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Inhibition of hypertonic saline induced cough by Loratadine in nonasthmatic patients with chronic cough

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We examined the effect of loratadine (10mg) on the number of coughs induced by ultrasonically nebulized hypertonic saline in nine patients with chronic cough and in ten normal volunteers using a randomized, double-blind cross-over method. Each subject inhaled hypertonic saline for one minute, and the numbers of coughs during the one-minute 4.5% NaCl inhalation and the 30-second period following 4.5% NaCl inhalation were counted. There was no difference in forced expiratory volume in one second (FEV_1) or maximum expiratory flow at 25% vital capacity (V_{25}) before to after one-minute hypertonic saline inhalation for either patients or normal subjects. There was also no significant difference in FEV_1 or V_{25} before to one hour after oral administration of loratadine. Placebo did not reduce the number of induced coughs for either patients or normal subjects, but loratadine significantly reduced the number of coughs for patients with chronic cough ($P = 0.012$). On the other hand, loratadine did not reduce the number of coughs by normal subjects. We conclude that in patients with chronic cough, the release of histamine or other chemical mediators or high sensitivity of cough receptors to histamine may be one of the reasons for persistence of chronic cough.

Introduction

Chronic persistent cough of unknown origin is a common clinical problem. Therapies have been devised for chronic cough of known cause such as post-nasal drip, asthma and gastroesophageal reflux[1]. Yet, the pathophysiological mechanisms responsible for chronic cough of unknown origin are not clearly known, although this condition is associated with airway inflammation with predominantly mononuclear-cell infiltrates and epithelial damage[2]. However, short-term of high doses of inhaled steroids do not always effect in patients with chronic cough[2]. Non-sedating selective H1antihistamines[3),4),5)] such as loratadine and terfenadine may be of clinical use for patients with chronic cough.

Hypertonic saline inhalation, which induces principally the release of histamine from airway mast cells, can induce bronchoconstriction in asthmatics, and this bronchoconstriction can be inhibited with H1antihistamines[6),7)] or nedocromil sodium[8)], and can not be inhibited with NK1 receptor antagonist[9)]. NK1 receptor antagonist do not also inhibit induced cough in asthmatics[9)]. Hypertonic saline inhalation causes cough and bronchoconstriction in asthmatics, and these responses are by separate neural pathways[10),11)]. On the other hand, it is reported in asthmatics that responsiveness to 4.5% NaCl inhalation

is significantly correlated with responsiveness to methacholine, but is not significantly correlated with responsiveness to water inhalation[12]. We previously experienced that loratadine significantly reduced the number of coughs induced by ultrasonically nebulized distilled water inhalation in patients with chronic cough[13]. However, the effect of H1antihistamine on ultrasonically nebulized hypertonic saline-induced cough has not been yet studied in non-asthmatic patients with chronic cough of unknown cause.

The aim of this study was to determine whether a selective H1antihistamine can reduce the number of coughs induced by ultrasonically nebulized hypertonic saline inhalation in non-asthmatic patients with chronic cough and normal volunteers. A randomized, double-blind cross-over method was used.

METHODS

Subjects

Nine non-asthmatic patients with chronic cough and ten normal subjects were the subjects of this study（see Table. 1）. All patients and subjects were non-smokers. The duration of cough was from two to twelve months. Examination of all patients included a respiratory questionnaire, physical examination, pulmonary function tests, and methacholine challenge tests. Methacholine challenge tests were performed three or five days before hypertonic saline inhalation cough challenge, and we excluded patients who exhibited hyperresposiveness on methacholine challenge tests. All patients had normal chest and sinus radiographs. None had any history of esophageal reflux, allergic rhinitis, or post-nasal drip. None were atopic, as determined by the finding of at least one positive reaction to skin tests in a battery of twelve common airborne antigens or specific IgE antibodies to aeroallergens or both. None of the patients had a history of post-viral infection, shortness of breath, wheezing at rest or use of ACE-inhibitors. None had a history of airway infection during the four-week period preceding the study. None took any medication, including H1antihistamines, preceding any examination in the study. Informed consent for participation in the study was obtained from each subject. The study was approved by the Ethics Committee of Osaka City University Hospital.

