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Cough Threshold for Capsaicin Increases by Azelastine in Patients with Cough-variant Asthma

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SUMMARY: To assess the effects of azelastine in patients with cough-variant asthma, we measured the cough threshold for capsaicin (the concentration required to elicit more than five coughs) in 16 patients with cough-variant asthma before and after 4 weeks of treatment with azelastine (2 mg; b.i.d.) or placebo. After treatment, coughing decreased in all patients and the cough threshold for capsaicin increased significantly, from 0.67 ± 0.30 μM to 4.76 ± 1.55 μM ($P<0.01$) in the azelastine group. However, the cough threshold for capsaicin did not increase significantly, from 0.86 ± 0.33 μM to 1.11 ± 0.35 μM ($P>0.10$) in the placebo group. These results suggest that azelastine inhibits coughing in patients with cough-variant asthma.

KEY WORDS: Azelastine hydrochloride, Capsaicin cough threshold, Cough-variant asthma.

INTRODUCTION

Reversible airway obstruction can be confirmed with spirometry, and asthma is often diagnosed from a history of episodic wheezing, but coughing is also common among patients with asthma. MacFadden and Corrao have reported cases in which chronic coughing was the sole representing manifestation of bronchial asthma, and they referred to this condition as a variant form of asthma or as cough-variant asthma.[1,2]

Azelastine is a novel antiallergy compound that demonstrates H1 receptor antagonist activity.[3,4] Azelastine also inhibits substance P (SP) release and antagonizes SP.[5] Recently, SP released from sensory nerves in the airway has been shown to be an endogenous substance causing coughing.[6] We examined the effect of azelastine on chronic coughing in patients with cough-variant asthma.

METHODS

Patients

Sixteen patients who were referred to our Pulmonary Division complained of chronic coughing and were given the diagnosis of cough-variant asthma, as defined by MacFadden and Corrao.[1,2] The study was done according to the Helsinki Agreement, and all patients gave their written informed consent to participate. This study was carried out in a double blind placebo-controlled fashion. There were 10 women and six men, and their ages ranged from 22 to 66 years. They reported that they had been coughing for from 8 to 24 weeks. None complained of shortness of breath or wheezing, either at rest or with exercise. None had postnasal drip or chronic bronchitis to explain the cough. A carefully taken history, physical examination, complete blood count, examination of expectorated sputum, sinus and chest roentgenograms were within normal limits. The values of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) and FEV_1 as a percent of FVC (FEV_1/FVC) were 3.70 ± 0.26 l, 2.98 ± 0.22 l and 81.1 ± 2.4% respectively (Table 1). Total eosinophil counts were slightly higher than normal in five of the 16 patients.

Measurement of airway hyperresponsiveness

Airway response to inhaled methacholine was assessed with an Astograph (TCK-6100H, Chest, Tokyo, Japan). This device uses the forced oscillation method to measure respiratory resistance and its reciprocal conductance, during tidal breathing.[7] Briefly, it consists of an aerosol delivery system, a loudspeaker and

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Table 1. Patients' characteristics.

Age	Sex	WBC (/μl)	Eosinophils (%)	IgE (U/l)	FVC (l)	FEV_1 (l)	FEV_1/FVC (%)	Dmin (mg/ml)
55	F	3500	13	503	2.99	2.18	72.9	12.5
33	F	6300	0	35	2.28	1.97	86.4	9.02
39	F	6500	1	291	3.59	3.01	83.9	11.2
38	F	6800	0	86	2.76	2.46	89.1	1.16
63	F	9600	2	21	3.31	2.71	81.9	3.06
26	F	8700	5	21	2.93	2.83	96.6	8.31
25	F	5300	1	83	3.49	3.23	92.6	11.7
66	M	4100	4	594	3.21	2.15	67.1	11.2
48	M	7000	11	58	3.59	2.52	70.2	7.53
25	F	6200	9	97	3.15	2.35	75.3	6.21
50	M	9100	7	66	5.49	4.64	84.5	11.8
22	M	5600	14	83	6.17	4.84	78.4	0.08
24	M	5300	21	1562	4.62	3.89	84.6	4.05
66	M	6800	5	19	3.57	2.88	81.5	12.0
45	F	7600	3	58	3.95	3.52	89.1	8.35
56	F	5600	3	853	3.58	2.43	63.1	0.10

box used to generate changes in air pressure described by a sine wave of constant amplitude at 3 Hz, and a system for computing respiratory resistance automatically from measured values of flow and pressure at the mouth. Resistance and conductance were measured during inhalation of aerosolized methacholine. Airway responsiveness to the methacholine was expressed as the geometric mean of the lowest concentration of methacholine associated with the start of a consistent decrease in conductance (Dmin, in mg/ml of inhalation). From the results of pilot studies of normal subjects and of patients with asthma, hyperresponsiveness was defined as a Dmin less than or equal to 12.5 mg/ml.[7] By this definition, all patients were hyperresponsive to inhaled methacholine. FVC and FEV_1 were measured with a dry-seal spirometer (Chestac 65V, Chest, Tokyo, Japan). To measure the output of the nebulizer, it was weighed before and after solutions containing 4 mg/ml of methacholine were aerosolized with a constant airflow of 6 l/min. The output was found to be approximately 0.15 ml/min.

