

Incidence of Captopril-Induced Cough in Newly Diagnosed Hypertensive Patients: Incidence in an Outpatient Medical Clinic Population in Iran in 2011-2012

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ABSTRACT

Introduction: In patients with uncomplicated primary hypertension (HTN), angiotensin converting enzyme inhibitors (ACEIs) are considered as monotherapy. In some studies, cough was not related to age, sex, underlying disease, or drug dosage. However, in previous studies, the incidence of cough was greater in females than males. The aim of this study is to determine the incidence of captopril-induced cough in patients with HTN and to evaluate some associated parameters such as sex and age. **Materials and Methods:** In this cross-sectional epidemiologic study, 877 patients with new onset HTN, referring to our outpatient clinic, were assessed and underwent treatment by captopril as first-line medical treatment. All patients were enrolled in four different age groups (<35, 36-45, 46-55 and >55 years old) and comparison was made between the groups. **Results:** The overall incidence of captopril-induced cough was 15.5%, with a significant difference between females and males and obviously a higher rate in females ($P=0.017$). In addition, cough was significantly more common in females than males in 36- to 45-year-old group (46.42% vs. 24.71%). The incidence of cough after treatment with captopril decreased by increasing age of patients and this reduction in both male and female patients was statistically significant ($P<0.001$). **Conclusion:** A persistent, dry cough in a hypertensive patient, treated by captopril, should be considered as an adverse effect of ACE inhibitor therapy. Our study demonstrated the higher incidence of cough in female patients, receiving captopril. Thus, identification of this adverse effect may prevent unnecessary treatment of patients using captopril.

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Introduction

In developed countries, the prevalence of hypertension increases with age, rising after the age of 30 years. By the age of 75 years, about 90% of males and females will have hypertension (1).

About three decades later the first angiotensin converting enzyme inhibitor (ACEI), captopril, was prescribed for the treatment of hypertension (2). In patients with uncomplicated primary hypertension, ACEIs as monotherapy provide antihypertensive effects equal to those obtained with other classes. More importantly, ACEI-based therapy has provided significant protection against cardiovascular (CV) disease and death when compared with

placebo, and comparable if not better protection than other classes of drugs (1).

The same angiotensin converting enzyme (ACE) that converts angiotensin I (A I) to angiotensin II (A II) is also responsible for inactivation of the vasodilating hormone Bradykinin (BK). By inhibiting the breakdown of bradykinin, ACEIs increase the concentration of a vasodilating hormone while decreasing the concentration of a vasoconstrictor hormone. The increased plasma kinin levels may contribute to the vasodilation and other beneficial effects of ACEIs, but they are also probably responsible for

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the most common and bothersome side effects of their use—a dry hacking cough (1). These results suggest that because ACE inhibitors impair metabolism of BK, it may result to the manifestation of cough in hypertensive patients receiving these drugs (3). Cough may begin as early as one week after the start of captopril. It begins with tickling sensation in the back of the throat, the cough is dry, non-productive and unresponsive to antitussive agents (4). The frequency of ACE inhibitor associated cough has been reported to range from 10-20% (5).

The reported prevalence of cough with ACE inhibitor therapy varies from 0.2 to 25%. In some studies the complication of cough was not related significantly to age, sex, underlying disease, drug dosage, or smoking status (6), but in other studies the incidence of cough was also greater in females than in males (7). Also, in some studies a genetic predisposing factors, especially in females, may increase ACEI-induced cough risk (8,9).

The cough is associated with pulmonary dysfunction but may not resolve for 3 weeks after the ACEI is discontinued. If a cough appears in a patient who needs an ACEI, an Angiotensin Receptor Blocker (ARB) or Direct Renin Inhibitor (DRI) should be substituted (1). Thus, our study goals are to determine the incidence of cough in patients newly starting to use captopril and, to compare the frequency of cough in different age and gender groups.

Materials and Methods

A cross-sectional epidemiologic survey in an Outpatient Medical Clinic Population in Iran in 2011-2012 was done. In this study, 877 patients with new onset HTN, attending in the outpatient department of Hazrat Rasoul referral Hospital, Kermanshah University of Medical Sciences were registered and underwent treatment by Captopril at first.

