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Effect of loratadine, an H_1 antihistamine, on induced cough in non-asthmatic patients with chronic cough

Shigehiro Tanaka, Kazuto Hirata, Naotsugu Kurihara, Junichi Yoshikawa, Tadanao Takeda

Abstract

Background **– H_1 antihistamines have been shown to have an antitussive effect in patients with asthma, postnasal drip, and allergic rhinitis. No study has been performed to determine whether orally administered H_1 antihistamines can reduce the number of coughs induced by stimulation of cough receptors in non-asthmatic patients with chronic dry cough.**

Methods **– The effect of loratadine (10 mg) on the number of coughs induced by ultrasonically nebulised distilled water (UNDW) was examined in 10 patients with nasal disease and in seven patients with unexplained chronic cough using a randomised, double blind crossover method. Eleven normal volunteers were also studied. Each subject inhaled UNDW for one minute, and the numbers of coughs during the one minute inhalation and the 30 seconds following it were counted.**

Results **– There was no difference in the results of pulmonary function tests performed before and one minute after UNDW inhalation for either patients or normal subjects. There was also no significant difference between the results of pulmonary function tests before or after oral administration of loratadine. Loratadine significantly reduced the number of coughs in patients with nasal disease and in those with unexplained chronic cough, but not in normal subjects.**

Conclusions **– The H_1 antihistamine loratadine reduces cough induced by UNDW. The release of histamine may contribute to the chronic cough in patients with unexplained chronic cough or nasal disease.**

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Keywords: H_1 antihistamine, chronic cough, distilled water challenge.

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Chronic cough of unknown cause is a common clinical problem. Specific treatments have been devised for patients with chronic cough with postnasal drip, asthma, and gastro-oesophageal reflux.[1] Pratter *et al* have reported an algorithm for the treatment of chronic cough and suggest that an H_1 antihistamine may be effective and that bronchoprovocation challenge is useful in investigation.[2] The newer non-sedating antihistamines such as loratadine and terfenadine may be clinically useful for patients with chronic cough.[3–5]

Ultrasonically nebulised distilled water (UNDW) inhalation can induce bronchoconstriction in asthmatic subjects and this bronchoconstriction can be inhibited with H_1 antihistamines, inhaled anticholinergic agents, β agonists, and disodium cromoglycate.[6–10] Protection against this bronchoconstriction may be independent of bronchodilation since it has been reported that oral terfenadine is a more effective inhibitor of distilled water-induced bronchoconstriction than is inhaled ipratropium bromide.[7] Bronchoconstriction associated with UNDW inhalation in asthmatic subjects is thought to occur as a result of direct osmotic changes in the mucosa or lining fluid that may change wall thickness, together with osmotically stimulated local mediator release.[11 12] However, in non-asthmatic subjects inhalation of UNDW has no direct effect on the size of the airway.[12] UNDW-induced cough is not caused by bronchoconstriction and is inhibited by inhaled lignocaine,[6] inhaled anticholinergic bronchodilators, and β adrenergic agonists.[13] However, the effect of H_1 antihistamine on UNDW-induced cough has not been systematically studied in non-asthmatic patients with chronic cough.

The aim of this study was to determine whether H_1 antihistamines, which are widely used antiallergic drugs, can reduce the number of coughs induced by UNDW inhalation in non-asthmatic patients with chronic cough and in normal volunteers, and whether they have an acute effect on the results of pulmonary function tests.

Methods

SUBJECTS

The three groups of subjects who took part in the study comprised 10 non-asthmatic patients with chronic cough and a history of nasal disease, seven non-asthmatic patients with unexplained chronic cough and no nasal disease, and 11 normal subjects. All patients and subjects were non-smokers.

The 10 patients (four men) with nasal disease were aged 24–60 years and had chronic cough of more than eight weeks duration. Four had a history of allergic rhinitis only, four had postnasal drip only, and two had a history of both allergic rhinitis and postnasal drip (table 1). The six patients with a history of allergic rhinitis had neither nasal discharge nor sneezing at the time of the study.

