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A Case of Atopic Cough Successfully Treated with the H1 Antagonist Epinastine Hydrochloride

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Abstract

A 38-year-old female patient with chronic persistent cough was diagnosed with atopic cough (eosinophilic bronchitis). To investigate the effect of a H1 antagonist epinastine hydrochloride (epinastine; 20mg/day, once daily), we evaluated cough scores, pulmonary function, capsaicin cough threshold, and bronchial hyperresonsiveness to methacholine before and after a 4-week treatment with epinastine. Treatment with epinastine resulted in a marked decrease in persistent cough. It also resulted in a marked improvement in capsaicin cough threshold. These results suggested that epinastine may be useful for treating patients with atopic cough and that histamine H1 receptor is related to the pathophysiology of atopic cough.

Introduction

Cough is one of the main symptoms of respiratory disease[1),2)]. Regarding atopic cough (eosinophilic bronchitis), it has been recently reported that chronic persistent non-productive cough is the only manifested clinical symptom in patients with atopic disposition, increased cough sensitivity, normal chest roentgenogram, and normal bronchial responsiveness[3),4)].

Epinastine hydrochroride (epinastine) has been shown to be a potent anti-histaminic agent with high affinity for histamine H1 receptors[5),6)]. In the present paper we report a case in which epinastine reduced prolonged cough and improved the capsaicin cough threshold, suggesting that epinastine is effective for the treatment of atopic cough and that histamine H1 receptor is related to the pathophysiology of atopic cough.

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Clinical Summary

A 38-year-old female patient visited Akita University Hospital on June 12, 2000, for non-productive cough that had persisted for 6 months. Although she had been treated with antibiotics and antitussive drugs by a general physician since January 2000, her cough had not improved. She had no history of asthma. 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. The patient was 158 cm tall and weighed 47 kg. Her blood pressure was 128/64 mmHg, with no difference between arms. Her pulse was regular (84 beats/min). No heart murmur was heard, and no rales were heard over either lung field. Otolaryngeal examination revealed no evidence of nasal allergy or chronic sinusitis.

As shown in Table 1, the patient's eosinophil differential was slightly increased and her IgE level was also elevated. The radioallergosorbent test (RAST) scores for house dust 1 (HD1), house dust mite (Der f), Japanese cedar, and dog skin were strongly positive (2+ to 3+). No abnormalities were detected by chest roentgenogram or electrocardiogram. Pulmonary function tests showed no appreciable occlusion, with a forced vital capacity (FVC) of 2.77 L, a forced expiratory volume in one second (FEV_1) of

Table 1. Laboratory findings on first visit

Hematology	Biochemistry	Serology and Immunology
ESR 11 mm/hr	T.P. 8.2 g/dl	CRP 0.0 mg/dl
RBC 412x10⁴/mm³	Alb 4.7 g/dl	IgE 481.1 IU/ml
Hb 13.7 g/dl	GOT 28 U/l	RAST HD1 3+
WBC 7800 /mm³	GPT 28 U/l	Der. f. 3+
N 31%	LDH 168 IU/l	Jap. cedar 3+
Eo 13%	ALP 62 U/l	Dog skin 2+
Baso 0%	T.Chol. 161 mg/dl	
Mono 7%	BUN 10 mg/dl	Sputum Eosinophil 13%
Lym 49%	Cr 0.7 mg/dl	
Plt 27.7x10⁴/mm³	Na 140 mEq/l	
	K 3.9 mEq/l	
	Cl 101 mEq/l	

Abbreviations: ESR; erythrocyte sedimentation rate, RBC; Red blood cell, Hb; hemoglobin, N;neutrophils, Eo;eosinophils, Baso;basophils, Mono;monocytes, Lym;lymphocytes, Plt;platelets, T.P.;total protein, Alb;albumin, GOT;glutamate oxaloacetate transaminase, GPT;glutamate pyruvate transaminase, LDH;lactate dyhydrogenase, ALP;alkaliphosphatase, T.Chol.;total cholesterol, BUN;blood urea nitrogen, Cr;creatinine, CRP;c-reactive protein

Table 2. Time course in pulmonary function test

	June 12, 2000	July 24, 2000
FVC (l)	2.77	2.85
FEV1 (l)	2.38	2.41
FEV1% (%)	85.9	84.6
PEF (l/s)	4.78	4.82
Ccap (μM)	0.08	10.0
Dmin (U)	50.0	50.0

Abbreviations:
FVC; forced vital capacity,
FEV1; forced expiratory volume in one second,
FEV1%; FEV1 as a percent of FVC (FEV1/FVC),
PEF; peak expiratory flow rate,
Ccap; capsaicin cough threshold,
Dmin; geometric mean of the lowest concentration of methacholine associated with the start of a consistent decrease in conductance (in mg/ml (unit) of inhalation)

2.38 L, FEV1 as a percent of FVC (FEV_1%) of 85.9%, and a peak expiratory flow (PEF) of 4.78 l/sec (Table 2). No significant changes in FVC, FE V_1, and PEF values were observed between pre-treatment and post-treatment values (Table 2) or between the morning and evening PEF values according to the symptom diary (data not shown).

