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Topical active H_1-antihistamines and their effect on nasal airway resistance

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Abstract
The introduction of a topically active H_1-antihistamine nasal spray Azelastine, has given an extra dimension in the management of allergic rhinitis. The drug acts rapidly and avoids the systemic adverse effects of antihistimines. An objective prospective study was performed to detect the effect of Azelastine nasal spray on nasal airway resistance. Twelve healthy adult volunteers with no rhinological problems were included in the study. Nasal cavities were sprayed with 280 μg (two puffs) of Azelastine nasal spray and the nasal airway resistance was measured with anterior rhinomanometry at intervals of 30 minutes for up to two hours. Our study has shown a statistically significant increase in the total nasal airway resistance following the use of Azelastine nasal spray in the absence of a subjective change in nasal airway resistance. There are substances when inhaled which can cause subjective improvement in nasal airway patency without changing the measured nasal airway resistance. However this medication gives no subjective change in nasal airway patency in spite of increasing nasal airway resistance.

Key words: Histamine H_1 receptor blockaders; Nose

Introduction

The introduction of topically active nonabsorbent antihistamines (TANAA) for the management of nasal allergies is a new concept and has stimulated considerable interest among rhinologists. Azelastine hydrochloride nasal spray is a rapidly acting medication which avoids the systemic effects of antihistamines giving considerable advantages over oral antihistamines. Antihistamines block the histamine receptors and furthermore inhibit the secretion of histamines in the inflammatory reaction which can be mediated by allergic reactions (Jackson, 1991).

Preliminary studies carried out have shown that Azelastine, 4-[*p*-chlorobenzyl]-2-[hexahydro-1-methyl-1H-azepine-4yl]–[2H]-phthalazinone hydrochloride, nasal spray is as effective as terfenadine tablets (60 mg) twice a day in the treatment of allergic rhinitis (Nolte *et al.*, 1989). In our clinical practice however we encountered some patients developing nasal obstruction after the use of Azelastine nasal spray (topical H_1-antihistamines). This motivated us to test the effects of topical H_1-antihistamines on the nasal airflow by objective assessment of the airflow with rhinomanometry.

Materials and methods

A prospective study was performed to detect the total nasal airway resistance on 12 healthy adults after topical application of Azelastine nasal spray and the total nasal airway resistance was measured objectively by using rhinomanometry.

Material

Twelve healthy adult volunteers (seven females, and five males, aged 25–57 years; mean 37 years) with no rhinological abnormalities or symptoms were included in the study. The total nasal airway resistance was measured using the Mercury® NR8 rhinomanometer.

Methods

After detailed history and clinical examination only people with a normal airway and no evidence of nasal pathology were selected for the study. The total nasal airway resistance was measured with the rhinomanometer. Then each nasal cavity was sprayed with 280 μg (two puffs) of Azelastine nasal spray. Rhinomanometric assessment of the nasal airway was performed at intervals of 30 minutes and the last measurement was carried out after two hours.

Active anterior rhinomanometry was performed with flow (cm^3:/:s) measured at a transnasal pressure of 150 Pa and the mask tube fixed with tape. Total nasal airway resistance is given in Pa/cm^3 per s. All measurements were carried out in the same room

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TABLE I

THE SLOPE OF THE TINAR (MEAN TOTAL INSPIRATION NASAL AIRWAY RESISTANCE) AND TENAR (MEAN TOTAL EXPIRATION NASAL AIRWAY RESISTANCE) *VERSUS* TIME GRAPH WAS CALCULATED FOR EACH INDIVIDUAL SUBJECT USING SIMPLE LINEAR REGRESSION. THESE DEMONSTRATE THAT BOTH TINAR AND TENAR SIGNIFICANTLY ($p < 0.05$) INCREASE OVER TIME AFTER APPLICATION OF AZELASTINE NASAL SPRAY

	TINAR	TENAR
No. of subjects	12	12
Mean slope	0.00053	0.00051
SD	0.00062	0.00073
95% Confidence interval for the slope	0.00014 to 0.00092	0.00005 to 0.00098
p-value	$p = 0.013$	$p = 0.034$

(with visual feedback for the testing person) in a sitting position as suggested by the committee report on standardization of rhinomanometry (Clement, 1984).

Each objective rhinomanometric measurement was preceded by a subjective assessment of the nasal airway by visual analogue, ranging from: −2 (nose completely open); −1 (nose open); 0 (normal); +1 (nose blocked) and +2 (nose completely blocked).

