

# A double-blind comparison of nasal budesonide and oral astemizole for the treatment of perennial rhinitis

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Sixty-nine outpatients with symptomatic perennial rhinitis were recruited to this double-blind, parallel-group study to compare budesonide nasal spray with oral astemizole. Following a 1-week run-in on placebo, 67 patients achieved a mean daily total symptom score of at least 4 (scoring for each symptom was 0 = none, 1 = mild, 2 = moderate, 3 = severe), and were randomized to study treatments – 33 to budesonide, 100 µg in each nostril morning and evening, and 34 to astemizole, one 10-mg tablet each morning, for a period of 4 weeks. No antihistamine preparations other than eye drops and no corticosteroids were permitted during the active treatment period. Patients recorded symptoms of blocked nose, runny nose, sneezing, itchy nose, sore eyes or runny eyes in diary cards each evening before retiring. Diary card data showed that there was significantly greater improvement in blocked nose, runny nose and runny eyes during the first 2 weeks of budesonide treatment than during the same period on astemizole. A similar, although non-significant, trend was observed for sneezing and itchy nose, but there was no apparent difference in the reporting of sore eyes. After 4 weeks, blocked nose and runny nose remained significantly less troublesome in the budesonide group. Both treatments were well-tolerated and no major adverse effects were reported. Patient ratings for treatment efficacy were significantly higher for budesonide than astemizole at both 2 weeks and 4 weeks.

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Perennial rhinitis, with or without an allergic component, is relatively common and is characterised by three main symptoms – sneezing, nasal discharge and blockage of the nasal passages (12). The most common types of therapy are oral H<sub>1</sub>-receptor antagonists (antihistamines) and topical glucocorticosteroids (GCS). Antihistamines competitively block the effect of the histamine released during an allergic response and thereby reduce symptoms of sneezing, itching eyes, runny nose and itchy throat, although they have little or no effect on nasal blockage (4). Topical GCS inhibit the inflammatory response at source and thus inhibit the release of other inflammatory mediators as well as histamine. They also reduce the sensitivity of irritant receptors in the nose and inhibit the secretory response to cholinergic stimulants (5) as well as producing local vasoconstriction. This wide spectrum of activity makes topical GCS highly effective in controlling the main symptoms of rhinitis, including nasal blockage. By virtue of their localized application, however, they have little effect on eye symptoms (9). We were in-

terested to compare the two types of therapy in our patients with perennial rhinitis. Astemizole is a recently introduced non-sedating antihistamine (11) which has been shown to be effective in the treatment of allergic perennial rhinitis (8) and hay fever (7, 13) and was also found to be more effective than chlorpheniramine in our Thai patients with perennial rhinitis (2). Hence astemizole was selected for comparison with budesonide, a potent topical GCS which has been shown to be effective in all types of rhinitis (3), including our perennial rhinitis patients (1).

## Patients and methods

### Patients

The study group was selected from patients attending the ENT Allergy Clinic at the Siriraj Hospital in Bangkok for treatment of their perennial rhinitis. Patients aged 16–70 years were eligible for entry, provided they had had symptoms of perennial rhinitis for at least 2 years preceding the study and were

suffering from at least two of the following typical symptoms: blocked nose, runny nose, itchy nose or sneezing bouts. They also had to complete a 1-week run-in on placebo during which they recorded any of these symptoms daily in diary cards (also runny eyes or sore eyes), using a severity scale of 0–3 where 0 = none, 1 = mild, 2 = moderate, 3 = severe. Their mean daily score during the run-in period (calculated from the sum of scores for all symptoms recorded) had to be at least 4 before they were eligible for randomization to study treatments.

Patients were excluded from study if they had received corticosteroid therapy during the 4 weeks prior to the study or had received hyposensitization therapy during the previous 12 months. Pregnant or lactating women were also excluded, as were any patients with bacterial, viral or fungal infection or with nasal complications, such as marked septal deviation or polyps.

