

Effect of terfenadine and budesonide on nasal symptoms, olfaction, and nasal airway patency following allergen challenge

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The study investigated the effect of the oral H_1 -blocker terfenadine on allergen challenge in subjects with nasal allergy in comparison with the topical steroid, budesonide. A randomized, placebo-controlled, double-blind, crossover study with 3 experimental days was performed outside the pollen season. Seventeen nonsmokers with hay fever (symptoms, positive skin prick test, and RAST against timothy) were treated for 14 days before each experimental day, where the response to nasal challenge with four different concentrations of timothy was measured every 15 min for 6 h. The nasal cavity dimensions were measured by acoustic rhinometry and the olfactory function as the threshold for the sense of smell of butanol. Nasal symptoms were determined by questionnaires. Both terfenadine and budesonide dry powder had an effect on the hay fever symptoms during nasal pollen challenge. Terfenadine was more efficient than budesonide against histamine-mediated symptoms such as sneezing and itching. Budesonide increased nasal airway dimensions better than terfenadine ($P < 0.01$). A marked effect of budesonide was seen 1–2 h after challenge, suggesting an effect on “early late phase” reaction in the nose. In 7/17 subjects, a significant ($P < 0.05$) improvement of olfactory function after budesonide treatment was seen. In conclusion, topical steroid (budesonide) is superior to antihistamine (terfenadine) in treatment of nasal congestion in hay fever, especially for the postchallenge reaction, and may, in some cases, relieve the decreased sense of smell during pollen challenge.

Key words: acoustic rhinometry; antihistamine; nasal blockage; olfactory function; topical steroid.

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At present, hay fever and other allergic manifestations in the nose are primarily treated pharmacologically by H_1 blockage or by topical steroids. H_1 blockers are primarily intended to act by preventing the H_1 receptor-histamine interaction. H_1 blockade is advocated in cases of itching, sneezing, or secretion. The effect of steroids is more complicated and not completely understood, but blockage of immune competent cells and inhibition of histamine release have been shown (17). Topical steroids have shown a significant effect on all nasal symptoms compared with placebo, and on rhinomanometric and nasal peak-flow measurements in allergic rhinitis (13, 20).

Only a few comparisons have been made between steroids and the new nonsedating antihistamines on blockage in hay fever (8, 9, 21), and although steroids are advocated in case of blockage instead of antihistamines (12,16), we find that further study by

acoustic rhinometry, a more recent objective method for evaluation of nasal patency, is justified.

In 10–15% of patients suffering from hay fever, loss of the sense of smell is a significant symptom (10) and may be related to changes in nasal airway patency. Some studies show a correlation between the feeling of nasal patency and the sense of smell (3, 7), whereas others do not (6), but correlation of nasal patency and olfactory function in allergic rhinitis has not previously been examined by objective methods.

Therefore, the present study has aimed to examine the effect of the H_1 blocker terfenadine in comparison with topically applied budesonide dry powder (Rhinocort® Turbuhaler®) on nasal patency, especially the time course, evaluated by acoustic rhinometry, symptoms, and threshold of smell in allergic subjects challenged by allergens.

