

Effects of topical budesonide and levocabastine on nasal symptoms and plasma exudation responses in seasonal allergic rhinitis

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This study compares the effects of two topical nasal treatments for allergic rhinitis, budesonide and levocabastine, on symptom development during seasonal pollen exposure. Additionally, the protective effects of drug treatments on allergen-challenge-induced responses (symptoms and microvascular exudation of plasma) are examined late into the pollen season. Forty-four patients with seasonal allergic rhinitis to birch pollen participated in this single-blind, randomized, and placebo-controlled study. Topical nasal treatment with either levocabastine (200 µg b.i.d.; $n=16$), budesonide (200 µg b.i.d.; $n=16$), or placebo ($n=12$) was instituted before the start of the pollen season and continued for 5 weeks until the end of the birch pollen season. The participants kept diaries for scores of nasal and ocular symptoms. Nasal allergen challenges with increasing doses of a birch pollen extract (10^2 , 10^3 , and 10^4 SQ-U) were carried out both before, when patients were asymptomatic and without treatment, and late into the pollen season. A nasal lavage followed each challenge, and the lavage fluid levels of albumin were measured as an index of the acute inflammatory response of the allergic mucosa. The birch pollen season was rather mild, producing only small increases in nasal symptoms. Budesonide treatment reduced the total nasal symptoms compared to placebo ($P<0.01$) and to levocabastine ($P<0.05$), while levocabastine treatment did not differ significantly from placebo. Ocular symptoms and use of rescue medication did not differ between placebo and the active treatments. At the end of the pollen season, both treatments reduced allergen-challenge-induced nasal symptoms compared to placebo ($P<0.01$). Only budesonide reduced allergen-challenge-induced increments of albumin levels in postchallenge nasal lavage fluids ($P<0.05$, in comparison with placebo). The results suggest that budesonide reduces both seasonal and allergen-challenge-induced nasal symptoms, while levocabastine is effective against allergen-challenge-induced symptoms also during the season. In addition, the topical steroid treatment, but not the antihistamine, inhibits the inflammatory exudation evoked by allergen challenge in patients with active seasonal disease.

**C. Svensson¹, M. Andersson¹,
L. Greiff¹, L.-O. Blychert²,
C. G. A. Persson³**

¹Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital, Lund;

²Janssen-Cilag AB, Västra Frölunda;

³Department of Clinical Pharmacology, University Hospital, Lund, Sweden

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Christer Svensson
Department of Otorhinolaryngology, Head and Neck Surgery
University Hospital
S-221 85 Lund
Sweden

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Topical glucocorticoids and topical antihistamines represent two treatments of allergic rhinitis. The topical steroids are known to exert a range of effects on cellular and mucosal inflammation and are considered generally efficacious antirhinitis drugs (1). Antihistamines antagonize the effects of endogenous histamine on different airway target cells and may even be more protective than topical steroids at acute experimental airway allergen chal-

lenge. Thus, while topical nasal steroids attenuate the allergen-challenge-induced nasal symptoms and physiologic indices of nasal inflammation (e.g., the plasma exudation response) occurring in the immediate phase after allergen challenge of allergic subjects who receive the challenge outside their active disease period (2), antihistamines seem to have a more pronounced effect and almost inhibit both nasal symptoms and mucosal exudation after

experimental nasal allergen challenge (3, 4). However, it may not be possible to draw conclusions about drug efficacy in allergic rhinitis from allergen-challenge studies involving subjects with near normal airways. Therefore, this study aimed to compare the effects of antihistamine and steroid drugs in patients having allergic airway inflammation for several weeks. Thus, it examined the effects of topical levocabastine and topical budesonide on symptoms of seasonal allergic rhinitis. In addition, the effects of these treatments were determined at an allergen challenge causing symptoms and plasma exudation late in the pollen season.

Material and methods

Study design

The study was performed in a single-blind and placebo-controlled design during the Swedish birch pollen season of 1992. The patients were randomized for three different topical treatments: levocabastine, budesonide, and placebo. Treatment started on 15 April and continued until 19 May. Nasal allergen challenges were performed before the birch pollen season during the first 2 weeks of March when the participants were asymptomatic and without treatment, and late into the pollen season (19 May) when the participants were symptomatic and on a study drug.