Patients with secondary HTN; cases with contraindication to ACEIs; with significant systolic heart failure; smokers; patients with concomitant respiratory disease e.g. bronchial asthma, chronic obstructive airway disease (COPD), pulmonary tuberculosis, respiratory neoplasm, cases with other pulmonary diseases; and patients with any other potential cause of cough were excluded from study. While the incidence of cough may be affected by other drug usage, we excluded those patients with concomitant treatment of cardiovascular and respiratory diseases from our study.

All patients were evaluated for occurrence of any dry, non-productive and unresponsive to antitussive agents cough following usage of captopril. Patients were followed up for six to eight months. On each visit besides checking their

blood pressure they were specifically questioned about proper usage the drug and occurrence of the cough as subjective finding. Also, the onset of captopril-induced cough ranged from within hours of the first dose two months after the initiation of therapy. But in most patients cough had begun about one week after the start of captopril, not considering the drug dosage. It mostly developed with a sensation like tickling in the back of the throat. The cough was dry, non-productive and unresponsive to antitussive agents and may also be paroxysmal and worst at night.

Our information was based on patient self-reporting of the presence or absence of cough on every visit.

Statistical Analysis

Patients were located in four different age groups: <35 years old, 36-45 years, 46-55 years, and >55 years; the groups containing 59,173,262 and 383 patients, respectively.

Statistical analysis was performed in these groups with Statistical Package for the Social Sciences (SPSS). The chi-square test was used to find association between different sex and age groups. P-value of <0.05 was considered statistically significant.

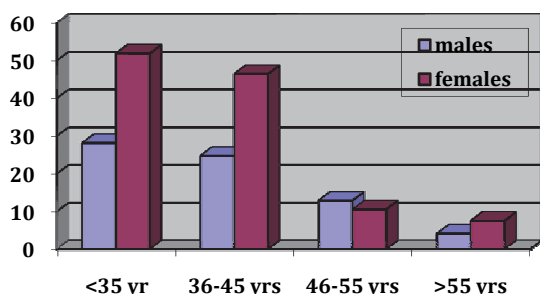
Results

In present study, captopril-induced cough developed about one week after start of the treatment. Among 877 patients, 418 were male and 459 were female. In overall patients the incidence of captopril-induced cough was 15.5% (18.3% in females vs. 12.4% in males). In the 36-45 years age group, the cough frequency was statistically significant higher in females than males (46.42 % vs. 24.71%, respectively) (P=0.003). In the age group 46 - 55years, captopril-induced cough was more common in males than females (12.87% vs. 10.55%) and in the age groups <35 years, 36-45 years and >55 years, the cough was more common in females than males and however it was clinically important but the differences were not statistically significant (51.85% vs. 28.12%, 46.42% vs. 24.71% and 7.48% vs. 4.08%, respectively). By considering the age of the patients, there was a significant difference between captopril-induced cough in females and males and obviously higher in females (P=0.017)

Among the different age groups, the cough was most common in patients younger than 35years (38.98%) and its occurrence decreased by aging, reached to 35.26% in patients with age 36 - 45 years and 11.45% in 46 - 55 years and 5.74% in patients older than 55 years. Patient characteristics and statistical analysis of the

Table 1. Comparison of the cough incidence among age and sex groups

Age groups	Males	Females	Cough in all patients	Cough in females	Cough in males	P value between sex groups cough incidence differences
<35->55 years (n=877)	418	459	136(15.5%)	84(18.3%)	52(12.4%)	0.017
<35 years (n=59)	32	27	23(38.98%)	14(51.85%)	9(28.12%)	0.063
36 – 45 years (n=173)	89	84	61(35.26%)	39(46.42%)	22(24.71%)	0.003
46 – 55 years (n=262)	101	161	30(11.45%)	17(10.55%)	13(12.87%)	0.567
>55 years (n=383)	196	187	22(5.74%)	14(7.48%)	8(4.08%)	0.152

**Figure 1.** Incidence of captopril-induced cough (as percentage) in different age groups

results were summarized in the Table 1. As illustrated in Figure 1, the incidence of cough after treatment with captopril decreased by increasing the age of the patients and this progressively reduction in both male and female patients was statistically significant ($P < 0.001$) (linear-by-linear association).

