

Brief communications

Effect of oxymetazoline on the early response to nasal challenge with antigen

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The ineffectiveness of antihistamines for relief of nasal congestion during symptomatic allergic rhinitis prompted combining them with orally active α -adrenergic agonists. These agents act through two adrenergic receptors to constrict capacitance vessels and restrict the blood supply to the nasal mucosa. The result is a decreased volume of blood in the sinusoids and less mucosal edema, which leads to improved nasal airflow. Topical, compared with systemic, administration of α -agonists provides a more rapid onset of action and greater efficacy with fewer systemic side effects.

To evaluate mediator release after nasal antigen challenge, we have used the technique of nasal lavage to recover nasal secretions.¹ In preliminary experiments, it became apparent that a robust nasal reaction was necessary for the demonstration of increased histamine release. The congestion that resulted from the nasal challenge, however, frequently interfered with the ability to lavage the nasal cavity. The intranasal use of oxymetazoline, an α_2 -agonist, before antigen stimulation provided a means to impede the development of nasal congestion and permit continued nasal lavages. In a limited number of individuals in whom lavage could be performed after a strong antigenic challenge, we originally found equivalent amounts of histamine release. The use of this agent has caused concern among some investigators, however, because of potential effects of oxymetazoline on mediator release. We have re-

Abbreviation used

NAR: Nasal airway resistance

cently developed a localized nasal challenge with antigen, which permits us to measure histamine release while simultaneously assessing the physiologic response in the absence of oxymetazoline premedication.

METHODS

Fourteen subjects with ragweed- and grass-allergic rhinitis participated in a double-blind, cross-over trial in which two sprays of oxymetazoline (Nostrilla 0.05%) were compared with placebo (saline solution). We measured nasal airway resistance (NAR) by anterior rhinomanometry, counted sneezes, and monitored the secretory response by using 8 mm filter paper discs to collect secretions from the nasal septum posterior to the mucocutaneous junction for 30 seconds. These discs were preweighed in an Eppendorf container (Sarstedt, Newton, N.C.) and reweighed after secretion collection. The difference in weights provided the volume of secretions collected after each challenge. Then, 300 μ l of saline solution was added to the Eppendorf tubes and incubated overnight at 4° C to elute the secretions for the measurement of histamine by means of a radioenzymatic assay with a sensitivity of 200 pg/ml.² Preliminary experiments determined that over 90% of histamine added to a disc could be recovered. All samples from an individual subject were measured in the same assay to reduce interassay variability.

The challenge protocol began with baseline measurements. Next, each subject's nose was lavaged five times with 10 ml of Ringer's lactate solution. A second set of baseline measurements was obtained. Oxymetazoline or placebo was then applied in random order. Ten minutes later, the subjects were challenged with 50 μ l of the diluent for the antigen by placing an 8 mm filter paper disc at the same site of the septum used for collecting nasal secretions. Secretions were collected at 30 seconds and at 2 minutes after the challenge. Sneezes were counted, and 8 minutes

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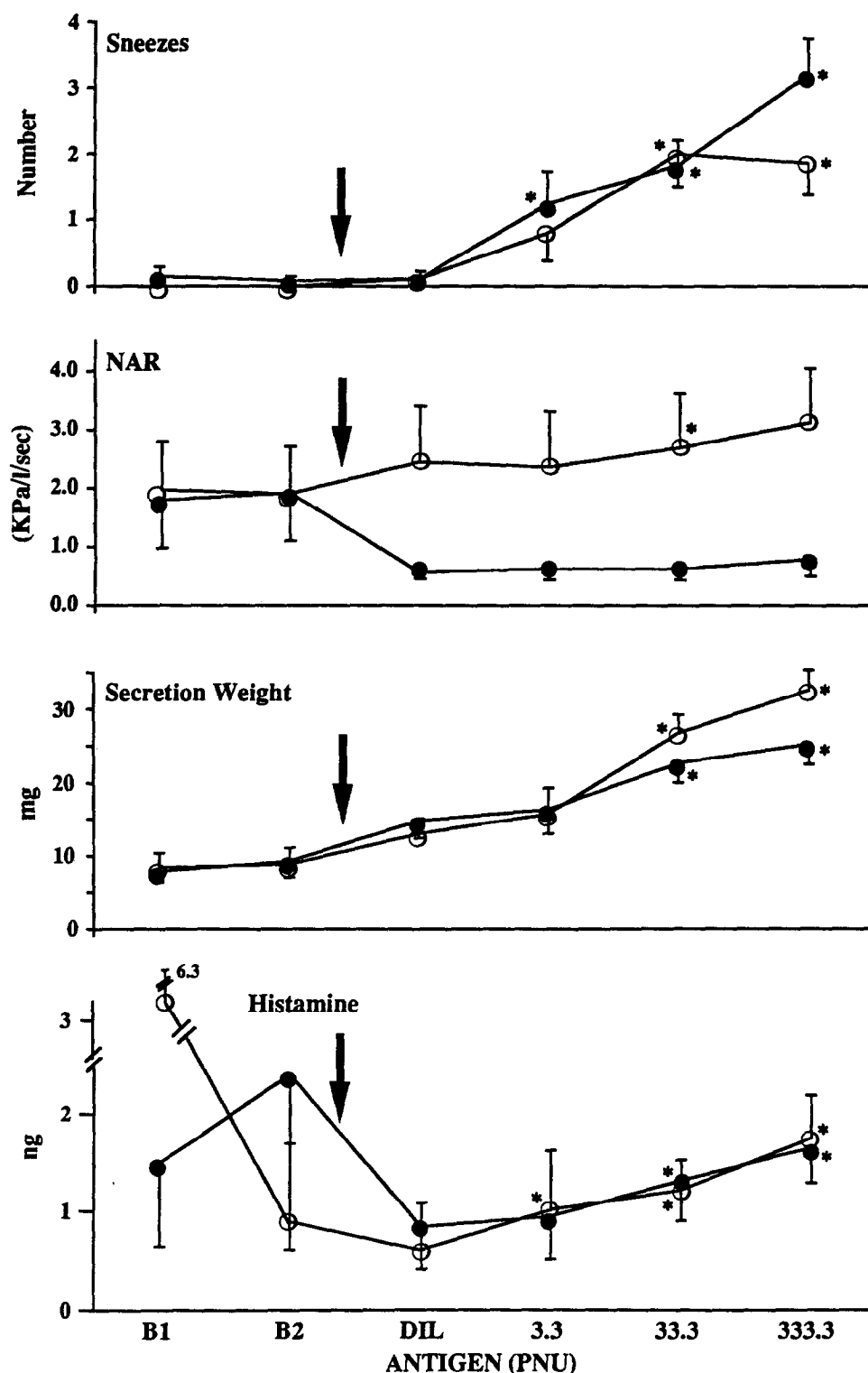