The seven non-asthmatic patients (two men) without nasal disease were aged 27–61 years

Table 1 Characteristics of patients and normal subjects

	Age	*Sex*	*FEV_1 (l) (% predicted)*	*Cough duration (months)*	*Atopy*	*Diagnosis*
Patients with nasal disease:						
1	49	F	1.85 (82)	6	–	PND
2	27	F	1.82 (77)	6	+	(AR)
3	51	F	1.93 (78)	4	–	PND
4	60	F	1.92 (107)	10	+	PND, (AR)
5	29	F	2.44 (84)	2	–	PND
6	44	F	2.54 (100)	2	+	(AR)
7	26	M	3.55 (88)	12	+	(AR)
8	29	M	4.10 (102)	3	–	PND
9	24	M	4.48 (106)	2	+	(AR)
10	44	M	3.30 (102)	2	+	PND, (AR)
Mean (SD)	38 (13)		2.79 (1.0)			
Patients with unexplained chronic cough:						
1	51	F	2.23 (104)	6	–	
2	29	F	2.81 (96)	12	–	
3	33	F	2.20 (81)	3	–	
4	61	F	1.98 (104)	6	–	
5	54	F	2.84 (138)	3	–	
6	27	M	4.24 (116)	36	–	
7	58	M	2.92 (103)	12	–	
Mean (SD)	45 (15)		2.74 (0.8)			
Normal subjects (n=11; 23–38 years; M:F, 6:5)						
Mean (SD)	28 (5.1)		3.55 (0.6)			

FEV_1 = forced expiratory volume in one second; + = at least one positive reaction to skin tests with a battery of 12 common airborne antigens or specific IgE antibodies to common aeroallergens or both; – = negative; PND = postnasal drip; AR = allergic rhinitis.

and also had chronic cough of more than eight weeks duration (range 2–36 months) (table 1).

Each patient made three visits to our laboratory. Patient examination included a respiratory questionnaire, physical examination, pulmonary function tests, and methacholine challenge tests. All patients had normal chest and sinus radiographs and none had any history of oesophageal reflux. Six of the patients with nasal disease were atopic as evidenced by at least one positive reaction to skin tests in a battery of 12 common airborne antigens or specific IgE antibodies to aeroallergens, or both. None of the patients had a history of postviral infection, shortness of breath, wheezing at rest, or use of ACE inhibitors.

The 11 normal subjects (six men) were aged 23–38 years and made two visits to our laboratory (table 1). None had a history of airway infection during the four week period preceding the study and none had taken any medication, including H_1 antihistamines, prior to the study.

Informed consent for participation in the study was obtained from each subject and the study was approved by the ethics committee of Osaka City University Hospital.

UNDW INHALATION COUGH CHALLENGE

UNDW inhalation tests based on the method of Anderson *et al*[14] were used with some minor modifications. One minute UNDW inhalation was used because, in a previous study in which three minute UNDW inhalations were used with 30 minute intervals between inhalations, tachyphylaxis occurred in normal subjects.[15] The UNDW aerosol was inhaled from an ultrasonic nebuliser (Devilbiss Ultra Neb 99, The Devilbiss Co, Somerset, Pennsylvania, 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 mm in internal diameter. The UNDW inhalation challenge was performed during tidal breathing over one minute with the subject wearing a noseclip. The mean output of the nebuliser without a two way valve was 15 l/min and particle diameter ranged from 0.5 μm to 5 μm. The mean (SD) output of the nebuliser with a two way valve during tidal breathing was 10 (0.7) l/min as measured with a Wright respirometer (Haloscale Compact, Ferraris Development and Engineering Co, UK) in seven normal volunteers after completion of their second day of the study. The mean (SD) amount of inhaled distilled water for the seven normal volunteers was 2.5 (0.3) ml. The number of coughs during the one minute UNDW inhalation and the 30 seconds immediately afterwards was counted by an observer who had been instructed only to count and record into a tape recorder. No further coughs were counted after this time. Coughs were defined as plosive events which occurred in singles or in runs. Each plosive event was counted individually and episodes of throat clearing were not counted. Pulmonary function tests (forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and maximum expiratory flow at 25% vital capacity (V_{25})) were performed every two minutes before and after UNDW inhalation with a Chestac-25 F System (Chest Co Ltd, Tokyo, Japan).

