Angiotensin-Converting Enzyme Inhibitor-Induced Cough

ACCP Evidence-Based Clinical Practice Guidelines

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Background: A dry, persistent cough is a well-described class effect of the angiotensin-converting enzyme (ACE) inhibitor medications. The mechanism of ACE inhibitor-induced cough remains unresolved, but likely involves the protussive mediators bradykinin and substance P, agents that are degraded by ACE and therefore accumulate in the upper respiratory tract or lung when the enzyme is inhibited, and prostaglandins, the production of which may be stimulated by bradykinin.

Methods: Data for this review were obtained from a National Library of Medicine (PubMed) search, which was performed in May 2004, of the literature published in the English language from 1985 to 2004, using the search terms “angiotensin-converting enzyme,” “angiotensin converting enzyme inhibitors,” and “cough.”

Results: The incidence of ACE inhibitor-induced cough has been reported to be in the range of 5 to 35% among patients treated with these agents. However, a much lower incidence has been described in studies of patients presenting for the evaluation of chronic cough. The onset of ACE inhibitor-induced cough ranges from within hours of the first dose to months after the initiation of therapy. Resolution typically occurs within 1 to 4 weeks after the cessation of therapy, but cough may linger for up to 3 months. The only uniformly effective treatment for ACE inhibitor-induced cough is the cessation of treatment with the offending agent. The incidence of cough associated with therapy with angiotensin-receptor blockers appears to be similar to that of the control drug. In a minority of patients, cough will not recur after the reintroduction of ACE inhibitor therapy.

Conclusions: In a patient with chronic cough, ACE inhibitors should be considered as wholly or partially causative, regardless of the temporal relation between the initiation of ACE inhibitor therapy and the onset of cough. Although the cessation of therapy is the only uniformly effective treatment for ACE inhibitor-induced cough, some pharmacologic agents have been shown to attenuate the cough.

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Key words: angiotensin-converting enzyme; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; bradykinin; capsaicin; cough; prostaglandins; substance P

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker

C hronic cough is a well-described class effect of the angiotensin-converting enzyme (ACE) inhibitors.\(^1\) The cough is typically dry and is associated with a tickling or scratching sensation in the throat. The incidence of ACE inhibitor-induced cough has been reported\(^1,2\) to be in the range of 5 to 35% among patients who have been treated with these agents. However, in prospective, descriptive studies\(^3-5\) that evaluated the etiology of chronic cough in patients presenting for evaluation of this symptom, ACE inhibitors were determined to be responsible in 0 to 3% of cases. ACE inhibitor-induced cough is not dose-dependent.\(^1\) Patients treated with ACE inhibitors for conges-
tive heart failure cough more frequently than those treated with these agents for hypertension. Cough due to ACE inhibitors occurs more commonly in women, nonsmokers, and persons of Chinese origin.

Cough may occur within hours of the first dose of medication, or its onset can be delayed for weeks to months after the initiation of therapy. Treatment with ACE inhibitors may sensitize the cough reflex, thereby potentiating other causes of chronic cough. Although cough usually resolves within 1 to 4 weeks of the cessation of therapy with the offending drug, in a subgroup of individuals cough may linger for up to 3 months.

Although the etiology of ACE inhibitor-induced cough remains an unresolved issue, new developments since the publication of the first American College of Chest Physician consensus panel report include studies implicating the bradykinin receptor as relevant to ACE inhibitor function as well as the cough associated with these medications. Several new therapeutic agents have been added to the list of drugs that may attenuate ACE inhibitor-induced cough in some patients. Furthermore, an accumulating body of evidence supports the concept that the angiotensin receptor blockers (ARBs) do not cause cough, including in those patients with a history of ACE inhibitor-induced cough. Data for this review were obtained from a National Library of Medicine (PubMed) search, which was performed in May 2004, of the literature published in the English language from 1985 to 2004, using the search terms “angiotensin-converting enzyme,” “angiotensin-converting enzyme inhibitors,” and “cough.”

