Bradykinin-Induced Cough Reflex Markedly Increases in Patients with Cough Associated with Captopril and Enalapril

UICHIRO KATSUMATA, KIYOHISA SEKIZAWA*, YUKO UJIE*,
HIDETADA SASAKI* and TAMOTSU TAKISHIMA

*The First Department of Internal Medicine, and
*Department of Geriatric Medicine, Tohoku University
School of Medicine, Sendai 980*

KATSUMATA, U., SEKIZAWA, K., UJIE, Y., SASAKI, H. and TAKISHIMA, T. *Bradykinin-Induced Cough Reflex Markedly Increases in Patients with Cough Associated with Captopril and Enalapril*. Tohoku J. Exp. Med., 1991, **164** (2), 103-109 — We studied the effects of angiotensin converting enzyme (ACE) inhibitors on cough responses to bradykinin (BK), substance P (SP) and citric acid in a double blind, random study on 10 hypertensive patients receiving ACE inhibitors. Of these patients, five had reported cough with ACE inhibitors. Cough responses to citric acid were similar between patients with and without cough, and SP up to 10^{-5} M did not cause cough in any of the subjects. BK caused cough at 13.4 ± 1.2 ($-\log$ M) in 5 patients with cough associated with ACE inhibitors, but it did not cause cough at concentrations up to 10^{-5} M in other 5 patients. One month after the withdrawal of ACE inhibitors, 5 patients were free from cough symptoms, and BK did not cause cough up to 10^{-5} M in these patients, except for one who coughed at 10^{-9} M, without changes in responses to citric acid. BK caused cough at 14.3 ± 0.7 ($-\log$ M) although BK_{1-7} , a major metabolite of BK by ACE, caused cough at 5.7 ± 0.7 ($-\log$ M) in another 3 patients with cough associated with ACE inhibitor. These results suggest that impaired metabolism of BK induced by ACE inhibitors may relate to the manifestation of cough in hypertensive patients receiving ACE inhibitors. — bradykinin; ACE inhibitor; dry cough; hypertension

Angiotensin converting enzyme (ACE) inhibitors, such as captopril and enalapril have been widely used in the treatment of systemic hypertension. However, persistent dry coughs have been often reported in hypertensive patients who have been treated with ACE inhibitors (Sesoko and Kaneko 1985; Semple and Herd 1986; Webb et al. 1986; Coulter and Edwards 1987). Hypertensive

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Address for reprints: Tamotsu Takishima, M.D., the First Department of Internal Medicine, Tohoku University School of Medicine, 1-1 Seiryō-machi, Aoba-ku, Sendai 980, Japan.

patients receiving ACE inhibitors are reported to show an increase in dermal responses to bradykinin (Ferner et al. 1989) and may develop angioedema through the impaired metabolism of bradykinin within subcutaneous tissues (Wood et al. 1987). Thus, it has been suggested that the impaired metabolism of bradykinin induced by ACE inhibitors is related to a dry cough. However, to our knowledge, there has been no data to support this hypothesis. We therefore undertook a study in healthy volunteers and hypertensive patients with and without coughs associated with ACE inhibitors to investigate the effects of ACE inhibitors on cough responses to citric acid, bradykinin (BK) and substance P (SP).

METHODS

We studied 5 normal male subjects and 10 patients with essential hypertension. None of the subjects had had a history of recent respiratory tract infection, and none had asthma nor rhinitis. None had a smoking habit.

Normal subjects (ranging in age from 29 to 33) were studied before and after the administration of captopril. Captopril (25 mg) or a matched placebo was given orally 2 hr before the study in a random fashion (Morice et al. 1987). Hypertensive patients, three men and seven women, aged 55 to 78 (mean, 68.8 years), with mild to moderate essential hypertension (sitting diastolic blood pressure, 95 to 104 mmHg before treatment), were studied while undergoing an antihypertensive regimen which included the administration of either captopril or enalapril for at least 1 month. None had clinical evidence of heart failure. Of these patients, five had reported a dry cough associated with captopril or enalapril before and during the study. The patients characteristics and treatment received are shown in Table 1. To eliminate any diurnal change in cough response, the challenges were carried out at the same time of day in each subject.

