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Oropharyngeal Angioedema Induced by Inhaled Histamine

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. FEV_1 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*

Youngil I. Koh, Inseon S. Choi

Division of Allergy, Department of Internal Medicine, Chonnam National University Medical School and Research Institute of Medical Science, Gwangju, Korea

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Address for correspondence
Inseon S. Choi, M.D.
Division of Allergy, Department of Internal Medicine, Chonnam National University Medical School, 8 Hak-dong, Dong-gu, Gwangju 501-757, Korea
Tel : +82-62-220-6571, Fax : +82-62-225-8578
E-mail : ischoi@chonnam.chonnam.ac.kr

INTRODUCTION

Inhaled histamine is as useful as methacholine for measuring airway responsiveness in asthmatics. However, such side effects as throat irritation, flushing, and headache are more frequent with histamine than with methacholine, and are dose-related (1). It is possible that the inhaled histamine produces severe adverse effects in asthmatics with increased end organ responsiveness to histamine.

The pathogenesis of urticaria and angioedema can involve the release of a diverse array of potential vasoactive mediators that arise from the activation of cells or enzymatic pathways, and histamine appears to be the major culprit (2). It has been reported that skin responses to histamine are enhanced in patients with chronic idiopathic urticaria (3). Therefore, inhaled histamine is likely to develop some adverse effects easily in patients with chronic idiopathic urticaria and/or angioedema. To our knowledge, the patient described herein is the first case of severe oropharyngeal angioedema developed during histamine inhalation challenge in an asthmatic patient with chronic idiopathic angioedema.

CASE REPORT

A 56-yr-old woman visited our clinic for evaluation of chronic cough and breathlessness. She had experienced mild angioedema episodes involving face and/or extremities without a family history. The episodes had no clear-cut association with any food, drugs or physical factors. Nephelometric assays (Behring, U.S.A.) showed normal C3 (135.4 mg/dL) and C4 (23.3 mg/dL) levels. Radial immunodiffusion assay (Binding Site, U.K.) showed that C1 esterase inhibitor was 37 mg/dL (normal range, 15-35 mg/dL). These findings could exclude the diagnosis of hereditary angioedema. On visit, she had no angioedema. Spirometry showed 1,980 mL (85% of predicted value) of forced expiratory volume in one second (FEV_1) and 2,550 mL (89%) of forced vital capacity. Skin prick tests with routine inhalants showed positive responses to *Dermatophagoides pteronyssinus* and *D. farinae.*

Regarding the diagnosis of asthma, methacholine challenge test was performed according to the standardized tidal breathing method (4). The concentration of methacholine that produced 20% fall in FEV_1 from baseline (PC_{20}) was over 25 mg/mL. Five days later, histamine inhalation challenge test was performed (4), inhaling doubling concentrations of histamine acid phosphate (Sigma Chemical Co., U.S.A.) from 0.03 to 16 mg/mL. FEV_1 fell by 37% from baseline at 3 min after inhalation of 8 mg/mL, resulting in histamine-PC_{20} of 4.59 mg/mL. Immediately thereafter, severe angioedema on face, lips, and oropharyngeal area, foreign body sensation at throat, and hoarseness occurred (Fig. 1). The angioedema was

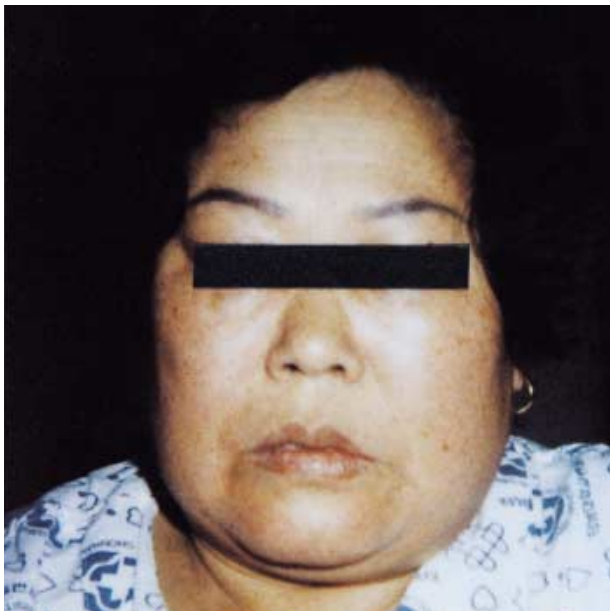

Fig. 1. Angioedema on face, lips, and oropharyngeal area developed immediately after inhalation of histamine concentration of 8 mg/mL.

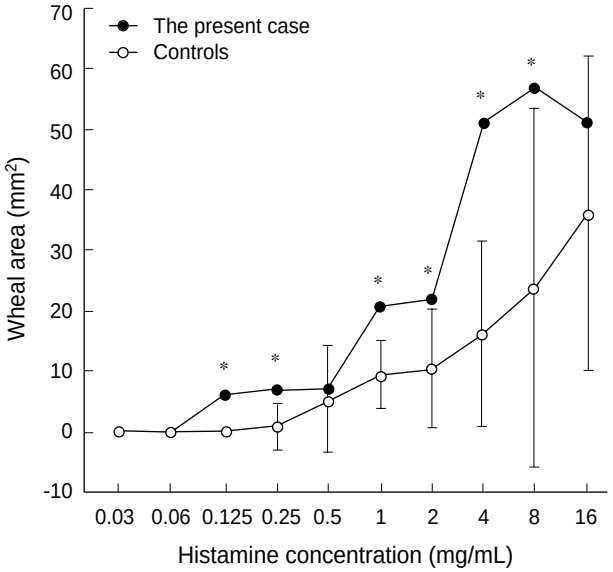

Fig. 2. Histamine dose-response curve of the present case (closed circles) and six controls (open circles). Skin wheal responses were measured in square millimeters. Error bars represent 2-fold standard deviation (SD). *means that wheal area of the present case was greater than the mean +2SD (cut-off values) of that determined from controls.

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.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 mm^2, respectively. The patient showed a greater skin responses to histamine (6.2, 7.1, 21.2, 22.1, 51.5, and 57.1 mm^2 for the doses of 0.125, 0.25, 1, 2, 4, and 8 mg/mL, respectively) than cut-off values (Fig. 2). Also, regression analysis showed that the intercept (25.9 mm^2) and slope (23.0) were greater than the cut-off values (20.6 mm^2 for intercept and 21.6 for slope) determined from six controls.

DISCUSSION

In the present case, the fact that oropharyngeal angioedema was induced by histamine, but not by methacholine, suggests that inhaled histamine is the culprit for the reaction. A vasodilation response of histamine is mediated through both H_1 and H_2 receptor subtypes, and this response is mediated in part by endothelium-derived relaxing factor (5). Although side effects to inhaled histamine are dose-related (1), the histamine concentration (8 mg/mL) producing the oropharyngeal angioedema in our patient was not very high. This may suggest that the increased end organ responsiveness to histamine enhances the effects of histamine at its receptors. Krause and Shuster (3) reported that the wheal and flare response to histamine was enhanced in patients with chronic idiopathic urticaria as compared with normal subjects. Similarly, our case of atopic asthma and chronic idiopathic urticaria showed a greater skin response to histamine 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.

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