Allergology International (1998) **47**: 147–151

Case Report

Effect of a leukotriene receptor antagonist on cough receptor sensitivity and allergen-induced cough in a patient with atopic cough variant asthma

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Abstract

A 24-year-old female patient with chronic dry cough, without wheezing and other symptoms, was diagnosed as atopic cough variant asthma (CVA) sensitized with house dust (HD) mite. To investigate the effect of a leukotriene (LT) receptor antagonist (pranlukast hydrate, ONON 450 mg/day), cough score, respiratory function, cough receptor sensitivity to capsaicin, airway inflammation evaluated by hypertonic saline inhalation and airway reactivity to histamine were studied before and after treatment for 4 weeks. Furthermore, the effect of a LT receptor antagonist on HD allergen-induced bronchoconstrictive and cough responses was investigated. Treatment with a LT receptor antagonist resulted in disappearance of cough, improvement of respiratory function, decrease in eosinophil percentage in induced sputum and increase in capsaicin and histamine threshold. Although bronchoprovocation with HD extract induced an immediate bronchoconstriction followed by cough responses before treatment, inhibition of both bronchoconstrictive and cough responses was observed after treatment. These results suggest that LT is involved in the mechanism of cough in this patient with atopic CVA.

Key words: asthma, atopy, cough variant asthma, leukotriene receptor antagonist.

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Received 16 September 1997. Accepted for publication 11 November 1997.

Introduction

It has been reported that chronic cough is the only manifested clinical symptom in patients with so-called cough variant asthma (CVA).[1,2] Episodic wheezing is one of the criteria of bronchial asthma, but there is no history of wheezing in CVA patients. Although the precise mechanisms responsible for the induction of cough in CVA patients are not clear, bronchodilators, such as β_2-agonists and theophylline are effective agents in relieving cough.[2]

Several chemical mediators have been reported to be involved in allergic reactions, including histamine, leukotrienes (LT), and thromboxane (Tx) A_2.[3] Indeed, receptor antagonists for these chemical mediators have been reported to improve asthma symptoms and also to inhibit allergen-induced bronchoconstriction.[4–6] In humans, much evidence suggests that LT is the major mediator responsible for an immediate bronchial response after the inhalation of an allergen.[5] Recently, it was reported that a Tx synthetase inhibitor was a useful drug for the management of CVA, but the effectiveness of a LT receptor antagonist has not been clearly demonstrated.[7]

In the present paper we report on a case in which a LT receptor antagonist improved cough and airway reactivity to both capsaicin and histamine and also improved eosinophilic airway inflammation detected by hypertonic saline-induced sputum. Furthermore, we demonstrate that inhalation of house dust extract resulted in cough induction followed by an immediate bronchial response and that the LT receptor antagonist inhibited both the allergen-induced cough and the bronchial response. These results suggest that inhalation of allergen results in the induction

of cough and that LT is a major chemical mediator involved in cough in this patient with atopic CVA.

Case Report

A 24-year-old female patient visited Kihara hospital because of a dry cough that had persisted for 3 months. She had no history of asthma or allergic rhinitis. Her cough usually began at night and often disturbed her sleep. The patient exhibited no wheezing, sputum, nasal discharge, fever or other symptoms, including gastroesophageal symptoms. No abnormalities were detected by chest X-ray film, electrocardiogram, analysis of arterial blood gas and respiratory function.

Laboratory findings detected increases in IgE, specifically house dust-, house dust mite- (Der f and Der p), Japanese cedar- and hinoki-specific IgE, in her serum (Table 1). Because CVA was suspected, several allergic examinations were performed. Cough receptor sensitivity to capsaicin was investigated according to methods described by Fujimura *et al.*[8] Airway inflammation was determined by calculating the percentage of eosinophils in hypertonic saline-induced sputum, as described previously.[9] Airway reactivity to histamine and house dust was examined by methods described previously.[10] Briefly, the patient inhaled doubling increasing concentration of histamine or a diluted solution of house dust extract (Torii Pharmaceuticals Co Ltd, Tokyo, Japan) for 2 min by tidal breathing. Increasing concentrations of histamine or house dust extract were administered until the forced expiratory volume in one second (FEV_1) decreased by more than 20% of the baseline value. Peak expiratory flow (PEF) and daily cough symptoms were monitored. A daily record of cough symptoms, including cough frequency, measured on a scale of 0–3 (0, no cough; 1, infrequent; 2, frequent; 3, very frequent); intensity, measured on a scale of 0–2

