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Effect of vasoconstrictor pre-treatment on obstruction, secretion and sneezing after nasal challenge with threshold and suprathreshold allergen doses*

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SUMMARY

Acute nasal allergen challenge produces airway obstruction which varies in amount and timing with the allergen dose delivered. To see whether different mechanisms might contribute variably to mucosal swelling with different amounts of allergen, we challenged sensitive volunteers with threshold and 10-times threshold allergen doses, with and without topical vasoconstrictor pre-treatment. The vasoconstrictor effectively eliminated obstruction at both allergen dose levels, suggesting that acute vascular changes were responsible for all the measurable obstruction seen with acute allergen provocation. Alpha-adrenergic vasoconstrictor pre-treatment was associated with increased weight of secretion and numbers of sneezes.

Key words: nasal allergen challenge, nasal vasoconstriction, nasal decongestion, oxymetazoline

INTRODUCTION

One of the cardinal features of the nasal allergic reaction is mucosal swelling leading to airway obstruction. When this reaction is induced by acute allergen provocation the swelling is asymmetrical (Brooks et al., 1991). This is probably a result of interaction between the allergic response and the underlying nasal cycle (Principato et al., 1970; Eccles, 1977; Brooks et al., 1991). We have found that the amount of nasal obstruction is allergen-dose related, reaching its maximum later and decreasing more slowly with higher allergen doses (Brooks et al., 1991).

The major cause of nasal mucosal swelling is distension of submucosal venous sinuses (Mygind, 1979). Decongestant vasoconstrictors empty these sinuses providing effective symptomatic benefit. Mucosal biopsy specimens from people with chronic rhinitis have shown mucosal oedema and inflammatory infiltrates which also contribute somewhat to nasal airway obstruction (Harlin et al., 1988).

We hypothesized that the slower-to-develop-and-remit congestion after suprathreshold allergen provocation reflected recruitment of a second, possibly non-vascular mechanism which was not triggered by exposure to threshold allergen doses. If this were the case, the more complex response to higher dose provocation might better approximate naturally-occurring allergic rhinitis than does the reaction after a threshold allergen stimulus.

In this study we sought to separate vascular and non-vascular contributions to nasal obstruction after allergen provocation. To accomplish this we used oxymetazoline (OMT), an effective vasoconstrictor used commonly as a topical decongestant. Our means of assessing mucosal swelling was unilateral measurement of Nasal Airway Resistance (NAR). We anticipated that mucosal swelling developing rapidly after threshold allergen dosing would be vascular in origin and would be eliminated by the vasoconstrictor. With suprathreshold dosing we expected that mucosal swelling on the lower resistance side might be non-vascular and would be little affected by the vasoconstrictor. On the higher resistance side, the vasoconstrictor should eliminate only the vascular contribution. This would result in partial elimination of the allergen-induced rise in resistance producing a similar congestive response on both sides of the nose.

MATERIALS AND METHODS

Subjects

Eleven subjects with seasonal allergic rhinitis participated. None were sensitive to allergens likely to be in the environment at the time of the study provocations. Table 1 lists sex,

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Table 1. Demographics of study participants.

sex	age	allergen (threshold)
F	25	ragweed (1:1,000)
F	36	ragweed (1:10,000)
M	38	ragweed (1:10,000)
F	42	ragweed (1:3,000)
F	42	bluegrass (1:10,000)
M	50	ragweed (1:10,000)
M	30	ragweed (1:3,000)
F	30	ragweed (1:10,000)
M	29	ragweed (1:10,000)
F	33	bluegrass (1:3,000)
F	35	ragweed (1:1,000)

age and allergen used for each of the volunteers. All were pollen sensitive, nine to ragweed and two to bluegrass. For six subjects the threshold was 1:10,000, the weakest concentration which we have found useful in studies of this type. There were seven women and four men ranging in age from 25 to 50 years. All were healthy except for their allergies. Each subject consented in writing to participate after being informed about the study's intent, design, risks and benefits. To identify each subject's level of sensitivity, we ran a diagnostic challenge sequence. This consisted of spraying the nose with allergen in dilutions of 1:10,000; 1:3,000; and 1:1,000. A positive response was more than 1 g of blown secretions or two or more sneezes in the 5 min following the challenge. When this response occurred, we stopped the sequence and designated the last allergen dilution used as that patient's threshold. After a lesser response, we waited 10 additional minutes and retreated with the next higher dose. All volunteers had to demonstrate challenge reproducibility in a second diagnostic challenge.

