Prevalence of cough among patients treated with angiotensin converting enzyme inhibitors

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Abstract

Purpose: The aim of this study was to assess the prevalence of cough, its causality and impact on patient adherence in patients taking angiotensin converting enzyme inhibitors. **Methods -** A cross sectional study was conducted in Ayder Referral Hospital, northern Ethiopia from April to June 2013. Patients who started either captopril or enalapril were interviewed for the occurrence of cough and its characteristics. Data were entered to EPI-info and analyzed using SPSS for windows version 16 statistical software. Logistic regression model was used to analyze variations in occurrence of cough among different factors. P value of less than 0.05 was considered statistically significant. **Results -** One hundred two patients were participated in this study. Of which, 54(52.9%) were females. About half of the respondents (53%) were between the ages of 40 to 60. Cough was observed in 30 (29.4%) patients. According to World Health Organizations causality scale, the reported cough was certain (drug induced) in 5 (7.1%) patients; possible in 10 (25%) patients; probable in 12 (10.7%) patients and unlikely in 3 (57.1%) patients. Significant statistical difference was observed between occurrence of cough and durations of treatment (P<0.05). There was no statistically significant difference in occurrence of cough with age, sex, ethnicity, residence, dose and type of ACEI. **Conclusion –** In this study, dry cough was more prevalent among patients on angiotensin converting enzyme inhibitors. Troublesome cough may affect patient's sleep and overall adherence to treatment. Health professionals should aware of the characteristics cough and manage accordingly.

Keywords: Cough, Angiotensin Converting Enzyme Inhibitors, Causality, Ethiopia

Introduction

Cardiovascular diseases (CVDs) are now being endemic worldwide, no longer limited to economically developed countries. At the beginning of the 20th century, CVD was responsible for fewer than 10% of all deaths worldwide. Today, that figure is about 30%, where 80% of the burden now occurring in developing countries [1,2]. In Ethiopia, cardiovascular disorders such as hypertension and heart diseases are becoming common and silent epidemic [3,4].

Angiotensin converting enzyme inhibitors (ACEI) have undoubtedly been one of the crucial developments in cardiovascular pharmacology over the last 30 years [5]. These drugs are used primarily for the treatment of hypertension and heart failure. ACEIs act in the angiotensin converting enzyme, a component of the blood pressure-regulating renin- angiotensin system, ultimately altering the peripheral resistance, renal function and cardiovascular structure [6, 7]. While the benefits of ACE inhibitors are important in CVDs, cough a troublesome side-effect is common to all ACE inhibitors. ACEI-induced cough is characterized as dry, non-productive, frequently associated with sore and itchy throat which may be persistant requiring termination of treatment [8, 9]. The incidence of ACEI-induced cough has been reported to range between 5% and 35% [10]. Study by Vegter and de Jong-van den Berg suggested that cough as a side effect of ACE-I is being missed and patients are treated with anti-tussive agents [11]. The reported prevalence of cough associated with use of ACE inhibitors was 14.9%, with 4.7% of patients interrupting treatment as a result. Similarly, the UKPDS (The United Kingdom Prospective Diabetes Study) Group noted that 4% of patients receiving captopril discontinued therapy due to cough [12]. Multiple factors such as genetic makeup, race, age, sex, disease state, and other exogenous factors such as co-prescribed drugs, and diet may alter a patient's susceptibility to ACEI associated cough.

To the best of available literature, no research has been done in Ethiopia related to the ACE inhibitors induced cough. This study was aimed to assess the prevalence of cough in patients treated with angiotensin converting enzyme inhibitors and assess its' causality, and impact on patient adherence.

Materials and Methods

This study was conducted in the ambulatory cardiovascular clinic of Ayder Referral Hospital situated in Mekelle town, northern Ethiopia, 783 kilometers far from the capital Addis Ababa. The hospital started giving referral and specialized medical services in 2008 to about 8 million inhabitants in its catchment area of northern Ethiopia. It provides a broad range of medical services to both in and out patients [13].

A cross sectional study was carried out from April to June 2013. Patients on ACE inhibitors were interviewed about occurrence of dry cough, its characteristics, measures taken and adherence their medication. Out patients on ACE inhibitors (either enalapril or captopril); on follow-up for at least three months in the ambulatory clinic; with age of 18 years and above and willing to participate after providing consent were included as study subjects.

The sample size required for the study was determined using the formula for single population proportion by considering the prevalence rate of cough 10% and 5% margin of error at 95% confidence level and finally adjusting for finite population correction a sample of 102 patients were selected. Systematic random sampling (sampling interval (k) of N/n (400/102 =4)) was used to enroll participants from the study population. The first patient was selected randomly and every fourth patient was included in the study.