### Study design

The study was performed as a double-blind, parallel-group comparison of budesonide (Rhinocort®) and astemizole (Hismanal®). All patients entered a 1-week placebo run-in period during which they were given placebo medication (both nasal aerosol and tablets) together with a supply of "rescue" short-acting antihistamine tablets (chlorpheniramine maleate) to be used only if symptoms were severe. Following the run-in period, patients were randomized to receive 4 weeks' treatment with either budesonide, two actuations (each containing 50 µg budesonide) in each nostril morning and evening (total daily dose of 400 µg budesonide administered by metered dose aerosol), plus one placebo tablet, or astemizole, one 10 mg tablet each morning before breakfast, plus two actuations of a placebo aerosol in each nostril morning and evening. Patients recorded symptoms on a 0–3 scale daily in diary cards throughout the study. No antihistamines or other preparations for the nasal condition (including oral corticosteroids) were permitted during the double-blind phase of the study, although intolerable eye symptoms could be treated with antihistamine eye drops. The consumption of the eye drops was recorded in the diary card.

Patients returned for follow-up visits after 2 and 4 weeks' active treatment. At each visit, the severity of the nasal and eye symptoms were recorded and adverse effects were checked by asking a non-leading question. Patients' assessments of treatment effectiveness were also recorded.

Skin prick tests and intracutaneous skin tests to six common allergens (house dust, house-dust mite,

Bermuda grass, careless weeds, cockroach and *Candida*) were performed on the patients prior to the double-blind treatment to determine the type of perennial rhinitis, i.e. allergic or non-allergic. Patients were considered to have allergic rhinitis if they showed positive skin prick tests or strong positive responses to at least two allergens tested in the intracutaneous skin tests.

### Statistical evaluation

Considering each individual symptom as the primary response variable, it was determined that a total of 60 patients, 30 on each treatment, would be sufficient to detect, with 80% power ( $\beta = 0.2$ ), a mean difference in symptom score of 0.6 between the treatment groups. This was with an estimated standard deviation of 0.8, using a two-sided test and a significance level of 5% ( $\alpha = 0.05$ ). The principal response variables were the symptom scores for blocked nose, runny nose, itchy nose, sneezing bout, runny eyes and sore eyes, recorded in the diary cards. The mean daily symptom scores during the 2nd and 4th weeks were compared between treatments by the Wilcoxon rank sum test and *p* values < 0.05 were considered to be significant. As there was an imbalance between treatment groups in the incidence of blocked nose during run-in, this symptom was compared between groups for weeks 2 and 4 by calculating the change from placebo run-in. Patients' ratings on effectiveness of medication were also compared between treatments by the Wilcoxon rank sum test.

## Results

### Patients

A total of 69 patients were recruited for study between June 1988 and March 1989, of whom 34 were randomized to the budesonide treatment group and 35 to the astemizole treatment group.

Demography for the two treatment groups was similar, although there were fewer males in the budesonide group (10/34 or 29%) than in the astemizole group (16/35 or 46%) and the mean age of the budesonide group was lower (27.8 years versus 31.3 years in astemizole group).