Study materials

Allergens used for diagnosis and provocation were obtained from Hollister-Stier (Spokane, USA). The hospital pharmacy provided 0.05% oxymetazoline. All volumes administered were 0.15 ml sprayed into each side of the nose using a locally fabricated sprayer which delivers rapidly and quantitatively (Brooks et al., 1981).

Assessment of response

We measured Nasal Airway Resistance (NAR) using a previously described posterior rhinomanometry system (Brooks et al., 1991). Measurements were made unilaterally at 5-min intervals beginning 20 min before the allergen exposure. After the allergen provocation, we measured NAR every 3 min for the first 15 min and at 5-min intervals through 40 min. We also collected blown secretions and counted sneezes for the first 15 min post-challenge.

Treatment/challenge sequences

Each subject was challenged with the following four sequences given in random order: (1) oxymetazoline (dosed twice at -20 and -3 min) followed by threshold allergen challenge; (2) oxymetazoline (dosed twice) followed by 10-times threshold allergen challenge; (3) placebo (dosed twice) followed by threshold allergen challenge; (4) placebo (dosed twice) followed by 10-times threshold allergen challenge. The challenge sessions were conducted at the same time of day and no less than one week apart.

Analysis of data

We designated high and low resistance sides of the nose based on NAR values in the last three measurements before allergen challenge. For each side of the nose, a change score was calculated by subtracting the mean pre-allergen challenge NAR measurement from each of the follow-up responses. The area under the resulting response curve (AUC) was obtained by inspection using the trapezoid rule. AUC scores for each patient were analyzed using an analysis of variance model incorporating factors for subject and treatment grouping. There were eight treatment groupings composed of the various combinations of high or low resistance, placebo or oxymetazoline pre-treatment and threshold or 10-times threshold allergen challenge. The sneezing and secretion scores were also analyzed using the above model. We used Proc GLM from SAS (SAS Institute, Inc., USA) to fit the analysis of variance models and the Least Square Means option to identify treatment group differences.

Ethical considerations

The study design and supporting documents were reviewed and approved by the Bronson Hospital Human Use Committee. All subjects consented in writing to participate before we undertook any study procedures.

RESULTS

Nasal Airway Resistance (NAR) measurements

We compared the effect of placebo or vasoconstrictor treatment on obstruction with threshold (T) and suprathreshold (10T) allergen provocation in the anticipated higher and lower resistance sides of the nose. Figure 1 plots results with placebo pre-treatment as mean changes in NAR after allergen provocation. As we noted previously (Brooks et al., 1991), compared with threshold stimulation, higher allergen doses produced greater obstruction which reached its peak later and lasted longer.

Figure 2 plots means of changes in NAR with 10T dosing, with and without vasoconstrictor (OMT) pre-treatment. We had hypothesized that OMT would suppress that part of the obstructive response due to vascular engorgement but exert minimal effect on obstruction due to edema or inflammatory infiltration. Since we postulated that vascular differences were the source of the asymmetry of response, it seemed likely that any obstruction developing after OMT pre-treatment would be about the same on both sides of the nose. The figure is partially consistent with that postulate in that asymmetry of response is not evident after OMT treatment. However, we had anticipated a measurable residue of non-

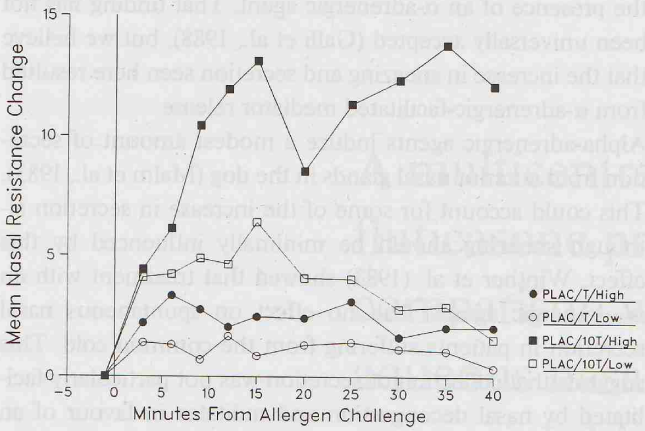

Figure 1. Mean Nasal Airway Resistance (NAR; cm H_2O/l/s) changes after allergen provocation with placebo (PLAC) pre-treatment. High(er) and Low(er) resistance sides of the nose were selected based on the three NAR values immediately preceding challenge. Values shown are changes from a baseline which is the mean of the five pre-challenge NAR measurements.

