Effects of Candesartan on Cough and Bronchial Hyperresponsiveness in Mildly to Moderately Hypertensive Patients With Symptomatic Asthma

Hiroshi Tanaka, MD; Shin Teramoto, MD; Kensuke Oashi, MD; Toyohiro Saikai, MD; Shintaro Tanaka, MD; Kazuhiro Suzuki, MD; Midori Hashimoto, MD; Shosaku Abe, MD

Background—Candesartan, an AT \(_1\) receptor antagonist, has been reported to have no association with persistent cough in subjects with hypertension, but there has been no study on the safety of its administration to hypertensive patients with symptomatic asthma. The aim of this study was to compare the adverse effects of candesartan and calcium antagonists on cough, pulmonary function, and bronchial hyperresponsiveness in these patients.

Methods and Results—Sixty mildly to moderately hypertensive patients with bronchial asthma received either candesartan (n = 30) or the calcium antagonists nifedipine or manidipine (n = 30) for 6 months. The candesartan group included 5 subjects with a history of ACE inhibitor–induced cough. There were no differences between the 2 groups in patient characteristics, ACE gene polymorphism, pulmonary function, or bronchial hyperresponsiveness to methacholine. Control of hypertension was the primary end point; new cough detected by self-administrated questionnaire and an increase in cough frequency by visual analog scale were the second end point. No patient complained of persistent cough. Neither mean visual analog scale score nor pulmonary functions changed during this study. Bronchial hyperresponsiveness had a tendency to improve in the candesartan group, but there was no difference between the 2 groups.

Conclusions—Incidence, frequency, and severity of persistent cough, pulmonary functions, and bronchial hyperresponsiveness did not change in either the candesartan or calcium antagonist group. It is suggested that candesartan is as effective and safe as calcium antagonists in the treatment of hypertension associated with symptomatic asthma. (Circulation. 2001;104:281-285.)

Key Words: angiotensin receptors hypertension asthma genes

ACE inhibitors are generally well-tolerated drugs, but persistent dry cough has been found to occur in 0.2% to 33% of patients and may be more common in women and the mongoloid race.1–3 ACE inhibitor–induced cough appeared to occur through the accumulation of substance P or bradykinin in the respiratory tract and subsequent stimulation of the cough reflex pathway.2,4 The mechanism for kinin accumulation with ACE inhibitors is the additional function of ACE as a kininase, which causes degradation of several kinin substrates. Candesartan is a novel angiotensin II antagonist, an AT \(_1\) receptor antagonist; it offers a more specific mechanism to inhibit the renin-angiotensin system and should not lead to kinin accumulation and cough. Recently, it was reported that AT \(_1\) receptor antagonists were not associated with cough in hypertensive patients with a history of ACE inhibitor–induced cough;4 however, there has been no report on its effect in patients with bronchial asthma.

The relation between ACE inhibitor–induced dry cough and the insertion/deletion (I/D) polymorphism of the ACE gene was reported in Japanese patients with hypertension, and frequencies of allele I in subjects with persistent cough were significantly higher than in those without the cough.5 Increased sensitivity of coughing after inhalation of aerosols of distilled water and bronchial hyperresponsiveness (BHR) to methacholine were observed in normotensive subjects with the II genotype.7 These studies suggested a strong association between allele I of the ACE polymorphism and increased airway hyperresponsiveness, which is a major manifestation of bronchial asthma. On the other hand, Malini et al8 reported that the urinary ratio of 11-dehydro thromboxane B \(_2\) (TXB \(_2\)) to 6-keto-prostaglandin F \(_{1\alpha}\) (PGF \(_{1\alpha}\)) of an ACE inhibitor–induced cougher was twice that of the control subject, suggesting that increased TXB \(_2\) and decreased prostacyclin might represent a marker of patients susceptible to ACE inhibitor–induced cough.