Bronchial response to inhaled methacholine (MCh) was assessed with an Astograph (TCK-6100H, Chest, Tokyo, Japan) for measurement of bronchial hyperresponsiveness (BHR). This device uses the forced oscillation method to measure respiratory resistance and its reciprocal conductance during tidal breathing.[7] Airway sensitivity to MCh was expressed as the geometric mean of the lowest concentration of MCh associated with the start of a consistent decrease in conductance {Dmin, in mg/ml (unit) of MCh inhalation}. Cough threshold was evaluated using capsaicin according to the method of Midgren et al.[8,9] In brief, capsaicin (Sigma) was dissolved in ethanol and diluted with 0.9% NaCl to 0.016, 0.08, 0.4, 2, 10, 50, and 250 μM. Capsaicin was inhaled during tidal breathing from a nebulizer (Nissho, Tokyo, Japan, output 0.5 ml/min, mean mass diameter 5 mm). Concentrations of capsaicin were increased until the patient coughed more than five times. The final concentration was taken as the cough threshold for capsaicin (Ccap: μM)[8),9)].

The patient evaluated her cough four times a day, every six hours, and recorded the cough points in the diary[9),10)]. The evaluations were "quite often" (21 times or more) - four points, "often" (11 to 20 times) - three points, "relatively often" (6 to 10 times) - two points, "not often" (5 times or fewer) - one point, and "none" - zero points. The total cough points in a day became the cough scores. Astograph results showed a normal value in BHR, with a Dmin of 50.0 units. In contrast, the capsaicin cough threshold was markedly increased, as indicated by a Ccap of 0.08 μM.

The patient was treated with epinastine (20mg/day, once daily) beginning on June 24, when testing had been completed. Her persistent cough began to improve clinically on treatment day 3. Treatment with epinastine also resulted in significant improvement in the cough scores based on patient diary entries (Figure 1). Although there was no marked difference between the pulmonary function test results before and after 4 weeks of treatment with epinastine, Ccap improved markedly, from 0.08 μM to 10.0 μM (Table 2) after treatment with epinastine. Dmin did not improve from the baseline value of 50.0 units, and the IgE level did not change after the 4-

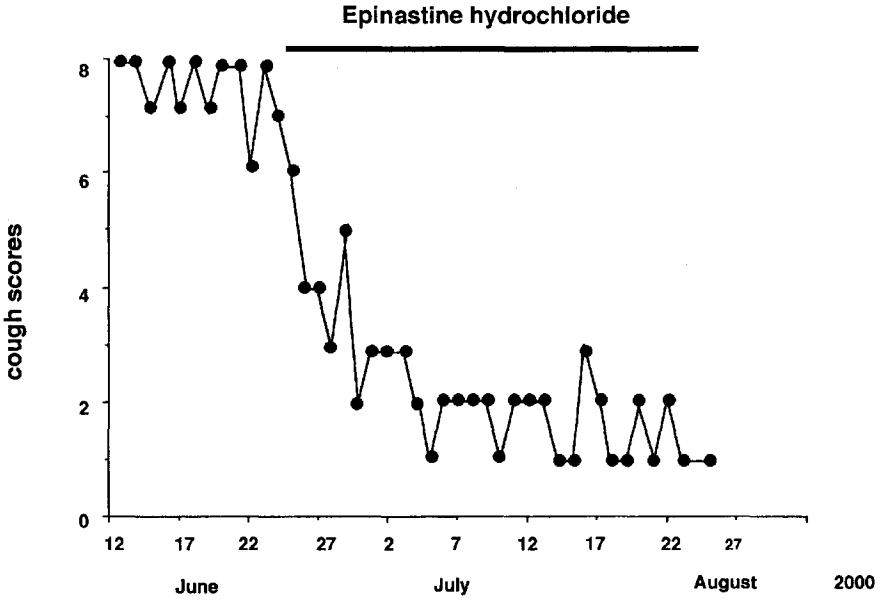

Figure 1. Changes in cough scores

week treatment with epinastine.

Discussion

Atopic cough, a disease occurring in patients having an atopic disposition was described by Fujimura, et al[3),4)]. Fujimura[11)] also reported that around 50% of cases of the chronic dry cough of unknown origin were atopic cough. The primary feature of atopic cough is non-productive cough, and it mainly appears in sleeping, early morning. Atopic cough can be easily induced by many factors, such as air conditioners, tobacco smoking, tension[3),4)]. It is considered that atopic cough is more abundant for the woman, especially in postmenopausal woman. The central pathophysiology of this disease is accentuation of cough receptor sensitivity resulting from eosinophilic inflammation of the large airways[3),4)]. Atopic cough is recently considered to be almost identical disease with eosinophilic bronchitis which has been reported by Gibson et al[12),13)].

