

Assessment of the allergic reaction in seasonal rhinitis: acoustic rhinometry is a sensitive and objective method

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Summary

Background Seasonal allergic rhinitis constitutes an excellent *in vivo* model of an allergic mucosal inflammatory reaction. This offers the opportunity of studying the fundamentals of allergic inflammation in addition to improvement of knowledge on the basal pathophysiological mechanisms of the disease. So far, monitoring methods of disease activity and treatment efficacy have mainly been based upon subjective assessments, illustrating the impact of introducing reliable objective methods.

Objective To investigate the allergic inflammatory reaction of seasonal rhinitis through different objective methods and evaluate these as indicators of disease activity and treatment efficacy.

Methods Functional parameters, i.e. acoustic rhinometry and nasal metacholine challenge, and biological markers, i.e. blood eosinophil count, eosinophil cationic protein in serum (s-ECP) and nasal lavage fluid (n-ECP), were assessed before and at peak pollen season in 27 patients with grass pollen induced rhinitis. Patients were randomized to either nasal corticosteroid or placebo treatment and recorded nasal symptom scores.

Results Acoustic rhinometry revealed a significant difference in favour of steroid treatment ($P < 0.05$) comparing nasal volumes before and during season. This difference primarily relied upon a decrease in the placebo group ($P = 0.05$). A reduction from baseline of s-ECP in the steroid group ($P < 0.01$) was obtained. N-ECP demonstrated a difference between treatment groups, although not significant. Symptom scores increased in all patients during the pollen season, although this was only significant in the placebo treated patients ($P < 0.01$). The remaining methods applied did not demonstrate further differences, either within or between treatment groups.

Conclusion Our results demonstrate acoustic rhinometry to be a sensitive and objective method of assessment of nasal obstruction. Furthermore, acoustic rhinometry and s-ECP reflect the impact of nasal steroid therapy on seasonal allergic rhinitis.

Keywords: allergic rhinitis, seasonal rhinitis, hayfever, acoustic rhinometry, nasal metacholine challenge, eosinophils, ECP, nasal lavage

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Introduction

Seasonal allergic rhinitis is a common disease [1], and its prevalence seems to be increasing [2]. Apart from the

annoying and troublesome nasal symptoms, the disease causes a declining quality-of-life, resulting from concomitant phenomena like headache, lack of concentration, social limitations and impairment of sleep [3], as well as economic consequences attributable to medical contacts, sick leave and medication expenses. Furthermore, recent data suggest allergic rhinitis is a significant risk factor for developing asthma later in life [4].

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Allergic rhinitis is triggered by an inflammatory reaction in the nasal mucosa, consisting of vasodilation, hypersecretion, cellular infiltration (e.g. of eosinophil granulocytes) and oedema [5]. It is important to improve knowledge of the condition and functional state of the nasal mucosa in allergic rhinitis, to develop tools for monitoring of disease activity, and develop a rational approach to treatment [6]. Until now, many studies of allergic rhinitis, especially regarding treatment efficacy, have used subjective endpoints as indicators of disease activity [7]. During recent years, several objective methods have evolved, to quantify the allergic inflammation and its functional impact.

The primary objective of the present study was to describe and assess some of the main pathophysiological factors in allergic nasal inflammation, i.e. oedema, hyperreactivity and eosinophil activity, and their consequences, by using different objective methods. Apart from providing knowledge about the impact of each of these factors in seasonal allergic rhinitis, the results could improve the understanding of their relationship in the pathogenesis of allergic inflammation. Moreover, the study aimed to evaluate the different methods of monitoring disease activity, and evaluate their sensitivity compared to commonly used symptom scoring. Finally, the ability of the different methods to evaluate the impact of therapy was studied by using local corticosteroid therapy, representing an effective treatment directed against the nasal inflammation [8].

Materials and methods

Study population

Twenty-seven adult patients (17 males, 10 females) aged 20–68 years, with monoallergy towards grass pollen, documented by either positive skin prick test or RAST, and symptoms of allergic rhinitis during at least the two latest grass pollen seasons, participated in the study. All were non-smokers and none had received any kind of corticosteroid treatment within the previous 6 months.

