

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

Jameel Nasser, MD, MSc* Khadija Al Aradi, MD*
Kubra 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.

Bahrain Med Bull 2018; 40(2): 97 - 99

Hypertension is a common worldwide chronic disease. In 2015, it was estimated that there were 874 million adults who had systolic blood pressure 140 mmHg or higher¹. Furthermore, hypertension is the most common preventable risk factor for cardiovascular morbidity and mortality².

Pharmacologic management of hypertension includes many major classes of drugs. Angiotensin-Converting Enzyme Inhibitors (ACEI) is one of them. In fact, ACEI is considered the first choice in many recent guidelines^{3,4}. ACEI have many indications in addition to blood pressure lowering. For example, many studies had found consistent beneficial effects in post-myocardial infarction, heart failure, and chronic kidney disease patients⁵. This led to the widespread use of these agents.

ACEI are well-tolerated by many patients, but cough is an adverse effect of these drugs, which can be troublesome⁶. Furthermore, ACEI-induced cough can result in a delay in diagnosis, unnecessary workup, misdiagnosis, and mistreatment due to inadequate knowledge of the treating physicians⁷⁻⁹.

The incidence and prevalence of ACEI-induced cough vary widely. Some found it to be as low as 3.2%, while others found

it to be as high as 60%. This variation could be explained by the type of population studied^{6,10-12}.

ACEI are commonly prescribed agents in primary care settings in Bahrain¹³. However, there are no studies regarding the incidence of their adverse effects.

The aim of this study is to evaluate the incidence of ACEI-induced cough among patients attending primary care settings.

METHOD

Newly diagnosed patients with hypertension attending two primary healthcare centers who were started on ACEI or ARB were included in the study from 2 January 2016 to 31 December 2016. During the study, the only available ACEI in primary care was Perindopril. It was available in free and fixed-dose combinations. Patients on either formulation were included. The following data were documented: age, sex, smoking, body mass index (BMI), and any concomitant co-morbid disease.

SPSS version 24 was used for data analysis. Frequencies of different variables were calculated. Chi-square test was used

* Consultant Family Physician
Ministry of Health
Kingdom of Bahrain
E-mail: jnasser66@yahoo.com

to assess the association between cough and gender, age group, and MBI. 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

Reasons for Exclusion	Number
No Answer	6
Wrong Telephone Number	4
Refused Treatment	1
Stopped Treatment	1
Did Not Take the Treatment	1
Language Barrier	1
No Contact Number	1
Total	15

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

Age Group (years)	Number (%)
<40	10 (12.5%)
40-49	24 (30%)
50-59	30 (37.5%)
≥60	16 (20%)
Total	80 (100%)

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

Co-morbidity	Number of Patients (%)
Obesity (BMI ≥ 30 kg/m ²)	32 (40%)
Diabetes	18 (22.5%)
Dyslipidemia	11 (14%)
Bronchial asthma	4 (5%)

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^{7,8,10,14}.

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 ACEI¹⁵.

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 study¹⁸.

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

- Forouzanfar MH, Liu P, Roth GA, et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. *JAMA* 2017; 317(2):165-182.
- Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report from the American Heart Association. <http://circ.ahajournals.org>. Accessed on 31 January 2018.
- Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. <http://professional.heart.org/statements> Accessed on 31 January 2018.
- Hypertension in Adults: Diagnosis and Management. <https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance#choosing-antihypertensive-drug-treatment> Accessed on 9 February 2018.
- Kaplan NM, Victor RG. Treatment of Hypertension: Drug Therapy. In: Goolsby J, ed. *Kaplan's Clinical Hypertension*. 11th edition. USA: Wolters Kluwer, 2015; 198-262.
- Lee Y, Chiang Y, Tsai JCR. Severe Nonproductive Cough and Cough - Induced Stress Urinary Incontinence in Diabetic Postmenopausal Women Treated With ACE Inhibitor. *Diabetes Care* 2000; 23(3):427.
- Vegter S, de Jong-van den Berg LT. Misdiagnosis and Mistreatment of a Common Side-Effect--Angiotensin-Converting Enzyme Inhibitor-Induced Cough. *Br J Clin Pharmacol* 2010; 69(2):200-3.
- Olsen CG. Delay of Diagnosis and Empiric Treatment of Angiotensin-Converting Enzyme Inhibitor-Induced Cough in Office Practice. *Arch Fam Med* 1995; 4(6):525-8.
- Lombardi C, Crivellaro M, Dama A, et al. Are Physicians Aware of the Side Effects of Angiotensin-Converting Enzyme Inhibitors? A Questionnaire Survey in Different Medical Categories. *Chest* 2005; 128(2):976-9.
- Ng LP, Goh PS. Incidence of Discontinuation of Angiotensin-Converting Enzyme Inhibitors Due to Cough, in a Primary Healthcare Centre in Singapore. *Singapore Med J* 2014; 55(3):146-9.
- Brugts JJ, Arima H, Remme W, et al. The Incidence and Clinical Predictors of Ace-Inhibitor Induced Dry Cough by Perindopril in 27,492 Patients with Vascular Disease. *Int J Cardiol* 2014; 176(3):718-23.
- Baker-Smith CM, Benjamin DK, Jr, Califf RM, et al. Cough in Pediatric Patients Receiving Angiotensin-Converting Enzyme Inhibitor Therapy or Angiotensin Receptor Blocker Therapy in Randomized Controlled Trials. *Clin Pharmacol Ther* 2010; 87(6):668-71.
- Nasser J. Hypertension in a Primary Care Setting: Control and Pattern of Prescribing. *Bahrain Med Bull* 2010; 32(3):100-104.
- Dicpinigaitis PV. Angiotensin-Converting Enzyme Inhibitor-Induced Cough: ACCP Evidence-Based Clinical Practice Guidelines. *Chest* 2006;129(1 Suppl):169S-173S.
- Tumanan-Mendoza BA, Dans AL, Villacin LL, et al. Dechallenge and Rechallenge Method Showed Different Incidences of Cough among Four ACE-Is. *J Clin Epidemiol* 2007; 60(6):547-53.
- Israili ZH, Hall WD. Cough and Angioneurotic Edema Associated with Angiotensin-Converting Enzyme Inhibitor Therapy. A Review of the Literature and Pathophysiology. *Ann Intern Med* 1992; 117(3):234-42.
- Singh NP, Uppal M, Anuradha S, et al. Angiotensin Converting Enzyme Inhibitors and Cough--A North Indian Study. *J Assoc Physicians India* 1998; 46(5):448-51.
- Grilo A, Sáez-Rosas MP, Santos-Morano J, et al. Identification of Genetic Factors Associated with Susceptibility to Angiotensin-Converting Enzyme Inhibitors-Induced Cough. *Pharmacogenet Genomics* 2011; 21(1):10-7.
- Morimoto T, Gandhi TK, Fiskio JM, et al. Development and Validation of a Clinical Prediction Rule for Angiotensin-Converting Enzyme Inhibitor-Induced Cough. *J Gen Intern Med* 2004; 19(6):684-91.
- Malini PL, Strocchi E, Fiumi N, et al. ACE Inhibitor-Induced Cough in Hypertensive Type 2 Diabetic Patients. *Diabetes Care* 1999; 22 (9):1586-7.