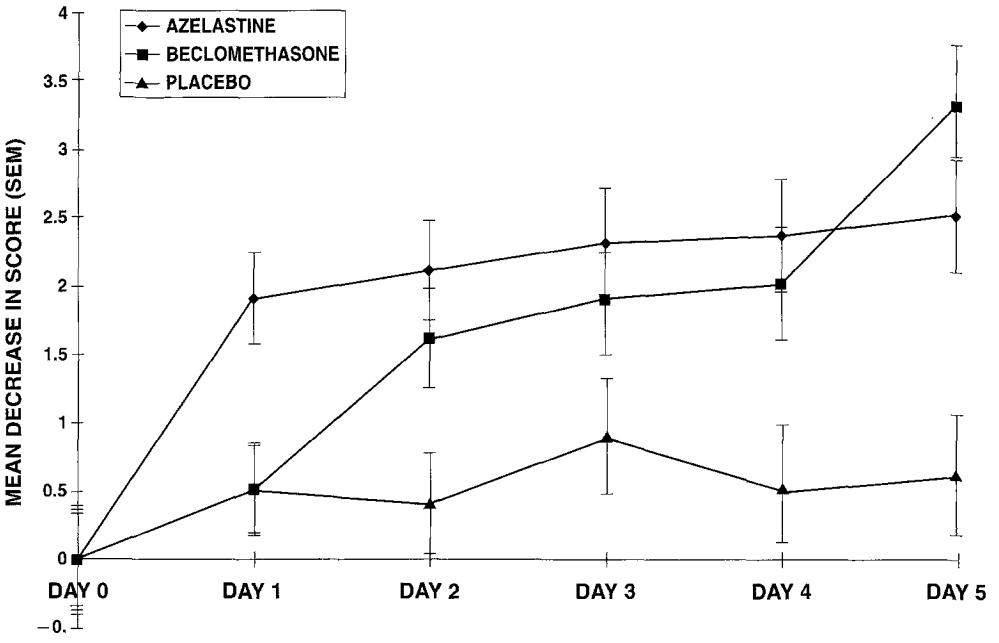
| | | |
|---|---|---|
| Sneezing | 0 | Absent |
| | 1 | Occasional |
| | 2 | Troublesome bouts of sneezing |
| | 3 | Frequent bouts of sneezing throughout the day |
| Nasal itching | 0 | Absent |
| | 1 | Occasional |
| | 2 | Present mostly but not a persistent distraction |
| | 3 | A constant annoying distraction |
| Rhinorrhea | 0 | Absent |
| | 1 | Occasionally present |
| | 2 | Requiring frequent nose blowing |
| | 3 | Persistent, very frequent nose blowing |
| Nasal stuffiness | 0 | Absent |
| | 1 | Some difficulty in nasal breathing |
| | 2 | Difficult to breathe through the nose, tendency to mouth breathe |
| | 3 | Unable to breathe through the nose |
| Eye itching | 0 | Absent |
| | 1 | Occasional |
| | 2 | Frequent |
| | 3 | Constant |
| Eye watering | 0 | Absent |
| | 1 | Occasional |
| | 2 | Frequent |
| | 3 | Constant |

The study was originally designed to detect a 20% difference between the two active groups, based on the assumption that an initial mean investigator composite score with 8 parameters would be 18 with a standard deviation of 5.9. After 1 and 2 weeks of therapy, respectively, the mean reduction in score would be $6 \pm 3$ and $12 \pm 6$. From these data, it was calculated that the required sample size per group was 88, assuming $\alpha = 0.05$ and $\beta = 0.2$.

TSSI was selected as the primary efficacy variable at the time of the study's design. TSSI data and patient symptom score data were analyzed using the Wilcoxon rank-sum test. VAS in the diary cards were analyzed using *t*-tests. Baseline values for all efficacy parameters were taken as the measurements recorded at the start of the treatment phase of the study. The reductions from baseline were tested within each treatment group using an analysis of covariance with the baseline score as the covariate. This was done to take into account differences between total symptom scores of the groups at baseline.