Patients

Forty-five patients with a clinical history of birch pollen-induced allergic rhinitis and a positive skin prick test to birch pollen extract (Soluprick®, ALK, Denmark) were included in the study. Informed consent was obtained from all subjects, and the study was approved by the local ethics committee and the Swedish Medical Products Agency. The study was performed according to the Declaration of Helsinki. None of the patients had any symptoms or signs of perennial allergic rhinitis or any other form of chronic nasal disease, nor did they have any structural abnormalities of the nose as revealed by anterior rhinoscopy. None of the participants had received previous immunotherapy. To achieve a high compliance, the participants came for weekly visits at the clinic. Nevertheless, one of the patients was excluded for noncompliance with the protocol, leaving 44 patients for evaluation. Their age and sex distribution were as follows: placebo group ($n=12$, female/male=3/9, mean age 23 [21–40] years), levocabastine group ($n=16$, female/male=5/11, mean age 27 [19–48] years), and budesonide group ($n=16$, female/male=6/10, mean age 26 [21–44] years).

Study drugs

The treatments were either 100 µg of levocabastine (Livostin®, Janssen Pharmaceutical, Belgium), or 100 µg of budesonide (Rhinocort® Aqua, Astra Draco, Sweden) in each nasal cavity twice daily, or placebo nasal spray. The subjects were provided with an allocation number, and the order of treatment proceeded according to a randomization scheme of the allocation numbers. Blindness with respect to levocabastine was maintained by identical appearance and taste of the active drug and placebo preparations. For practical reasons in the hospital pharmacy, the placebo spray was provided only for levocabastine, a circumstance which the participants were unaware of (the drugs were delivered by a nurse who was not informed of the placebo design).

Rescue medication

Levocabastine (0.05%) eye-drops (Livostin, Janssen Pharmaceutical, Belgium) and naphazoline chloride (0.1%) eye-drops (Rimidol®, UCB, Belgium) were allowed (one drop in each eye 1–2 times daily) if more than mild ocular symptoms occurred. A nasal spray containing a decongestant agent, xylomethazoline (1%) (Otrivin®, Ciba-Geigy, Switzerland), was allowed (one spray in each nostril 1–3 times daily) if more than mild nasal symptoms appeared. All use of rescue medicine was to be noted in the diary sheets.

Birch pollen counts

The birch pollen grains were counted with the aid of a Burchard pollen trap located in Malmö, 20 km from Lund. Birch pollen occurrence was expressed as daily mean pollen grains/m³ of filtered air.

Symptom scores

Nasal and ocular symptoms were estimated each morning (evaluation of the symptoms experienced during the last 24 h) and scored separately on a diary card where 0=none, 1=mild, 2=moderate, and 3=severe symptoms.

Nasal allergen challenge and lavage

A nasal allergen challenge test was performed before (March) and at the end of the pollen season (May) at about 2 p.m. Diluent (manufacturer's diluent for the allergen extract) and increasing doses (10^2 , 10^3 , and 10^4 SQ-U) of a birch pollen extract (Aquagen®, ALK, Denmark) were sprayed into one nasal cavity with a mechanical pump spray