**Recommendation**

1. In patients presenting with chronic cough, in order to determine that the ACE inhibitor is the cause of the cough, therapy with ACE inhibitors should be discontinued regardless of the temporal relation between the onset of cough and the initiation of ACE inhibitor therapy. The diagnosis is confirmed by the resolution of cough, usually within 1 to 4 weeks of the cessation of the offending agent; however, the resolution of cough may be delayed in a subgroup of patients for up to 3 months. Quality of evidence, low; net benefit, substantial; grade of recommendation, B.

**Pathogenesis**

The mechanism of ACE inhibitor-induced cough remains unclear. Possible protussive mediators include bradykinin and substance P, which are degraded by ACE and therefore accumulate in the upper airway or lung when the enzyme is inhibited; and prostaglandins, the production of which may be stimulated by bradykinin. Bradykinin-induced sensitization of airway sensory nerves has been proposed as a potential mechanism of ACE inhibitor-induced cough. Some evidence has suggested that the therapeutic effect of ACE inhibitors may involve the activation of bradykinin receptors, and that bradykinin receptor gene polymorphism is associated with the cough that is related to ACE inhibitors. The enhancement of bronchial responsiveness does not appear to be a relevant mechanism. Subjects with ACE inhibitor-induced cough demonstrate increased cough reflex sensitivity to experimental stimulation with capsaicin, which resolves after the discontinuation of therapy with the inciting drug.

**TREATMENT**

The only uniformly effective intervention for ACE inhibitor-induced cough is the cessation of therapy with the offending agent. Numerous small studies have evaluated various drugs as potential therapies (Table 1). Agents demonstrating the ability to attenuate cough due to ACE inhibitors in randomized, double-blind, placebo-controlled trials include inhaled sodium cromoglycate, theophylline, sulindac, indomethacin, the calcium-channel antagonists amlopidine and nifedipine, ferrous sulfate, and the thromboxane receptor antagonist picotamide (not available in the United States). In open-label, uncontrolled studies, agents shown to suppress ACE inhibitor-induced cough include the γ-aminobutyric acid agonist baclofen, the thromboxane synthetase inhibitor ozagrel, and aspirin, 500 mg/d (low-dose therapy with aspirin was found to be ineffective).

One randomized, double-blind, parallel-group, controlled trial demonstrated that about 30% of patients with ACE inhibitor-induced cough who had been challenged and dechallenged twice did not develop cough after a third trial of ACE inhibitor therapy. Therefore, in patients whose cough resolves after the cessation of ACE inhibition therapy and for whom there is a compelling reason to treat with these agents, a repeat trial of ACE inhibitor therapy may be attempted.

**Recommendations**

2. In patients presenting with chronic ACE inhibitor-induced cough, discontinue therapy.
with the drug because it is the only uniformly effective treatment. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

3. In patients whose cough resolves after the cessation of therapy with ACE inhibitors, and for whom there is a compelling reason to treat with these agents, a repeat trial of ACE inhibitor therapy may be attempted. Quality of evidence, fair; net benefit, substantial; grade of recommendation, A

4. In patients for whom the cessation of ACE inhibitor therapy is not an option, pharmacologic therapy, including that with sodium cromoglycate, theophylline, sulindac, indomethacin, amlodipine, nifedipine, ferrous sulfate, and picotamide that is aimed at suppressing cough should be attempted. Quality of evidence, fair; net benefit, substantial; grade of recommendation, B

Theoretically, the recently introduced ARBs should not induce cough, because their mechanism of action does not involve the inhibition of ACE with the resultant elevation of tissue levels of bradykinin and substance P. Indeed, losartan, the first ARB that was approved for clinical use, has been associated with a low incidence of cough, similar to that of the diuretic hydrochlorothiazide, in patients with a history of ACE inhibitor-induced cough.13 Numerous comparative trials28,29 have subsequently been performed, demonstrating the lower incidence of cough associated with several ARBs compared to that with ACE inhibitors.