## Results

Thirty-one general practitioners returned validated data on a total of 291 patients. Forty-seven patients dropped out in the run-in phase, mainly because they did not achieve the minimum symptom score required to enter the treatment phase. The three treatment groups were compared with respect to age (median age for all patients = 35 years), sex, height, weight, co-existing disease at entry to the study and history of seasonal allergic rhinitis. No significant differences were found for any of these parameters. Hence, 83 patients received azelastine, 83 beclomethasone and 77 placebo. Compliance with the medication regimen was checked using the diary cards and returned medication bottles. When patients did not com-



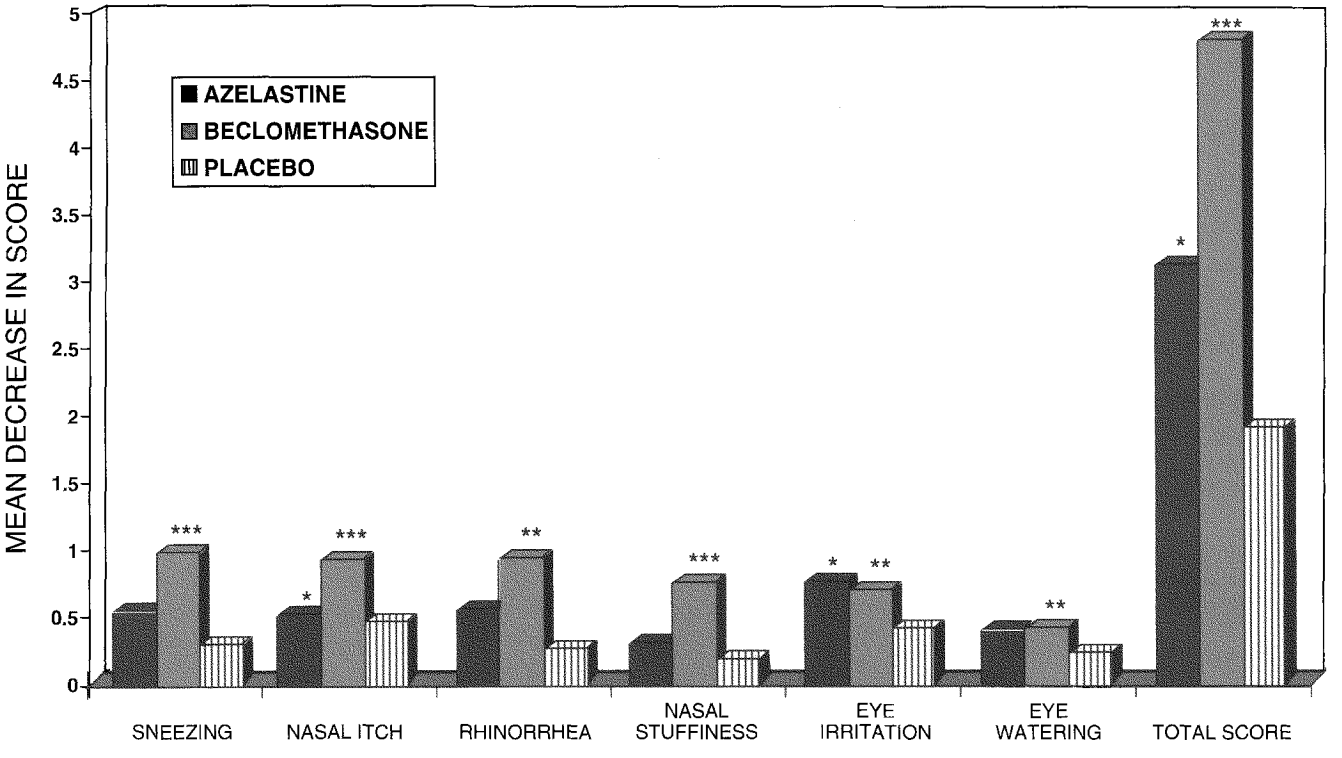




**Fig. 1** Diary card total symptom score decrease between days 1 and 5 after treatment with either azelastine or beclomethasone

**Fig. 2** Overall reductions in patient diary card scores. Statistical significance compared to placebo: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$

plete the treatment phase, data were included for analysis up to the time they were considered evaluable. Of the 24 patients who failed to complete the treatment phase, 3 patients were withdrawn for adverse events (1 in the beclomethasone group, 2 in the placebo group), 15 for lack of efficacy (8 in the placebo group, 4 in the azelastine group and 3 in the beclomethasone group), 2 for lack of compliance and 4 for deviations of the protocol. There was no statistically significant difference in patient withdrawals between the three groups.

