Candesartan Cilexetil Is Not Associated With Cough in Hypertensive Patients With Enalapril-Induced Cough

P.H. Tanser, L.M. Campbell, J. Carranza, J. Karrash, P. Toutouzas, and R. Watts, for the Multicentre Cough Study Group

The aim of this study was to evaluate the occurrence of dry cough during treatment with candesartan cilexetil, enalapril, or placebo in patients with hypertension and a history of angiotensin converting enzyme (ACE)-inhibitor–related cough. Patients with confirmed cough during an enalapril (10 mg) challenge period, followed by no cough during a placebo dechallenge period were randomized to 8 weeks of double-blind treatment with candesartan cilexetil (8 mg) (n = 62), enalapril (10 mg) (n = 66), or placebo (n = 26). Incidence and severity of dry cough was evaluated by the symptom assessment questionnaire, frequency of dry cough by a visual analog scale, and the possible impact on quality of life by the minor symptom evaluation (MSE) profile. The percentage of patients with cough was significantly lower with candesartan cilexetil (35.5%) than with enalapril (68.2%, P < .001), and did not differ between candesartan cilexetil and placebo (26.9%, P > .20). Patients coughed less frequently and with less severe cough with candesartan cilexetil than with enalapril, and similarly with candesartan cilexetil and placebo. Changes in the MSE profile were minor, although candesartan cilexetil had better scores for contentment than placebo (P = .03), and also tended to be associated with better sleep than enalapril (P = .08). In hypertensive patients with ACE-inhibitor–induced cough, the incidence, frequency, and severity of dry cough was significantly lower with candesartan cilexetil than with enalapril, and no different from that found with placebo. Am J Hypertens 2000;13:214–218

© 2000 American Journal of Hypertension, Ltd.

KEY WORDS: Cough, quality of life, hypertension, candesartan cilexetil, enalapril, placebo.

Angiotensin converting enzyme (ACE) inhibitors are generally well tolerated drugs, but a persistent and dry cough has been found to occur in 15% to 40% of patients and may be more common in women and the Mongoloid race.1,2 In patients with hypertension, usually an asymptomatic state, the irritating cough appears to be a frequent reason for noncompliance or switching to an alternate therapy.3

The ACE-inhibitor–mediated cough appears to oc-
cur through the accumulation of tachykinins or bradykinin in the respiratory tract and subsequent stimulation of the cough reflex pathway.\(^4,5\) The reason for kinin accumulation with ACE inhibitors is that ACE also functions as a kininase, causing degradation of several kinin substrates. The angiotensin type 1 (AT\(_1\)) receptor blockers offer a more specific mechanism to inhibit the renin-angiotensin system and should not lead to kinin accumulation and cough.

Candesartan is a new, selective AT\(_1\)-receptor blocker, with a tight binding to, and a slow dissociation from, the receptor.\(^6\) It is administered orally as candesartan cilexetil, which is rapidly and completely converted to the active compound candesartan during absorption from the gastrointestinal tract.\(^7\)

The present study investigated the effect of candesartan cilexetil on the incidence, frequency, and severity of dry cough when compared with enalapril or placebo in hypertensive patients with previous ACE-inhibitor–induced cough. A secondary objective of the study was to evaluate the effect of these treatments on quality of life.

**PATIENTS AND METHODS**

**Patients** Male and female outpatients aged 20 to 80 years with primary hypertension and a history of ACE-inhibitor–induced cough were eligible to participate. Exclusion criteria were those that could affect cough, such as obstructive pulmonary disease, smoking, and concomitant medication including nonsteroidal anti-inflammatory drugs, aspirin, codeine, and other antitussive agents. Further criteria for exclusion were secondary or malignant hypertension, sitting diastolic blood pressure (DBP) >105 mm Hg or systolic blood pressure (SBP) >180 mm Hg, severe cardiovascular, liver, renal, or allergic disease, renal artery stenosis or transplantation, past or present drug abuse, childbearing potential, or hypersensitivity to study drugs.

All patients provided written consent to participate in the study, and an independent ethics committee for each study center approved the study protocol. The study was performed according to good clinical practice and the principles stated in the declaration of Helsinki.

**Study Design** The study was a multicenter, randomized, double-blind comparison of candesartan cilexetil (8 mg), enalapril (10 mg), and placebo, with groups unbalanced 2:2:1 in patient numbers, and with the possibility to add hydrochlorothiazide (12.5 mg) during the double-blind treatment if DBP was >105 mm Hg. All study drugs were administered in the morning once daily. Other antihypertensive treatment and drugs with potential to affect cough were withdrawn and not allowed during the study. Eligible patients entered a 1 to 4-week enalapril (10 mg) challenge period, and those who experienced dry cough according to the symptom assessment (SA) questionnaire on two consecutive visits continued to a 1- to 4-week placebo dechallenge period. To be randomized, patients’ cough had to resolve and be absent on two consecutive visits. The double-blind period was completed after 8 weeks of treatment, or when the patient reported dry cough on the SA questionnaire, whichever came first.