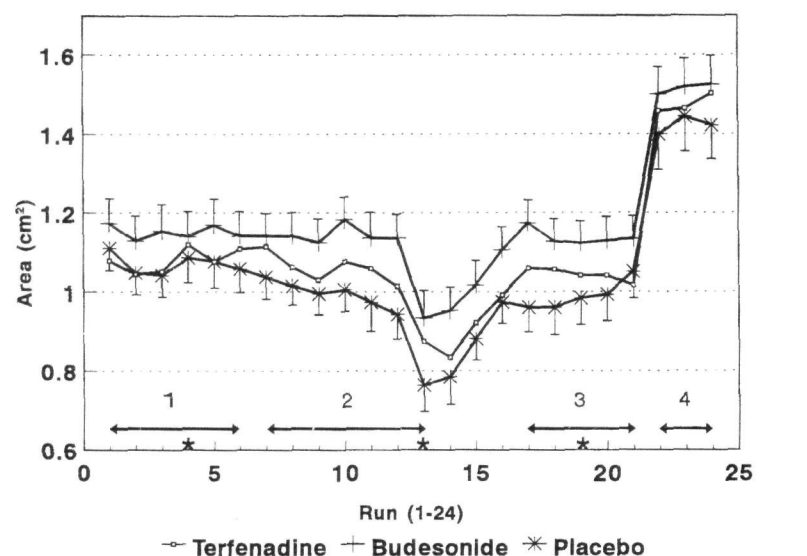
Material and methods

The study was performed during the winter outside the pollen season. Eighteen subjects with typical hay fever symptoms in the season, positive skin prick test, and RAST against timothy of at least class 3 (3.5–17.5 PRU/ml) were included in the study. One subject left the study for personal reasons before the first experimental day. Seventeen subjects completed the study and are included in the results. The subjects were recruited among nonsmoking outpatients and were volunteers of Caucasian race without previous operation in the nose, gross nasal pathology, severe asthma, or other diseases in the airways except hay fever. The subjects' characteristics were as follows: mean age: 25.4 years (23–33 years) (three women, 14 men; weight: 70.52 kg (60–90 kg); height: 179.0 cm (169–189 cm); duration of hay fever: 15.6 years (4–25 years); and mean RAST: 22.3 PRU/ml (13.3–34.2 PRU/ml). The study was approved by the regional ethics committee and the National Board of Health, and was performed according to the Declaration of Helsinki.

The study was designed as a randomized, placebo-controlled, double-blind, crossover study. It was divided into three parts: 1) 14 days of treatment with nasal steroid and placebo tablets followed by a nasal challenge day, 2) 14 days of treatment with antihistamine tablets and placebo inhalation followed by a nasal challenge day, and 3) 14 days of treatment with placebo inhalation and placebo tablets followed by a nasal challenge day. There were two washout periods of 7 days between each part. The study therapy was the H_1 blocker terfenadine (120-mg tablets (Teldanex®)) and budesonide (100- μ g/dose (Rhino-cort® Turbuhaler®)) in each nostril.

The experiments were performed in a climatic chamber (temperature = 22°C, relative humidity = 45%, air changes = 8/h). Each experimental day had a duration of 6 h. It included an initial rest period of 30 min, and was divided into four sections (Fig. 1): 1) a baseline period of 90 min in duration to map the nasal cycle of the subject and to determine the initial olfactory threshold, 2) a nasal allergen challenge period of 90 min in duration with four provocations with increasing concentrations of allergen, 3) a postchallenge period lasting 1 h for determination of olfactory threshold, acoustic measurements, rest, and determination of olfactory threshold again before decongestion, and 4) maximal decongestion with xylometazoline (Otrivin®, two sprays in each nostril, 1%, 0.14 ml/spray) to obtain a reference minimally influenced by the actual state of the mucosa.

The challenge was performed by installation of 0.15 ml solution of allergen (Alk, Timothy Aqua, 100 000 SQ-U/ml = 10 HEP) in concentrations of 10, 100, 1000, and 10 000 SQ-U/ml on the anterior



1: Baseline 2: Challenge 3: Post challenge 4: Decongestion *: Olfactory measurements

Fig. 1. Minimum cross-sectional area as function of time (run) for different treatments. Pollen challenge was performed immediately after run numbers 6, 8, 10, and 12. Standard error of mean is indicated for budesonide and placebo. Notice especially baseline and postchallenge difference between treatments.

part of the inferior turbinate on each side. The solution was instilled by means of a small-angled cannula during anterior rhinoscopy, with the subject sitting in an upright position to obtain a precise application in every challenge. Precautions were taken to avoid any instrumentational contact with the nasal mucosa.

The nasal volume and minimum cross-sectional area were measured by acoustic rhinometry, as described previously (11), every 15 min. Three measurements were performed in each nostril, alternating between the two sides. Such a set of measurements defines a run and was performed every 15 min. In total, 24 runs were made.