Discussion

ACE inhibitors as Captopril, are being used increasingly to treat hypertension. In general, ACEIs are well tolerated and have a low incidence of adverse effects (a dry cough is the most common) (4). In our study, we observed the incidence of captopril-induced cough in overall patients was 15.5%. A review of literature by Zafar Israeli & Hall estimated the incidence of captopril induced cough range from 0.7% to 48% (10).

In Muhammad et al. study, dry cough incidence with captopril in Pakistan was 17.3% (4) and in a research, McNally showed that however, the frequency of captopril-induced cough is not established definitely, but in his investigations it occurs in 5% to 15% of patients using captopril for a long time (11).

In Wyskida et al. study, a higher ACEI-induced cough incidence in women was found, confirming Grilo et al. results of their published article showing women are more susceptible to ACE inhibitor-induced cough (8,9). Several other studies confirmed this subject that in females the risk of this adverse drug reaction is more common than males (12, 13, 14). The prevalence of ACE inhibitor induced-cough varies widely among previous series and has been reported to be in the range of 5 to 35% among patients treated with these agents (15). For example, Wood et al. showed a 13 percent prevalence of

cough among ACE inhibitor users (2). In a recent crossover trial in elderly patients being treated for mild to moderate hypertension, Woo and colleagues reported cough in 7 of 40 (18%) subjects receiving captopril (16). In McKinney W. et al study the prevalence of cough in patients using captopril was 19% (15). The beginning of ACE inhibitor-induced cough ranges from few hours after the first dose to months after starting the treatment. During ACEI medical therapy period, often the cough develops in the early course of treatment (17). In present study, captopril-induced cough developed about one week after start of the treatment. Cough resolution usually occur within 1 to 4 weeks after the termination of therapy, but it may last for up to 3 months. This kind of cough has not been revealed to be dose dependent. However, as an important limitation of our study, the Data of the cough resolution symptoms with discontinuation of medical treatment and recurrence on re-challenge were not available. The only effective treatment for ACE inhibitor-induced cough is discontinuing the treatment with this drug (18). Results of Mc Ewan et al. and Wood R. studies, demonstrated ACEI-induced cough were not dose dependent (2,19).

Our study showed that cough is more common in females than males (18.30% vs. 12.44%) and it is significantly more common in females than males in the age group less than 46 years. In another study, the incidence of captopril induced cough was more common in females as compared to males (14.3% vs. 12.0%) (4). Whatever the age is lower, this difference is more pronounced. In both genders, whatever the age is lower, cough is more common and cough is most common in young females less than 35yrs.

Thus, in the patients younger than 46 yrs, especially in females, occurrence of cough following use of ACE.I as captopril is expected more frequently than conceived former, and in these patients prescription of ARBs is reasonable (20).

While published data established the incidence of cough has increased over the last two decades (21), if the clinician is unable to recognize that the cough may be related to ACEI therapy, patients may be subjected to extensive and unnecessary evaluations, diagnostic tests, and consultations (4). However, another ACEI

replacement should not be rechallenged, because almost always the cough will recur. Usually after a few days of captopril cessation cough will subside (22). A short-term trial of withdrawal of captopril or substitution of another type of antihypertensive drug is an inexpensive, easy way to determine if the ACEI is the cause of cough (4, 18). Our results suggest that in young female patients because of high incidence of ACEI-induced cough (such as captopril-related cough) ARB drugs replacement should be considered as the first line medical treatment in hypertension.

Conclusion

A persistent, dry cough in a hypertensive patient using captopril as medical treatment, should be considered as an adverse effect of ACE inhibitor therapy. Female sex seems to increase the captopril-induced cough risk. A short-term trial of captopril termination is an inexpensive and easy way to evaluate if this drug is the cause of cough. Present study determined that the incidence of captopril-induced cough decreases by increasing the age of patients and this progressively reduction in both male and female hypertensive patients is statistically significant.

We recommend that determination of this adverse effect as the most common side effect of ACEIs (e.g. captopril) may prevent unnecessary treatment of patients using captopril.

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Conflict of Interest

The authors declare no conflict of interest.

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