Study design

The study methods, comprising of functional (i.e. acoustic rhinometry and nasal metacholine challenge) and biochemical parameters (i.e. blood eosinophil granulocyte count, serum and nasal lavage content of eosinophil cationic protein (ECP)), were carried out twice, the first time immediately before the grass pollen season and the second time 4 weeks later at the expected time of maximal pollen count. Each visit was extended over 2 consecutive days, because of the possible immediate interference of the

methods applied. The first study visit was followed by a 1-week baseline period, after which the patients received either Fluticasone propionate (Flixonase[®]) 200 µg o.d. or placebo administered as nasal aqueous spray, in a double-blind, randomized fashion. All patients had the opportunity to use antihistamines (Acrivastine) and eyedrops (Chromoglicate) as relief medication, apart from 12 h before each study visit.

During the full study period all patients kept a diary, in which they scored daily for three different symptoms, i.e. sneezing, runny and blocked nose, according to a linear scale ranging from 0 (no symptoms) to 3 (disabling symptoms). Eye symptoms and use of antihistamines were also recorded. Finally, during the treatment period, the patients had to mark daily their use of study medication to check compliance.

A group of 10 healthy adults (four males, six females) aged 30–56 years, without any history or signs of allergic disease, served as normal controls for blood and serological parameters at study entry.

Acoustic rhinometry

Acoustic rhinometry was chosen to express the degree of mucosal oedema, as this method directly measures cross-sectional area or volume of the nasal cavity. Thus, changes in these values within weeks to months will reflect changes in thickness of the nasal mucosa. This method is based upon acoustic measurements [9]. Briefly, a generated sound impulse is passed into one nostril, and the reflection from the nose is registered by a piezo-electric microphone. After amplification, a computerized analysis (Nadap v2.05) of intensity and time delay from the resulting signals is able to determine the cross-sectional areas and the volume of the nasal cavity. In the present study cross-sectional areas were measured as minimum and at 1.3 cm, 3.3 cm, 4.0 cm and 6.4 cm from the nostril. Nasal volumes were estimated to a distance of 12 cm from the nostril. The sum of right and left nasal cavity values were used for analysis. Values were obtained as a mean of three measurements with a maximum allowed variation of 5%.

Nasal metacholine challenge

The degree of nasal reactivity was assessed by challenge with metacholine bromide dissolved in saline. Saline and then doubling concentrations of metacholine, from 0.03 mg/ml to a maximum 64 mg/ml, were nebulized into each nostril using a nasal spray delivering 0.13 ml/dose. The nasal response was measured as the highest of three consecutive inspiratory peak flows on a Youlton peak flow meter 90 s after each dose. The reactivity was

expressed in terms of the metacholine concentration resulting in a 20% reduction of nasal inspiratory peak flow compared to the post-saline value (PC_{20} metacholine). It was intended to estimate nasal congestion as an expression of the degree of mucosal hyperresponsiveness, and evaluate a potential parameter.

Biochemistry

The number of eosinophil granulocytes in peripheral blood was determined by counting in a Fuchs-Rosenthal chamber.

For measurements of serum ECP (s-ECP), serum was isolated by sedimentation (60 min, 20°C) followed by centrifugation (10 min, 4°C, 1600 g). The resulting serum samples were kept at -80°C until analysis. ECP analysis was carried out by fluorescence-emission-immunoassay (CAP-FEIA[®] system, Pharmacia AB). Nasal lavage was applied, modified from a previously described method [10]; 4 ml of saline were instilled through each nostril with the patient seated, the head extended 45° from horizontal, and the nasopharynx occluded voluntarily by the soft palate. After 15 s the fluid was recovered passively into a tube and placed on ice until centrifugation (10 min, 4°C, 1600 g). The supernatant was kept at -80°C until analysed for ECP content (n-ECP) in the same way as the serum samples. Before the lavage the patients were asked to blow their noses. A single baseline wash was performed in each nostril.

Finally total serum IgE (ELISA) and allergen specific IgE (FEIA) were determined at study entry.

Pollen count

Grass pollen was counted daily throughout the study period using a Burkard trap and expressed as number/m³ air (Fig. 1).

Statistics

For each variable analysed, the difference between visits was used. Between treatment comparisons were performed using unpaired *t*-test. Within treatment comparisons were done by paired *t*-test. Normal assumptions were checked by using normal plots. Checks for homogeneity of variances in the treatment groups were done by Bartlett's test. If any of the assumptions were violated, logarithmic transformation was applied. If inappropriate, non-parametric statistics were applied (Wilcoxon or sign test). Analyses were performed using SAS software (v6.08).