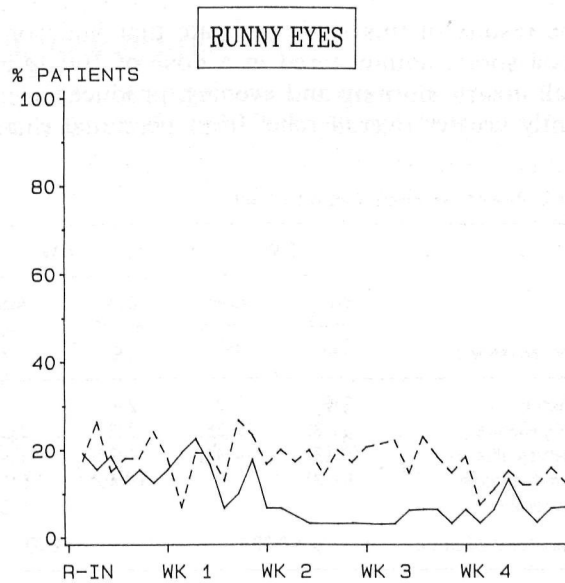
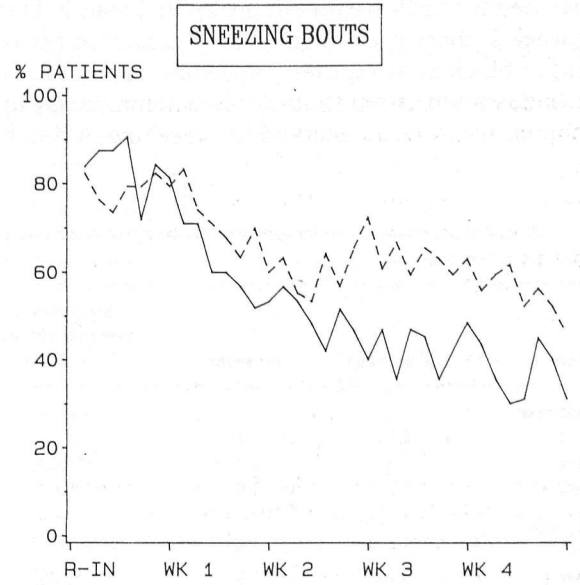
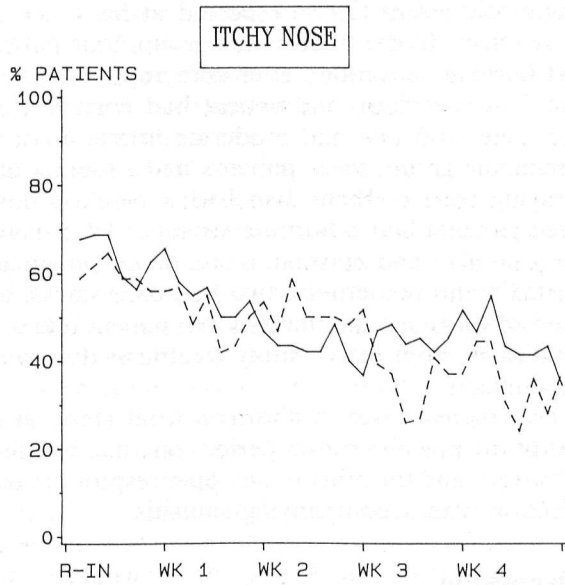
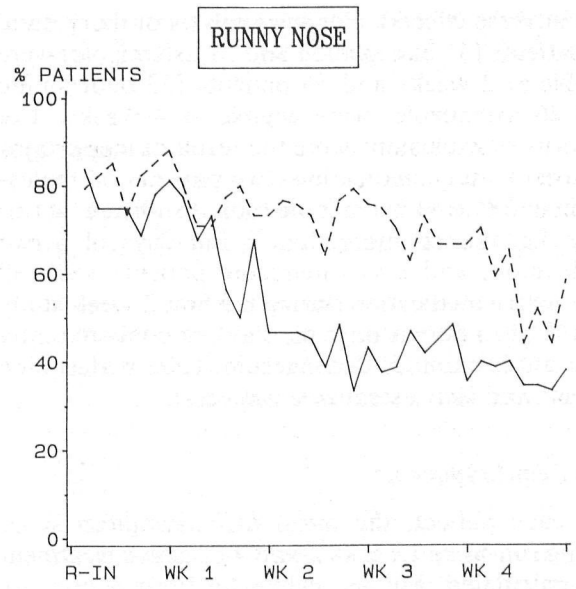
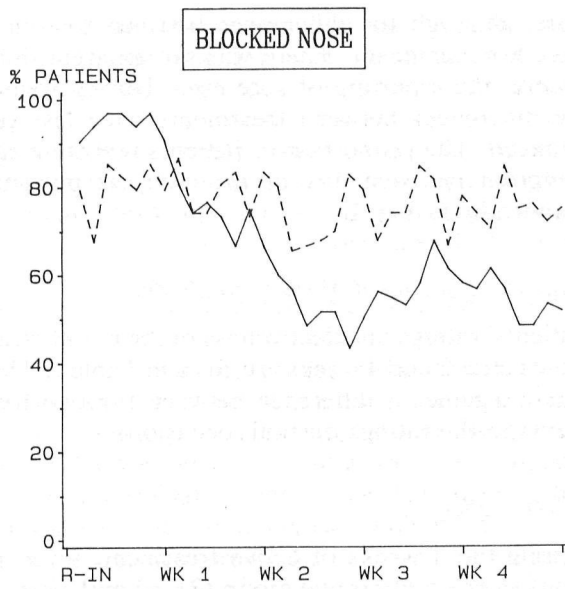
Sixty-six patients received skin prick tests and intracutaneous tests, and results indicated atopy in 62 patients (32 budesonide, 30 astemizole).