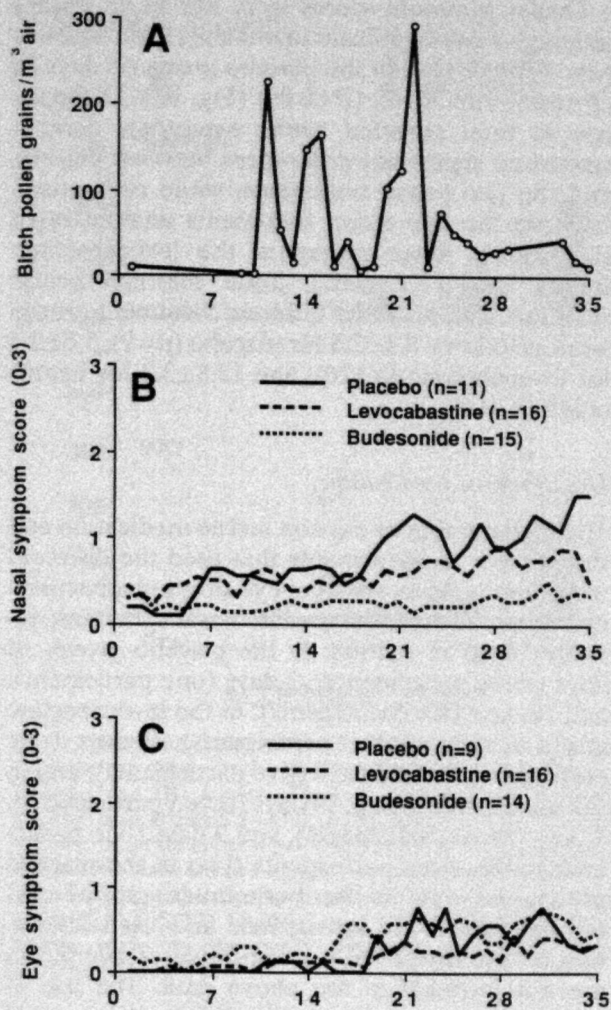


Fig. 1. A) Birch pollen occurrence (grains/m³ filtered air), B) daily nasal symptom scores (mean), and C) daily ocular symptom scores (mean) in different treatment groups during study period (15 April–19 May).

device delivering 100 μ l per actuation. Nasal lavage with a "nasal pool" device (0.9% saline at room temperature; volume: 14 ml; duration: 2.5 min) was performed 10 min after each challenge, as previously described (5). Before the challenges, the nasal mucosa was cleaned from accumulated secretions by two quick lavages (duration: 30 s each), which were not collected. The lavage fluid was immediately centrifuged (400 g) for 10 min and the supernatant frozen (-20°C) for later analyses. During the challenge procedure, the patients rated their nasal symptoms (secretion and blockage) on a symptom score sheet, and the number of sneezes was counted. The nasal symptoms were rated from 0 to 3 where 0=none, 1=mild, 2=moderate, and 3=severe symptoms. The number of sneezes was counted and transformed into a score where 0=0 sneezes, 1=1–4 sneezes, 2=5–9 sneezes, and

3= ≥ 10 sneezes. A total nasal symptom score was calculated as the sum of the blockage, secretion, and sneezing scores.

Albumin assay

Albumin was measured by a radioimmunoassay sensitive to 6.25 ng/ml. Rabbit anti-human albumin (Dakopatts, Copenhagen, Denmark) was used as antiserum, and standard human serum (Calbiochem, San Diego, CA, USA) as standard. Iodination was performed by a lactoperoxidase method (6) to a specific activity of 2 mCi/nmol. Tracer and standard (or sample) were mixed with antiserum before adding goat antirabbit antiserum (Astra Draco, Lund, Sweden). The bound fraction was measured with a gamma counter (Clinigamma; Pharmacia Diagnostica Norden, Uppsala, Sweden). The intra- and intercoefficient of variations were 5% and 10%, respectively.

Statistics

A nonparametric analysis of variance (Kruskal-Wallis) was used to compare intergroup differences (seasonal symptoms and responses to nasal allergen provocation). If a statistical significance emerged, further calculations with the Mann-Whitney U-test were done for comparison between the treatment groups. Another nonparametric analysis of variance (Friedman test) was used for calculation/comparison of intragroup changes (seasonal symptoms and responses to nasal allergen challenge) followed by further calculations with the Wilcoxon signed-rank test. A *P* value less than 0.05 was considered significant. All values are given as mean $\pm$ SEM.

Results

The diary cards from two participants (belonging to the placebo and the budesonide groups, respectively) were incompletely filled in and therefore not evaluable. All other diary cards were evaluable. While all participants partook in the preseasonal allergen challenge in March, five of them failed to carry out the allergen challenge in May (two, two, and one belonging to the placebo, levocabastine, and budesonide groups, respectively). While data from the diaries of these five participants were included in statistical evaluation, data from the allergen challenge in March were excluded. Three participants (two from the placebo group and one from the budesonide group) misunderstood the instructions and used levocabastine eye-drops daily for the entire study period irrespective of ocular symptoms. Eye symptom data from these three participants were therefore excluded from statistical evaluation.