Table 1. Laboratory findings on arrival

Hematology	
WBC (/mm^3)	3800
Ba (%)	0.0
Stab (%)	2.0
Seg (%)	64.0
Eo (%)	3.0
Mo (%)	4.0
Ly (%)	27.0
RBC (/mm^3)	407×10^4
Hb (g/dL)	12.4
Hct (%)	41.0
PLT (/mm^3)	21.5×10^4
Biochemistry	
TP (g/dL)	6.4
GOT (IU/L)	18
GPT (IU/L)	12
LDH (IU/L)	264
γ-GTP (IU/L)	16
T-Bil (mg/dL)	0.36
BUN (mg/dL)	12.6
Cr (mg/dL)	0.9
Na^+ (mEq/L)	144
Cl^- (mEq/L)	107
K^+ (mEq/L)	4.2
Serology and Immunology	
CRP (mg/dL)	0.2
IgE (IU/mL)	499
RAST (UA/mL)	
House dust 1	34.07
House dust 2	26.60
Der. f.	21.40
Der. p.	21.40
Japanese cedar	49.67
Hinoki	7.70

WBC, white blood cells; BA, basophil; Stab, stabed form of leukocyte; Seg, segmented form of leukocyte; Eo, eosinophils, Mo, monocytes; Ly, lymphocytes; RBC, red blood cells; HB, hemoglobin; Hct, hematocrit; PLT, platelets; TP, total protein; GOT, aspartate aminotransferase; GPT, glutamate–pyruvate transaminase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein.

Table 2. Clinical course

	Before	ONON
Cough score (mean/week)	70	1
Spirometry		
FVC (L)	3.53	3.8
%FVC	114	113
FEV_1 (L)	3.18	3.7
FEV_1 %	90	92.2
$\dot{V}_{50}$ (L/s)	3.80	4.39
$\dot{V}_{25}$ (L/s)	1.71	2.29
PEF (L/min)	459	539
CR sensitivity (μmol/L)	15.6	250
Ratio of eosinophils in induced sputum (%)	8.7	3.1
PC_{20} (μg/mL)	780	1660

Cough score, respiratory function and several allergic examinations were investigated before and after treatment with the leukotriene receptor antagonist ONON (450 mg/day) for 4 weeks. Improvement of cough score and respiratory function, including morning peak expiratory flow (PEF) were noted after treatment. Although increases in cough receptor (CR) sensitivity to capsaicin, airway reactivity to histamine (PC_{20}) and the percentage of eosinophils were noted before treatment, a remarkable improvement of all examinations was observed after treatment. All examinations were evaluated again 2 h after taking ONON (225 mg).

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; $\dot{V}_{50}$, $\dot{V}_{25}$, expiratory flow at the half and last middle half of time, respectively.

