Angiotensin-Converting Enzyme Inhibitors and Cough*

Prevalence in an Outpatient Medical Clinic Population

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To determine the frequency of ACE inhibitor cough in an outpatient medical clinic population, a cross-sectional epidemiologic survey using mailed questionnaires was done. Patients were randomly selected from a computerized hospital pharmacy data base. The overall prevalence of cough was 19 percent in the ACE inhibitor groups compared with 9 percent in the hydrochlorothiazide-treated group. The observed odds ratio for cough among ACE inhibitor users was 2.3 (95 percent CI, 1.02 to 5.00). This study is the first systematic investigation of frequency and characteristics of ACE inhibitor cough that includes a control group. Our results suggest that cough may more frequently accompany treatment with ACE inhibitors than has been previously reported. We recommend that physicians specifically inquire about cough in patients taking an ACE inhibitor. Recognition of this side effect may prevent unnecessary testing and treatment of patients receiving ACE inhibitors. (Chest 1991; 99:36-39)

ACE = angiotensin-converting enzyme; CI = confidence interval

Although pre-marketing studies did not suggest that cough was an important side effect of ACE inhibitors, cough is now recognized to occur in 1 to 10 percent of patients receiving these drugs.1-15

Accumulated case studies have reported that the large majority of individuals who develop ACE inhibitor cough are women.9,12,15,16 However, previous studies have not systematically inquired into the development of symptoms in men nor have their investigators used a control group to compare the frequency of cough in patients taking ACE inhibitors vs other medications. Therefore, we undertook a cross-sectional epidemiologic study with two goals: first, to determine the prevalence and characteristics of cough in patients using ACE inhibitors, and second, to compare the frequency of cough with that of patients in a control group.

**METHODS AND STUDY DESIGN**

Following approval of this study by the human research review committee, the computerized pharmacy data base of the Clement J. Zablocki Veterans Administration Medical Center was programmed to generate a list of all patients who were receiving either an ACE inhibitor or hydrochlorothiazide. Using random number tables, 100 persons prescribed captopril, 100 persons prescribed enalapril and 200 persons prescribed hydrochlorothiazide were identified. Individual drug profiles were reviewed to insure that study participants were prescribed either one of the study medications but not both. A questionnaire form with a self-addressed stamped return envelope was then mailed to each selected person.

The questionnaire was designed to determine: (1) whether the patient was currently using ACE inhibitors or hydrochlorothiazide; (2) the dosage of the respective medication; (3) whether the patient had ever been given a diagnosis of bronchitis, emphysema or congestive heart failure; (4) whether the patient reported any allergies, history of asthma or wheezing or current cigarette smoking; (5) the characteristics of any cough, if present, including its duration and severity; (6) whether any medication was taken to suppress the cough; and (7) whether the cough was reported to the patient's physician.

Cough was considered to be present if respondents indicated that they had been bothered by a cough during the prior month and if they had had symptoms for at least two weeks without an identifiable cause, such as an acute respiratory infection. All survey responses were evaluated for the presence or absence of self-reported cough by a reviewer who was blinded to the patient's medication use.

All statistical analyses were performed using the Statistical Package for the Social Sciences—version X (SPSS-X). Differences in proportions were compared using the chi-square test, and differences in means were analyzed using the Student two-tailed t test. Differences were considered statistically significant if p<0.05.

**Table 1—Study Design: VA Pharmacy Data Base, Random Selection**

<table>
<thead>
<tr>
<th>Pertinent Study Data</th>
<th>Captopril (n = 100)</th>
<th>Enalapril (n = 100)</th>
<th>Hydrochlorothiazide (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaires returned (n = 304 [76%])</td>
<td>81</td>
<td>71</td>
<td>152</td>
</tr>
<tr>
<td>Current use of drug (n = 265 [66%])</td>
<td>74</td>
<td>53</td>
<td>138</td>
</tr>
<tr>
<td>Answered cough question (n = 252 [63%])</td>
<td>65</td>
<td>50</td>
<td>137</td>
</tr>
</tbody>
</table>

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36 ACE Inhibitors and Cough (Sebastian et al)
RESULTS

Questionnaires were returned by 304 (76 percent) of the 400 persons selected. Thirty-nine patients were no longer using ACE inhibitors or hydrochlorothiazide and 13 patients did not answer the question concerning cough, leaving 252 evaluable responses (Table 1). The characteristics of the 115 respondents in the ACE inhibitor group and the 137 users of hydrochlorothiazide are displayed in Table 2. There was no difference in mean age; use of the medication to treat hypertension; history of allergies, wheezing or asthma, chronic bronchitis, emphysema, or current cigarette smoking. More persons in the ACE inhibitor group reported a history of congestive heart failure than did respondents in the hydrochlorothiazide group (25 of 115 = 23 percent vs 12 of 137 = 10 percent, p = 0.01). Twenty-two persons (19 percent) in the ACE inhibitor group and 13 (9 percent) of the hydrochlorothiazide group satisfied the case definition for cough (odds ratio for ACE inhibitor use, 2.3; 95 percent CI, 1.02 to 5.00).