## Diary card data

Analysis of the patient's diary card symptom score reductions between baseline and days 1–5 of treatment showed that on the 1st day of treatment the azelastine group experienced a significantly larger reduction in total symptom

score compared to both placebo and beclomethasone. Reductions in score for the azelastine group were significant for all individual symptoms except sneezing and eye watering. This trend continued until day 5 (Fig. 1). At day 1 beclomethasone showed no significant difference versus placebo for any symptoms.

Taking the whole 2-week study treatment period into consideration, individual symptom scores for the azelastine-treated group were in all cases reduced when compared to placebo. However, these changes only reached statistical significance for nasal itching and eye irritation. The beclomethasone-treatment group showed statistically significant reductions compared to placebo for all six symptom scores by the last day (Fig. 2).

For the patient's VAS symptom scores recorded on the diary cards, both the azelastine- and beclomethasone-treated groups showed a significant reduction in all symptom scores compared to placebo at the end of the treatment period. There were no significant differences detected between azelastine and beclomethasone (Fig. 3).

### Investigator symptom scores

The baseline values for TSSI for the three groups were 7.32 for azelastine, 8.46 for beclomethasone, and 8.42 for placebo. Overall at the end of the study azelastine showed a significantly larger reduction in TSSI when compared to placebo ($P = 0.0292$). Beclomethasone showed a significantly larger reduction than both placebo ($P = 0.0001$) and azelastine ($P = 0.0126$). When considering individual nasal symptoms assessed by the investigators, azelastine was significantly better than placebo for sneezing and rhinorrhea, but not for nasal stuffiness or nasal itching. Beclomethasone was effective for all these parameters. For eye symptoms, azelastine was significantly better than placebo for eye irritation, but not for eye watering. In contrast, beclomethasone showed no significant advantage for either symptom (Fig. 4).

**Table 2** Summary of adverse events occurring in three or more patients using either topical azelastine or beclomethasone

| Adverse event | Azelastine | Beclomethasone | Placebo | Total of each event |
|---|---|---|---|---|
| Headache | 2 | 6 | 4 | 12 |
| Bitter taste/smell | 5 | 0 | 0 | 5 |
| Epistaxis | 2 | 1 | 2 | 5 |
| Nasal irritation | 0 | 1 | 3 | 4 |
| Sneezing | 2 | 0 | 2 | 4 |
| Pharyngitis | 2 | 1 | 1 | 4 |
| Cold | 1 | 1 | 2 | 4 |
| Nausea | 3 | 0 | 0 | 3 |
| Burning sensation in nose | 1 | 2 | 0 | 3 |
| Upper respiratory tract infection | 2 | 0 | 1 | 3 |
| Chest tightness | 0 | 2 | 1 | 3 |
| Asthma | 2 | 0 | 1 | 3 |

### Tolerance

No serious adverse events occurred (Table 2), although three patients withdrew from the study due to adverse events. One patient in the beclomethasone group withdrew due to loss of smell. Two patients in the placebo group also withdrew: one had nasal irritation and another had an increase in nasal stuffiness. Bitter taste was reported by five patients (6%) in the azelastine group, but no other event was thought to be due to the medication given. In particular, there were no complaints of drowsiness in any of the treatment groups.

## Discussion

All three measurements used in this study – namely, patients' diary card scores, VAS and investigators' scores (TSSI) – showed that both azelastine and beclomethasone were significantly more effective than placebo in relieving the symptoms associated with seasonal rhinitis. At the end of the 2-week treatment period beclomethasone showed a greater decrease in symptom scores as assessed weekly by TSSI and daily diary card rating scores. However, daily assessments when patients used VAS showed no significant differences in efficacy between azelastine and beclomethasone for any symptom. A correlation was confirmed previously between the results of VAS and categorical rating scales for assessing overall seasonal rhinitis symptoms although a correlation for individual rhinitis symptoms has been shown to be poor [6]. This is possibly due to the ability of the VAS to allow greater discrimination of symptom intensity. From the 1st day of treatment, the daily diary card measurements revealed the faster onset of azelastine's action when compared to that of beclomethasone. Rapid symptom relief is important clinically in such conditions as seasonal rhinitis when medication is used on an "as required" basis. The delayed onset of action of many intranasal steroids in seasonal allergic rhinitis is now well established [7].

