Inhaled histamine used to measure airway responsiveness produces some side effects more frequently than does methacholine. It is possible that the inhaled histamine induces the side effects in asthmatics with increased end organ responsiveness to histamine. A 56-yr-old woman with chronic idiopathic angioedema presented with asthma-like symptoms. Methacholine challenge test was performed, with a negative result. Five days later, histamine inhalation test was done. FEV1 fell by 37% after inhalation of histamine concentration of 8 mg/mL. Immediately thereafter, severe angioedema on face, lips, and oropharyngeal area, foreign body sensation at throat, and hoarseness occurred. To assess end organ responsiveness to histamine, skin prick tests with doubling concentrations of histamine (0.03-16 mg/mL) were carried out on the forearm of the patient and six age- and sex-matched asthmatic controls. The wheal areas were measured. The patient showed greater skin responses than the controls. Regression analysis showed that the intercept and slope were greater than cut-off levels determined from six controls. The patient showed an increased skin wheal response to histamine, indicating the enhanced end organ responsiveness to histamine, which is likely to contribute to the development of the oropharyngeal angioedema by inhaled histamine.

**Key Words**: Angioneurotic Edema; Histamine; Bronchial Provocation Tests
apparently observed and spontaneously resolved 4 hr later.

To assess end organ responsiveness to histamine, skin prick tests with doubling concentrations of histamine from 0.03 to 16 mg/mL were performed in duplicate on the forearm of the patient and six age- and sex-matched controls with atopic asthma. All subjects submitted a written consent to participate in the study. Fifteen minutes after the histamine prick test, the wheals corresponding to each of histamine concentrations were drawn directly on the arm. Tape was applied, removed, and glued onto a transparency, permitting an exact tracing of each area. All areas were calculated after scanning and integration using the computer program Adobe Photoshop and were analyzed using the public domain National Institutes of Health (NIH) Image program (developed at the US NIH and available on the Internet at http://rsb.info.nih.gov/nih-image/). The cut-off value of the skin response was determined from mean plus 2-fold standard deviation of wheal area from the controls. The cut-off values for doses of 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, and 16 mg/mL were determined as 0, 0, 0, 4.7, 14.2, 15.2, 20.3, 32.0, 54.0, and 62.7 mm², respectively. The patient showed a greater skin responses to histamine (6.2, 7.1, 21.2, 22.1, 51.5, and 57.1 mm² for the doses of 0.125, 0.25, 1, 2, 4, and 8 mg/mL, respectively) than cut-off values compared with age- and sex-matched atopic asthmatics, indicating the enhanced end organ responsiveness to histamine, which may contribute to the occurrence of the oropharyngeal angioedema by inhaled histamine.

In addition, Kanny et al. (6) showed that abnormal passage of histamine across the intestinal barrier could result either from intestinal hyperpermeability and/or a deficit in the enzymatic catabolism of histamine in chronic idiopathic urticaria, postulating a deficit in diamine oxidase in the enterocytes. The increased absorption of inhaled histamine across the oropharyngeal mucosa may in part play a role in the development of
the angioedema in the present case.

Although airway responsiveness to histamine correlated closely with responsiveness to methacholine (1), our case showed different airway responses to both stimuli. Spector and Farr (7) reported that atopic asthmatics were more reactive to histamine than to methacholine. However, further investigations are needed to verify this.

Taken together, in case the histamine bronchial provocation test is performed in asthmatics with a history of chronic idiopathic urticaria and/or angioedema, a possibility of severe oropharyngeal angioedema by inhaled histamine should be considered.

REFERENCES

1. Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. Thorax 1978; 33: 705-10.
2. Kaplan AP. Urticaria and angioedema. In: Middleton E, Jr. editors, Allergy: Principles & Practice. St. Louis: Mosby-Year Book, Inc., 1998; 1104-22.
3. Krause LB, Sluster S. Enhanced wheal and flare response to histamine in chronic idiopathic urticaria. Br J Clin Pharmacol 1985; 20: 486-8.
4. Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O Byrne PM, Anderson SD, Juniper EF, Malo JL. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur Respir J 1993; 6(Suppl 16): 53-83.
5. Dachman WD, Bedarida G, Blaschke TF, Hoffman BB. Histamine-induced venodilation in human beings involves both H1 and H2 receptor subtypes. J Allergy Clin Immunol 1994; 93: 606-14.
6. Kanny G, Moneret-Vautrin DA, Schohn H, Feldman L, Mallie JP, Guenat JL. Abnormalities in histamine pharmacodynamics in chronic urticaria. Clin Exp Allergy 1993; 23: 1015-20.
7. Spector SL, Farr RS. A comparison of methacholine and histamine inhalations in asthmatics. J Allergy Clin Immunol 1975; 56: 308-16.