Table 3 demonstrates that the prevalence of cough in patients taking captopril (11 of 65 = 17 percent) did not differ significantly from the prevalence of cough in patients who were taking enalapril (11 of 50 = 22 percent).

Of the 252 respondents who reported that they were using either of the study drugs, only 129 (51 percent) reported the dosage of their respective medication. For these patients, the prevalence of cough did not vary by dosage of ACE inhibitor or hydrochlorothiazide when these groups were dichotomized at the median dose (Table 4).

Characteristics of the 22 persons in the ACE inhibitor group and the 13 persons in the hydrochlorothiazide group reporting cough are outlined in Table 5. There was no difference between the groups in mean age, current smoking status, history of wheezing or asthma, emphysema, or congestive heart failure. However, more hydrochlorothiazide users than ACE inhibitor users reported a history of chronic bronchitis (1 of 22 = 5 percent vs 5 of 13 = 42 percent, p = 0.04). Cough associated with ACE inhibitor use has been previously reported as dry and nonproductive.5,13,14,15,17,18 No statistically significant differences in the characteristics of cough were noted between the ACE inhibitor and hydrochlorothiazide users (Table 6).

DISCUSSION

This study shows that patients using ACE inhibitors have a high (19 percent) prevalence of cough. This is statistically more common than cough occurring in patients using a control medication.

Prevalence estimates of ACE inhibitor cough vary widely among previous series. These differences may reflect, in part, patient selection and referral bias. The largest available series of captopril users (n = 4,849) reported a cough prevalence of 0.7 percent.19 However, the cough estimates from smaller series are considerably higher. For example, Hood et al4 showed a 13 percent prevalence of cough among

Table 3—Prevalence of Cough by Specific ACE Inhibitor

<table>
<thead>
<tr>
<th>Subject Features</th>
<th>Captopril</th>
<th>Enalapril</th>
<th>Total ACE Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate subjects</td>
<td>65</td>
<td>50</td>
<td>115</td>
</tr>
<tr>
<td>Subjects who reported cough</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>% of subjects who reported cough</td>
<td>17%</td>
<td>22%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Table 4—Prevalence of Cough by Medication Dosage*

<table>
<thead>
<tr>
<th>Medication</th>
<th>&lt;75 mg</th>
<th>≥75 mg</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough +</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cough -</td>
<td>10</td>
<td>17</td>
<td>p = NS</td>
</tr>
<tr>
<td>Enalapril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough +</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cough -</td>
<td>12</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough +</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cough -</td>
<td>34</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

* +, present; -, not present.

Table 5—Analysis of Coughers Only

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ACE Inhibitors (n = 22)</th>
<th>Hydrochlorothiazide (n = 13)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>61 ± 13</td>
<td>62 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers</td>
<td>11 (52%)</td>
<td>3 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Wheezing, asthma</td>
<td>7 (32%)</td>
<td>8 (62%)</td>
<td>NS</td>
</tr>
<tr>
<td>Emphysema</td>
<td>2 (10%)</td>
<td>1 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (17%)</td>
<td>2 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>1 (9%)</td>
<td>5 (42%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
ACE inhibitor users. In a recent crossover trial in elderly patients being treated for mild to moderate hypertension, Woo and colleagues reported cough in 7 of 40 (18 percent) subjects receiving captopril compared with 0 of 15 subjects receiving treatment with triamterene and hydrochlorothiazide. Another pharmaceutical survey suggested a cough prevalence of 1.3 percent among 2,677 patients treated with enalapril compared with 0.9 percent in patients receiving placebo. Among 546 patients treated with enalapril for congestive heart failure, Warner et al reported a cough prevalence of 2 percent. Post-marketing surveillance studies of enalapril (n = 13,713 patients) suggests a prevalence of drug-induced cough that averages almost 3 percent. In a recent retrospective analysis, Gibson reported that 22 of 209 (11 percent) patients taking enalapril were required to discontinue this therapy because of intractable cough.