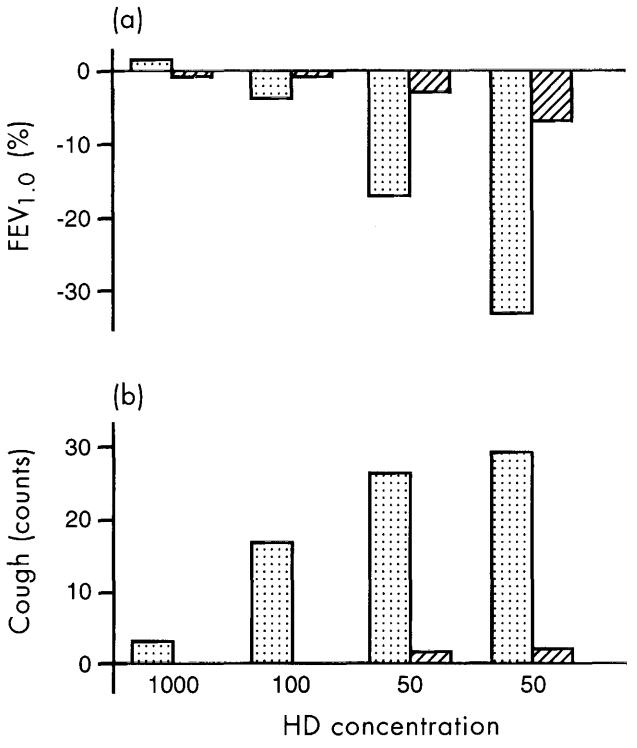

Fig. 1 Effect of a leukotriene (LT) receptor antagonist on (a) bronchial obstruction and (b) cough after inhaling the allergen house dust extract (HD; wt/vol). Bronchoprovocative inhalation of HD immediately induced cough before obvious bronchoconstriction. Two inhalations of 1:50 diluted concentrations of HD resulted in an immediate bronchial response with audible wheezing. After treatment with the LT receptor antagonist pranlukast hydrate (ONON; 450 mg/day) for 4 weeks, the inhalation test was performed again with pretreatment with ONON (225 mg) 2 h before challenge. Both cough and bronchoconstriction were inhibited by pretreatment with ONON. The percent decrease in FEV_1 and the total number of coughs for 5 min after inhalation of each dilution of HD are shown. (▩), without ONON pretreatment; (▨), responses after ONON pretreatment.

(0, no cough; 1, weak; 2, strong), and dyspnea, measured on a scale of 0–1 (0, no dyspnea; 1, dyspnea), were recorded four times a day (morning, day time, evening, night time). The mean cough score for the week was calculated. The results of these examinations are summarized in Table 2. An increase in the percentage of eosinophils and airway reactivity to histamine and a decrease in PEF were observed. Capsaicin inhalation in this patient resulted in data similar to those observed in healthy females. Inhalation of house dust extract resulted in the induction of cough immediately after challenge and a dose-dependent increase in the number of coughs was observed (Fig. 1). After two inhalations of 1:50 diluted house dust extract, an immediate bronchial response appeared and wheezing was detected with frequent cough. Because the frequency and intensity of the cough were so severe, inhalation of a β_2-agonist was necessary. Bronchoconstriction and cough were immediately improved by the inhalation of a β_2-agonist. A late bronchial response was not observed after inhalation challenge.

Because LT is one of the major chemical mediators responsible for the immediate bronchial response in asthma, the patient was treated with a LT receptor antagonist (pranlukast hydrate (ONON), 450 mg/day; ONO Pharmaceutical Co. Ltd, Tokyo, Japan) for 4 weeks and all clinical tests were performed again. Treatment with the LT receptor antagonist resulted in an improvement of the cough score, PEF, cough receptor sensitivity to capsaicin, percentage of eosinophils in induced sputum and airway reactivity to histamine (Table 2). Furthermore, both the house dust extract-induced cough and the immediate bronchial response were markedly inhibited by pretreatment with the LT receptor antagonist (Fig. 1).

Discussion

Patients with a chronic cough and without a history of wheezing and dyspnea but with normal baseline spirometery and hyperreactive airway, have been diagnosed as CVA. Characteristic of the cough in CVA patients is the excellent response of the cough to bronchodilatory agents, such as β_2-agonists and theophylline. Recent guidelines for the diagnosis of asthma have emphasized the existence of eosinophilic inflammation in the airway that is closely associated with airway hyperreactivity.[11–13] Although there was no history of wheezing, increases in the percentage of eosinophils and airway reactivity to histamine were detected in the patient in the present study. Inhalation of allergen resulted in the induction of cough followed by bronchoconstriction; both were relieved by the inhalation of a β_2-agonist. These results demonstrate that it is likely that chemical mediators released during the immediate bronchial response may be responsible for the induction of cough after the inhalation of allergen.