METHACHOLINE CHALLENGE

The methacholine provocation challenge test was performed three or five days before UNDW inhalation using the method described by Makino *et al*.[16] In brief, aerosols were generated with a nebuliser at an air flow rate of 5 l/min. At five minute intervals each subject inhaled the aerosol for two minutes during quiet breathing through the mouth. An isotonic 0.9% saline solution was inhaled first, followed by methacholine in concentrations ranging from 20 to 10 000 μg/ml in doubling

increments. The FEV_1 was measured before and after inhalation of the saline solution and after each inhalation of methacholine. When the change in FEV_1 from the baseline after the inhalation of saline was 10% or less in all subjects, inhalation of methacholine was started. The test was continued until the FEV_1 had fallen by 20% or until the highest concentration of methacholine had been administered. The threshold was defined as the lowest concentration of methacholine that produced a 20% fall in FEV_1 (PC_{20}) which was calculated by linear interpolation between the last two data points on the dose-response curve or was expressed as 10 000 μg/ml if there had been no response.

STUDY DESIGN

A randomised, double blind, crossover method was used. In the afternoon of the visit to the laboratory on day 1 each subject inhaled UNDW for one minute and the number of coughs during the inhalation and the 30 seconds following it were counted. One tablet of loratadine (10 mg, Schering-Plough, Osaka, Japan) or one tablet of an identical placebo (starch) were then administered in a randomised double blind fashion. One hour later one minute UNDW inhalation was repeated and the number of coughs was again counted. Intervals of one hour between UNDW inhalations were used because of the pharmacokinetics of loratadine.[3 4] The second day of the study was two days after day 1. Each subject inhaled UNDW for one minute and the number of coughs was counted. Placebo or loratadine were then administered, whichever had not been given on day 1. One hour later one minute UNDW inhalation was performed and the numbers of coughs were counted again.

STATISTICAL ANALYSES

The results are expressed as mean (SD) but the numbers of coughs, FEV_1, and V_{25} values are expressed as mean (SE). Comparison of pretreatment UNDW challenges between days 1 and 2 was performed using a two tailed Student's *t* test. The repeatability of the pretreatment UNDW cough challenges was assessed using the method of Bland and Altman.[17] The mean number of coughs on days 1 and 2 was plotted against the difference between the means, both expressed on a logarithmic scale. Pretreatment differences in the number of coughs between groups were examined using the Mann-Whitney U test. Differences in the numbers of coughs from baseline to treatment were analysed using the Wilcoxon's rank sum test which compared intragroup differences. The Mann-Whitney U test was used to compare differences in the numbers of coughs from control to treatment between the different groups. Changes in recorded FEV_1 and V_{25} were analysed using analysis of variance (ANOVA). Values of $p < 0.05$ were taken to indicate statistical significance.

Results

There was no significant difference in the number of coughs before treatment on days 1 and 2. The calculated coefficient of repeatability for the UNDW challenge was 0.21 (fig 1). Tachyphylaxis did not occur during the one minute UNDW inhalation in any of the patients or the normal subjects. The two groups of patients with chronic cough each had a significantly larger response to UNDW inhalation testing than did the normal subjects (fig 2). Neither placebo nor loratadine had any effect on the number of coughs in normal subjects and placebo had no effect in either of the patient groups. However, compared with placebo, loratadine significantly reduced the number of coughs in both patients with nasal disease ($p = 0.005$) and those with unexplained chronic cough ($p < 0.05$) (fig 3). There was no difference in the amount of cough reduction between the two groups of patients. Since there was no significant difference in FEV_1 or V_{25} before and after UNDW inhalation or before and after oral administration of placebo or loratadine in either patients or normal subjects, loratadine had no acute effect on bronchodilation one hour after its oral administration. Patients exhibited no hyperresponsiveness on methacholine challenge tests.