Hypertonic Saline Inhalation Cough Challenge

The 4.5% NaCl inhalation tests were performed using the method of Anderson et al[14] with some minor modifications. A 4.5% NaCl aerosol was inhaled from an ultrasonic nebulizer（Devilbiss Ultra Neb 99, The Devilbiss Co., Somerset, PA, USA）through a mouthpiece connected to a two-way valve（Igarashi's non-rebreathing valve, Igarashi Medical Co., Japan）with tubing 70 cm in length and 22

Table 1. Characteristics of patients and normal subjects

Patients	Age	Sex	FVC（L）（% pred）	FEV_1（L）（% pred）	FEV_1/ FVC	Cough duration（months）
1	53	F	94	116	0.89	4
2	37	F	109	94	0.97	5
3	29	F	108	85	0.95	2
4	57	F	97	109	0.83	12
5	45	F	83	119	0.88	3
6	56	F	113	98	0.88	6
7	29	M	100	107	1.00	2
8	63	M	93	134	0.84	12
9	25	M	89	102	0.91	6
Mean	44		98	107	0.91	5.8
SD	14		10	15	0.06	3.8
Normal subjects（n＝10. aged 25-40 yrs, five males and five females）						
Mean	30		98	98	0.91	
SD	5.3		14	7	0.04	

mm in internal diameter. The 4.5% NaCl inhalation challenge was performed during tidal breathing over one minute with the subject wearing a nose clip. The mean output of the nebulizer without a two-way valve was 15L/min, and particle diameter ranged from 0.5μm to 5μm. The number of coughs during the one-minute 4.5% NaCl inhalation and the 30-second period after 4.5% NaCl inhalation were counted by an observer who had been instructed only to count and record in a tape recorder. No coughs after the later, 30-second period were counted. Coughs were defined as plosive events, occurring in singles or in runs. Each plosive event was counted individually. Episodes of throat clearing were not counted. Pulmonary function tests (FVC: forced vital capacity, FEV_1: forced expiratory volume in one second, V25: maximum expiratory flow at 25% vital capacity; Chestac-25 F System, Chest Co., Ltd, Tokyo) were performed every two minutes before and after 4.5% NaCl inhalation.

Study Design

Days 1 and 2

In the afternoon of the visit to our laboratory on Day 1, each subject inhaled 4.5% NaCl for one minute, and the number of coughs during the one-minute 4.5% NaCl inhalation and the 30-second period after 4.5% NaCl inhalation were counted. Then one tablet of loratadine (10mg, Schering-Plough, Osaka, Japan) or one tablet of a placebo identical in appearance was orally administered in a randomized, double-blind fashion. Sixty minutes later, one-minute 4.5% NaCl inhalation was performed, and the number of coughs was counted again. Taking into consideration the pharmacokinetics of loratadine, 60-minute intervals were included between 4.5% NaCl inhalations[3),4)]. On Day 2 of the study, which was two days after Day 1, each subject inhaled 4.5% NaCl for one minute, and the number of coughs was counted. On Day 2, either placebo or loratadine was administered, whichever was not administered on Day 1. Sixty minutes later, one-minute 4.5% NaCl inhalation was performed, and the numbers of coughs were counted again.