FIG. 1. The effect of premedication with oxymetazoline on antigen challenge. The challenge protocol is shown on the abscissa. *B*, Baseline measurement; *Dil*, diluent for the antigen extracts. Doses of antigen extracts were 3.3, 33.3, and 333.3 PNU. Responses after oxymetazoline are indicated by *closed circles* and those after placebo by *open circles*. The *solid vertical arrows* represent the time of administration of either oxymetazoline or placebo sprays. Data are expressed as means $\pm$ SEM for 14 subjects. * $p \leq 0.05$ versus respective diluents.

after the challenge, NAR was measured. Two minutes later the subjects were challenged with 3.3 PNU of antigen, and the measurements were repeated. The cycle was repeated with 33.3 and 333 PNU of antigen. The two challenge days were separated by 2 weeks.

The measurements obtained at 30 seconds and 2 minutes after each challenge were averaged and analyzed with the use of nonparametric statistics and expressed as means $\pm$ SEM to show the variability in the data. A Friedman analysis of variance was first done within each curve; and, if differences were found, the Wilcoxon signed-rank test was applied to compare antigen values with those of diluent. Comparisons between oxymetazoline and placebo were performed on total changes from diluent challenge. Total changes from the second set of baseline measurements were used when effects of oxymetazoline or placebo on NAR were compared.

RESULTS

High levels of histamine were present in baseline nasal secretions, which were reduced by lavage (Fig. 1). The administration of oxymetazoline decreased NAR. On the placebo day, antigen induced significant increases from the diluent response in sneezing, NAR, secretion weight, and histamine (Fig. 1). The response to antigen after oxymetazoline treatment showed increases in sneezing, secretion weights, and histamine but no change in NAR. Comparison of total changes from diluent after active therapy and placebo showed that sneezing increased from 4.32 ± 1.07 with placebo to 6.11 ± 1.1 with oxymetazoline ($p < 0.01$) and secretion weights decreased from 36 ± 6.3 mg with placebo to 19.8 ± 4.7 mg with oxymetazoline ($p < 0.04$) but that there was no significant change in histamine (2.18 ± 1.04 vs 1.4 ± 1.47 ng; placebo vs oxymetazoline). When the total changes from the second baseline were compared, there was a significant decrease in NAR after oxymetazoline administration, -5.04 ± 2.83 as compared with placebo administration, 3.05 ± 2.09 kPa/L/sec ($p < 0.01$). Because the volume of the secretions and the concentration of histamine recovered were known, we calculated the concentration of histamine in nasal secretions. No differences were found in these parameters between treatments. In other experiments in which this model was used, nonallergic subjects who were challenged with antigen or allergic subjects who were challenged with diluent did not release histamine or demonstrate changes in NAR, sneezing, or secretion weights (data not shown).

DISCUSSION

The results of this study are clear. Oxymetazoline decreases NAR. When applied before nasal challenge, it prevents the development of nasal obstruction and causes a slight decrease in the volume of secretion and a slight increase in the sneezing response. Oxymetazoline, however, does not affect histamine release.

These results are consistent with results of published reports. Watase and Okuda³ showed that phenylephrine caused no change in sneezing or secretions but had a marked effect on nasal congestion. Druce et al.,⁴ using laser Doppler velocimetry, and Bende et al.,⁵ using xenon clearance, both showed a 25% to 50% decrease in blood flow. The decrease in blood flow could contribute to the small decrease in the volume of secretions measured. Oxymetazoline acts through α_2 -receptors, which are presynaptic and postsynaptic.⁶ They regulate the release of norepinephrine and possibly cholinergic nerve activity, which could account for the small differences detected between treatments. Oxymetazoline alone can induce sneezing, which may have been potentiated by antigen stimulation.⁷

This study supports our prior impression about the lack of effect of oxymetazoline on antigen induced histamine release. Our results pertaining to histamine release after nasal challenge with antigen have been supported by some investigators. We suspect that the differences are related to two factors. First, the robust antigenic stimulation needed to consistently detect histamine release produces nasal congestion, which alters the ability to lavage the nasal cavity. Smaller degrees of stimulation can cause significant increases in histamine, but with less consistency. Second, the high baseline levels of histamine need to be reduced by serial lavages before changes can be detected. Conversely, it is easier to detect changes in biochemical markers with low basal levels.

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