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BRIEF CLINICAL UPDATE

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# Angiotensin-Converting Enzyme Inhibitor Induced Cough Among Asians

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## *Introduction*

Angiotensin-converting enzyme (ACE) inhibitors have added a new dimension to the treatment of hypertension, congestive heart failure and post myocardial infarction, and are now playing an important role in the treatment of endothelial dysfunction.<sup>1</sup> In hypertensive diabetic patients, and particularly those with albuminuria, treatment with ACE inhibitors may forestall the deterioration of renal function and diminish albuminuria.<sup>2</sup> Unloading therapy in congestive heart failure with the use of ACE inhibitors along with the use of diuretics and digoxin has added another important adjunct in the care of a difficult situation, especially in patients with hypertension as well as diabetes mellitus. While the benefits of ACE inhibitor treatment are important in cardiovascular diseases, coughing is a troublesome side-effect common to all ACE inhibitors, sometimes requiring termination of treatment. Among our patient population, an inordinately high number of patients develop ACE inhibitor induced cough, especially among Asian women where the incidence of cough is much higher than the statistics quoted in the PDR and the literature.

A brief review of the literature regarding gender and ethnic differences in the incidence of ACE inhibitor induced cough will be presented as well as speculation on the etiology and treatment of the cough.

## *Discussion*

The literature is replete with articles concerning cough induced by ACE inhibitors and the incidence of the cough ranges from 3.7% to as high as 33%. In general, the literature supports the fact that ACE inhibitor related cough is slightly higher in females than males, and the evidence suggests that there may be some ethnic differences as well.<sup>3</sup> The incidence of cough is apparently not dose related, as small doses as well as high doses cause similar problems.

Our patient population, consisting mostly of Asians of Japanese extraction, not matched for age, sex, prior medical history, duration of hypertension or smoking, has shown a high incidence of cough,

particularly among the Asian women many of whom had to cease treatment due to troublesome coughing. Although the number of patients was small, the incidence of ACE inhibitor induced cough was estimated to be at about 45% among the Asian women with approximately 15% of the patients ceasing treatment. Male patients did not seem to have as much difficulty, but about 30% reported ACE inhibitor induced cough and roughly 5% required cessation of treatment.<sup>4</sup>

In hypertensive Chinese patients, Woo and Chan noted that patients treated with a combination therapy of isradipine (a calcium channel blocker) and lisinopril experienced a high incidence of cough. The coughing rate was 40%, which was much higher than those reported in hypertensive Caucasian patients. They speculated there were racial differences in the pharmacokinetics of ACE inhibitors resulting in a higher concentration of kinins and increased reactivity to kinins in the bronchial smooth muscles.<sup>3</sup>

Woo and Nicholls reported a high incidence of cough in hypertensive Chinese patients treated with either captopril or enalapril. The incidence of cough occurred at 46% in the captopril group and 41% in the enalapril group with controls at 11.1%. Coughing was not related in any significant manner to age, sex, underlying disease, drug dosage, or smoking history.<sup>5</sup>

Woo and associates found a difference in ACE inhibitor induced cough in an age and sex matched controlled study involving Chinese patients in Hong Kong and Caucasian patients in New Zealand. Both treatment groups had an increased incidence of cough but the Chinese patients had a much higher rate. Up to 53% of the Chinese patients experienced cough with controls at 10% while 18% of the Caucasian patients had cough with controls at 5%. They concluded that the difference indicated an enhanced susceptibility for developing ACE inhibitor induced cough among Chinese patients.<sup>6</sup>

Elliott reported how frequently ACE inhibitors were discontinued due to cough in black patients. He noted that black patients, particularly female patients, had a high incidence of cough. There was a higher

Table 1. ADOPT and ASCEND Trials

	Caucasians	Blacks	Hispanics	Asians
ADOPT (n=12,275)	4.9% (n=9807)	4.1% (n=1656)	2.6% (n=495)	13.8% (n=217)
ASCEND (n=10,782)	5.4% (n=8548)	3.5% (n=1445)	4.9% (n=466)	14.4% (n=222)

rate of discontinuation due to cough compared to other ethnic groups, suggesting that there may be "race or ethnic-related differences".<sup>7</sup>

In the ADOPT and ASCEND studies conducted by Parke-Davis regarding their product quinapril, cough induced by ACE inhibitors according to race comparing Caucasians, Blacks, Hispanics, and Asians indicated that Asians had the highest incidence of coughing.(Table 1) No definite conclusions could be made, however, as the Asian population was quite small and not matched for age, sex, smoking history, prior ACE inhibitor therapy, other medical history, or duration of hypertension. Nevertheless, Asians tended to have the highest incidence of cough, 13.8% in the ADOPT Trial and 14.4% in the ASCEND Trial.<sup>8</sup>

#### *Suggested Mechanisms for ACE Inhibitor Induced Cough*

The cough reflex is mediated by the vagus nerve through the afferent C fiber via the type J receptors in the respiratory tract. Bradykinin and substance P induce the formation of prostaglandin E2, and the accumulation of prostaglandin E2 in the C fiber receptors leads to coughing.<sup>9</sup> Since angiotensin-converting enzyme degrades bradykinin, the use of ACE inhibitors may result in an increased level of bradykinin. The increased level of bradykinin is proposed to cause an accumulation of prostaglandin E2 which leads to coughing. In heart-lung transplant patients with denervated cholinergic nerve, ACE inhibitor treatment led to cough which suggested a local accumulation of bradykinin.<sup>10</sup> Bradykinin had also exhibited a bronchoconstrictor effect on the human respiratory tract.<sup>11</sup>