TOTAL NASAL SYMPTOM SCORE (0-9)

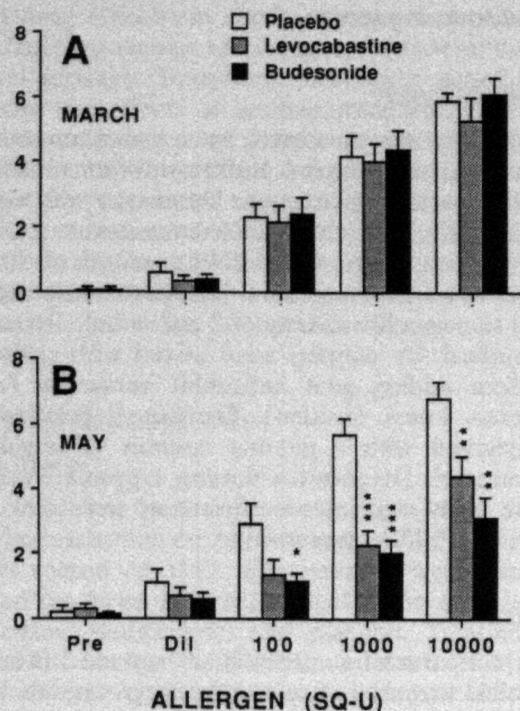


Fig. 2. Intergroup comparison of allergen-challenge-induced nasal symptoms ($\pm$ SEM) (A) before (March) and (B) at end (May) of pollen season. Placebo ($n=10$), levocabastine ($n=14$), budesonide ($n=15$). * $P<0.05$, ** $P<0.01$, *** $P<0.001$ (placebo vs treatment groups). All comparisons levocabastine vs budesonide were without statistical significance.

Pollen occurrence and daily symptoms

Due to technical problems with the Burkhard pollen trap, we were not able to receive pollen counts for every day during the study period (Fig. 1A). The first birch pollen peak appeared on 25 April (study day 11). The birch pollen season was mild with only 6 days of pollen counts above 100 grains/ m^3 filtered air.

There was a significant increase in nasal symptoms for the placebo-treated group on the following days: study days 15, 19–20, 22–24, 26–28, and 31–35 ($P<0.05$ – 0.001 ; comparison with day 1) (Fig. 1B). Comparison of total seasonal nasal symptoms (calculated as the sum score for the entire treatment period) demonstrated significantly fewer symptoms in the budesonide-treated group than with both placebo ($P<0.01$) and levocabastine treatment ($P<0.05$), while there was no statistically significant difference between levocabastine and placebo treatment. Total seasonal nasal symptom scores for the different treatment groups were as follows: 25.5 ± 4.7 for placebo ($n=11$), 19.4 ± 3.9 for levocabastine ($n=16$), and 8.1 ± 3.2 for budesonide ($n=15$).

Ocular symptom scores were low in all groups although some significant increments from baseline (day 1) were seen in the placebo group on days 26 ($P<0.05$) and 30–32 ($P<0.05$) (Fig. 1C). Comparison of total seasonal ocular symptoms demonstrated no significant differences between placebo and the two active treatments, while comparison between the two active treatments demonstrated significantly lower scores in the levocabastine-treated group ($P<0.05$). Total seasonal ocular symptom scores for the different treatment groups were as follows: 8.2 ± 2.5 for placebo ($n=9$), 5.6 ± 2.4 for levocabastine ($n=16$), and 12.8 ± 3.2 for budesonide ($n=14$).

Use of rescue medication

The total number of days on rescue medication and the number of participants that used the different medications (levocabastine eye-drops, naphazoline eye-drops, and xylometazoline nasal spray, respectively) were as follows: in the placebo group, 10 days (three participants), 2 days (one participant), and 28 days (six participants); in the levocabastine group, 9 days (three participants), 9 days (one participant), and 20 days (five participants); and in the budesonide group, 59 days (seven participants), 8 days (three participants), and 9 days (one participant). The three participants (two in the placebo group and one in the budesonide group) that misunderstood the instructions and used levocabastine eye-drops daily irrespective of symptoms are not included in the above data. The use of naphazoline eye-drops and xylometazoline nasal spray was low in all treatment groups and without statistically significant differences. There seemed to be an overuse of levocabastine eye-drops in the budesonide group, but this difference did not reach statistical significance ($P=0.09$ for comparison with Kruskal-Wallis; $P<0.05$ for comparison with Mann-Whitney U-test levocabastine vs budesonide).