The amount of "rescue" medication (chlorpheniramine tablets) taken during the run-in period was similar for both groups.

Of these 69 patients, two had to be withdrawn from further study at the end of the placebo run-in

Fig. 1. Percentage of patients recording symptoms of blocked nose, runny nose, itchy nose, sneezing, runny eyes or sore eyes daily in diary cards during treatment with either budesonide (—) or astemizole (---).

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(see adverse effects). For the analysis of diary data, 62 patients (31 budesonide and 31 astemizole) were eligible at 2 weeks and 56 patients (30 budesonide and 26 astemizole) were eligible at 4 weeks. The majority of exclusions were the result of inappropriate use of study medication (two patients on budesonide and one on astemizole took insufficient active drug, i.e. missed more than 3 full days of active medication, and two astemizole patients took all their active medication during the first 2-week study period, i.e. a double dose per day), or concomitantly used antihistamines/decongestant (one budesonide patient and four astemizole patients).

### Diary card symptoms

For each patient, the mean daily symptom score during run-in and weeks 2 and 4 of active treatment was calculated. Median values for these scores are presented for each treatment group in Table 1. During week 2, there was a significantly greater improvement in blocked nose, runny nose and runny eyes in the budesonide group than in the astemizole group. A similar trend was observed for sneezing and itchy

Table 1. Median\* daily symptom scores for each treatment during run-in and weeks 2 and 4 of active treatment

| Symptom        | Budesonide | Astemizole | Significance of treatment difference<br>P |
|----------------|------------|------------|-------------------------------------------|
| Blocked nose   |            |            |                                           |
| run-in         | 1.64       | 1.14       |                                           |
| week 2         | 0.57       | 1.0        | **0.0001                                  |
| week 4         | 0.71       | 1.0        | **0.01                                    |
| Runny nose     |            |            |                                           |
| run-in         | 1.0        | 1.07       |                                           |
| week 2         | 0.43       | 1.0        | 0.007                                     |
| week 4         | 0.14       | 0.5        | 0.29                                      |
| Sneezing bouts |            |            |                                           |
| run-in         | 1.0        | 1.14       |                                           |
| week 2         | 0.50       | 0.86       | 0.13                                      |
| week 4         | 0.21       | 0.57       | 0.2                                       |
| Itchy nose     |            |            |                                           |
| run-in         | 1.0        | 0.57       |                                           |
| week 2         | 0.07       | 0.57       | 0.2                                       |
| week 4         | 0.21       | 0.07       | 0.34                                      |
| Sore eyes      |            |            |                                           |
| run-in         | 0.29       | 0.29       |                                           |
| week 2         | 0.0        | 0.0        | 0.75                                      |
| week 4         | 0.14       | 0.0        | 0.25                                      |
| Runny eyes     |            |            |                                           |
| run-in         | 0.0        | 0.0        |                                           |
| week 2         | 0.0        | 0.0        | 0.005                                     |
| week 4         | 0.0        | 0.0        | 0.51                                      |

\* Median calculated from individual mean daily symptom scores calculated for each week of the study. \*\* Difference between treatments calculated on changes from baseline, as baselines were not well matched.

nose, although the differences between treatments were not significant. There was no apparent difference in the reporting of sore eyes. During week 4, the differences between treatments were less pronounced. The proportion of patients reporting each symptom on each day of the study is presented graphically in Fig. 1.