Substance P, a protein bronchoconstrictor, is also metabolized by angiotensin-converting enzyme. When ACE inhibitor treatment is administered, substance P levels may increase resulting in an accumulation of prostaglandin E2 in the C fiber receptors. The accumulation of prostaglandin E2 stimulates the cough reflex.<sup>12</sup>

Patients treated with ACE inhibitors showed increased sensitivity to cough when challenged with capsaicin, an irritant. Aerosol inhalation of citric acid

prior to treatment with an ACE inhibitor also led to increased sensitivity to cough.<sup>13</sup> Increased sensitivity to methacholine inhalation was seen in seven out of eight patients with ACE inhibitor induced cough.<sup>9</sup> In general, ACE inhibitor treatment decreases the cough threshold leading to increased sensitivity to the cough reflex.

On the supposition that ACE inhibitor induced cough is genetically determined, the various genes encoding angiotensin-converting enzyme, chymase, and B2 bradykinin were studied, but no connections were found. Further studies are necessary to determine whether genetic factors are involved in the observed differences in cough.<sup>14</sup>

#### *Clinical Presentation and Management*

The cough is described as being a troublesome dry cough, without wheezing, typically starting from 1-7 days after the onset of therapy to as late as several weeks after the initiation of treatment. The cough usually subsides within 4-7 days after cessation of treatment, but may continue for as long as 3-4 weeks. The symptoms are apparently common to all ACE inhibitors, including those primarily tissue-bound such as quinapril and others that are found predominantly in the serum such as lisinopril. Chest x-ray and ENT examinations are normal.<sup>9</sup>

At times, the diagnosis of ACE inhibitor induced cough may be difficult to establish, particularly if the patients have asthma, COPD, allergic rhinitis, or congestive heart failure since coughing is frequently a symptom which complicates these disorders. Rather than having the patient undergo expensive testing, the simplest maneuver would be to stop the ACE inhibitor for one week. However, if the cough continues following cessation of the ACE inhibitor, then those conditions that may cause coughing should be investigated and treated aggressively. If the cough resolves, the patient may be restarted on the ACE inhibitor.

If the cough persists, stop the ACE inhibitor and try another class of medication. However, if the cough is mild and tolerable and the patient has a medical need to continue ACE inhibitor treatment, then the patient should be encouraged to continue taking the ACE inhibitor. There have been reported cases of

spontaneous subsidence of cough after 3-4 months.<sup>15</sup> An alternative treatment of ACE inhibitors is angiotensin II receptor blockers. Angiotensin II receptor blockers do not lead to cough and do not decrease the degradation of bradykinin as does the ACE inhibitor.<sup>16</sup> However, the beneficial effects of angiotensin II receptor blockers on myocardium, diabetic nephropathy or congestive heart failure have not yet been established.

Patients with congestive heart failure, diabetic nephropathy, acute myocardial infarction, or diabetes may have the medical need to continue ACE inhibitor therapy despite the cough. Drugs, such as NSAIDs, sodium cromoglycate, theophylline, and Baclofen, may be prescribed to alleviate the cough. However, NSAIDs such as sulindac and indomethacin have been prescribed to alleviate ACE inhibitor induced cough with inconsistent results.<sup>9</sup>

Sodium cromoglycate given by inhalation at 20 mg four times a day resulted in a favorable response in 4 out of 5 patients, but larger trials are necessary to establish definitive conclusions.<sup>17</sup>

Theophylline given to a series of 10 patients with ACE inhibitor induced cough at a dosage of 8.5 mg/kg orally once a day while providing no bronchodilation resulted in a beneficial effect with reduction in cough. Again, further studies are necessary to make any definitive conclusions, particularly as this drug has many drug interactions as well as need for monitoring blood levels.<sup>18</sup>

Baclofen, a gamma aminobutyric acid agonist used in the treatment of muscle spasticity associated with spinal cord injury and multiple sclerosis, was utilized in a preliminary study of 7 patients with ACE inhibitor induced cough who were suffering from hypertension and congestive heart failure some of whom had diabetes mellitus. Response was quite good without adverse effects at low doses starting with 5 mg three times a day and ending with 10 mg three times a day. However, no final conclusion can be made until additional controlled studies in progress are completed.<sup>19</sup> Thus, there is no proven therapeutic treatment for the patient with severe coughing who must remain on the ACE inhibitor treatment.

### Conclusion

Studies indicate ethnic differences in the incidence of ACE inhibitor induced cough with Asians having the highest incidence. Studies further show Asian females

have a greater incidence of cough as compared to Asian males. Involvement of larger numbers of patients as well as adequate controls, however, are necessary to produce any definitive conclusions.

At this time, no known genetic differences adequately explain the apparent increased incidence of ACE inhibitor induced cough among females in general or among the various ethnic groups. Additional genetic studies are necessary to determine the potential involvement of genetic factors in ACE inhibitor induced cough.

No definite conclusion can be made as to the etiology of the ACE inhibitor induced cough, but the accumulation of bradykinin as an initial step appears to be a popular concept. Further investigation must be pursued to determine the connection between bradykinin and the cough.

No ideal therapy exists for the treatment of ACE inhibitor induced cough. However, if the patient can tolerate the cough, there is no need to stop ACE inhibitor treatment as spontaneous remissions may occur. In a small pilot study, treatment with baclofen showed promise in alleviating cough among those patients who must stay on ACE inhibitor treatment.

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