Ethics

The study was approved by the local scientific ethics committee (County of Aarhus). All patients gave informed consent in writing before entering the study.

Results

Twenty-seven patients were randomized, 13 received intranasal steroid treatment and 14 received placebo. Baseline characteristics of patients and controls are listed in Table 1. No significant differences were observed between the two treatment groups. Compared to the controls, patients with allergic rhinitis had significantly higher levels of both total serum IgE ($P < 0.01$) and allergen specific serum IgE ($P < 0.001$). Acoustic rhinometry (Fig. 2) showed comparable nasal volumes at entry between treatment groups (steroid 68.4 ± 5.2 ml, placebo 71.8 ± 4.9 ml (mean $\pm$ SEM)).

During the pollen season a minor increase of nasal volume was demonstrated in the steroid group (72.5 ± 5.7 ml), in contrast to a marked decrease in the placebo treated patients (60.9 ± 3.7 ml). This difference of change in nasal volumes between groups was significant ($P < 0.05$) and primarily caused by the lower levels within the placebo group ($P = 0.05$). Minimal cross-sectional area revealed a decrease in the placebo group (1.30 ± 0.10 cm² to 1.23 ± 0.11 cm²) compared to an increase in the steroid group (1.19 ± 0.09 cm² to 1.26 ± 0.11 cm²) during the season. However, neither this nor any of the other cross-sectional areas measured (data not shown), were able to demonstrate significant differences between or within treatment groups ($P > 0.2$ for all comparisons).

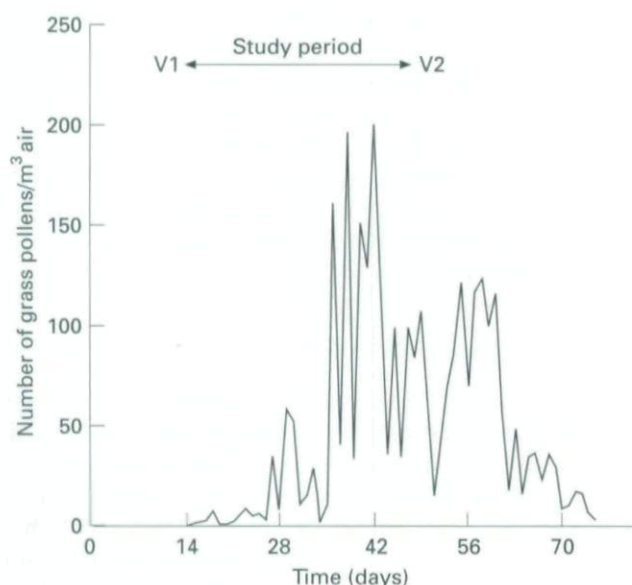


Fig. 1. Daily pollen counts in Aarhus, Summer 1994.

Table 1. Baseline characteristics of study population

	Steroid	Placebo		Controls	
Age (yr)	33.7 (20–52)	40.6 (24–68)	ns	40.5 (30–56)	ns
Gender (M/F)	6/7	11/3	ns	4/6	ns
Eosinophils (m/L)*	200 ± 30	243 ± 30	ns	118 ± 29	<i>P</i> < 0.05
Serum IgE (kU/L)*	100.8 ± 23.6	66.4 ± 10.9	ns	21.7 ± 7.6	<i>P</i> < 0.01
RAST grass (PRU/L)*	8.6 ± 1.6	6.6 ± 1.9	ns	0.0	<i>P</i> < 0.001

* Mean ± SEM at study entry.

Nasal metacholine challenge likewise showed only minute changes between the mean preseasonal and seasonal levels of PC₂₀ metacholine in steroid (0.00 ± 0.20 mg/ml) and placebo groups (-2.21 ± 2.10 mg/ml), and no significance was obtained in the comparison of changes both within and between treatments. It is, however, worth noticing the low range of PC₂₀ metacholine (0.5–3.0 mg/ml) in both groups throughout the study.

Blood eosinophil counts (Fig. 3) at study entry were almost equal in the steroid ($200 \pm 30 \times 10^6/L$) and the placebo treated patients ($243 \pm 30 \times 10^6/L$), and significantly higher (*P* < 0.01) than the mean level of the controls ($118 \pm 29 \times 10^6/L$). During the season these values demonstrated minor insignificant elevations in

both steroid ($212 \pm 34 \times 10^6/L$) and placebo groups ($307 \pm 44 \times 10^6/L$).