The methacholine inhalation challenge test is used to assess airway reactivity, and it stimulates the adverse effect of endogenous mediators on bronchial smooth muscle in hyper-
reactive subjects, therefore providing a diagnosis of airway sensitivity. We hypothesize that AT1 receptor antagonists may not be associated with cough or airway kinin accumulation even in asthmatic patients who show increased BHR, and if so, cough and BHR will not be worsened during the use of an AT1 receptor antagonist. However, there have been no studies on the incidence, frequency, and severity of dry cough and changes in BHR resulting from long-term therapy with AT1 receptor antagonists in patients with symptomatic bronchial asthma. To investigate the safety of an AT1 receptor antagonist in these patients, we conducted a multicenter, genetically controlled, active placebo-controlled, parallel group study on 6-month therapy with candesartan. We found no significant changes in incidence, frequency, and severity of dry cough; pulmonary functions; and BHR to methacholine in either the candesartan or calcium antagonist group. It is suggested that candesartan is as effective and safe as calcium antagonists in the treatment of hypertension associated with symptomatic asthma.

**Methods**

**Study Population**

A total of 62 outpatient subjects were enrolled in this study. Patients ranged from 41 to 78 years of age and had primary hypertension with symptomatic and stable bronchial asthma. None of these patients had experienced symptoms of upper respiratory tract infection or seasonal allergies for ≥4 weeks before enrollment. Exclusion criteria were secondary or malignant hypertension; sitting diastolic blood pressure (DBP) >105 mm Hg or systolic blood pressure (SBP) >180 mm Hg; and severe cardiovascular, liver, or renal diseases. The previous daily antihypertensive drugs used by the 62 patients consisted of 10 mg mandipine (n=24), 20 mg long-acting nifedipine (n=21), 5 mg imidapril (n=5), 5 mg enalapril (n=4), 2.5 mgamlodipine (n=4), 40 mg furosemide (n=2), and 4 mg nilvadipine (n=2). All subjects were recruited from Sapporo Medical University Hospital and Tomokomai Prefecture Hospital after giving informed consent for the study and ACE gene examination.

Asthma was diagnosed by use of the American Thoracic Society criteria for bronchial asthma, consisting of the symptoms of episodic cough, wheezing, and dyspnea and an increase of ≥15% in the forced expiratory volume in 1 second (FEV1) in response to bronchodilator. Severity of asthma was defined by the guidelines published by the National Institutes of Health, according to which 23 of the 60 patients had mild, 30 had moderate, and 7 had severe asthma. Of the 60 subjects, 9 were current smokers. Fifty-seven asthmatic patients were treated with inhaled beclomethasone dipropionate (200-1600 µg/d) and inhaled β2-agonist was used when required according to the guidelines. No patients were treated with an oral anti-inflammatory drug.

**ACE Gene Polymorphism**

Genomic DNA was prepared from peripheral blood leukocytes by standard method. A 287-bp I/D polymorphism in intron 16 of the ACE gene was examined by polymerase chain reaction. Polymerase chain reaction products were subjected to electrophoresis in agarose gels, and genotype was determined. A 190-bp fragment without the insertion (D allele) and a 490-bp fragment with the insertion (I allele) were observed, and 3 genotypes appeared as II, ID, and DD.

**Study Protocol**

This was a multicenter, ACE genetically controlled, active placebo-controlled study with parallel-group design that compared 4 mg candesartan (once daily) and matching placebo calcium antagonists consisting of either 20 mg nifedipine (10 mg twice daily) or 10 mg mandipine (once daily). We chose 4 mg candesartan because ACE inhibitor–induced cough was reported not to have a dose-related effect, and all enrolled patients had been in excellent BP control with a low dose of each antihypertensive agent mentioned in the Study Population section. In a previous study in Japanese patients with mild to moderate hypertension, the cumulative efficacies rates of candesartan were 15% at 1 mg/d, 38% at 2 mg/d, 60% at 4 mg/d, and 76% at 8 mg/d. And if the adverse effect of cough would be subclinical as a result of a low dose of candesartan, the methacholine inhalation challenge test would detect the subtle airway inflammation. With informed consent, all previous antihypertensive agents were withdrawn 2 weeks before administration. All subjects received these drugs for 6 months, before and after which we examined the incidence, frequency, and severity of cough; pulmonary functions; and BHR to inhaled methacholine. The primary end point was control of hypertension; in the event of sitting DBP >95 mm Hg or SBP >150 mm Hg 1 month after treatment, we would double the dose of each drug administered. The second end point was the adverse effect of dry cough or an increase in cough frequency by visual analog scale (VAS).