Our beclomethasone-treated group experienced a greater relief of eye irritation and eye watering than would be anticipated with a steroid preparation. This result could in part be explained by the lack of true blinding in the study due to the characteristic taste of azelastine. It is possible that this taste factor made patients aware of azelastine as the test compound resulting in a bias towards beclamethasone which was packaged in an easily recognized bottle. This factor highlights the difficulty of obtaining a true blinding in a study with two nasally administered treatments.

Results of nasal stuffiness scores (using both the four-point scale and VAS) showed a definite improvement for the azelastine-treated patients. This is contrary to the established belief that antihistamines do not improve nasal blockage. The results of the current study support those of Davies et al. [2] showing that azelastine significantly improved symptoms in patients with perennial allergic rhinitis.

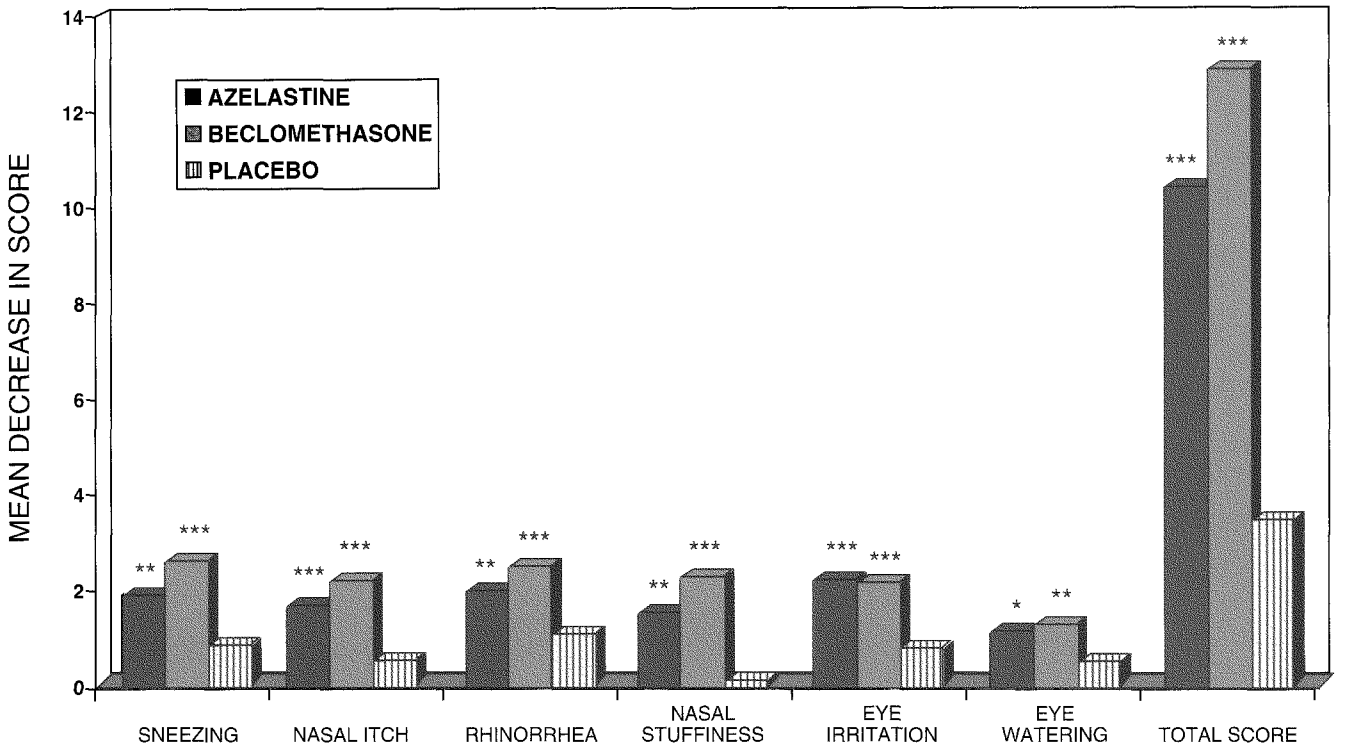