S-ECP (Fig. 4) in the steroid group ($14.54 \pm 4.35 \mu g/l$) as well as in the placebo group ($13.55 \pm 1.71 \mu g/l$), were significantly higher, when compared with the control group ($4.02 \pm 0.46 \mu g/l$) before season (*P* < 0.001). In the season the level of the steroid treated patients decreased to $8.11 \pm 1.65 \mu g/l$ (*P* < 0.01). A minor decline to $11.87 \pm 1.70 \mu g/l$ was noticed in the placebo group (ns). No significant difference was found when comparing the changes in the two groups.

All except one patient in the steroid group were able to comply with the nasal lavage procedure. The mean recovery rates in the groups at the two visits ranged from 58.8% to 65.2% and no significant differences were present, either within or between the groups. The ECP

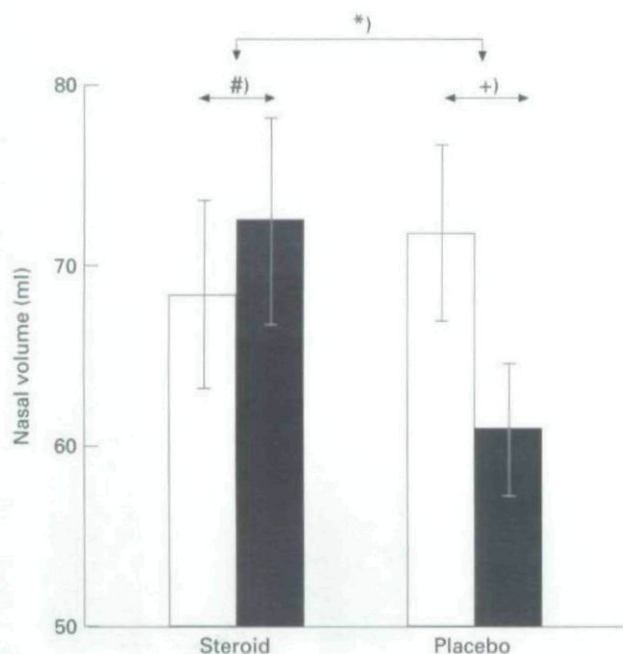


Fig. 2. Acoustic rhinometry expressed by total nasal volume (mean ± SEM). #) = ns; +) = *P* = 0.05; *) = *P* < 0.05). □ = before season; ■ = during season.

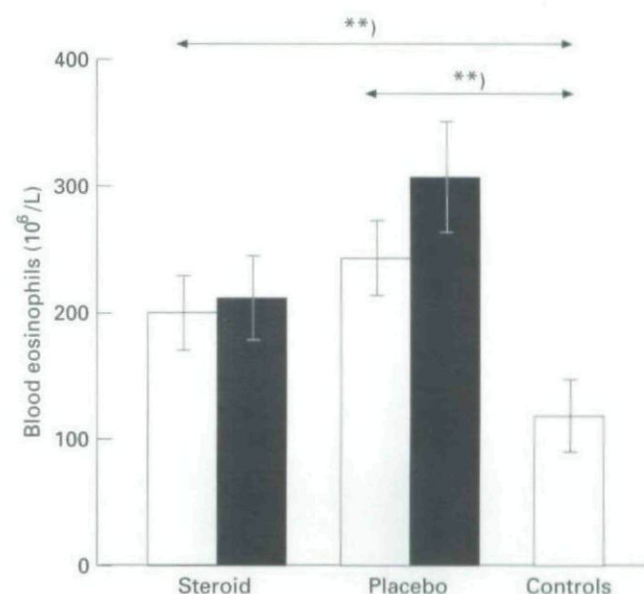


Fig. 3. Number of eosinophils in peripheral blood (mean ± SEM). **) = *P* < 0.01). □ = before season; ■ = during season.

content of nasal lavage fluid (Fig. 5) was at visit 1 similar in the steroid ($3.74 \pm 1.08 \mu\text{g/l}$) and the placebo group ($3.30 \pm 0.57 \mu\text{g/l}$). During the season levels in the steroid treated patients decreased to $2.75 \pm 0.45 \mu\text{g/L}$, while an increase was observed in the placebo treated patients to $5.10 \pm 1.38 \mu\text{g/L}$. These changes in both treatment groups were non-significant, but a comparison of the changes gave a tendency towards a difference ($P = 0.07$).