**Assessments**

Frequency of cough was reported by making a cross on a VAS score, ie, a straight horizontal line 100 mm in length, with 0 mm labeled “none of the time” and 100 mm labeled “all of the time.” Severity of cough was assessed by a symptom assessment questionnaire by means of a 5-grade Likert scale (not at all, a little, moderately, quite a bit, and extremely). The incidence of cough was defined by any of the responses on the Likert scale, except “not at all.” BP was measured on the same arm at each visit with a mercury sphygmomanometer with a cuff of appropriate size but not standardized in relation to study drug intake or time of day. After 5 minutes of rest, sitting SBP and DBP were measured to the nearest 2 mm Hg. Adverse events were recorded either from spontaneous reports by the patient or in response to an open, nonspecific question (eg, “Have you had any health problems since we last met?”).

**Spirogram and Bronchial Responsiveness**

FEV1 was measured with a standard spirometer (Chestac 55V, Chest). Predicted FEV1 was calculated by the following forms of method of Berglund: male predicted FEV1 = (L) × 3.44 × height (m) × 0.033 × age (y) − 1.00, and female predicted FEV1 = (L) × 2.67 × height (m) × 0.027 × age (y) − 0.54. BHR was examined by the continuous methacholine inhalation method with simultaneous measurement of respiratory resistance (Rrs; cm H2O · L−1 · s−1) developed by Takishima et al. Briefly, we prepared ten 2-fold incremental concentrations of methacholine chloride diluted in physiological saline from 49 to 25 000 µg/mL. Each methacholine aerosol was inhaled for 1 minute through Bird micronebulizers (Bird Corp), with an output of 0.25 L/s. Rrs was measured by the 3-Hz forced oscillation method. After baseline Rrs (physiological saline inhalation) was recorded, methacholine aerosols were inhaled during tidal breathing without the pause while Rrs was continuously measured. The inhalation continued until the measuring Rrs was >2-fold the baseline Rrs level. Respiratory conductance (the reciprocal of Rrs) was plotted, and the cumulative dose of methacholine that decreased respiratory conductance to 65% of the baseline level was obtained as PD35Grs from each dose-response curve. This parameter was measured in terms of a unit defined as 1-minute inhalation of 1 mg/mL methacholine. The values were expressed as logPD35Grs. Ishii et al reported that the logPD35Grs values in this simple continuous inhalation provocation test were significantly correlated (r=0.80) with those in a more complex standard intermittent method; methacholine aerosols with stepwise incremental concentrations are inhaled during tidal breathing for 2 minutes at 5 minutes after the end of each inhalation period by means of the forced oscillation method. All bronchial challenge studies were performed at approximately the same time of day for each subject.
Measurement of Urinary 11-Dehydro-TXB\textsubscript{2} and 6-Keto-PGF\textsubscript{1\alpha}

Urinary 11-dehydro-TXB\textsubscript{2} and 6-keto-PGF\textsubscript{1\alpha} were assayed as described elsewhere. Briefly, indomethacin was added to a 3-hour urine sample and stored at \(-20\)°C until measurement. These eicosanoids were measured with the 11-dehydro-TXB\textsubscript{2} [\(^{125}\text{I}\)] radioimmunoassay kit (New England Nuclear) and the 6-keto-PGF\textsubscript{1\alpha} [\(^{125}\text{I}\)] assay system (Amersham International). The measurements were corrected by the urine creatinine content, and levels were expressed as picograms per milligram of creatinine. The recovery rates of tritiated 11-dehydro-TXB\textsubscript{2} and 6-keto-PGF\textsubscript{1\alpha} were 61.5% and 67.4%, respectively.

Statistical Analysis

Results are expressed as mean±SD. Baseline data between the 2 treatment groups were compared by use of the Mann-Whitney U test for continuous variables and by the \(\chi^2\) test for categorical variables. Changes in the frequency and severity of cough, pulmonary function tests, and BHR to methacholine were analyzed nonparametrically with the Wilcoxon rank-sum test. The incidence of cough according to the Likert scale at the last visit was analyzed by use of the Mantel-Haenszel test. Statistical significance was assumed at \(P<0.05\).

Results

A total of 62 hypertensive patients with bronchial asthma were enrolled in this study and divided into 2 treatment groups: a candesartan-treated group and a calcium antagonist-treated group. However, 1 patient in the candesartan group withdrew because of gastric discomfort, and 1 subject in the calcium antagonist group withdrew because of headaches. Therefore, analysis was done on 30 subjects in each group. No significant differences were demonstrated between the 2 groups with regard to demographics and baseline characteristics (Table 1), as well as duration of hypertension and previous antihypertensive therapy.