Statistical Analyses

Results are expressed as means (SD), but numbers of coughs (Fig. 2.3) are expressed as means (SE). Comparison of results of pretreatment 4.5%

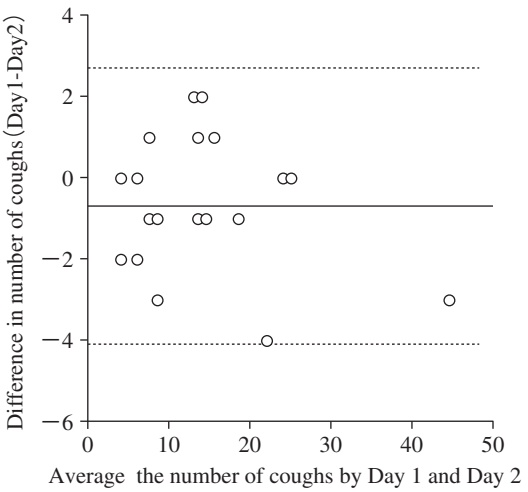

Fig. 1. Repeatability of pretreatment number of coughs induced by 4.5% NaC1 inhalation in all subjects.

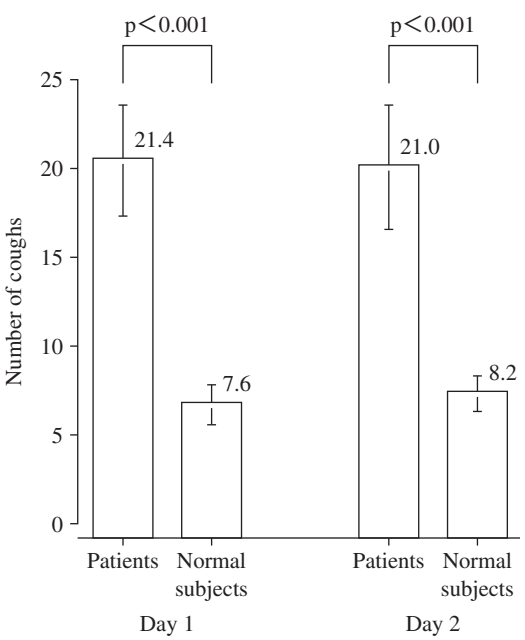

Fig. 2. Comparison of pretreatment number of coughs induced by 4.5% NaC1 inhalation between patients and normal subjects.

Table 2. Changes in FEV_1 or V_{25} from control to each period of 1-minute 4.5% NaCl inhalation in placebo day and loratadine day（(P) = placebo day.（L) = loratadine day）

Patients	4.5% NaCl inhalation			4.5% NaCl inhalation		
	control →	after →	drug →	before →	after	p
FEV_1（L）	2.92（0.8）	2.82（0.8）	Placebo	2.90（0.7）	2.87（0.8）	n.s
FEV_1	2.92（0.8）	2.83（0.8）	Loratadine	2.87（0.7）	2.83（0.7）	n.s
Normal subjects						
	control →	after →	drug →	before →	after	p
FEV_1	3.42（0.6）	3.39（0.6）	Placebo	3.35（0.7）	3.34（0.6）	n.s
FEV_1	3.44（0.6）	3.44（0.6）	Loratadine	3.38（0.6）	3.35（0.6）	n.s