Nasal allergen challenge

Intergroup comparison. Allergen provocation in March (before pollen season and treatment) revealed no differences between the groups in challenge-induced nasal symptoms (Fig. 2A). The lavage fluid levels of albumin showed some small differences (Fig. 3A). After diluent provocation, the budesonide group exhibited higher levels than the placebo and levocabastine groups ($P<0.05$). After 100 SQ-U, the placebo group and the budesonide group had higher levels than the levocabastine group ($P<0.05$ and $P<0.01$, respectively), and after 1000 SQ-U, the budesonide group had higher

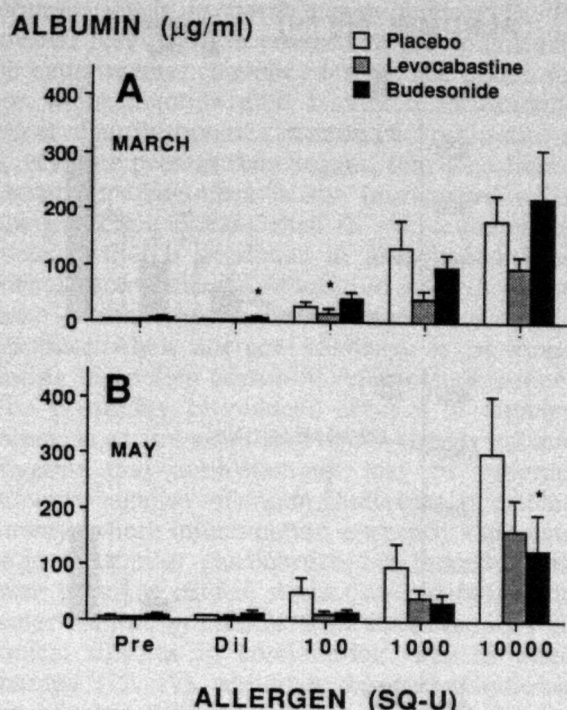


Fig. 3. Intergroup comparison of allergen-challenge-induced nasal lavage fluid levels of albumin ($\pm$ SEM) (A) before (March) and (B) at end (May) of pollen season. Placebo ($n=10$), levocabastine ($n=14$), budesonide ($n=15$). * $P<0.05$ (placebo vs treatment groups). Comparison of levocabastine vs budesonide demonstrated significantly higher levels of albumin in budesonide-treated group after challenge with diluent (Dil) ($P<0.05$), 100 SQ-U ($P<0.01$), and 1000 SQ-U ($P<0.05$) in March, while no statistically significant differences were detected in May.

levels than the levocabastine group ($P<0.05$). At allergen provocation in May, both budesonide and levocabastine treatment reduced allergen-challenge-induced nasal symptoms compared to the placebo-treated group (Fig. 2B). There were no statistically significant differences in challenge-induced nasal symptoms between the two drug regimens by the intergroup comparisons in May. The lavage fluid levels of albumin were numerically lower with both treatments compared to placebo at all provocation doses in May. However, these differences were statistically significant for budesonide only after the highest allergen dose (comparison to placebo) (Fig. 3B). There were no differences in lavage fluid levels of albumin between the two drug regimens.

Intragroup comparison. Both preseasonal (March) and seasonal (May) nasal allergen challenges produced dose-dependent increases in nasal symptoms and in albumin-levels of nasal lavage fluids in all three groups of participants ($P<0.001$, Friedman test) (Figs. 4 and 5). The challenge-induced nasal

responses in the placebo-treated group exhibited no evident increases during the pollen season (neither change reached statistical significance). Within the budesonide-treated group, both allergen-challenge-induced symptoms and albumin levels were significantly reduced in May, while no significant reduction was noted within the levocabastine-treated group (Figs. 4 and 5).

Discussion

Besides confirming the clinical efficacy of topical budesonide in seasonal allergic rhinitis, this study demonstrates that this drug inhibits the plasma-exudation response and the nasal symptoms evoked by allergen challenge carried out at the end of the pollen season. This study further demonstrates that a b.i.d. dose regimen of a topical antihistaminic drug protects the rhinitic airways late in the season against allergen-challenge-induced symptoms. Although both types of drugs showed significant treatment effects, the steroid treatment possessed a more general efficacy than the antihistamine, including effects on the plasma exudation response.