**Assessments** The SA questionnaire measures the severity of symptoms, including dry cough, by means of a five-graded Likert scale (not at all, a little, moderately, quite a bit, and extremely).\(^8,9\) The incidence of dry cough was defined as those with any of the responses on the Likert scale, except “not at all.” The frequency of cough was reported by making a cross on a visual analog (VA) scale, 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.” Quality of life was assessed by 15 of the original 24 items in the minor symptom evaluation (MSE) profile,\(^10\) which were categorized into three separate dimensions: contentment, vitality, and sleep. The MSE profile uses a 100-mm VA scale, with the lower end of the scale indicating positive feelings and the higher end of the scale negative feelings.

Blood pressure was measured on the same arm at each visit using a mercury sphygmomanometer with a cuff of appropriate size, but not standardized in relation to study drug intake or time of the day. After 5 min of rest, sitting systolic and diastolic blood pressure was measured to the nearest 2 mm Hg. Heart rate was measured by pulse palpation for 30 seconds immediately after recording the blood pressure.

Adverse events were recorded, either from spontaneous reports by the patient, or in response to an open, nonspecific question (such as “Have you had any health problems since we last met?”), or as observed by the study personnel.

**Statistical Evaluation** The change in the severity of dry cough was analyzed nonparametrically using the Wilcoxon rank sum test, stratified for center. The incidence (proportion of patients) of dry cough according to the Likert scale at the last visit was analyzed using the Mantel-Haenszel test, stratified for center. The change from randomization to the end of double-blind treatment in the frequency of dry cough was calculated by analysis of covariance. The linear model included center and treatment as factors and baseline (value at randomization) as a covariate. The MSE profile, regarding the change in the three dimensions contentment, vitality, and sleep, was analyzed using the same linear model as described above. Centers with few patients were pooled before the code was
broken. Estimates and 95% confidence intervals (CI) for the true mean treatment differences with respect to cough were calculated. The P-values for the corresponding tests of equal true means are also presented.

RESULTS

In total, 301 patients were enrolled in the study, of whom 156 were randomized to double-blind treatment. Reasons for discontinuation prior to randomization were absence of cough during enalapril challenge (n = 71), failure of cough to resolve during placebo dechallenge (n = 29), adverse events (n = 21), and other reasons (n = 24). As two patients had no post-randomization assessments of cough, the intention-to-treat population consisted of 154 patients, all with the diagnosis of primary hypertension. The patients ranged in age from 32 to 80 years, and their mean age was 60 years. The groups were similar with regard to demographics and baseline characteristics (Table 1), as well as duration of hypertension and previous antihypertensive therapy.

Severity, Incidence, and Frequency of Cough At randomization all patients’ severity of dry cough according to the Likert scale was “not at all,” as this was an inclusion criterion. At the end of the study, scores for the enalapril group were more evenly distributed across different grades of cough, whereas scores for the placebo and candesartan cilexetil groups were skewed toward less cough, with most patients giving the score “not at all” (difference in change versus baseline; P < .001 candesartan versus enalapril, P > .20 candesartan versus placebo). Based on the responses in the Likert scale (any of the scores: a little, moderately, quite a bit, and extremely), the estimated proportion of patients that reported cough at the end of the study is presented by treatment group in Figure 1. The proportion of patients with cough was 26.9% in the placebo group, 35.5% in the candesartan cilexetil group (P > .20 versus placebo), and 68.2% in the enalapril group (P < .001 versus candesartan cilexetil).

Similar results were obtained when changes in the frequency of dry cough from randomization to last visit according to a 100-mm VA scale were compared: there was a significant deterioration with enalapril compared with candesartan cilexetil (mean difference 12.9 mm, 95% CI 5.2 to 20.5 mm, P = .001), whereas no significant difference was found between placebo and candesartan cilexetil (mean difference in favor of candesartan cilexetil 2.1 mm, 95% CI 2.8 to 11.2 mm, P = .20).

MSE Profile Treatment with candesartan cilexetil did not compromise patients’ well-being. For contentment, candesartan cilexetil was superior to placebo (mean difference 7.6 mm, 95% CI 0.7 to 14.4 mm, P = .03), and for vitality and sleep there were similar nonsignificant trends. Candesartan cilexetil tended to be associated with better sleep than enalapril (mean difference 5.5 mm, 95% CI −0.6 to +11.5 mm, P = .08).