Blood Pressure

No patient had DBP >95 mm Hg or SBP >150 mm Hg 1 month after treatment; therefore, we did not double the dose of drugs administered. Baseline SBP was 152±14 mm Hg in candesartan patients and 153±13 mm Hg in calcium antagonist subjects. Six months after treatment, these values declined to 130±15 and 129±16 mm Hg, respectively. Baseline DBP was 92±6 mm Hg in the candesartan group and 93±8 mm Hg in the calcium antagonist group; these levels also declined to 79±5 and 80±8 mm Hg, respectively, after treatment.

Incidence, Frequency, and Severity of Cough

At the start of this study, the incidence of cough was not significantly different between the 2 groups (36.7% versus 30.0%), and at the end of treatment, there were no increases (36.7% versus 33.3%). The frequency of cough (VAS score) was 20.8±19.9 mm for the candesartan group and 19.8±17.7 mm for the calcium antagonist group, and there was no significant difference between before and after treatment (Table 2 and the Figure). Similar results were obtained with regard to severity of cough with no significant difference.

TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Candesartan Group (n=30)</th>
<th>Calcium Antagonist Group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±9</td>
<td>60±12</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>15/15</td>
<td>15/15</td>
</tr>
<tr>
<td>Current smoker, n</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>152±14</td>
<td>153±13</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>92±7</td>
<td>93±8</td>
</tr>
<tr>
<td>ACE genotype, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>allele I</td>
<td>0.70</td>
<td>0.68</td>
</tr>
<tr>
<td>allele D</td>
<td>0.30</td>
<td>0.32</td>
</tr>
<tr>
<td>Cough Incidence, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency, VAS, mm</td>
<td>20.8±19.9</td>
<td>19.8±17.7</td>
</tr>
<tr>
<td>Severity, n</td>
<td>19/10/1</td>
<td>21/8/1</td>
</tr>
<tr>
<td>Baseline urinary eicosanoids</td>
<td></td>
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<tr>
<td>TXB\textsubscript{2}, pg/mg creatinine</td>
<td>860±454</td>
<td>915±502</td>
</tr>
<tr>
<td>PGF\textsubscript{1\alpha}, pg/mg creatinine</td>
<td>274±124</td>
<td>301±156</td>
</tr>
<tr>
<td>Ratio of TXB\textsubscript{2}/PGF\textsubscript{1\alpha}</td>
<td>3.73±2.94</td>
<td>3.85±3.12</td>
</tr>
<tr>
<td>Therapy, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Long-acting nifedipine</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Mandipine</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
</table>

*Likert scale 0—not at all, 1—a little; 2—moderately.

Pulmonary Functions and BHR to Methacholine

As shown in Table 2, there were no significant differences in FEV\textsubscript{1}, \%FEV\textsubscript{1}, or BHR to methacholine (logPD35Grs) during the 6-month therapy. The values of logPD35Grs had a tendency to decrease in candesartan group (\(P=0.089\)) but with no differences between the 2 groups.

Discussion

This is the first report to ascertain that AT\textsubscript{1} receptor antagonist affects asthmatic symptoms, pulmonary functions, and BHR to methacholine in the long-term treatment of systemic hypertensive patients with symptomatic asthma. Recently, it was reported that 7 days of therapy with the AT\textsubscript{1} receptor antagonist losartan at recommended dosages did not enhance BHR in subjects with mild stable asthma. Angiotensin II is an octapeptide hormone that stimulates a variety of physiological responses that support arterial blood pressure, and it may contribute to the pathogenesis of hypertension, heart failure, and diabetic nephropathy. On the other hand, plasma angiotensin II levels have been reported to be elevated during asthma exacerbation. Alternative angiotensin II–producing pathways besides the ACE-dependent ones were chymase- or
cathepsin G–dependent pathways. Chymase is abundant in mast cells and is released during IgE-mediated allergic reactions. Intravenous infusion of angiotensin II into stable asthmatic patients enhances BHR to inhaled methacholine, and angiotensin II causes bronchoconstriction in mildly asthmatic patients. Recently, Myou et al reported that the AT1 receptor antagonist losartan slightly improved BHR to methacholine in asthmatic subjects. It was suggested that the AT1 receptor antagonist might function favorably on not only systemic hypertension but also bronchial inflammation in symptomatic asthmatics. However, in the present study, a tendency toward improvement in BHR to methacholine was observed in both the candesartan and calcium antagonist groups during the 6-month treatment. In our study, 90% of patients were treated with inhaled corticosteroid, which may mask the effect of an AT1 receptor antagonist. To evaluate the true effect of this drug on airway hyperresponsiveness, further prospective studies of asthmatic patients without inhaled corticosteroid are required.