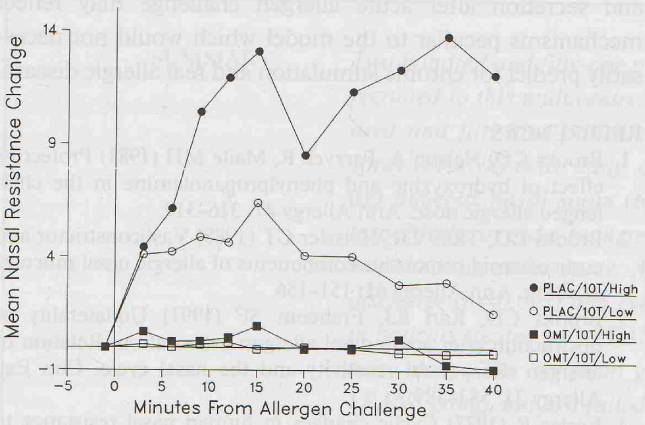

Figure 2. Mean Nasal Airway Resistance (cm H_2O/l/s) changes after suprathreshold (10T) allergen provocation. Higher and lower resistance sides, placebo (PLAC) or oxymetazoline (OMT) pre-treatment.

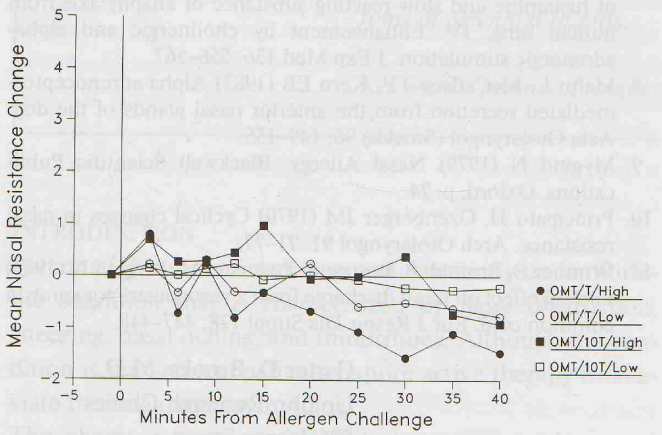

Figure 3. Mean Nasal Airway Resistance (cm H_2O/l/s) changes after allergen provocation. All sides receiving oxymetazoline (OMT) pre-treatment.

vascular swelling after OMT and this we do not see. The vasoconstrictor has effectively suppressed post-10T allergen-induced swelling suggesting that this was due entirely to vascular engorgement.

Figure 3 plots obstructive responses to threshold (T) and suprathreshold (10T) allergen doses with OMT pre-treatment. The T and 10T plots are essentially superimposable though some scatter is evident. Statistical testing indicates that it is unlikely that these results differ. Thus, vasoconstrictor pre-treatment has eliminated measurable differences in response between the two sides of the nose and between the T- and 10T-allergen-provoking doses. There is no evidence of a non-vascular contribution to allergen-induced nasal obstruction at any dose level studied.

Sneezing and secretion

Table 2 contains mean numbers of sneezes and mean weight of blown secretions obtained during the 15 min after allergen provocation. In all cases these measures indicated greater severity of response after vasoconstrictor pre-treatment. With 10T allergen provocation, the placebo/OMT differences were highly significant.

Table 2. Number of sneezes and weight of secretions in 15 min after threshold (T) and suprathreshold (10T) allergen dosing, with and without oxymetazoline (OMT) pre-treatment.

	sneezes		secretions	
	number mean	proba-bility	weight mean	proba-bility
T allergen/OMT	4.18	0.0105	2.37	0.0747
T allergen/no OMT	1.18		1.45	
10T allergen/OMT	6.73	0.0006	3.75	0.0023
10T allergen/no OMT	2.55		2.10	