Atopic cough shows no increase in fundamental bronchial hyperresponsiveness, nor is there airway reversibility by bronchodilators such as $\beta 2$ adrenoceptor agonists. Though environmental fungus is identified in some cases as an antigen, the causal antigen in the majority of cases is currently considered to be uncertain[14),15)]. With respect to diagnosis, it is necessary to differentiate atopic cough from many other diseases which cause chronic cough, such as cough variant asthma[16),17)], laryngeal allergy[18)], and gastroesophageal reflex disease[19),20)]. Based on the current situation, the diagnostic criteria of atopic cough were outlined in a workshop by the Japanese Research Society for Chronic Cough and Atopic Cough[21)] (Table 3).

Based on the facts that our patient demonstrated an increased capsaicin cough threshold and normal bronchial responsiveness to MCh, and satisfied the above-mentioned diagnostic criteria, we diagnosed her with atopic cough. We administered the H1 receptor antagonist epinastine hydrochloride to our patient. As a result, the persistent cough decreased directly after epinastine administration, and the cough scores improved on day 3 of daily epinastine administration, and became 1 point after 4 weeks of treatment. In addition, the capsaicine cough threshold, which was 0.08 μM at pre-administration of epinastine improved markedly to 10 μM at post-administration of epinastine. Our data suggest that epinastine was very effective for treating atopic cough, and that histamine release from mast cells was related to the pathophysiology of this disease as well as to eosinophilic inflammation.

Table 3. Diagnostic criteria of atopic cough

1. non-productive cough lasting more than 8 weeks without stridor or dyspnea
2. atopic disposition or eosinophilia in induced sputum
3. no airway reversibility
4. normal bronchial responsiveness
5. increased cough sensitivity
6. non-effectivenes of bronchodilators
7. no abnormal finding in chest roentgenogram
8. normal pulmonary function test

Histamine has been shown to increase vascular permeability in bronchial circulation and to stimulate the rapidly adapting stretch receptors (RARs), which are thought to be one of peripheral cough receptors[22),23)]. Histamine H1 receptor antagonists have also been reported to inhibit RARs and to have anti-allergic effects that antagonize chemical mediator-induced bronchoconstriction and reduce irritants, including inhaled antigen, which, in turn, may reduce the tone of nerve fibers related to the cough reflex in animals[23),24)]. Thus, epinastine, a histamine H1 antagonist, may reduce cough in atopic cough.

Recently, unmyelinated c-fiber has also been shown to play an important role in the peripheral cough reflex[22),25)]. Histamine has been reported to stimulate c-fibers and induce cough[26),27)]. In addition, azelastine, a histamine antagonist, has been shown to inhibit the release of substance P from the c-fiber in guinea-pigs[28)]. Thus, another possible mechanism of antitussive effect of epinastine might be related to the inhibition of c-fibers in the airway.

It is reported that epinastine posesses

serotonin 1b receptor (5HT1b) partial agonistic action in addition to its anti-histaminic action[29),30)]. Recently, it has been clarified that the serotonin receptor has an important role in stimulatory transmission in the cough center of the medulla[22)]. Future research will examine the mechanism of antitussive action of epinastine in atopic cough in detail not only in terms of its anti-histaminic action but also in relation to serotonin receptor subtype in the cough center.

Summary

Epinastine suppressed persistent non-productive cough in our patient with atopic cough, and the capsaicin cough threshold significantly improved after treatment with epinastine. Though it is indicated that histamine is concerned in the pathophysiology of atopic cough, the precise mechanism and usefulness of epinastine should be explored in more detail by conducting a case-controlled study of the drug in a large sample size at multiple institutions.

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塩酸エピナスチンが有効だったアトピー咳嗽の１例

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要　旨

慢性咳嗽を訴える38歳の女性がアトピー咳嗽（好酸球性気管支炎）と診断された．ヒスタミンH1拮抗薬である塩酸エピナスチン（エピナスチン；１日１回20mg投与）の効果を確かめる目的で，咳点数，呼吸機能，カプサイシン咳閾値，メサコリンに対する気道過敏性を，エピナスチン投与前と投与４週後に評価した．エピナスチン投与後，咳嗽は著明に減少し，さらに，カプサイシン咳閾値は顕著に改善した．これらの結果から，エピナスチンがアトピー咳嗽患者の治療に有用であり，アトピー咳嗽の病態生理にヒスタミン受容体が関与している可能性が示唆された．