The olfactory threshold of *n*-butanol was measured by a triangle olfactometer, a standard instrument for measurement of olfactory sensitivity (5). The subject was asked to identify the one of three tubes containing the test gas (the two others contained pure air) in each of six funnels with increasing gas concentrations. The lowest correctly identified concentration out of six defined the olfactory threshold. The olfactory threshold for butanol was tested three times; before and immediately after the challenge and 3 h after challenge. The subjective feeling of nasal symptoms was evaluated by questionnaire. Each symptom – blockage, itching, sneezing, and secretion – was rated on a visual linear analog scale (100 mm, ranging from no symptoms to intolerable symptoms). The subjective evaluations were done at 15-min intervals during the experimental day. On the three different experimental days, the study was performed at the same hour of the day, and by the same investigator.

The data were analyzed by analyses of variance, correlation analyses, and Student's *t*-test (SAS Ver-

sion 6.08, SAS Institute). A *P* value less than 0.05 was considered to be significant; one between 0.05 and 0.1 was considered to be a tendency.

Results

The overall effect of treatments showed a significant effect of budesonide and a tendency to an effect of terfenadine on nasal cavity dimensions (Table 1). Due to the distribution of the score data, it was not possible to make an overall evaluation of these data.

During baseline measurements before challenge (Fig. 1, baseline), a tendency to a higher minimum cross-sectional area was recorded during treatment with budesonide. Similarly, the variability of the nasal mucosa (i.e., the variation in total minimum area), calculated as the coefficient of variation ($CV = SD/mean$) for the first five measurements (runs 1–6), was significantly lower for budesonide ($5.3 \pm 0.5\%$ (SEM)) than terfenadine ($7.4 \pm 0.7\%$) and placebo ($7.5 \pm 0.8\%$) ($P = 0.018$).

The results of pollen challenge (Table 1, section 3) were calculated by analysis of variance for all measurements during challenge, i.e., runs 7–13 (Fig. 1, challenge). Budesonide significantly increased nasal dimensions. A minor effect of terfenadine was also recorded. Evaluation of the data separately at each provocation step by *t*-tests both with and without correction for baseline differences gave similar results. Symptom score data were evaluated separately (*t*-tests) at each provocation step: 10, 100, 1000, and 10 000 SQ-U/ml (runs 7, 9, 11, 13) for the four score

variables: itch, sneeze, secretion, and blockage (Fig. 2). At 10–100 SQ-U/ml, only small differences were seen between the different treatments in nasal scores. After challenge with 1000 SQ-U/ml, an effect of both terfenadine and budesonide was seen on itching and sneezing. A tendency ($P < 0.1$) to an effect of budesonide on secretion and blockage was also recorded. After challenge with 10 000 SQ-U/ml, the protective effect of terfenadine was recorded in all symptoms. At this challenge step, terfenadine was superior to budesonide except against blockage. Only minor and nonsignificant effects of budesonide compared with placebo were recorded.

After pollen challenge, i.e., during runs 17–21, the most pronounced difference between budesonide and placebo on nasal dimensions was recorded. There was no effect of terfenadine (Fig. 1, post-challenge; Table 1, section 4).

The effect on olfactory function of treatment was tested. Neither test of variance or nor *t*-test of the separate three olfactory measurements on each experimental day, nor other tests on all subjects showed any overall effect of treatment. Examination of the relationship between nasal cavity dimensions and olfactory function showed a correlation in 7/17 subjects. In these subjects, larger dimensions involved a more sensitive olfactory function (lower threshold). These seven subjects were selected as a subpopulation of all 17 subjects to test the effect of treatment on olfaction. Immediately after challenge, no significant differences between the effects on olfaction of placebo and topical steroid were seen

Table 1. Results of acoustic measurements for different parts of study (overall effect, effect on baseline, effect during challenge, postchallenge effect). *P* values were calculated from variance model including all measurements. Differences between treatments with *P* values larger than 0.1 were regarded as nonsignificant