### Patients' assessment of study treatment

Patients' ratings on effectiveness of their study treatments after 2 and 4 weeks are given in Table 2. There was a significant difference between the two treatments in the ratings on both occasions.

### Adverse effects

During the 4 weeks of active treatment, seven patients in the budesonide group (21%) and 10 in the astemizole group (29%) reported at least one adverse effect. In the budesonide group, four patients had burning sensations after spraying (one patient also had sneezing), one patient had epistaxis, one had acne, and one had moderate urticaria. In the astemizole group, three patients had sneezing after spraying (one of them also had a blocked nose), three patients had a burning sensation after spraying (one also had epistaxis), one other patient had epistaxis and tenderness, two had drowsiness, and one had dizziness and nausea. No patient had to be withdrawn from active study treatment due to adverse effects.

Two patients were withdrawn from study at the end of the placebo run-in period, one due to edema of the face and the other to an upper respiratory tract infection with accompanying sinusitis.

### Discussion

The results of this study indicate that budesonide nasal spray, administered in a dose of 100 µg into each nostril morning and evening, produces significantly greater overall relief from perennial rhinitis

Table 2. Patients' assessment of study treatment

| Patient assessment         | 2 W                   |                        | 4 W                   |                        |
|----------------------------|-----------------------|------------------------|-----------------------|------------------------|
|                            | Bude<br>n = 33<br>(%) | Astem<br>n = 34<br>(%) | Bude<br>n = 33<br>(%) | Astem<br>n = 34<br>(%) |
| Ineffective                | 2 (6)                 | 7 (21)                 | 2 (6)                 | 7 (20.5)               |
| Slightly effective         | 6 (18)                | 13 (38)                | 7 (21)                | 7 (20.5)               |
| Moderately effective       | 19 (58)               | 14 (41)                | 11 (33)               | 14 (41)                |
| Extremely effective        | 6 (18)                | —                      | 13 (40)               | 5 (15)                 |
| Not recorded               | —                     | —                      | —                     | 1 (3)                  |
| Significance of difference | p = 0.001             |                        | p = 0.03              |                        |

symptoms than astemizole 10 mg given orally each morning. Skin tests indicated atopy in almost all patients tested, suggesting that their rhinitis was allergic rather than non-allergic in origin.

Our study showed that during the first 2 weeks of active treatment, patients in the budesonide group had significantly less blocked nose and runny nose than those in the astemizole group, and during week 4 blocked nose remained significantly less in the budesonide group. The difference between the treatments in relieving blocked nose is as predicted from their pharmacological profiles (see introduction) and has been noted previously in our patients (1, 2) as well as being reported in other studies comparing budesonide with both the older sedative antihistamine, dexchlorpheniramine maleate (6) and the newer non-sedative antihistamine, terfenadine (10) in seasonal rhinitis. Our results also showed the superior efficacy of budesonide in relief of runny eyes. This is, perhaps, unexpected in view of its localized action in the nose. It should be emphasized, however, that only a small proportion of patients in this study suffered from eye symptoms either before or during the study treatment (Fig. 1).

The study indicates that neither drug eliminated the symptoms of perennial rhinitis completely in all patients, although 40% of the budesonide group found the treatment extremely effective after 4 weeks and 33% found it moderately effective. Only 15% of the patients on astemizole found it extremely effective and 41% moderately effective. Both drugs were well tolerated and were associated with no major adverse effects. In conclusion, there was greater relief from perennial rhinitis symptoms (as recorded daily in diary cards) in patients treated with budesonide than in patients treated with astemizole, and this was borne out by their overall assessment of the two treatments at the end of the study period.

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