Three types of tests were used to induce cough and were performed in a random manner on separate days within the same week. Aerosols of BK, SP, and citric acid were generated by a nebulizer ('De Vilbiss 646). The nebulizer output was 0.15 ml/min, with particles of aerodynamic mass mean diameters, $2.5 \mu\text{m}$ (the manufacture's specifications). BK and SP (Sigma Chemical Co. Ltd., St. Louis, MO, USA) were dissolved in saline (5 ml) providing a hundred times incremental concentrations from 10^{-17} M to 10^{-5} M. Fresh solutions were made up on each day, and stored on ice until used. Citric acid (Wako Chemicals, Osaka) was dissolved in saline and made into two-fold incremental concentrations from 0.03% to 18%. After the first set of experiments were carried out, five patients complaining of a dry cough stopped taking captopril or enalapril and received another antihypertensive regimen. One month after stopping ACE inhibitors, we repeated the previous experiment on those five patients.

Subjects tidally breathed nebulised solutions through a two-way low resistance valve, with a 30 liter reservoir bag interposed to ensure constant delivery of solution. Cough was recorded by a heated pneumotachograph (Fleisch No. 2; Dynasciences, Blue Bell, PA, USA) mounted on the expiratory ports of the valve. The cough response to the inhalation of each aerosolized solution was analyzed for each subject by determining the subject's cough threshold (Eschenbacher et al. 1984). Cough threshold was the concentration at which the subject coughed at least 5 times, provided that the subject also coughed at two subsequent solutions of higher concentrations (Eschenbacher et al. 1984). Cough was recorded during a 1 min period of exposure to a given concentration of solution and over a subsequent 3 min observation period. Subjects inhaled saline aerosol (control) first, then inhaled each aerosolized solution starting from the lowest concentration. We waited 3 min between each administration. We measured the vital capacity (VC) and forced expiratory volume at 1 sec (FEV_1) before and after the experiments using a spirometer (Tatebe, Tokyo). The

reservoir bag and two-way valve were changed between each subject, and after each study, they were washed in water to ensure that the drugs deposited on their walls had been removed.

We attempted to determine whether BK_{1-7} , a major metabolite of BK by ACE, causes cough. Other hypertensive patients, three women, aged 60 to 72 (mean, 67.3 years), with cough, who had taken enalapril were tested with either BK or BK_{1-7} in a double blind, random fashion.

Results are reported as mean $\pm$ s.e. For statistical analysis we employed a one-way analysis of variance, Duncan's multiple-range test, and the Wilcoxon signed-ranks test. Significance was accepted at $p < 0.05$.

RESULTS

Saline aerosols did not cause cough in all subjects under all conditions. None of the normal subjects coughed at concentrations of up to 10^{-5} M BK, either before or after captopril. Table 1 shows that the dosage of captopril and enalapril, age and pulmonary function tests were similar in the patients with and without cough, although the patients with cough were all women. Table 2 shows that SP did not cause cough in either group at concentrations of up to 10^{-5} M, and both groups showed a similar cough threshold to citric acid. Fig. 1 shows cough responses to bradykinin in patients with cough. Bradykinin-induced cough was not concentration dependent, and tachyphylaxis occurred during the challenge. BK caused cough at the concentration of 13.4 ± 1.2 ($-\log M$) in patients with cough, although