mean（SD）

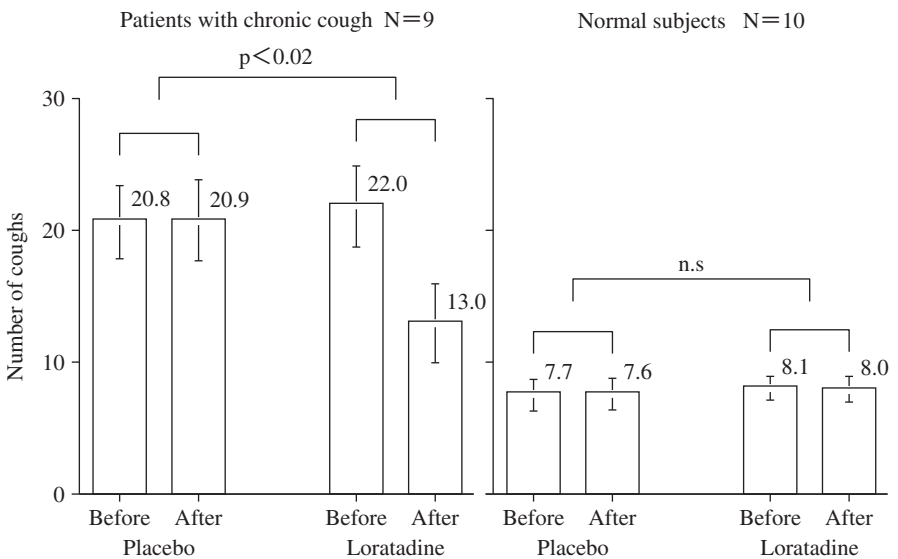

Fig. 3. The effect of oral administration of loratadine on the number of coughs induced by 4.5% NaC1 inhalation.

NaCl challenges between Days 1 and 2 was performed using the two-tailed Student's t-test. The repeatability of results of the pretreatment 4.5% NaCl cough challenges was assessed using the Bland-Altman method[15]. The mean number of coughs from the Days 1 and 2 was plotted against the difference between the means. Pre-treatment differences in the number of coughs between groups were examined using the Mann-Whitney U-test. Differences in numbers of coughs from baseline to treatment were analyzed using Wilcoxon's rank-sum test when comparing intragroup differences. Changes in recorded FEV_1 were studied by analysis of variance（ANOVA）. Findings of $p<0.05$ were taken to indicate statistical significance.

RESULTS

There was no significant difference between pretreatment numbers of coughs on Days 1 and 2（$p=0.8$）. The calculated coefficient of repeatability for 4.5% NaCl challenge was 3.4（Fig. 1）. Patients with chronic cough had a significantly larger response to 4.5% NaCl inhalation testing than did the normal subjects（Fig. 2）. Neither loratadine nor placebo had any effect on number of coughs in normal subjects,

and placebo had no effect on this parameter in any subject group. However, compared with placebo, loratadine significantly reduced the number of coughs in patients with chronic cough ($p<0.02$) (Fig. 3). There was no significant difference in FEV1 or V25 before to after 4.5% NaCl inhalation or before to after oral administration of placebo or loratadine in either patients or normal subjects (Table. 2).

DISCUSSION

This study showed that for non-asthmatic patients with chronic cough, oral administration of loratadine, a selective H1antihistamine, loratadine significantly reduced cough induced by 4.5% NaCl inhalation. This finding suggests that it provides indirect evidence that, in at least some patients with chronic cough, histamine release or high sensitivity to histamine response to change in airway osmolarity contributes to the cough. This finding is similar to our experience that loratadine significantly reduced the number of coughs induced by ultrasonically nebulized distilled water inhalation in patients with chronic cough[13]. In asthmatics, however, responsiveness to 4.5% NaCl inhalation is not significantly correlated with responsiveness to distilled water inhalation[12]. These suggest that 4.5% NaCl inhalation and distilled water inhalation may relate to differences in the nature mediators released or synthesized in response to each challenge for asthmatics[12], but for patients with chronic cough, both may be similar irritant resulting in producing cough.

A previous study showed that in non-asthmatics larger amounts of hypertonic saline produce small increases in non-specific reactivity, and confirmed that substantial osmotic challenge does not change airway calibre[12,16]. The findings of no significant difference in FEV_1 or V_{25} before to after 4.5% NaCl inhalation or before to after oral administration of placebo or loratadine in either patients or normal subjects indicate that loratadine had no acute effect on bronchodilation one hour after its oral administration. The findings of the present study suggest that loratadine reduces the number of coughs induced by 4.5% NaCl inhalation by an H1antihistamine effect rather than an anticholinergic effect.