Symptom scores of sneezing, blocked and runny nose, as well as the combined score increased from baseline in both groups (Fig. 6). The increase from baseline was only significant in placebo treated patients ($P < 0.05$). When comparing changes for each of the symptoms between treatment groups, a difference was seen, although not reaching level of significance, i.e. blocked nose ($P = 0.10$), runny nose ($P = 0.08$) and sneezing ($P = 0.07$). Antihistamine intake (Fig. 6) increased significantly in both treatment groups during the season ($P < 0.01$), while no inter-treatment differences were observed ($P = 0.66$). Eye symptoms increased equally in both groups ($P < 0.01$, data not shown).

Discussion

An important factor of allergic rhinitis, both regarding symptomatology and pathophysiology, concerns the degree of nasal obstruction. Apart from subjective assessments of nasal airflow and rhinoscopic inspection,

rhinomanometry, expressing nasal resistance, presents a long used and thoroughly investigated method of estimating nasal airway patency in pathophysiological studies [11] and studies on treatment efficacy [12,13]. However, several questions have been raised on the technique, such as which parameters to use [14,15] and their correlation with rhinoscopic examination [16], as well as the measure's correlation to the degree of subjective nasal blockage [17].

Acoustic rhinometry presents a more recent and so far less used method of measuring nasal airway patency. This technique is based on acoustic reflections and offers certain advantages as it requires a minimum of cooperation from test persons, is reproducible and correlates highly with results from CT scans as well as rhinomanometry [9].

Our results, although obtained in a rather small population, were able to significantly demonstrate the involvement of mucosal inflammation with subsequent nasal obstruction, as shown by the decrease in nasal volume. Considering cross-sectional areas, expressed both as minimum and at various distances from the nostril, we were not able to obtain any significant differences, neither between nor within treatment groups during the season. This is in contrast to common acceptance of this parameter being the most reliable of acoustic rhinometry. However, allergic rhinitis represents an overall affection of the nasal mucosa

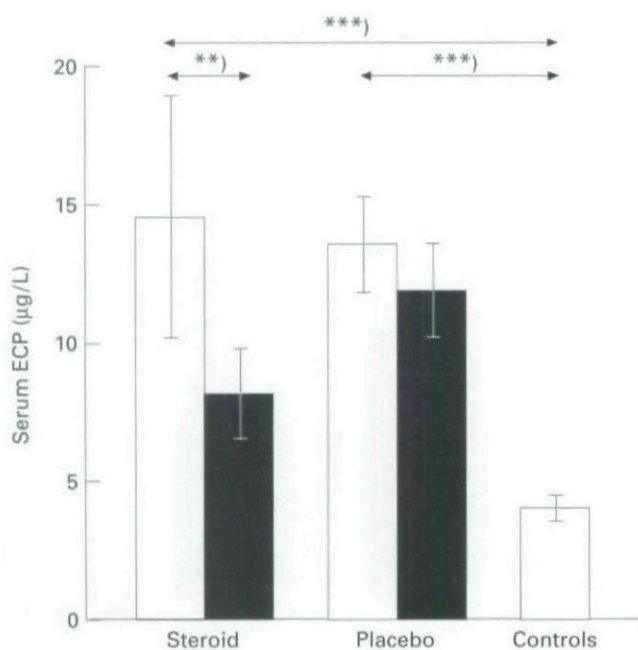


Fig. 4. Serum-ECP (mean $\pm$ SEM). ** = $P < 0.01$; *** = $P < 0.001$. $\square$ = before season; $\blacksquare$ = during season.

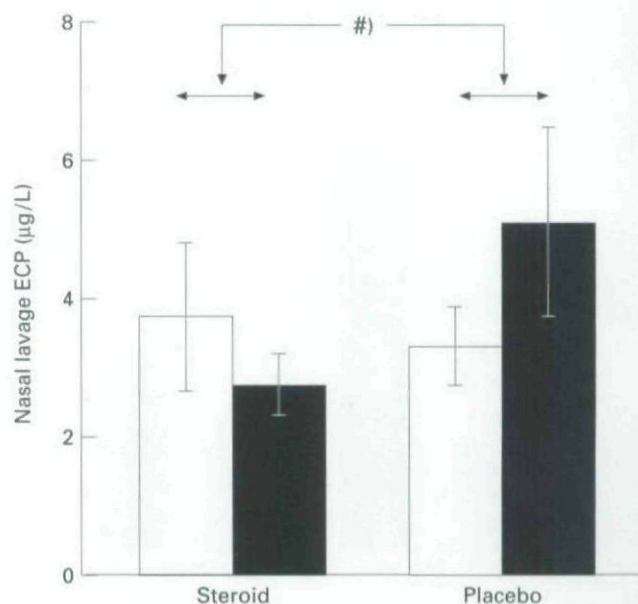


Fig. 5. ECP content of nasal lavage fluid (mean $\pm$ SEM). # = ns; $P = 0.07$. $\square$ = before season; $\blacksquare$ = during season.