Capsaicin inhalation challenge

Capsaicin (Sigma) was dissolved in ethanol and diluted with 0.9% NaCl to 0.016, 0.08, 0.4, 2, 10, and 50 μM. Coughing was induced as described by Midgren et al.[8] Briefly, capsaicin was inhaled during tidal breathing from a nebulizer (Nissho, Tokyo, Japan, output 0.5 ml/min, mass median diameter 5 μM). Concentrations of capsaicin were increased until the patients coughed more than five times. The final concentration was taken as the cough threshold for capsaicin.

Statistical analysis

All data are expressed as means ± SEM, and were analysed with Student's *t*-test (two-tailed) for paired samples. A P value of <0.05 was taken as significant.

RESULTS

After a 4-week course of treatment, all patients in the azelastine group reported that they were coughing less. The cough threshold for capsaicin had increased significantly by that time in the azelastine group (from 0.67 ± 0.30 μM to 4.76 ± 1.55 μM, $P<0.01$, Fig. 1). The cough threshold for capsaicin did not increase significantly in the placebo group (from 0.86 ± 0.33 μM to 1.11 ± 0.36 μM, $P>0.10$, Fig. 2). The values of Dmin did not change significantly in the azelastine group (7.01 ± 1.72 mg vs. 9.63 ± 0.95 mg, $P>0.10$, Fig. 3). The values of Dmin did not change significantly in the placebo group (7.55 ± 1.51 mg vs. 8.52 ± 1.48 mg, $P>0.10$, Fig. 4). Neither FVC nor FEV_1 changed significantly in either azelastine or placebo group.

DISCUSSION

After 4 weeks of treatment with azelastine all patients with cough-variant asthma reported that they were coughing less, and the cough threshold for capsaicin was significantly increased. These data suggest the effectiveness of azelastine on coughing in cough-variant asthma.

Azelastine is a novel antiallergy compound that

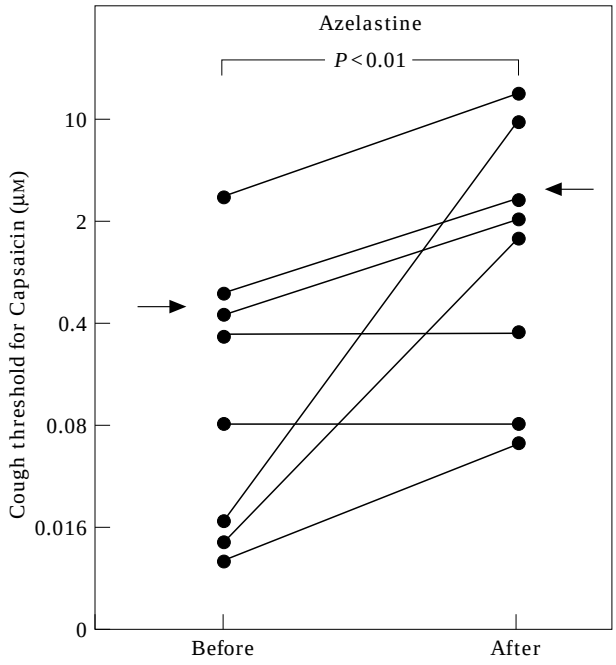

Fig. 1 Cough threshold for capsaicin before and after 4 weeks of treatment with azelastine (2 mg; b.i.d.). Means shown by arrows.

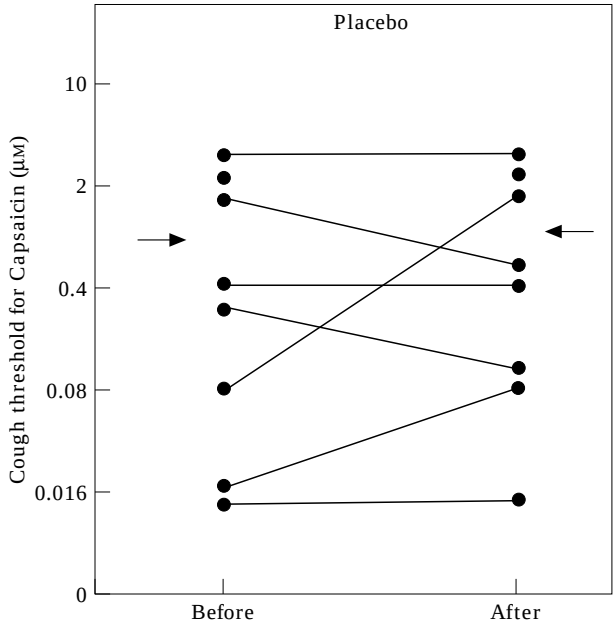

Fig. 2 Cough threshold for capsaicin before and after 4 weeks of treatment with placebo. Means shown by arrows.