Data were collected through face to face interview and data abstraction from patient medical records. Two nurses trained particularly for this purpose collected the data. A pretested structured questionnaire was developed in English version then translated into local language (Tigrigna). The Tigrigna version was used for interview. Data about socio-demographics (age, sex, marital status, educational status, ethnicity and residence) were obtained by interviewing the patients. Patients were also interviewed if they had symptom of cough and those responded yes were asked about its characteristics in terms of onset and duration; temporal relation with initiation of their medications; relieving or provocative factors; nature and severity; effect of drug discontinuation or re-introducing (if any) and impact on adherence. The type, dose and indication of ACE inhibitor; co-morbid respiratory disease or infections; baseline and subsequent laboratory values were collected from the patient treatment charts and laboratory notes.

Operational definitions

Causality: Cough associated with the use of ACE inhibitors was classified based on the World Health organizations (WHO) causality scale [14]. The following criteria were used to classify cough causality: temporal relationship of cough to initiation of treatment, absence of drug or diseases that can cause cough, discontinuation effect and re-introducing effect.

- **Certain**:- All of the four criteria are fulfilled.
- **Probable**:- All of the criteria are fulfilled except re-introducing effect.
- **Possible**:- All of the criteria are fulfilled except discontinuation and re-introducing effect.
- **Unlikely**:- None of the four criteria are fulfilled.

Nonadherence: A patient missed at least two doses of his/her treatments in the last month.

The study was conducted after ethical approval was obtained from ethics review committee of College of Health Sciences, Mekelle University. Letter of permission was written to the medical director of Ayder Referral Hospital. Patients were interviewed after obtaining consent and each patient data were kept confidential.

Data were cleaned, coded and entered in to Epi-info version 7. Then, data were transferred into a statistical software, SPSS for windows version 16. Descriptive statistics was computed to describe the number and percentages of patient socio-demographics, disease and medication characterstics. The relationship between cough and variables (age, sex, marital status, educational status, ethnicity, residence, co-morbidities, type, dose and duration of ACE inhibitor treatment) was assessed by univariate and multivariate binary logistic regression. Backward elimination (likelihood ratio) was used as variable selection method. Estimates of risk factor were expressed as odds ratio (OR), at 95 % confidence interval (CI). P value of less than 0.05 was considered significant. The processed data were organized and presented using tables and graphs.

Results

A total of 102 patients were interviewed in the study. Out of this, 54(52.9%) were females. About half (53%) of the respondents were between the aged of 40 to 60. Seventy five (73.5%) respondents were married, while 5(4.9%), 22(21.6%) were single and divorced. Majorities (93.1%) of the participants belong to the Tigray ethnic group and were from Mekelle city and its catchment area (Table 1).

The most common indications of ACE inhibitor were hypertension alone (40.2%), followed by hypertension and congestive heart failure (19.6%), and congestive heart failure alone (15.7%). Majority (98.0%) of the respondents were on Enalapril while the remaining 2 patients were on Captopril. No patients had any respiratory disease condition (chronic obstructive pulmonary disease, asthma, allergic rhinitis, and tuberculosis) that can be a cause for acute or chronic cough. However, 26 (25.5%) had cough at the time of diagnosis likely due to congestive heart failure and respiratory infections. The most common drugs co-prescribed with ACE inhibitors

were Hydrochlorothiazide alone in 22 (22.4%); spironolactone + furesamide + digoxin in 11(11.2%) patients and Hydrochlorthiazide + nifidipine in 6(6.1%) patients. Overall cough was reported in 30(29.4%) patients receiving an ACE inhibitor. Eleven (39.3%) patients reported the onset of cough was after two months of starting ACE inhibitor therapy while 9 (32.1%) patients reported cough with onset before treatment (Table 2).

Thirty three (32.4%) patients reported missing at least two doses of their treatments in the last month. The main reasons reported for non-adherence were forgetfulness 10(30.3%) feeling better 4 (12.1%), cough affecting sleep 6 (18.2%) economic reasons 5(15.2%) (Fig. 1). Five patients who reported cough had discontinued their medication and reported disappearance of cough. Cough was reappeared when the health provider attempted to reintroduce at lower dose of the drug. For the management of cough, antibiotics and antitusive drugs were prescribed in about 6 (20%), and 5 (16.7%) patients respectively.

According to WHO causality scale, the reported cough was certain (ACE inhibitors induced) in 5 (7.1%) patients, possible in 10 (25%) patients, probable in 12 (10.7%) patients and unlikely in 3 (57.1%) patients (Fig. 2).

There was no significant difference in the prevalence of cough with respect to age, sex, ethnicity, marital and educational status, place of residence, indication, type and dose of ACEIs. Cough was found significantly associated with duration of ACEI treatment (P<0.05). Cough was prominent in those patients on ACEI for less than two years as compared to patients treated for more than two years (Table 3).