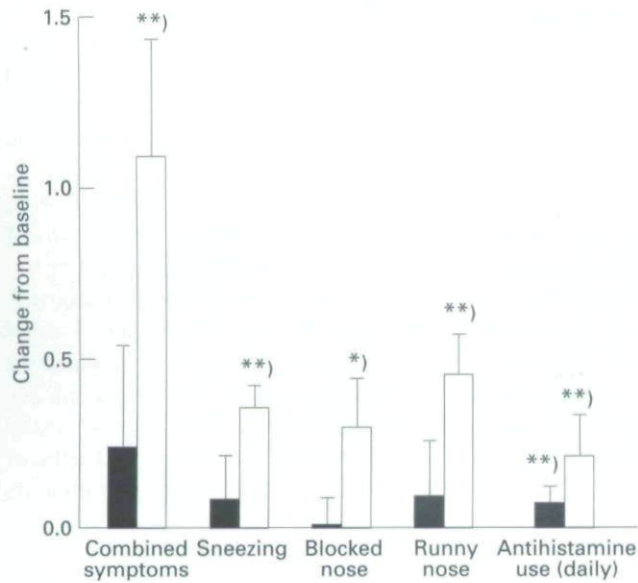


Fig. 6. Change in the score of combined and individual nasal symptoms from baseline to treatment. Change in daily use of antihistamines from baseline to treatment (number of tablets/patient) (mean $\pm$ SEM). * = $P < 0.05$; ** = $P < 0.01$. □ = placebo; ■ = steroid.

and as such the volume parameter may be more sensitive in discovering changes, as shown by the present data.

The method confirmed the efficacy of local corticosteroid therapy, represented by Fluticasone, in preventing the mucosal swelling during the season. This is according to results from previous studies [18,19] and confirms the value of the method in quantifying changes in nasal obstruction and as a tool for monitoring therapy in allergic rhinitis. A possible way of refining the technique in allergic rhinitis could be to diminish the distance of measurement from the nostril, i.e. to evaluate only the anterior parts of the nasal cavity. This would enhance reproducibility of the test as well as confine measurement to the part of the nose affected most by the inflammatory process. The pathogenesis of nasal hyperreactivity (NHR) is still controversial, especially when compared to the well-described phenomenon of bronchial hyperresponsiveness. The main problems appear to be a low level of specificity as well as an apparent lack of homogeneity in methodology applied and patients studied so far [20].

It is well established that metacholine is capable of inducing nasal congestion [21,22]. Our patients revealed a marked degree of NHR, expressed as nasal metacholine challenge PC₂₀, throughout the whole study period compared to results obtained in previous studies [21,23]. This could suggest NHR to be present at the beginning of the season (i.e. before or at very low allergen exposure), which contrasts with earlier findings in patients with

seasonal rhinitis [24]. Those data were, however, based upon allergen challenge outside season and did not account for the possibility of a priming effect by minimal amounts of pollen just before season or any cyclical variation of non-specific reactivity in seasonal rhinitis, as could be indicated by the present results. Our data demonstrate that treatment with intranasal corticosteroid does not alter the degree of NHR, similar to results obtained in challenge studies with histamine [25] and cold, dry air [26].