Discussion

The findings of this study show that, for non-asthmatic patients with chronic cough, the H_1 antihistamine loratadine, when given orally in a dose of 10 mg, significantly reduces cough induced by UNDW inhalation. This finding is important because it provides indirect evidence that, in at least some patients with chronic cough and a history of nasal diseases and some with unexplained chronic cough and no nasal disease, histamine release in response to a change in osmolarity of the airways contributes to the cough. Loratadine, when orally administered an hour before pulmonary function tests, had no acute bronchodilating effects in this study. It is clear that cough and bronchoconstrictor reflexes are mediated through different afferent neural pathways.[7 18-20] However, it has been shown that the bronchodilating effect may be one of the reasons for inhibition of cough induced by UNDW inhalation in normal volunteers, in

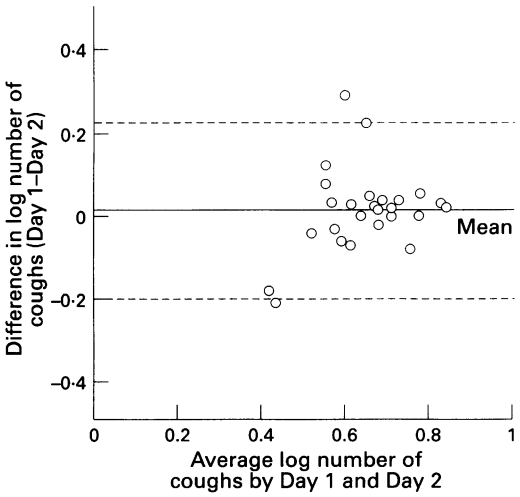

Figure 1 Repeatability of pretreatment number of coughs induced by UNDW inhalation in all subjects (n = 28).

patients with upper respiratory tract infections, and in those with asthma.[13 21 22] If coughing in the patient groups receives a contribution from heightened perception due to conductance changes, H_1 antihistamines can decrease specific airways conductance, thereby increasing FEV_1 or V_{25}. A previous study reported that both distilled water and hypertonic saline produced small increases in non-specific reactivity in non-asthmatic subjects and confirmed that substantial osmotic challenge does not change airway calibre.[12] Although the authors of that study used a larger amount of UNDW than in our study, in four subjects V_{25} was measured and had a plateau similar to that of specific airways conductance.[12] In our study FEV_1 and V_{25} were not significantly changed in either the patients or the normal subjects. Our findings suggest that loratadine reduces the number of coughs induced by UNDW inhalation by an H_1 antihistamine effect rather than by an anticholinergic effect.

The patient groups had a significantly larger response to UNDW inhalation than did normal subjects which indicated that both patients with nasal disease and those with unexplained chronic cough had a higher degree of cough sensitivity than normal subjects. In a study in which three minute UNDW inhalations with 30 minute intervals between inhalations were used, tachyphylaxis occurred in normal subjects.[15] No tachyphylaxis occurred in either patients or normal subjects in our study using one minute UNDW inhalation and 60 minute intervals between inhalations. These findings suggest that patients with chronic cough exhibit an abnormally excessive reaction to stimulation of cough receptors by UNDW inhalation.