TABLE 1. *Subject characteristics and pulmonary function test results*

Subject No.	Age (years)	Sex	L (% of predicted value)		Drug	Dosage of drug
			VC	FEV ₁		
1 ^a	78	F	2.08 (110)	1.77 (148)	Enalapril	2.5 bid
2 ^a	72	F	2.15 (104)	1.72 (113)	Captopril	12.5 tid
3 ^a	70	F	2.08 (102)	1.83 (114)	Captopril	12.5 tid
4 ^a	67	F	1.93 (98)	1.56 (110)	Enalapril	2.5 bid
5 ^a	70	F	1.73 (95)	1.45 (99)	Enalapril	2.5 bid
Mean $\pm$ s.e.	71 $\pm$ 2		(102 $\pm$ 3)	(117 $\pm$ 8)		
6	55	M	3.91 (104)	3.36 (108)	Enalapril	2.5 bid
7	78	M	2.74 (102)	2.33 (117)	Enalapril	2.5 bid
8	74	F	2.35 (106)	1.90 (119)	Enalapril	2.5 bid
9	67	M	3.94 (100)	3.11 (126)	Captopril	12.5 tid
10	55	F	2.94 (99)	2.35 (114)	Captopril	12.5 tid
Mean $\pm$ s.e.	66 $\pm$ 5		(102 $\pm$ 1)	(117 $\pm$ 3)		

^aSubjects had ACE inhibitor-related cough.

VC, vital capacity; FEV₁, forced expiratory volume in 1 s. "Dosage of drug" indicates the dosage received before and during study. bid, twice per day; tid, three times per day; F, female; M, male.

TABLE 2. *Pulmonary function test results and cough threshold*

Subject No.	Baseline		After BK		Threshold of cough ($-\log M$)				
	VC	FEV ₁ (% of predicted value)	VC	FEV ₁	During			Withdrawal	
					SP	CA	BK	CA	BK
1 ^a	110	148	106	141	<5	2.8	15	3.0	<5
2 ^a	104	113	107	118	<5	4.1	15	3.4	<5
3 ^a	102	114	103	113	<5	1.6	13	2.0	<5
4 ^a	98	110	102	107	<5	5.2	15	4.4	9
5 ^a	95	99	92	102	<5	2.9	9	2.1	<5
Mean $\pm$ S.E.	102 $\pm$ 3	117 $\pm$ 8	104 $\pm$ 3	116 $\pm$ 7	<5	3.3 $\pm$ 0.6	13.4 $\pm$ 1.2*	3.0 $\pm$ 0.4	ND
6	104	108	103	109	<5	1.4	<5	ND	ND
7	102	117	98	121	<5	6.2	<5	ND	ND
8	106	119	109	113	<5	2.0	<5	ND	ND
9	100	126	102	122	<5	3.6	<5	ND	ND
10	99	114	100	116	<5	5.8	<5	ND	ND
Mean $\pm$ S.E.	102 $\pm$ 1	117 $\pm$ 3	102 $\pm$ 2	116 $\pm$ 2	<5	3.8 $\pm$ 1.0	<5	ND	ND

^aSubjects had ACE inhibitor-related cough.

VC, vital capacity; FEV₁, forced expiratory volume in 1 s; SP, substance P; CA, citric acid; BK, bradykinin; During, during treatment with ACE inhibitor; Withdrawal, after withdrawal of ACE inhibitor. ND, not determined.

*Significant difference between patients with and without cough is indicated by $p < 0.01$.

Fig. 1. Effects of increasing concentrations of bradykinin on cough responses in individual patients with spontaneous cough. Cough responses were not concentration-dependent.

it did not cause cough at concentrations of up to 10^{-5} M in patients without cough (Table 2). BK, SP and citric acid did not alter VC and FEV₁ significantly in normal subjects before and after captopril, or patients with or without cough (Table 2). The patients with cough recovered from their symptoms in an average time of 13 days (from 7 to 21 days) after the withdrawal of ACE inhibitors. One month after the withdrawal of the drug, four patients did not cough at concentrations of up to 10^{-5} M BK and one patient showed an increase in cough threshold to BK from 10^{-15} M to 10^{-9} M, although the cough threshold for citric acid was similar (3.3 ± 0.6 vs. 3.0 ± 0.4 ; $-\log M$; $p > 0.3$). BK₁₋₇ caused cough at the concentration of 5.7 ± 0.7 ($-\log M$), significantly higher than that of 14.3 ± 0.7 ($-\log M$) in BK in the patients with cough ($n = 3$; $p < 0.01$).