Eosinophil granulocytes constitute one of the major pathogenetic characteristics of the allergic inflammation seen in seasonal rhinitis [5,27,28]. Moreover, localization of eosinophils in the nasal mucosa enhance their state of activation [5,29], reflected by a higher degree of releasability of ECP and other granular proteins [30,31]. An interesting finding in the present study was significantly raised levels of both eosinophils and s-ECP in allergic patients throughout the study period compared to the controls. The most unexpected finding was, however, unaltered levels of s-ECP in placebo-treated patients during season, where one would anticipate an increase, as has been observed in asthmatics during natural pollen exposure [32]. In contrast n-ECP values revealed a fall in the steroid group and an increase in the placebo group although this was not significant. It should be emphasized that we measured the native concentration of ECP in the nasal fluid. The reason for doing so grew from the viewpoint of the nasal mucosa being a target organ for eosinophils; the amount of ECP would reflect the degree of inflammatory activity, whereas peripheral blood, merely being a transport medium, is known to possess only minute amounts of ECP in plasma [33]. By measuring the native ECP concentration at the target organ, an expression of the actual eosinophil degranulation taking place was obtained. The lower levels of n-ECP in the present study compared to levels obtained in previous studies [34,35], must rely upon the difference of technique and the lavage volume used. Neither of the former studies were, however, able to reveal any differences between preseasonal and seasonal levels of n-ECP, although an increase was demonstrated after allergen challenge [34].

Several explanations could be proposed for the apparent discrepancy of eosinophils/s-ECP and n-ECP in the placebo group. One would be that eosinophils are recruited from bone marrow to peripheral blood and activated to some extent at the beginning of season, by a priming effect of non-detectable amounts of pollen or by some kind of cyclical variation as postulated for NHR. Recruitment to the target organ, however, requires a higher degree of allergen exposure and this may account for the n-ECP rise during season, as activated eosinophils accumulate in the nasal mucosa. In accordance with

this, it has been demonstrated in challenge studies that direct allergen exposure is necessary to gain eosinophil influx into the tissue [27,36]. Furthermore, accumulation, activation and lifespan of eosinophils at inflammatory sites are known to be dependent upon several mediators, especially interleukin-5 [36,37], mainly derived from T-lymphocytes, although both eosinophils and mast cells possess the capacity of synthesizing this cytokine [38].

The role of the eosinophil in the mucosal allergic inflammation obviously not only depends on the eosinophil, but is also influenced by other cell types and mediators present in response to allergen exposure either during season or by challenge. Another possible reason for the observations could be the existence of a chronic inflammatory hibernating condition dramatically aroused by seasonal allergen exposure, as indicated by previous studies [35,39]. This explanation seems, however, to be less well documented. Further data, i.e. values throughout the entire year, are needed to clarify the question.

The current results illustrate the efficacy of corticosteroid therapy on the activation state of eosinophils expressed as s-ECP and n-ECP, thereby confirming data from previous studies [30,31,34,40]. The significant decrease in s-ECP levels of the steroid group are particularly interesting, as it appears after a small dose of topically applied corticosteroid with only little expected systemic absorption. Hence, the decrease must be due to either minute amounts of steroids in the systemic circulation inflicting upon eosinophils or, more likely, an inhibitory signal from a less inflamed nasal mucosa to blood eosinophils or their precursors.

Symptoms constitute an important parameter in the assessment of allergic rhinitis, especially relating to treatment efficacy [41,42]. In this study, we used three main symptoms of seasonal rhinitis, and each of these as well as their combination revealed significant increases in the placebo patients during season, while minor non-significant increases were seen in the steroid group. When comparing the changes between treatment groups a difference was observed, almost reaching the level of significance. This lack of significance was probably caused by the relatively small number of patients and the marked variation of values. The present data thus emphasize symptom scoring as a valuable parameter, although demanding relatively large populations to present significance. Objections could be made against the patients being allowed to use antihistamines, but although a significant rise of intake was seen in both groups, no difference was observed between the groups. The increase of eye symptoms was correlated to allergen exposure, as indicated by the pollen counts.

The results of the present study regarding both hyper-reactivity and inflammatory parameters (i.e. eosinophils

and ECP) suggest a certain degree of allergic readiness at the beginning of the season. Pollen exposure then initiates the mucosal allergic reaction, eliciting mucosal swelling (as indicated by rhinometric data) and inflammation (as indicated by elevated n-ECP), inducing the well-known symptoms of seasonal rhinitis. The reason for this preseasonal state remains unsolved, although priming or cyclical variation are possible explanations of the phenomenon. Our data demonstrate acoustic rhinometry to be a sensitive and objective method for measuring nasal obstruction and reflecting the impact of nasal steroid treatment, exemplified by Fluticasone, in seasonal rhinitis, even in this small population. Treatment efficacy was also shown by s-ECP. N-ECP may be a potential monitoring parameter of disease activity and treatment efficacy, although further studies are needed to define its value.

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