Iron Supplementation Inhibits Cough Associated With ACE Inhibitors

Sang-Chol Lee, Seung Woo Park, Duk-Kyung Kim, Sang Hoon Lee, Kyung Pyo Hong

Abstract—Dry cough is the most common limiting factor of ACE inhibitor (ACEI) use. Generation of NO, a proinflammatory substance on bronchial epithelial cells, is increased by ACEI. Using a randomized, double-blind, placebo-controlled trial, we tested the hypothesis that supplementing iron, an inhibitor of NO synthase, may reduce the cough associated with ACEI use. The subjects were 19 patients who had developed ACEI-induced cough. After a 2-week observation period, they were randomized to a daily morning dose of either 256-mg ferrous sulfate as a tablet or placebo for a treatment period of 4 weeks. The subjects were requested to fill out a cough diary by scoring the daily severity of the cough on a scale of 0 to 4. Mean daily cough scores for the last week of the observation and treatment period were compared. Changes in blood cell count and serum iron and ferritin concentration between the 2 periods were evaluated. Mean daily cough scores during the observation and treatment periods were 3.07±0.70 and 1.69±1.10, respectively, for the iron group and 2.57±0.80 and 2.35±1.22, respectively, for the placebo group, showing a significant reduction in cough scores with iron supplementation (P<0.01) but not with placebo. Three subjects in the iron group showed almost complete cough abolition. No significant changes in laboratory data were observed in either group. In conclusion, iron supplementation successfully decreases ACEI-induced cough. This effect may be related to the decrease of NO generation associated with the inhibition of NO synthase activity in bronchial epithelial cells.

Key Words: angiotensin-converting enzyme inhibitors ■ cough ■ iron

The ACE inhibitor (ACEI) is one of the most widely used drugs in the field of cardiovascular medicine. However, ACEI use is limited because of its various side effects, of which the most troublesome and frequent is a persistent dry cough.1–3 Dry cough has been reported to occur in 5% to 39% of the patients who are prescribed ACEI, and in most cases, the drug has to be discontinued because of this annoying side effect.1

The mechanism that induces ACEI-induced dry cough has not yet been fully elucidated. There have been observations and trials reporting that the increment of prostaglandin synthesis or bradykinin accumulation associated with ACEI use is responsible for this effect.4–6 Other reports have proposed that tachykinins, such as substance P, are the main substance responsible for the development of cough.7 However, results of controlled trials involving ACEI-induced cough suppression with the use of antagonists of the above substances have been controversial.

The administration of ACEI is known to cause an increase in NO generation.8 NO is known to have inflammatory effects on bronchial epithelial cells,9 which themselves generate NO by certain stimuli, such as cytokines or lipopolysaccharides.10,11 Because it is evident that NO can exert deleterious effects on these cells and act as a pathological agent causing asthma and other respiratory tract diseases,12,13 ACEI-induced cough may also be associated with an increase of NO generation in bronchial epithelial cells.

NO is generated by the enzyme NO synthase (NOS), which is a heme-related enzyme. NOS activity is known to be associated with in vivo iron concentration, and supplementation of iron has been reported to decrease the generation of NO or diminish NO-related cell damage.14–16 On the basis of these findings, we sought to determine whether iron supplementation is effective in controlling ACEI-induced cough with a randomized, double-blind, placebo-controlled trial.

Methods

Subjects

The subjects were 19 Korean patients who had developed persistent dry cough while taking ACEI for various reasons. They included 6 men and 13 women, whose mean age was 59.9±12.2 years. An ACEI-induced cough was defined as a dry cough that occurred with ACEI use and subsided within 7 days after discontinuation of the drug. Evidence of organic pulmonary disease was ruled out by physical examination and chest x-rays in each of the patients. There was no significant difference in clinical characteristics between the treatment and placebo groups. Table 1 shows the characteristics of the subjects. All subjects gave informed consent, and the study was...
approved by the ethical committee of the Samsung Medical Center and Samsung Biomedical Research Institute, Seoul, Korea. The study was performed according to the guidelines of the above-mentioned ethical committee.

Randomization and Medication

Observation Period

Patients completed a cough diary during an initial 2-week observation period while taking ACEI only. They were asked to score their cough severity according to the following scale: 0, no cough; 1, which was only a tickling sensation on the throat; 2, mild cough, which did not interfere with daily activities; 3, moderate cough, which was tolerable but severe enough to interrupt daily activities for some time; and 4, severe cough, which persisted and interfered with most of the daily activities or disturbed sleep at night. Each day was divided into two 12-hour periods. The daytime period began at 8:00 AM and ended at 8:00 PM, and the nighttime period began at 8:00 PM and ended at 8:00 AM. Patients were asked to fill in cough scores for each period.