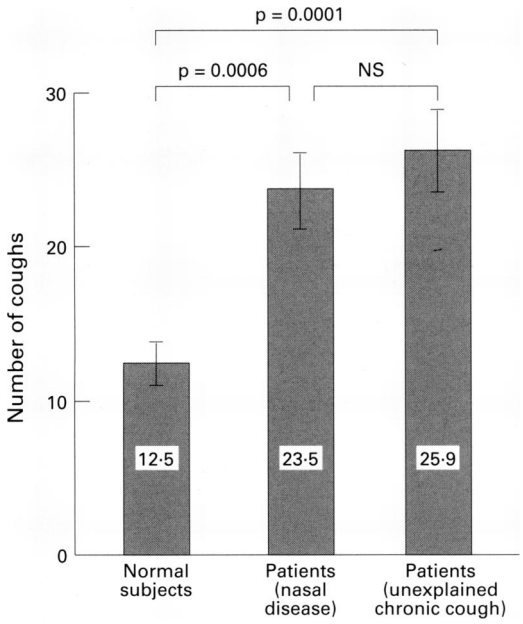

Figure 2 Comparison of pretreatment number of coughs induced by UNDW inhalation in the three groups.

H_1 antihistamines are known to be effective in the treatment of cough in patients with nasal disease.[23] In our study six patients had a history of allergic rhinitis but had no evidence of nasal discharge at the time of examination. Based on previous reports[1 2 24] they should be diagnosed as having postnasal drip secondary to rhinitis. The cause of cough in patients with allergic rhinitis is unclear, but it is generally thought to be due to postnasal drip secondary to rhinitis. In these patients histamine release may be one of the reasons for chronic cough. Postnasal drip may cause mechanostimulation of pharyngeal or laryngeal receptors with normal sensitivity. Prominent nasal obstruction with mouth breathing and loss of nasal air conditioning may lead to chronic irritation with enhanced sensitivity of afferent cough nerves.[25] Further studies are required to identify the mechanism of chronic cough in patients with postnasal drip.

The finding that treatment of patients with unexplained chronic cough requires a longer period of time than treatment of those with nasal disease suggests that a difference exists between these two groups, but a large difference was not found in this study. Patients with unexplained chronic cough should be followed up whether or not they have asthma.

H_1 antihistamines inhibit the release of histamine and leukotrienes produced by eosinophils and mast cells.[26–28] Chronic cough in non-asthmatic patients has been shown to be associated with airway inflammation by the presence of eosinophils and metachromatic cells and epithelial damage.[24 29] The findings of this study show that, in non-asthmatic patients with chronic cough, H_1 antihistamines significantly reduce coughing induced by UNDW inhalation without affecting FEV_1 or V_{25}. We

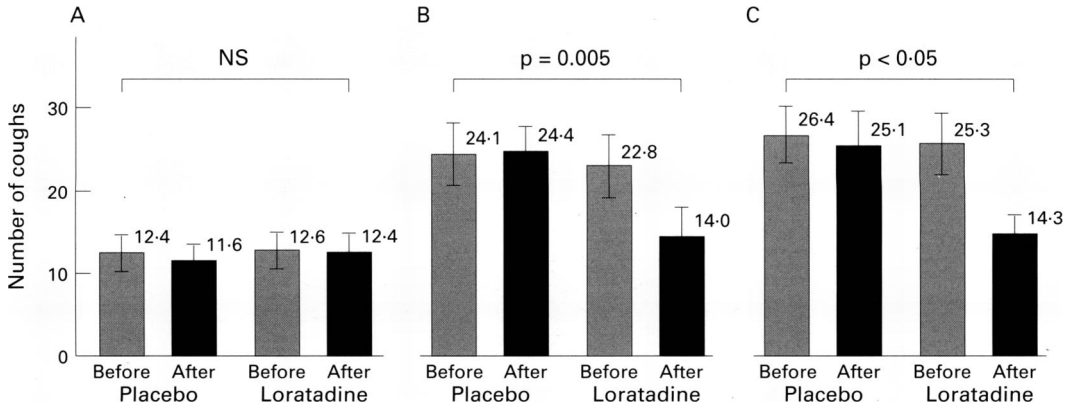

Figure 3 Effect of oral administration of loratadine on the number of coughs induced by UNDW inhalation in (A) normal subjects, (B) patients with nasal disease, and (C) patients with unexplained chronic cough.

conclude that the H_1 antihistamine loratadine reduces cough induced by UNDW, and that in patients with unexplained chronic cough or nasal disease the release of histamine may contribute to the chronic cough.

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