Safety and Tolerability There was a mean reduction in sitting DBP of 0.6 mm Hg in the placebo group, compared with 5.0 mm Hg with candesartan cilexetil and 3.5 mm Hg with enalapril. Similar reductions compared with placebo occurred in SBP. Changes in heart rate in the different groups were around 1 beat per minute.

More patients reported cough as an adverse event with enalapril (31%) compared with candesartan cilex-

### TABLE 1. PATIENT CHARACTERISTICS AT BASELINE

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 26)</th>
<th>Candesartan Cilexetil (n = 62)</th>
<th>Enalapril (n = 66)</th>
<th>Total (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men/women</td>
<td>10/16</td>
<td>22/40</td>
<td>25/41</td>
<td>57/97</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>61 (8)</td>
<td>60 (11)</td>
<td>60 (11)</td>
<td>60 (10)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>22</td>
<td>49</td>
<td>54</td>
<td>125</td>
</tr>
<tr>
<td>Mongoloid</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>12</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>29 (5)</td>
<td>28 (5)</td>
<td>29 (5)</td>
<td>29 (5)</td>
</tr>
<tr>
<td>DBP, mm Hg, mean (SD)</td>
<td>92 (7)</td>
<td>93 (8)</td>
<td>94 (9)</td>
<td>93 (8)</td>
</tr>
<tr>
<td>SBP, mm Hg, mean (SD)</td>
<td>154 (15)</td>
<td>152 (12)</td>
<td>154 (15)</td>
<td>153 (14)</td>
</tr>
</tbody>
</table>

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
etil (16%), or placebo (11%), supporting the cough evaluation by the SA questionnaire and the VA scale. All treatments were well tolerated, and after cough the most common adverse events with placebo were dry mouth, flush, headache, and aggravated hypertension; with candesartan cilexetil, respiratory infection and dizziness; and with enalapril, headache and back pain. In total, 11 patients withdrew because of adverse events, 3 taking placebo, 5 taking candesartan cilexetil, and 3 taking enalapril (excluding cough where the protocol mandated withdrawal).

DISCUSSION

Other studies in “unselected” hypertensive patients without a prior history of cough have also shown less cough with candesartan cilexetil than with enalapril. For example, a study by Arakawa et al reported cough in 14.5% of enalapril-treated patients compared with 0.7% of candesartan cilexetil-treated patients.

Our findings correspond well with those of a previous study of patients with ACE-inhibitor–related cough in which the incidence of cough assessed by the SA questionnaire was 72% with lisinopril, 29% with losartan, and 34% with hydrochlorothiazide. Similar data have also been found with valsartan compared with lisinopril and hydrochlorothiazide. Collectively, these trials indicate that dry cough is a class effect of the ACE inhibitors, which is not shared by the AT1-receptor blockers.

The present study used the MSE profile to detect the possible influence of cough on the quality of life. For contentment and vitality, both active treatments tended to give a better outcome than placebo (P = .03, candesartan cilexetil versus placebo regarding contentment), but there was a trend for candesartan cilexetil to be associated with better sleep than enalapril or placebo. A reason for the relatively small changes in the MSE profile may result from the fact that patients were discontinued as soon as any coughing was experienced. Another explanation may be the limited study size—usually larger studies are needed to detect effects on quality of life, and this study was not of sufficient size to detect changes in the MSE profile.

Previously, it has been reported in a case–control study that ACE-inhibitor–related cough is associated with some deterioration in well-being (sore throat, depression, and fatigue). However, further studies would be required for a more comprehensive evaluation of the effect of cough during ACE-inhibitor treatment on quality of life.

In conclusion, dry cough is a side effect specific to ACE-inhibitor therapy and is not evoked by intervening with the renin–angiotensin system by AT1-receptor blockers, such as candesartan cilexetil.

REFERENCES

12. McInnes GT, Istad H, Keinänen-Kiukaanniemi S, van Mierlo HF: Combination of candesartan cilexetil/hydrochlorothiazide 8/12.5 mg has a similar antihypertensive effect and is better tolerated than lisinopril/hydrochlorothiazide 10/12.5 mg (abstract). Am J Hypertens 1998;11:109A.

APPENDIX

Participating principal investigators in the Multicentre Cough Study Group were: Australia: J. Karrasch, Kippa Ring; R. Gordon, Greenslopes; G. MacDonald, Little Bay; G. Stokes, St. Leonards; R. Watts, Port Lincoln; D. Miller, North Adelaide; B. Jackson, Preston; H. Krum, Prahran. Canada: P.H. Tanser, Hamilton; D. Spence, R. Luton, London; S.