Treatment Period

At the end of the observation period, blood samples were drawn from the subjects for evaluation of hemoglobin, hematocrit, serum iron concentration, total iron binding capacity (TIBC), and ferritin measurements. After sampling, they were randomized to either an iron group, which received 256 mg of ferrous sulfate once daily as a tablet (early morning dose), or a placebo group. The randomization was arranged by a pharmacist who was in charge of distributing the medication according to a predetermined randomization table, and neither the subject taking the drug nor the physician prescribing it was aware of which group the subject belonged to. During the 4-week treatment period, subjects were asked to fill in a cough diary in a manner identical to that used in the observation period. After the 4-week treatment period, blood sampling was repeated in a manner identical to that performed at the initiation of the treatment period.

Analysis

Cough scores of the last week of the observation period and the last week of the treatment period were evaluated. Mean daily cough scores, which were defined as the mean of the total sum of the cough scores during the last week, and mean daytime and nighttime cough scores were compared. Laboratory data acquired from blood samples that were taken at the end of the observation and treatment periods were also compared. Data were expressed as mean±SD. Analysis was performed with the use of the SPSS software package for Windows (SPSS Inc). Change in mean daily, daytime, and nighttime cough scores and change in laboratory data were analyzed and compared between the 2 groups using the Wilcoxon signed rank sum test. A value of $P<0.05$ was considered significant.

Results

The mean daily cough score in the iron group was 3.07±0.70 at the final week of the observation period and 1.69±1.10 at the final week of the treatment period, showing a significant
were 3 subjects who showed near-complete cough abolition in the iron group, with a mean daily cough score of <1. No significant difference in cough scores was found between the daytime and nighttime periods in either group. In the 7 hypertensive patients, no significant change in blood pressure was observed between the end of the observation period and the treatment period.

No significant difference was observed in basal hemoglobin, hematocrit, ferritin, iron, and TIBC levels between the iron and placebo groups. An increase in mean ferritin levels with medication could be found in the iron group (68.15±32.86 and 86.03±25.78 μg/L before and after iron supplementation, respectively), but this difference did not reach a significant level (P=0.14). No significant change in ferritin levels was observed in the placebo group, which was as expected (102.47±46.17 and 98.97±41.58 μg/L before and after placebo administration, respectively). There were no significant changes in hemoglobin, hematocrit, iron, or TIBC levels with administration of either ferrous sulfate or placebo (Table 3). No notable complications associated with ferrous sulfate administration were reported.

### Discussion

Dry cough is the most often reported and troublesome complication associated with ACEI use, but its mechanism remains to be clarified. The incidence of ACEI-induced cough varies in published reports, ranging from 5% to 39%, but it is evident that the cough is a major limitation in terms of continuing the medication. The frequency of cough has been reported to be higher in women and nonsmokers for unexplained reasons.17-19

There have been various reports that have tried to explain the mechanism of this side effect. Bradykinin and prostaglandins are the most frequently proposed causes of the cough, and many studies using nonsteroidal anti-inflammatory drugs, such as sulindac and indomethacin, have been undertaken to attempt to abolish this side effect and thus allow continued medication.5,20,21 Tachykinins, such as substance P, have also been proposed as a possible cause of the dry cough, and disodium cromoglycate has been tested for control of the cough by inhibiting tachykinin activity.22,23 However, because no reports have clearly demonstrated successful termination of the dry cough with intervention of any kind or have clarified the mechanism behind this side effect, the question concerning the mechanism and method of control of dry cough remains open.

One of the mechanisms believed to be associated with the vasodilatory effect of ACEI involves the increased generation of NO through various mechanisms, including the induction of NOS and this is now known to be one of the major mechanisms of vasodilatation or reduction of myocardial oxygen consumption due to ACEI use. Besides its vasodilating effect, NO is also known to have proinflammatory effects on various kinds of cells, and its production is one of the mechanisms of the macrophage-mediated destruction of target cells. Furthermore, NO is known to be released in excess in bronchial epithelial cells of asthma patients and has been reported to be an important pathogenic effector in pertussis and other respiratory tract diseases caused by

### TABLE 2. Change in Mean Overall Daily, Daytime, and Nighttime Cough Scores

<table>
<thead>
<tr>
<th>Groups</th>
<th>Observation Period</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>3.07±0.70</td>
<td>1.69±1.10*</td>
</tr>
<tr>
<td>Daytime</td>
<td>2.86±0.86</td>
<td>1.51±1.00*</td>
</tr>
<tr>
<td>Nighttime</td>
<td>3.29±0.73</td>
<td>1.87±1.24*</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>2.57±0.80</td>
<td>2.35±1.22</td>
</tr>
<tr>
<td>Daytime</td>
<td>2.37±0.73</td>
<td>2.37±1.23</td>
</tr>
<tr>
<td>Nighttime</td>
<td>2.78±0.97</td>
<td>2.33±1.21</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.01 between treatment and observation period.
inflammation. Since ACEI medication causes an increase in NO concentration not only in endothelial cells but also in various kinds of other cells, ACEI-induced cough may be associated with an excess of NO in bronchial epithelial cells.