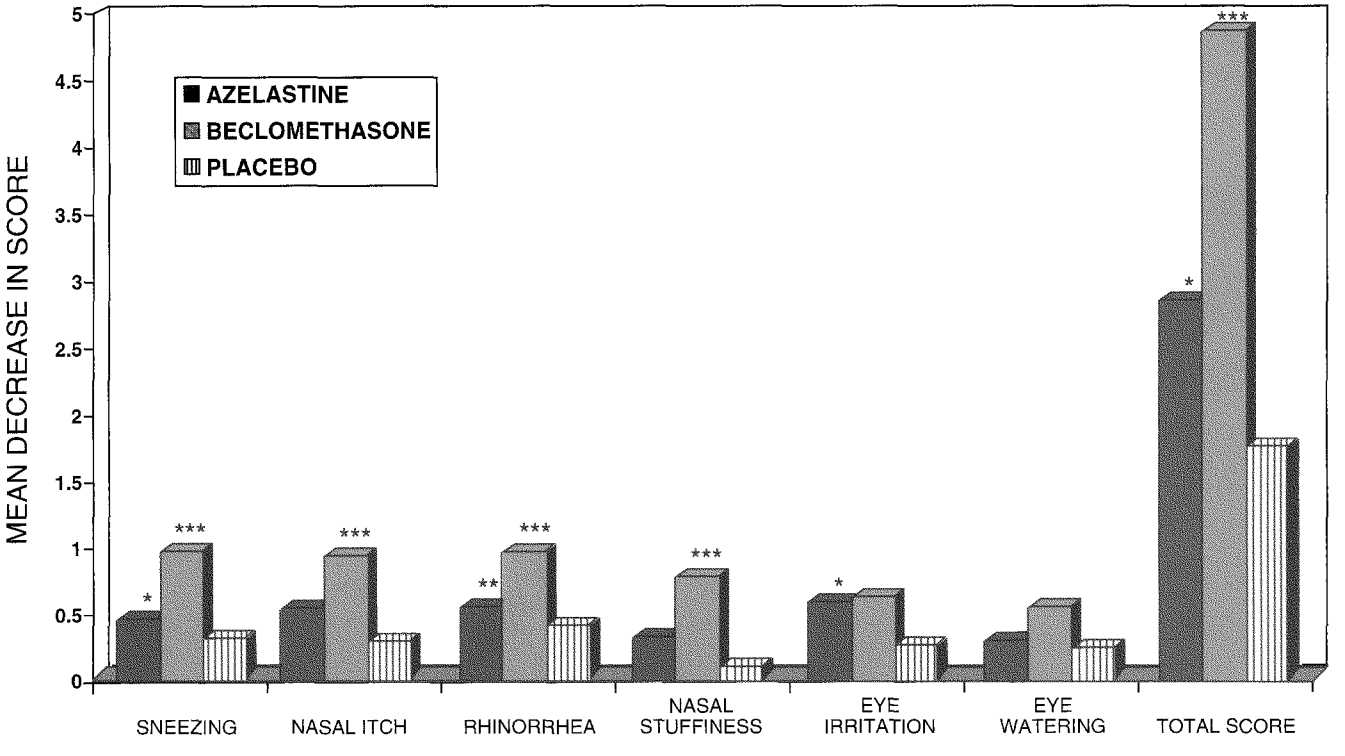



**Fig. 3** Overall reductions in patient visual analogue scores. Statistical significance compared to placebo: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$

**Fig. 4** Overall reductions in investigator symptom scores. Statistical significance compared to placebo: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$

Our present findings have shown that both intranasal azelastine and intranasal beclomethasone are effective drugs for the treatment of seasonal allergic rhinitis. Both drugs were well tolerated and the sedation reported following systemic antihistamine use was not seen when using intranasal azelastine. This finding is in agreement with other studies using this preparation [5].



**Acknowledgements** The authors would like to thank the General Practice study group who performed this study in the south of England, Glaxo Group Research Limited who provided beclomethasone and beclomethasone placebo, and Dr. Jane Bold for her help with this project.

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