	Minimum area $\pm$ SEM (cm ²)	<i>P</i> value	Volume $\pm$ SEM (cm ³)	<i>P</i> value
Overall effect				
Terfenadine	1.03 $\pm$ 0.050	(T-B) $P < 0.01$	16.45 $\pm$ 0.539	(T-B) NS
Budesonide	1.11 $\pm$ 0.057	(B-P) $P < 0.005$	16.98 $\pm$ 0.524	(B-P) $P < 0.01$
Placebo	0.99 $\pm$ 0.055	(T-P) NS	15.74 $\pm$ 0.497	(T-P) $P < 0.1$
Effect on baseline				
Terfenadine	1.08 $\pm$ 0.045	(T-B) $P < 0.1$	17.93 $\pm$ 0.588	(T-B) NS
Budesonide	1.15 $\pm$ 0.062	(B-P) $P < 0.1$	17.57 $\pm$ 0.528	(B-P) NS
Placebo	1.06 $\pm$ 0.056	(T-P) NS	17.07 $\pm$ 0.594	(T-P) NS
Effect during challenge				
Terfenadine	1.01 $\pm$ 0.052	(T-B) $P < 0.025$	15.88 $\pm$ 0.573	(T-B) NS
Budesonide	1.09 $\pm$ 0.058	(B-P) $P < 0.005$	16.40 $\pm$ 0.581	(B-P) $P < 0.01$
Placebo	0.94 $\pm$ 0.054	(T-P) $P < 0.1$	15.09 $\pm$ 0.510	(T-P) $P < 0.05$
Postchallenge effect				
Terfenadine	1.04 $\pm$ 0.053	(T-B) $P < 0.005$	16.19 $\pm$ 0.505	(T-B) $P < 0.025$
Budesonide	1.14 $\pm$ 0.055	(B-P) $P < 0.001$	17.15 $\pm$ 0.504	(B-P) $P < 0.001$
Placebo	0.99 $\pm$ 0.064	(T-P) NS	15.46 $\pm$ 0.518	(T-P) NS