Both topical corticosteroids and antihistamines have previously proven effective in the treatment of seasonal allergic rhinitis (7, 8). Pelucchi et al. have also compared intranasal azelastine and beclomethasone dipropionate (9). They demonstrated that both drugs were superior to placebo and that the glucocorticoid treatment was slightly more effective than the antihistamine (9). Previous studies have shown levocabastine employed in the present doses to be more effective than placebo and to have an efficacy like that of oral antihistamines (8, 10, 11). The present study could not fully confirm this antihistaminic efficacy, possibly because these previous studies included a larger number of patients than the current study. However, the present study could confirm a superior clinical efficacy of topical steroids in seasonal allergic rhinitis (9, 12, 13).

In contrast to most previous allergen-challenge experiments carried out outside the pollen season when the participants are asymptomatic, the present participants were subjected to allergen challenge in the laboratory when they had an ongoing allergic disease due to natural pollen exposure. The present challenge design was selected to ensure a significant acute allergic reaction during natural disease and to disclose pharmacologic effects on this response. A previous study on the effect of topical levocabastine on nasal allergen-challenge-induced symptoms demonstrated that the presently used dose had a duration of at least 12 h with strongest effect between 4 and 10 h

TOTAL NASAL SYMPTOM SCORE (0-9)

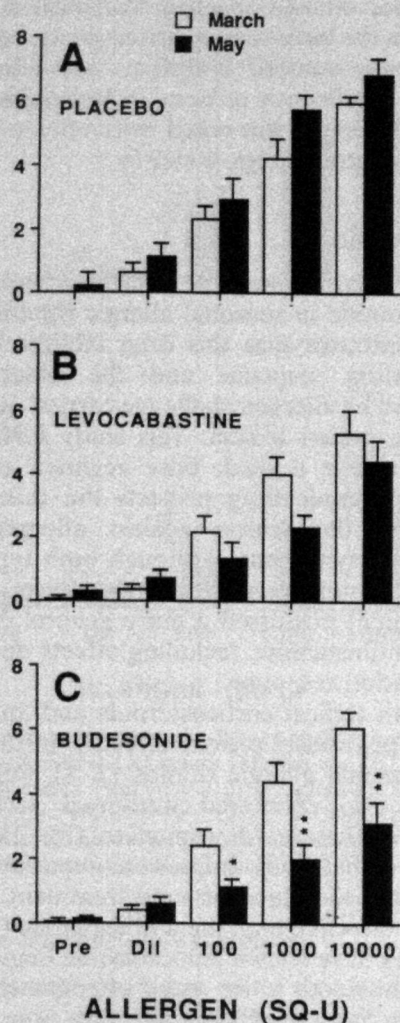


Fig. 4. Intragroup comparison of allergen-challenge-induced nasal symptoms ($\pm$ SEM) before (March) and at end of (May) pollen season. Placebo ($n=10$), levocabastine ($n=14$), budesonide ($n=15$). * $P<0.05$, ** $P<0.01$ (comparison March vs May for each group).

(14). The allergen challenge in the present study was performed well within this time interval (dosage on a b.i.d. regimen and the allergen challenge performed at 2 p.m.). Intranasal allergen challenge both before and at the end of the pollen season induced dose-dependent nasal symptoms as well as increased levels of albumin in postchallenge lavage fluids in all groups. For unknown reasons, the exudative response showed some variations between the groups before the season, making the intergroup comparison of this parameter uncertain. Accordingly, we consider intragroup comparison preferable in this study. There was a tendency for allergen challenge to produce stronger symptoms and plasma-exudative responses in the placebo

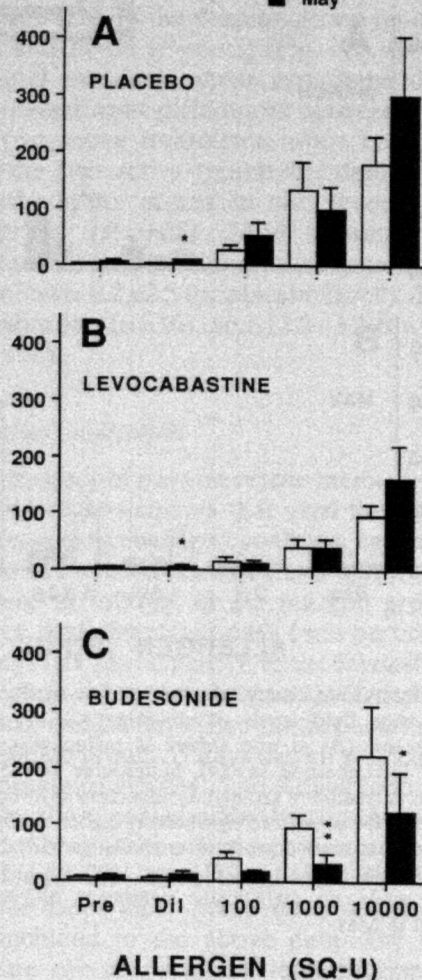
ALBUMIN (μ g/ml)