Statistics

Statistics were done with simple linear regression analysis. Statistical significance was defined as $p < 0.05$.

Results

Rhinomanometry

The mean total inspiration nasal airway resistance (TINAR) increased after application of Azelastine nasal spray with a mean slope of 0.00053 (Table I). See Figure 1 for means ± standard errors *versus* time.

The mean total expiration nasal airway resistance (TENAR) also increased in time with a slope of 0.00051 (Table I). In fact 11 out of the 12 volunteers showed an increase in TINAR as well as an increase in TENAR over time.

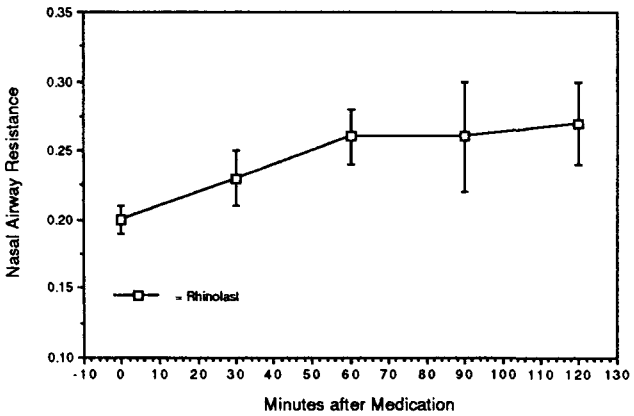

FIG. 1

Azelastine and the mean total inspiration nasal airway resistance (TINAR) in relation to time.

There is a statistically significant increase in the total nasal airway resistance following the use of Azelastine nasal spray.

Subjective

The median subjective score of the control measurement (time 0) as well as for times 30, 60, 90 and 120 minutes was 0. There was no statistically significant change in the subjective score of the nasal airway patency in relation to time.

Discussion

Antihistamines have anticholinergic, sedative, local anaesthetic and antiserotonin effects. Antihistamines also reduce histamine release and block histamine receptors in an inflammatory process which reduces the vascular permeability which can be triggered following an allergic reaction (Togias *et al.*, 1986; Jackson, 1991). The use of H_1-antihistamines results in less sneezing, itching and rhinorrhea, while the use of H_2-antihistamines results in vasconstriction (Jackson, 1991). Disadvantages of systemic antihistamines are their slow onset and adverse effects, mainly the dry mouth, sedation, headaches and blurred vision (Naclerio *et al.*, 1990; Jackson, 1991).

Allergic rhinitis is a common ENT problem for which there is no entirely satisfactory treatment. The commonly recommended treatment includes topically active nonabsorbent steroids with, or without, systemic antihistamines. The major drawback of the antihistamines is systemic side effects. The availability of topically active nonabsorbent antihistamines for use in the nose provides an extra dimension in the management of allergic rhinitis which avoids the adverse effects of systemic antihistamines.

The prospective study which we have carried out has shown a statistically significant increase in the total nasal airway resistance with time when antihistamines were applied topically to the nasal mucosa. This finding is quite contrary to expectations. It appears that the spray caused swelling of the nasal mucosa increasing the total nasal airway resistance. This did not correlate with the subjective sensation with time of nasal airway patency after topical application of these antihistamines to the nasal mucosa in our study.

The site of maximum nasal airway resistance is the same in healthy people as in people with allergic rhinitis (Wight *et al.*, 1988). Therefore we can conclude Azelastine nasal spray is capable of causing an increase in total nasal airway resistance in people with allergic rhinitis.

Our study has shown that Azelastine nasal spray increases the total nasal airway resistance, although all volunteers felt that there was no change in nasal airway patency. Therefore it can be assumed that a substance in the Azelastine probably stimulated the nerve endings responsible for detection of nasal airway patency. This phenomenon has been pre-

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viously described for substances like menthol and eucalyptus (Burrow *et al.*, 1983). Unlike these stimulants there is an objective increase in the total nasal airway resistance with Azelastine indicating this substance may be more stimulating than eucalyptus or menthol.

Conclusion

Azelastine nasal spray increases the total nasal airway resistance objectively in healthy people. Although previous studies have shown Azelastine reduces the runny nose and sneezing, in allergic rhinitis it does not decrease the total nasal airway resistance, one of the major problems of allergic rhinitis.

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