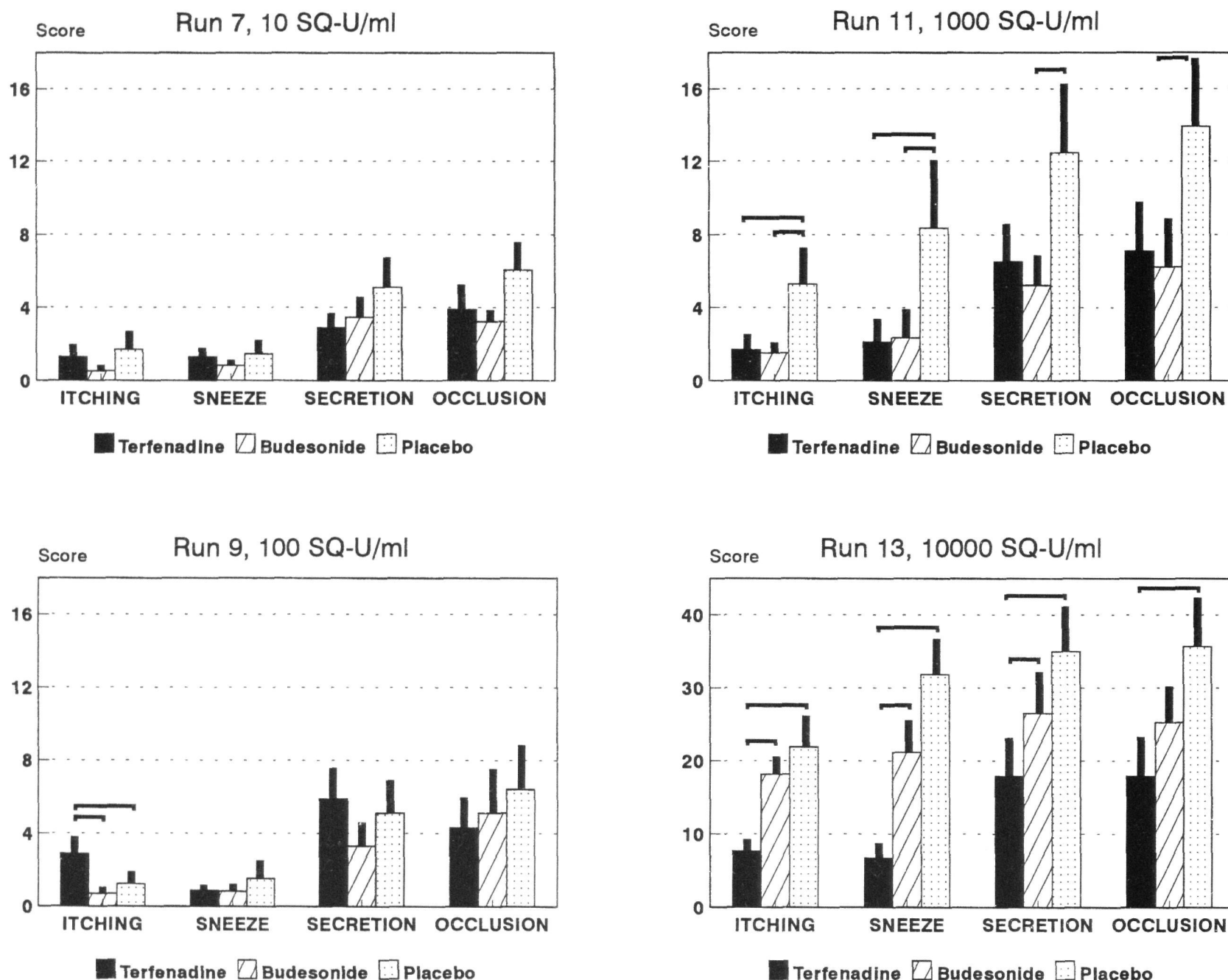


Fig. 2. Nasal symptoms (plus SEM) immediately after four challenge steps for different treatments. Sharp brackets indicate differences between treatments with P values less than 0.1. Notice different ordinate in run 13.

($P = 0.14$), but during the postchallenge period a significantly improved olfactory function ($P = 0.038$) was seen in the seven selected subjects during steroid treatment (mean olfaction threshold $\pm$ SEM: terfenadine: 3.0 ± 0.44 , budesonide: 2.43 ± 0.40 , placebo: 3.43 ± 0.65)

Correlation analysis of demographic data revealed no correlation between the RAST value and the duration of disease, age at start of disease, present age, or height of the subjects. A positive correlation between the decongested minimum cross-sectional areas and the heights of the subjects was found ($r = 0.61$, $P = 0.012$). Correlation between nasal occlusion scores and the acoustic measurements was examined for each subject. Seven subjects showed low correlation ($r < 0.5$, $n = 63$) between total cross-sectional area and occlusion score. These subjects had a larger mean total minimum area than the subjects with high correlation ($P = 0.03$), indicating

that there may be a threshold area above which no occlusion is observed (Fig. 3).

Discussion

Topical steroid and antihistamine have different effects on the allergic response due to interaction with different allergic mechanisms elicited by pollen challenge. Terfenadine inhibits sneezing, early release of histamine, and histamine binding to receptors. Oral steroid inhibits late histamine release and topical steroid inhibits both early and late release of histamine, and other mediators including cytokines (17).

The primary findings of the study were as follows. Budesonide tended to constrict the mucosa before any challenge. Budesonide was clearly superior to terfenadine with regard to the congestion of the nasal mucosa during pollen challenge. There was no effect of terfenadine in the postchallenge period, but there