Fig. 5. Intragroup comparison of allergen-challenge-induced nasal lavage fluid levels of albumin ($\pm$ SEM) before (March) and at end of (May) pollen season. Placebo ($n=10$), levocabastine ($n=14$), budesonide ($n=15$). * $P<0.05$, ** $P<0.01$ (comparison March vs May for each group).

group at the end than before the pollen season, but this tendency did not reach statistical significance. Budesonide treatment significantly (both inter- and intragroup comparison) reduced both nasal symptoms and the plasma exudative response. Levocabastine was effective in reducing allergen-challenge-induced nasal symptoms (intergroup comparison) at the end of the pollen season, but had no significant effect on the exudative response. (The mean levels of albumin in postchallenge nasal lavages were lower for the levocabastine group than the placebo group at the allergen challenge in May, but these differences did not reach statistical significance.) These data may be compared with findings in perennial allergic rhinitis that treatment with levocabastine for 1 week reduced allergen-challenge-induced nasal symptoms, but not the

albumin levels in nasal lavage fluids (15). The present results are in contrast to previous studies on experimental challenge outside the pollen season which demonstrated a marked antiexudative effect of antihistamines, including levocabastine (3, 4, 16). The present data suggest that the effect of histamine antagonism is less pronounced in ongoing allergic disease than in the acute allergic reaction that is produced in allergic individuals without active disease. Mediators other than histamine would thus cause the plasma-exudation response when allergen challenge is performed during the pollen season in symptomatic patients. The possibility of reduced efficacy of antihistamines on an airway mucosa that is already inflamed suggests that antihistamines may be especially effective against allergen challenge in diseased airways where inflammation is already suppressed (e.g., by topical glucocorticoids). Indeed, results from previous clinical studies have demonstrated fewer rhinitic symptoms with antihistamines and topical steroids in combination than in monotherapy (12, 17), although the pathophysiologic mechanisms remain to be investigated in detail.

Mucosal exudation of plasma is initiated through release of different cellular mediators with the capability to induce endothelial cell separation in postcapillary venules belonging to the profuse superficial microcirculation of the airways (18). The extravasation of plasma is promptly followed by luminal entry of a bulk plasma exudate which is an efficient elimination route (rather than promoting mucosal edema). The epithelial passage is a noninjurious paracellular flux of bulk plasma, possibly driven by hydrostatic forces, with the epithelial cell-line operating with a valve-like mechanism (18). As first demonstrated a decade ago (19), microvascular-epithelial exudation of plasma in the airways is evoked by many common mediators including histamine, PAF-acether, leukotrienes, and bradykinin. Effects on mediator-releasing cells or on mediator receptors at venular endothelial cells may thus modulate the allergen-exposure-evoked plasma exudation process. In previous studies, we have demonstrated that baseline mucosal exudation of plasma is increased in seasonal allergic rhinitis and that topical corticosteroids attenuate this process (20). The antiexudative effect of topical corticosteroids that has been demonstrated in seasonal allergic rhinitis may reflect a global anti-inflammatory efficacy of these drugs, including the inhibition of mucosal inflammatory cells, rather than merely a direct antileakage effect on the endothelial cells (21, 22).

In conclusion, this study confirms the clinical efficacy of topical budesonide in the treatment of seasonal allergic rhinitis. Furthermore, it demon-

strates the ability of both levocabastine and budesonide to attenuate allergen-challenge-induced nasal symptoms. Only budesonide reduced the plasma-exudative response to the allergen challenge at the end of the pollen season. Thus, whereas the topical antihistamine treatment maintained a symptom-reducing capacity, the topical steroid exhibited both anti-inflammatory and symptom-reducing capacity in this study of seasonal allergic rhinitis.

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