In our study, the 5 asthmatic patients with a history of ACE inhibitor–induced cough in the candesartan group did not note persistent cough. ACE inhibitor–induced cough appeared to occur through the accumulation of bradykinin, substance P, and/or prostaglandins in the airways. The mechanism for bradykinin and substance P accumulation with ACE inhibitors is via the additional function of ACE as a kininase, which causes degradation of several kinin substrates. These mediators can induce bronchoconstriction, increase the sensitivity of the cough reflex, stimulate the asthmatic neurogenic inflammation (ie, substance P), act through neurokinin-1 receptor, induce airway constriction, increase the vascular permeability and mucus secretion, and stimulate the release of histamine and tumor necrosis factor-α from mast cells. Bradykinin is a potent bronchoconstrictor in asthmatic patients that induces coughing and a sensation of chest tightness and stimulates the arachidonic acid pathway, which can produce bronchoconstrictive prostaglandins. On the other hand, nifedipine and indomethacin have been shown to attenuate the persistent cough associated with administration of ACE inhibitor through the inhibition of prostaglandin synthesis. Candesartan and losartan were reported not to be associated with cough in hypertensive patients with a history of ACE inhibitor–induced cough. From our results, this tendency may also apply to asthmatic patients.

The relation between ACE inhibitor–induced dry cough and the I/D polymorphism of ACE gene in intron 16 was reported in Japanese patients with hypertension but not in white subjects, and the frequencies of allele I in subjects with persistent cough were significantly higher than in those without the cough. Increased sensitivity of coughing after inhalation of aerosols of distilled water and BHR to methacholine was observed in normotensive subjects with the II genotype. Tomita et al reported that among Japanese asthmatic patients, 35.2% were type II, 52.1% type DI, and 12.7% type DD; in our 60 subjects, there were 28 with type II, 27 with type DI, and 5 with type DD. Our 5 ACE inhibitor-induced coughing subjects consisted of 2 with type II and 3 with type DI. The association between allele I of ACE polymorphism and airway hyperresponsiveness has been suggested; therefore, we divided the patients into 2

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**TABLE 2. Effects of 6-Month Course of Oral Candesartan or Calcium Antagonists**

<table>
<thead>
<tr>
<th></th>
<th>Candesartan Group</th>
<th>Calcium Antagonist Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Cough (VAS score, mm)</td>
<td>20.8±19.9</td>
<td>19.0±18.5</td>
</tr>
<tr>
<td>Spirogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.68±0.49</td>
<td>1.57±0.47</td>
</tr>
<tr>
<td>%FEV1</td>
<td>77.3±23.6</td>
<td>76.6±20.7</td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td>0.43±0.38</td>
<td>0.51±0.45</td>
</tr>
</tbody>
</table>

Changes in cough frequency by VAS before and after 6-month antihypertensive treatment.
groups in a genetically controlled fashion. On the other hand, Malini et al reported that the urinary ratio of 11-dehydro TXB2 to 6-keto-PGF1α of ACE inhibitor–induced coughers was twice that of control subjects, suggesting that increased TXB2 and decreased prostacyclin might represent a marker of patients susceptible to ACE inhibitor–induced cough. We compared this ratio between the candesartan and calcium antagonist groups and found no significant difference. From the 2 above-mentioned data-informed points of view, there was no difference between the 2 groups.

In conclusion, the incidence, frequency, and severity of persistent cough, pulmonary functions, and airway hyperresponsiveness were not different between the candesartan and calcium antagonist groups. It was suggested that an AT1 receptor antagonist was safe even in hypertensive patients with symptomatic asthma.

References

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_Circulation_. 2001;104:281-285
doi: 10.1161/01.CIR.104.3.281

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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