There are 2 known isoforms of NOS that have been identified. One is the constitutive form, which can be found mainly in neuronal and endothelial cells, and the other is the inducible form (iNOS), which is mainly found in macrophages, epithelial cells, and hepatocytes. Bronchial epithelial cells exhibit both constitutive NOS and iNOS activity, but iNOS is the main isoform of concern when relating to the subject of inflammation or cell damage. The activity of NO and NOS, especially iNOS, is known to be associated with iron concentration. NOS is itself a heme-bound molecule, and NO is known to express its effect by binding to the iron portion of guanylyl cyclase. Meanwhile, as Weiss et al have reported, the activity of cellular iNOS is known to be decreased by iron supplementation. This is thought to be a result of the regulation of iNOS mRNA and has been proposed to be a part of a feedback regulation between iron metabolism and the NO-NOS pathway. Furthermore, an animal study has shown that in vivo loading of iron decreases the release of NO by alveolar macrophages, and other reports have also shown that treatment with iron compounds can delay NO-induced cell damage in animal hepatocytes.

According to these findings, NO-mediated inflammatory responses may be reduced with iron supplementation. On the basis of these facts, we hypothesized that a change in serum iron concentration may affect ACEI-associated effects and side effects related to NO, possibly abolishing dry cough.

As we show in the present study, supplementation of iron clearly showed a beneficial effect in most of the subjects, and this effect could not be found in the placebo group. Furthermore, a near-total disappearance of the dry cough could be found in 3 patients who received iron supplementation. This dramatic effect of iron supplementation on dry cough may require further explanation, but according to our hypothesis and the results of previous studies, iron may be the key element in the control of the dry cough mechanism. As mentioned above, association of this element with NOS, especially iNOS activity, may be the mechanism of this effect. In short, supplementation of iron decreases the activity of iNOS, which results in reduced generation of NO in bronchial epithelial cells and macrophages and may consequently suppress the dry cough initiated by ACEI use.

A substantial increase in ferritin concentration was detected on iron supplementation, but the mean concentration after the supplementation was not significantly higher than that of the subjects who took the placebo. When the effect of supplementation is considered, this may well be found to be puzzling. However, this may be accounted for by the following: 4 weeks of iron supplementation may be a relatively short period for change in ferritin levels, and individual differences in NOS activity and iron dependence of the enzyme may be present.

Probably the most significant limitation of the present study was that we were unable to perform a crossover study to confirm the effect of iron supplementation. This was because after iron administration a considerable amount of time is required for the iron level to drop to the level that requires repeated supplementation. Because of this, immediate crossover was not considered to be of any real value in terms of further validating our results. Another limitation of the present study was that we did not perform an analysis of the exhaled level of NO itself or of the change in the level of NO with iron supplementation. This analysis, and perhaps studies using direct NO inhibitors, may be required to further confirm the present results. Also, the relatively small sample size of our subjects is another limitation of the present study.

In conclusion, supplementation of iron successfully diminishes ACEI-induced dry cough, and this fact supports the hypothesis that ACEI-induced cough may be associated with excessive generation of NO in bronchial epithelial cells. This finding requires further investigation, in vivo and in vitro.

Acknowledgment
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References

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Iron Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>134.3±8.1</td>
<td>136.3±6.0</td>
</tr>
<tr>
<td>Hct, %</td>
<td>39.58±2.65</td>
<td>40.78±2.51</td>
</tr>
<tr>
<td>Iron, µmol/L</td>
<td>13.39±1.89</td>
<td>15.00±2.88</td>
</tr>
<tr>
<td>TIBC, µmol/L</td>
<td>55.97±5.03</td>
<td>57.37±2.13</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
<td>68.15±32.86</td>
<td>86.03±25.78</td>
</tr>
</tbody>
</table>

Values are mean±SD. Hb indicates hemoglobin; and Hct, hematocrit.

P>0.05 between all before- and after-treatment values and between iron and placebo groups.


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