**Recommendation**

5. In patients in whom persistent or intolerable ACE inhibitor-induced cough occurs, therapy should be switched, when indicated, to an ARB, with which the incidence of associated cough appears to be similar to that for the control drug, or to an appropriate agent of another drug class. Quality of evidence, good; net benefit, substantial; grade of recommendation, A

### Summary of Recommendations

1. In patients presenting with chronic cough, in order to determine that the ACE inhibitor is the cause of the cough, therapy with ACE inhibitors should be discontinued regardless of the temporal relation between

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study</th>
<th>Patients, No.</th>
<th>Age, yr</th>
<th>Dosing</th>
<th>Results</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium cromoglycate</td>
<td>Hargreaves and Benson19</td>
<td>10</td>
<td>49-77</td>
<td>10 mg inhaled qid, for 14 d</td>
<td>Reduction in 9/10 patients</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Cazolla et al20</td>
<td>10</td>
<td>33-74</td>
<td>8.5 mg/kg po qd, for 14 d</td>
<td>Remission in 8/10 patients</td>
<td></td>
</tr>
<tr>
<td>Sulindac</td>
<td>McEwan et al21</td>
<td>6</td>
<td>46-66</td>
<td>200 mg po qd, 7 d</td>
<td>37% reduction in cough score</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Fogari et al22</td>
<td>33</td>
<td>42-65</td>
<td>50 mg po bid, 14 d</td>
<td>Eliminated in 27%, significantly reduced in 69% of patients</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Fogari et al22</td>
<td>33</td>
<td>42-65</td>
<td>5 mg po qd, 14 d</td>
<td>Eliminated in 6%, significantly reduced in 61% of patients</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Fogari et al22</td>
<td>33</td>
<td>42-65</td>
<td>30 mg po qd, 14 d</td>
<td>Eliminated in 3%, significantly reduced in 51% of patients</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>Lee et al23</td>
<td>19</td>
<td>59.9 ± 12.2</td>
<td>256 mg po qd, 28 d</td>
<td>45% reduction in mean cough score</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Picotamide</td>
<td>Malini et al24</td>
<td>9</td>
<td>39-89</td>
<td>600 mg po bid, 14 d</td>
<td>Significant reduction/elimination in 8/9 patients</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Dicpinigaitts25</td>
<td>7</td>
<td>43-73</td>
<td>5–10 mg po tid, 28 d</td>
<td>64% reduction in mean cough score</td>
<td></td>
</tr>
<tr>
<td>Ozagrel</td>
<td>Umemura et al26</td>
<td>10</td>
<td>60 ± 11</td>
<td>200 mg po qd, 30–60 d</td>
<td>Reduced or eliminated in 8/10 patients</td>
<td>0.012</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Tenenbaum et al27</td>
<td>14</td>
<td>63 ± 11</td>
<td>500 mg po qd, 7 d</td>
<td>Reduced or eliminated in 8/9 patients</td>
<td>&lt; 0.002</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD or range.
the onset of cough and the initiation of ACE inhibitor therapy. The diagnosis is confirmed by the resolution of cough, usually within 1 to 4 weeks of the cessation of the offending agent; however, the resolution of cough may be delayed in a subgroup of patients for up to 3 months. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

2. In patients presenting with chronic ACE inhibitor-induced cough, discontinue therapy with the drug because it is the only uniformly effective treatment. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

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4. In patients for whom the cessation of ACE inhibitor therapy is not an option, pharmacologic therapy, including that with sodium cromoglycate, theophylline, sulindac, indomethacin, amlodipine, nifedipine, ferrous sulfate, and picotamide that is aimed at suppressing cough should be attempted. Quality of evidence, fair; net benefit, intermediate; grade of recommendation, B

5. In patients in whom persistent or intolerable ACE inhibitor-induced cough occurs, therapy should be switched, when indicated, to an ARB, with which the incidence of associated cough appears to be similar to that for the control drug, or to an appropriate agent of another drug class. Quality of evidence, good; net benefit, substantial; grade of recommendation, A

REFERENCES
26 Umemura K, Nakashima M, Saruta T. Thromboxane \( A_2 \) synthetase inhibitor suppresses cough induced by angiotensin converting enzyme inhibitors. Life Sci 1997; 60: 1583–1588