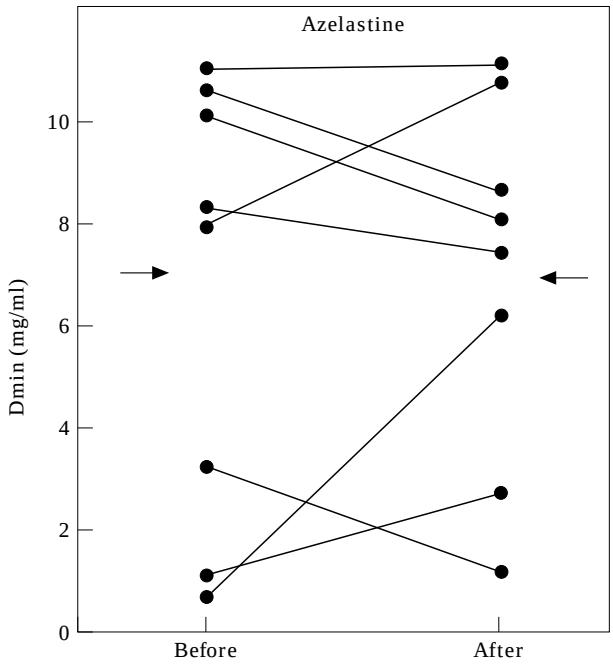

Fig. 3 Dmin before and after 4 weeks of treatment with azelastine. (Dmin: lowest concentration of methacholine associated with the start of a consistent decrease in conductance (mg/ml).) Means shown by arrows.

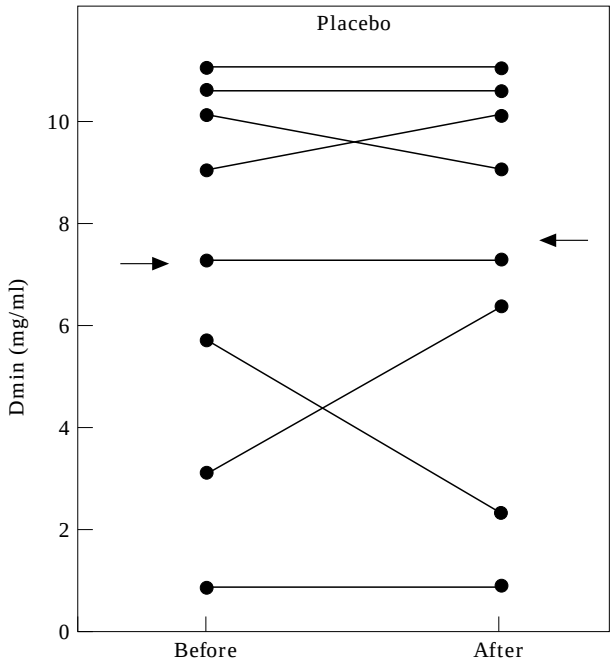

Fig. 4 Dmin before and after 4 weeks of treatment with placebo. Means shown by arrows.

appears to act through several interrelated mechanisms. Azelastine has histamine H1 receptor antagonist activity and also inhibits histamine release from mast cells following antigen and non-antigen stimuli.[9,10] However, Studham and Fuller found that terfenadine can affect the cough reflex, and that its effect is not related to H1 antagonism.[11] Therefore, the effect of azelastine on coughing need not be related to the H1 antagonism. Azelastine prevents eosinophil degranulation and activation[12,13] and inhibits the synthesis of leukotriene B4 (LTB4) and LTC4 in human eosinophils[14] contributing to its bronchial anti-inflammatory activities. However, in the present study, the value of Dmin which is the index of bronchial

hyperresponsiveness did not change after 4 weeks of treatment of azelastine, suggesting that the effectiveness of azelastine on coughing may not be related to the antiinflammatory effect of this agent.

Azelastine also inhibits SP release in the nose and lungs of patients with asthma.[15] Azelastine also inhibits non-adrenergic non-cholinergic neurotransmission which is mediated by SP, mainly by a prejunctional mechanism and partly by postjunctional depression.[5] Recently, SP has been shown to be an endogenous substance that can cause coughing.[6] Considering these data together, we speculate that the effectiveness of azelastine in cough-variant asthma is related to inhibition of non-adrenergic non-cholinergic nerves and/or antagonism to SP. Although this is a possible hypothesis, the precise mechanism in vivo and in vitro remains to be defined in the near future.

We conclude that azelastine can be an effective antitussive agent in cough-variant asthma, and that a placebo-controlled study in a larger group of patients is warranted.

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