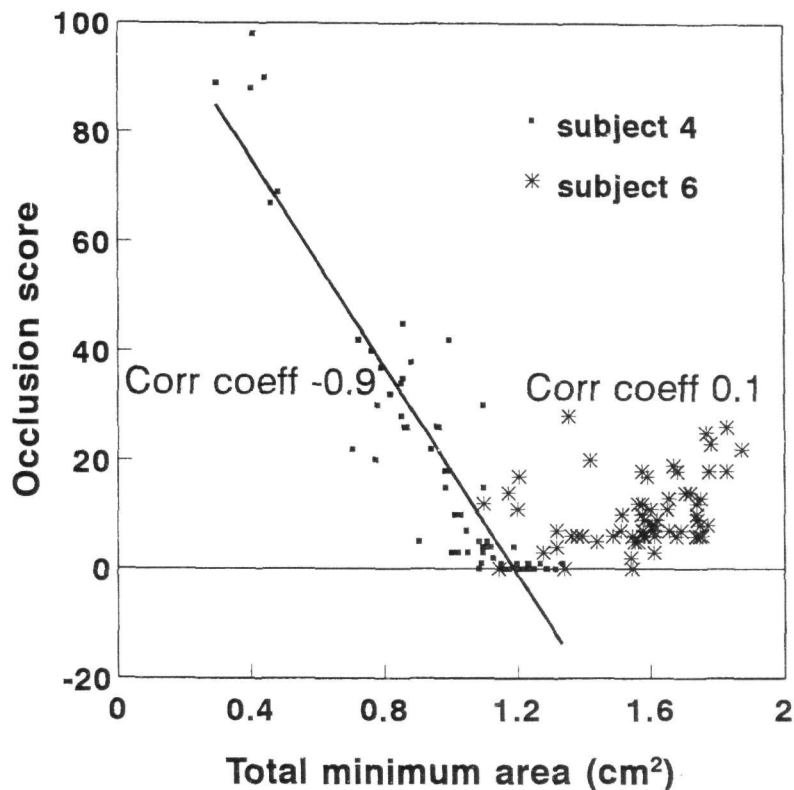


Fig. 3. Correlation between nasal occlusion score and total minimum cross-sectional area in two different subjects. No relationship in one subject with areas above 1.2 cm². Increasing sense of occlusion in one subject with areas below 1.2 cm².

was a highly significant effect of budesonide, showing a fast and complete return to the baseline values after challenge. A correlation between the measured nasal cavity dimensions and the olfactory threshold was found in 7/17 subjects. In these subjects, a benefit of budesonide treatment was seen during challenge on the olfactory function.

The subjects were prick test negative to the most common allergens except grass pollen, and two were known to be positive to house-dust mites and had no complaints of any kind regarding house dust. Budesonide showed no vasoconstrictor effect and did not influence nasal patency (evaluated by nasal peak flow) per se in nonallergic subjects (15), but it has previously been shown that allergen-induced specific and nonspecific nasal reactions are inhibited by topical glucocorticosteroids (1).

In this study, the immediate congestion of the mucosa during challenge was found to be significantly reduced during budesonide treatment, but only a minor effect was seen for terfenadine. Only budesonide revealed a highly significant postchallenge effect on nasal volume and minimum cross-sectional area.

A late-phase response in the lower airways seen 6–10 h after challenge has been well described, but in the nose the late-phase response, expressed as nasal congestion, is more uncertain and has not been demonstrated convincingly, although an early influx of eosinophils, mast cells, and neutrophils (2) has been seen. In the present study, the response of the

nasal mucosa in the period after challenge (1–2 h) was modified by budesonide, but not by terfenadine, and other studies (14) may also indicate that the “late-phase inflammatory response” in allergic challenge in the nose may be seen within a few hours, in contrast to 10–14 h in the lower airways. An explanation for this “early late phase” may be *in situ* cell differentiation (4) or fast recruitment of active cells (19). Further investigations are needed to verify this observation (“early late phase”) and to describe the mechanism.

The olfactory test in the present study revealed an effect of topical steroid in a selected group of subjects with correlation between the nasal geometry and the olfactory threshold. Various reasons for lack of effect in all subjects might be suggested. The change of nasal cavity volume during nasal challenge may be too small to induce modifications of the airflow eddies around the olfactory cells. The changes in the nasal mucosa during a pollen challenge outside the pollen season are rapid and of short duration compared with more chronic influence of the nasal mucosa during the pollen season. With the triangle olfactometer, the smell of compounds other than butanol may be impaired, but not detected.

The analysis of the score data revealed a large variability in the correlation between nasal blockage score and the nasal volume (or minimum area) among different subjects. Subjects with large cavities seem to have more difficulty in subjectively evaluating their nasal cavity dimensions during pollen challenge. Apart from intersubject variability, another important factor may be that the four different rhinitis symptoms may influence each other. When massive sneezing, itching, and secretion occur, it may be difficult to be “objective” when scoring nasal stuffiness or blockage on a symptom card. A study of symptoms during the pollen season with more natural pollen exposures showed a convincing effect of topical steroids on symptom scores (18).

In conclusion, the results of the present study confirmed that a topical steroid (budesonide) is superior to an antihistamine (terfenadine) in treatment of nasal congestion in hay fever, especially in the postchallenge reaction. This could indicate the presence of an “early late phase” reaction in the nose. In some cases, topical steroids may relieve a decreased sense of smell during pollen challenge.

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