There may be several reasons why our results and those of other recent studies of ACE inhibitor cough show a much higher prevalence than the 1 to 2 percent previously reported. First, cough is a common symptom that is not traditionally associated with drug use. The onset of cough may be delayed, relative to the initiation of the drug and may not be directly attributed to the use of the medication. Because our study design asked patients to respond to specific questions about cough, our results might not be directly comparable to other studies which report the prevalence of spontaneous, patient-initiated complaints. Second, the diagnosis of drug-related cough often is difficult to confirm because of the necessity of excluding other multiple causes. Unlike many of the previous reports in the literature, our patients had multiple potential etiologies for cough, including COPD.

As observed in Table 2, more persons using ACE inhibitors than hydrochlorothiazide also had associated congestive heart failure. This is not surprising since ACE inhibitors are being used with more frequency than thiazide diuretics to treat congestive heart failure. The high apparent prevalence of cough among hydrochlorothiazide users is most likely related to the presence of concomitant chronic bronchitis and emphysema but, as noted in Table 5, percentages of positive respondents for all categories of COPD were similar to users of ACE inhibitors.

**Study Limitations**

Our study has several important limitations that should be recognized. (1) The study population is predominantly an older group of male veterans and might not be representative of other populations. For example, previous reports of ACE inhibitor cough have emphasized a striking female predominance. The reasons for this female predominance are not well explained, but may represent an unwillingness of males spontaneously to report symptoms to their physicians. (2) Our information was based strictly on patient self-reporting of both the presence or absence of cough and whether the patient's physician had previously diagnosed a confounding condition such as COPD or congestive heart failure. Our study methods might explain the higher prevalence of cough when our results are compared with those of previously published reports. (3) Because this is a cross-sectional survey, no inferences can be made about the relationship between starting medication and the development of cough. Data on the resolution of cough symptoms with discontinuation of medication and recurrence on re-challenge is not available from our questionnaire. Other reports have shown that this relationship exists.

**Importance**

For several reasons, it is important for clinicians to recognize that a patient's cough may be a side effect of ACE inhibitors. First, failure to recognize the possible relationship between a patient's respiratory symptoms and ACE inhibitor use may lead to unnecessary investigations. The patients described in published case reports and case series have had various combinations of diagnostic tests: chest x-ray films, sputum cultures, pulmonary function tests including bronchoprovocation with methacholine, allergy evaluations, ENT consultation, and in one case fiberoptic bronchoscopy. Second, empiric treatments such as antitussives, bronchodilators and antibiotics are ineffective; patients may obtain relief from their cough only if its relationship to the offending drug is recognized and the ACE inhibitor is discontinued. Third, in patients with congestive heart failure, cough may be misinterpreted as a sign of worsening failure. It may be particularly difficult to determine the exact etiology of cough in these patients. If the cough is related to use of the medication, then increasing the dose of ACE inhibitors will not help the cough and might increase the chance of other dose-related side effects. On the other hand, stopping these afterload
reducing agents in patients with congestive cardiac failure might increase their symptoms if their cough is due to underlying congestive heart failure.

Our study is important because it is the first controlled study to evaluate the use of ACE inhibitors in a general medicine clinic population. Many of our patients have multiple medical disorders and thus many potential reasons to cough. It is indeed possible that many of our patients who reported cough may have other etiologies for this symptom. Additional studies are needed to determine if there are subgroups of patients who might be particularly susceptible to developing this side effect, such as asthmatic subjects or those with known bronchial hyperreactivity.

**Comment**

In summary, employing a questionnaire answered by a predominantly older group of male patients treated with either ACE inhibitors or hydrochlorothiazide, we have found that the self-reported prevalence of cough among ACE inhibitor users is 19 percent compared with 9 percent in a hydrochlorothiazide-treated group. This prevalence of ACE inhibitor cough is much higher than reported by most previous studies. Our results suggest that cough may be significantly underreported by patients to their physicians.

We believe that close observation of ACE inhibitor users is necessary to avoid continued cough, and the costs of needless laboratory studies and antitusive therapy. The increasing usage of ACE inhibitors for treatment of hypertension and congestive heart failure mandates this closer observation. We recommend that physicians specifically inquire about cough in their patients who are receiving an ACE inhibitor. While we do not advocate that physicians need to discontinue this medication in all patients who report symptoms of cough, such a trial would seem to be appropriate for some patients with persistent or severe symptoms.

**References**