Considering recent reports, it is likely that the cough is elicited on the basis of the cough receptor sensitivity and bronchoconstriction.[14,15] Patients with a chronic cough without a hyperreactive airway often possess hypersensitivity to inhaled capsaicin, the active ingredient of red pepper that produces a cough by stimulating C-fiber endings.[16] Anti-histamine receptor 1 antagonists are

often effective in relieving cough in these patients.[8] In contrast, bronchodilators are often effective in patients with CVA.[2] This evidence suggests that bronchoconstriction caused by the chemical mediators released from inflammatory cells may contribute to the mechanisms that induce cough.

In atopic asthma, inhalation of allergen results in the release of several chemical mediators, including histamine, Tx, platelet activating factor and LT. The protective effects of receptor antagonists for these chemical mediators have revealed that LT is the major chemical mediator responsible for allergen-induced airway obstruction.[5] Although it has been reported that LT receptor antagonists also have a protective effect against exercise-, aspirin- and cold air-induced asthma, the effectiveness for the cough observed in patients with CVA has not yet been clearly demonstrated.[17–19] In the present study, we have shown that inhalation of allergen resulted in the induction of cough before obvious bronchoconstriction and a dose-dependent increase in the frequency of cough was elicited by the immediate bronchial response in this patient with atopic CVA. Treatment with a LT receptor antagonist for 4 weeks resulted in an improvement of airway inflammation, airway reactivity to histamine and cough receptor sensitivity to capsaicin. Furthermore, remarkable inhibition of allergen-induced cough and bronchial obstruction by pretreatment with the LT receptor antagonist strongly supports LT as a major chemical mediator for eliciting cough in this patient. It is unlikely that the allergen-induced cough response was suppressed by pretreatment with the LT receptor antagonist solely because of its bronchodilator effect as few coughs were induced after two inhalations of a 50:1 dilution of house dust extract after treatment when FEV_1 had decreased by 7%. In contrast, 17 coughs were counted after inhalation of a 100:1 dilution extract before treatment when FEV_1 had decreased by 3.5%. The fact that cough receptor sensitivity to capsaicin changed from 7.6 to 250 mmol/L also suggests that LT was involved in the cough receptor sensitivity and, thus, may have led to an improvement of cough in this patient following treatment with the LT receptor antagonist.

It has been reported that tachykinins, such as substance P and neurokinin A, are involved in cough mechanisms. Inhalation of capsaicin results in the release of tachykinins from the airway sensory nerves, which induces cough in guinea pigs.[20] Inhalation of LTD_4 caused bronchoconstriction and plasma exudation in guinea pigs that were, in part, due to tachykinins released from the airway sensory nerves, because pretreatment with a specific neurokinin receptor antagonist significantly inhibited these responses.[21] In healthy human subjects, bronchoconstriction accompanied by cough has been induced after inhalation of LTC_4 and LTD.[4,22] Although we did not measure the concentration of substance P in the sputum, previous studies and our observations suggest that LT may release tachykinins after the allergen is inhaled and, thus, the LT receptor antagonist was effective in relieving cough in our patient.

The relationship between airway cough receptor sensitivity and airway reactivity to non-specific spasmogens has been reported to be independent.[23] In the present study, treatment with the LT receptor antagonist for 4 weeks resulted in an improvement of airway inflammation and airway reactivity to histamine. We cannot disregard the possibility that cough receptor sensitivity to capsaicin was improved by an alteration of airway inflammation. Further studies are necessary to elucidate the relationship between the severity of airway inflammation and cough receptor sensitivity.

In conclusion, in the present study we reported on a case with atopic CVA in which treatment with a LT receptor antagonist improved cough and cough receptor sensitivity to capsaicin and inhibited allergen-induced cough and bronchial obstruction.

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