DISCUSSION

Engorged submucosal vascular sinuses cause most of the mucosal swelling which obstructs the allergic nose (Mygind, 1979). With an acute threshold allergic stimulus the engorgement develops rapidly reaching its maximum in about 5 min (Brooks et al., 1991). It also fades rapidly, returning to pre-challenge levels within half an hour. In our previous studies it was notably one-sided, probably reflecting unilateral vascular reactivity related to the nasal cycle. With a suprathreshold allergen provocation, the same subjects showed a greater congestive response on both sides of the nose which was slower to reach its peak and much slower to disappear. This led us to wonder if the higher dose of allergen was recruiting other, non-vascular sources of mucosal swelling. Mucosal biopsies from patients with chronic rhinosinusitis show oedema, cellular infiltrates and thickened basement membranes (Harlin et al., 1988). Almost certainly this contributes to swelling of the mucosa although what fraction of these patients' nasal obstruction is contributed by non-vascular mechanisms is not clear. We have shown that, in

patients with ragweed hayfever, thorough dosing with a topical vasoconstrictor was insufficient to return NAR values to levels measured pre-seasonally (Brooks et al., 1988). When multiple doses of systemic corticoid were added to the vasoconstrictor, pre-seasonal NAR levels could be achieved. One interpretation of that finding was that the obstruction not reversed by the vasoconstrictor reflected non-vascular, corticoid-sensitive inflammatory swelling.

Having noted differences in timing and extent of allergic swelling induced by different levels of allergen stimulation, we hypothesized that different mechanisms were involved. Those not of vascular origin might be revealed by suppressing engorgement of the submucosal sinusoids with a vasoconstrictor. Expecting that a one-sided obstructive response related to the nasal cycle would be a vascular phenomenon, we anticipated that vasoconstrictor pre-treatment would suppress assymetry of obstruction. Further, after suprathreshold (10T) provocation, it should leave residual tissue swelling which would be reflected in higher resistance in both sides of the nose.

The experimental results are partly consistent with the hypothesis. Figure 3 shows that with OMT pre-treatment allergen provocation produced similar NAR patterns at both allergen levels and on both sides of the nose. The vasoconstrictor suppressed the asymmetry of response indicating that the source of the asymmetry was vascular. However, there was no sustained increase in NAR with higher allergen dosage failing to support the hypothesis that greater allergen dose was recruiting non-vascular mucosal swelling. Nasal obstruction due to oedema or inflammatory infiltration was either absent or too small to be detected by the measuring methods used in this study. The greater amount and different pattern of obstruction after 10T allergen provocation was apparently an extension of the same mechanisms involved at the threshold (T) level.

In this study we measured nasal resistance for 40 min post-challenge and had terminated our observations by the time late-phase-associated obstruction would occur. In earlier, unpublished studies we tried to assess late obstructive response using NAR measurement and patient's estimates of blockage, but could never discern any consistent pattern. In other studies, also unpublished, we found that in most subjects nasal eosinophil response first appeared 6 h after acute allergen challenge and peaked at about 24 h. We have never examined the effect of an α-adrenergic agonist on this response, but the more severe catarrhal responses after OMT (Table 2), suggest that such a study might be worth doing.

The increases in numbers of allergen-induced sneezes and weight of secretions after oxymetazoline pre-treatment were striking. Since secretion weight was based on the amount blown from the nose, one might argue that the decongested state after oxymetazoline made the secretions more easily recoverable. It is also possible that in a decongested state the mucosa was more accessible to allergen or to the effects of allergen-induced mediators. Kaliner et al (1972) reported that mediator release from shocked human lung was increased in the presence of an α-adrenergic agent. That finding has not been universally accepted (Galli et al., 1988), but we believe that the increase in sneezing and secretion seen here resulted from α-adrenergic-facilitated mediator release.

Alpha-adrenergic agents induce a modest amount of secretion from anterior nasal glands in the dog (Malm et al., 1983). This could account for some of the increase in secretion although sneezing should be minimally influenced by this effect. Winther et al. (1983) showed that treatment with an α-adrenergic agonist had no effect on spontaneous nasal secretion in patients suffering from the common cold. This suggests that collection of secretion was not particularly facilitated by nasal decongestion and militates in favour of an acute mast cell effect. Occasionally, patients report that decongestant nose drops increase running and blowing, but we have attributed this to greater ease of drainage after decongestion. We would not, based on these study results, recommend that patients avoid topical vasoconstrictors fearing that they might worsen nasal secretion. The possibility of rebound congestion is a substantially greater threat. The finding in this study of OMT-associated increases in sneezing and secretion after acute allergen challenge may reflect mechanisms peculiar to the model which would not necessarily predict for chronic stimulation and real allergic disease.

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