DISCUSSION

Our major findings were that ACE inhibition markedly increased the tussive effect of inhaled BK in the patients who reported cough while taking ACE inhibitors as part of an antihypertensive regimen, and that these patients recovered from symptoms in association with the decrease in cough response to BK after the withdrawal of ACE inhibitors.

The fact that all the patients who coughed while taking ACE inhibitors were women is similar as previously described in the literature. The cough was mild, easily tolerated by all patients, and resolved itself within one month after the withdrawal of ACE inhibitors.

A recent report showed that ACE inhibition potentiated capsaicin-induced cough reflex in normal subjects (Morice et al. 1987). It was suggested that SP released from sensory C-fibers by inhaled capsaicin is associated with the mechanisms responsible for cough associated with ACE inhibition (Morice et al. 1987). However, SP did not cause cough with ACE inhibition in any of the subjects in the present study, suggesting that SP is unlikely as a mechanism responsible for cough associated with ACE inhibition. Likewise, bronchoconstriction is not responsible for BK-induced cough in patients with cough, because pulmonary functions did not differ before and after BK inhalation.

Another possibility is that this type of medication could induce bronchial hyperresponsiveness leading to a cough (Salena 1986). However, Sala et al. (1986) did not find a difference in methacholine responsiveness after captopril treatment in asthmatic subjects with hypertension. More recently, Boulet et al. (1989) reported that hypertensive patients who developed cough during captopril treatment did not show an increase in responsiveness to inhaled methacholine.

Adverse effects of ACE inhibitors including angioedema (Wood et al. 1987), cough (Sesoko and Kaneko 1985), flushing and diarrhoea have putatively been ascribed to BK. However, ACE inhibition is reported to have no effect on airway reactivity and cough reflex to inhaled BK in asthmatic subjects (Dixon et al. 1987), suggesting that ACE inhibition may not cause cough in asthmatic subjects

without spontaneous cough. Thus, the present study is partly in agreement with the previous study that ACE inhibition did not cause an increase in cough response to inhaled BK in normal subjects and hypertensive patients without spontaneous cough.

BK caused cough at very low concentrations in patients with cough. However, similar findings have been reported in the cases of awake guinea pigs that coughed during inhalation of SP and capsaicin (Kohrogi et al. 1988, 1989). An increase in cough responses to BK induced by ACE inhibitors in patients with cough seems to be related to the class of drug rather than to individual compounds, since it occurred with both captopril and enalapril. ACE can hydrolyze bradykinin (Erdo 1979) and SP (Matsas et al. 1984; Thiele et al. 1985) as well as the formation of angiotensin II from angiotensin I (Yang et al. 1971). ACE degrades BK more rapidly and with higher specificity than it degrades SP (Turner et al. 1985). Although ACE is concentrated along the luminal surface of the vascular endothelium (Caldwell et al. 1976), it also exists in the tissues of the airways in humans (Johnson et al. 1985). ACE inhibition may therefore increase the susceptibility of the cough receptors to BK from either the vascular or epithelial side. BK₁₋₇, a major metabolite of BK by ACE (Turner et al. 1985), had only a weak effect on cough reflex in patients who coughed with inhaled BK at low concentrations, suggesting that impaired metabolism of BK is involved in the increase in cough response to BK in those patients. Furthermore, an increase in cough response to BK was reversible in association with the disappearance of symptoms without changes in cough response to citric acid, suggesting that the mechanisms responsible for the increase in cough response to BK are intimately related to cough associated with ACE inhibitors, although the present study can not address the reason why cough reflex to BK increased only in the patients with cough associated with ACE inhibitors. Because BK caused cough at very low concentrations in patients with spontaneous cough, cough receptors might become sensitive to bradykinin, with a resulting increase in susceptibility to either endogenous and exogenous BK.

Inhibition of neutral endopeptidase is reported to potentiate cough response to SP in awake guinea pigs (Kohrogi et al. 1988, 1989) and SP is the best substrate to neutral endopeptidase (Turner et al. 1985). Thus, a balance between substrate and substrate specific enzyme activity may be important for regulating cough reflex in the body, and enzyme inhibitors may be useful tools for further research toward an understanding of the most common respiratory symptom of cough.

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