It is clear that cough and bronchoconstrictor reflexes are mediated through different afferent neural pathways[10,11,17]. Indeed, bronchoconstriction induced by hypertonic saline inhalation is mediated by the release of histamine[6], but analysis of induced sputum has revealed no difference in sputum histamine level between asthmatics and normal subjects[18]. These finding suggest that asthmatics may have a high degree of sensitivity to the bronchoconstrictor effects of hypertonic saline inhalation without change in sputum histamine concentration. On the other hand, in this study the patient group had a significantly larger response to 4.5% NaCl inhalation than did normal subjects. These findings suggest that patients with chronic cough exhibit an abnormally excessive reaction to stimulation of cough receptors by 4.5% NaCl inhalation. It is not clear why hypertonic saline induces bronchoconstriction in asthmatics and excessive cough in non-asthmatic patients with chronic cough. Both asthmatics and patients with chronic cough have a bronchial epithelial damage with inflammatory cells[2,18,19,20], but it is not clearly known that following stimulation with histamine, asthmatics reflex bronchoconstriction and patients with chronic cough reflex cough occur and are mediated through a different neural pathways. Further study will be needed to clarify these mechanisms, and it will be necessary to follow up patients with chronic cough whether they have asthma or not.

H1antihistamines inhibit the release of histamine and leukotrienes produced by eosinophils and mast cells[21,22,23]. H1antihistamines are known to be effective in the treatment of cough in patients with nasal disease[1,24], and may be of clinical use for patients with chronic cough.

The findings of the present study show that in non-asthmatic patients with chronic cough, H1antihistamine significantly reduces coughing induced by 4.5% NaCl inhalation, and that cough receptors in these patients have a high degree of sensitivity to irritation. We conclude that the H1antihistamine loratadine reduces cough induced by hypertonic saline inhalation, and that in patients with chronic cough

the release of histamine or the high sensitivity of cough receptors to histamine may contribute to cough. Hypertonic saline in Ralation is mostly wed for sputum induction to evaluate airway in flammation.[25)]

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REFERENCES

1）Irwin, R. S et al *Am Rev Respir Dis.* 123：413-417（1981）
2）Boulet, L-P et al *Am J Respir Crit Care Med.* 149：482-489（1994）
3）Roman, I.J et al *Clin Rev Allergy.* 11：89-110（1993）
4）Mauser, P.J et al *Eur J Pharmacol.* 182：125-129（1990）
5）Clissold, S.P et al *Drugs.* 37：42-57（1989）
6）Sheppard, D et al *Am Rev Respir Dis.* 127：691-694（1983）
7）O'hickey, P.S et al *Thorax* 44：650-653（1989）
8）Rodwell, L. T et al *Am Rev Respir Dis.* 146：1149-1155（1992）
9）Fahy, J.V et al *Am J Respir Crit Care Med.* 152：879-884（1995）
10）Higenbottam, T et al *Bull Br Physiopathol Respir.* 20：553-562（1984）
11）Eschenbacher, W. L et al *Am Rev Respir Dis.* 129：211-215（1984）
12）Smith, C. M et al *Eur Respir J.* 3：144-151（1990）
13）Tanaka. S et al *Eur Respir J*（abstract）：96s（1994）
14）Anderson, S. D et al *Thorax.* 38：284-291（1983）
15）Bland, J. M et al *Lancet.* ：307-310（1986）
16）Antoniou, D et al *Eur Respir J.* 3：1117-1121（1990）
17）Karlsson, J. A et al *J Appl Physiol.* 65：1007-1023（1988）
18）Fahy, J.V et al *Am Rev Respir Dis.* 147：1126-1131（1993）
19）Gibson, P. G et al *Lancet.* 17：1346-1348（1989）
20）Pin, I et al *Thorax.* 47：25-29（1992）
21）Campbell, A. M et al *Int Arch Allergy Immunol.* 101：308-310（1993）
22）De Weck, A. L et al *Int Arch Allergy Immunol.* 101：326-32（1993）
23）Naclerio, R. M et al *Am Rev Respir Dis.* 142：167-17（1990）
24）Ciprandi, G et al *Ann Allergy, asthma and Immunology.* 75：115-120（1995）
25）Brightling, E. C Chest. C29：1344-1348（2006）