High Incidence of Cough among Users of Angiotensin-Converting Enzyme Inhibitors

Jameel Nasser, MD, MSc* Khadija Al Aradi, MD*
Kobra Sayed Ebrahim, MD* Ahmed Omran, MD, MSc*

Objective: To evaluate the incidence of cough among patients newly diagnosed with hypertension initiated on Angiotensin-Converting Enzyme Inhibitors (ACEI).

Design: A Prospective Study.

Setting: Two primary healthcare centers, Bahrain.

Method: Newly diagnosed patients with hypertension who were initiated on ACEI or angiotensin receptors blockers (ARBs) were included in the study. The patients were followed for one year starting from 2 January 2016 to 31 December 2016. The following data were documented: age, sex, smoking, body mass index (BMI), and concomitant co-morbid diseases, the onset of cough, duration, drug discontinuation, and the cough disappearance after discontinuation.

Result: Eighty patients were included in the analysis. Sixty-five (81%) patients received ACEI and 15 (19%) were on ARBs. Forty-three patients (54%) were females. Cough developed in 24 (37%) patients. Perindopril was the only ACEI prescribed. The mean cough onset is 12.7 days. After stopping or changing the drug, the mean for cough disappearance was 13.3 days. There was a statistically significant gender difference in ACEI-induced cough. Cough developed in 17 (70.8%) females compared to 7 (29.2%) males; P=0.044. There was no significant difference regarding age (P=0.79) or BMI (P=0.37).

Conclusion: The incidence of cough is unexpectedly high among our newly diagnosed hypertensive patients initiated on Perindopril. It is much higher among females. Larger study is needed to examine this common, often intolerable, adverse effect.
to assess the association between cough and gender, age group, and BMI. P-value of 0.05 or less was considered as statistically significant difference.

RESULT

Initially, ninety-five patients who started ACEI were included in the study, fifteen patients were excluded, see table 1.

Table 1: Reasons for Exclusion

<table>
<thead>
<tr>
<th>Reasons for Exclusion</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Answer</td>
<td>6</td>
</tr>
<tr>
<td>Wrong Telephone Number</td>
<td>4</td>
</tr>
<tr>
<td>Refused Treatment</td>
<td>1</td>
</tr>
<tr>
<td>Stopped Treatment</td>
<td>1</td>
</tr>
<tr>
<td>Did Not Take the Treatment</td>
<td>1</td>
</tr>
<tr>
<td>Language Barrier</td>
<td>1</td>
</tr>
<tr>
<td>No Contact Number</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

Eighty patients were included in the study. Sixty-five (81%) patients received ACEI, and 15 (19%) were on ARB. Forty-three patients (54%) were females. Eight (10%) patients are non-Bahrainis. The age group distribution is shown in table 2.

Table 2: Patients’ Age Groups

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Number (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>10 (12.5%)</td>
</tr>
<tr>
<td>40-49</td>
<td>24 (30%)</td>
</tr>
<tr>
<td>50-59</td>
<td>30 (37.5%)</td>
</tr>
<tr>
<td>≥60</td>
<td>16 (20%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>80 (100%)</strong></td>
</tr>
</tbody>
</table>

ACEI were prescribed for a diagnosis of primary hypertension in all patients. The co-morbidities were documented, see table 3.

Table 3: Patients’ Co-Morbidities

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (BMI ≥ 30 kg/m²)</td>
<td>32 (40%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (22.5%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

There were no patients with a diagnosis of COPD or heart failure. Six (7.5%) patients were current smokers.

Cough developed in 24 (37%) patients using ACEI. None of those on ARB developed cough. The mean cough onset was 12.7 days (minimum 2 days, maximum 90 days). The mean for cough disappearance after stopping or changing the drug, was 13.3 days (minimum 2 days, maximum 60 days). There was a statistically significant gender difference in ACEI-cough.

It developed in 17 (70.8%) females compared to 7 (29.2%) males, P=0.044. There was no significant difference regarding age (P=0.79) or BMI (P=0.37).

DISCUSSION

The duration of the study was favored because ACEI induced-cough and/or its recognition by the treating physician can persist in some patients for long duration\(^7,8,9,10\). The study showed that 37% of patients who were started on ACEI for primary hypertension developed cough within two weeks. It lasted for a maximum of 2 months. The cough was more common in females, but it was not related to age or BMI.

The reported incidence of ACEI-induced cough varies markedly. One of the main reasons is the racial differences. In a study among predominantly Europeans who used Perindopril, the incidence was 3.9%\(^11\). Whereas, in a study among predominantly Chinese patients, it reached up to 60%\(^6\). In another study, where 68% of the patients were Chinese, the incidence was around 30%\(^10\). However, none of them used Perindopril. A perindopril-induced cough was reported to be lower compared to other ACEI\(^15\).

The study showed a significant gender difference in the incidence of cough. It is more common among females which is a consistent finding in several other studies\(^7,10,16,17\). That could be related to genetic polymorphisms in certain genes including ACEI which is sex-specific that provide protection in males while increasing the susceptibility in females as found in a genetic study\(^18\).

No significant association of age or BMI with ACEI-induced cough was found, which could be due to the small sample size. For the same reason, we did not do statistical test to examine the association of cough with other patients’ comorbidities. Females and older age (>65 years) are two known predictors for ACEI-induced cough\(^11,19\). Further, diabetes, heart failure, respiratory diseases (including asthma and COPD) were found to be risk factors for ACEI-induced cough\(^6,16,20\).

Finally, this is the first study in the kingdom to examine the incidence of Perindopril-induced cough. Recall bias could not be excluded in our study, the short duration of appearance and resolution after discontinuation of the drug in these relatively healthy subjects with few comorbidities suggest correlation. However, a larger sample size is needed to confirm our finding.

CONCLUSION

The incidence of cough is unexpectedly high among our newly diagnosed hypertensive patients initiated on Perindopril. It is much higher among females. A larger study is needed to examine this common, often intolerable, adverse effect.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important
 intellectual content; and (3) final approval of the manuscript version to be published. Yes.

**Potential Conflicts of Interest:** None.

**Competing Interest:** None.

**Sponsorship:** None.

**Acceptance Date:** 14 April 2018.

**Ethical Approval:** Approved by the Council of Budaiya Health Center, Bahrain.

**REFERENCES**