Discussion

In this study, the prevalence of cough was 29.4%. This is lower than the prevalence (44%) reported in Chinese patients [14] however, this is higher than those reported from Nigeria (20.2%), India (24.39%), Poland (7.1%), Canada (10.1%) [15].This differences may be related to environmental, racial and genetic difference. East Asian ethnicity remained a risk factor for cough while African-American ethnicity was protective (negative risk). The higher prevalence of cough in this study as compared to study done in Nigerians might be due to differences in study design. In the Nigerian case, data were collected based on patient-initiated spontaneously reporting. Factors such as cigarette smoking, chronic obstructive pulmonary disease, asthma and previous history of tuberculosis seem to contribute to an increase in its occurrence.

It has been classically postulated that ACEI-induced cough is a “class effect” of these drugs. A recent study has found differences among ACEIs of cilazapril, enalapril, perindopril and imidapril. The incidence of cough was greater in patients receiving cilazapril and enlapril, compared with those treated with perindopril and imidapril [16]. Enalapril had a higher incidence of associated cough (25%) than captopril(12%) or cinalapril(13**%)** [17]. However in this study, cough was observed only in patients on enalapril treatment. The number of patients on Captopril was small (two patients) thus it is difficult to estimate the difference and further studies are necessary to draw definite conclusions.

Cough was observed more common among women in a study by Morimoto et al [18]. Similar a reviw by Omboni et al found significantly more women than men experienced cough (3.8% vs 1.3%, P = 0.042) [9]. However, in this study not significant difference was observed with respect to sex. A report from post marketing surveillance data showed that patients aged 65 to 79 had a higher incidence of adverse events compared with younger patients [18]. In this study it is difficult to show a difference in ethnicity of ACEIs associated cough because most of the subjects (>90%) were Tigray ethnic group.

The onset of cough in relation to initiation of ACEIs is not clear. Cough sometimes appears at the start of therapy and while in others later on in the course of treatment. In Turkey, in 59% of patients the onset of cough was after the first month of treatment [17]. However, in this study cough was more common after the second month of treatment. In this study 33 (32.4%) patients reported missing at least two doses of their treatments in the last month. The main reasons reported for non-adherence were forgetfulness (30.3%), and cough affecting sleep (18.2%). Similar studies from Nigeria, China, and Italy reported 8%, 10%, 23.8% of patients discontinued their ACEI respectively because of persistent cough affecting sleep [9, 14, 19].

The mechanism of ACE inhibitor-induced cough remains unresolved, but likely involves the protussive mediators bradykinin and substance P, agents that are degraded by ACE and therefore accumulate in the upper respiratory tract or lung when the enzyme is inhibited, and prostaglandins, the production of which may be stimulated by bradykinin. A trial of drugs might be considered, however the most effective treatment for ACE inhibitor-induced cough is the cessation of the treatment [10].

In one study nonsteroidal anti-inflammatory drugs (NSAIDs) such as sulindac and indomethacin was attempted to abolish the side effect and thus enabling the patients to continue medication [20,21]. In Asia, theophylline given to a series of 10 patients with ACE inhibitor induced cough at a dosage of 8.5 mg/kg orally once daily while providing no bronchodilation resulted in a beneficial effect with reduction in cough [8]. In Netherlands, the estimated frequency of antitussive use for the treatment of ACEI-induced dry cough was 15% [11]. In line with the study in Netherlands 5(17.9%) patients were treated with antitussive agents in our study, but no patient was treated with NSAIDs or theophylline.

Conclusion

In this study, dry cough was prevalent among patients on ACE-inhibitors. It was not related with age, sex, ethnicity, dose and type of ACE inhibitor but was more prominent after the second month of treatment. Troublesome cough may affect patient's sleep and overall adherence to treatment. Health professionals should aware of the characteristics and management of cough associated with ACE inhibitors thus impact of cough on patient adherence, quality of life and unnecessary treatments can be minimized.

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Tables and Figures

Table 1. Socio-demographic characteristics of respondents (N=102)

Variables		N (%)
Sex	Male	48(47.1%)
	Female	54(52.9%)
Age	18-39	19(19%)
	40-60	53(53%)
	>60	28(28%)
Educational status	Illiterate	45 (44.1%)
	Primary school	27 (26.5%)
	Secondary school	17 (16.7%)
	College/university	13 (12.7%)
Ethnicity	Oromia	2(2%)
	Amhara	4(3.9%)
	Tigray	95(93.1%)
	Afar	1(1%)
Marital status	Married	75 (73.5%)
	Single	5(4.9%)
	Divorced	22(21.6%)
Residence	Mekelle city	72 (70.6%)
	Rural area	30(29.4%)

Table 2. Distribution of clinical and medication related characteristics

Variables		N (%)
Indication of ACE inhibitor	HPN alone	41(40.2%)
	HF alone	16(15.7%)
	HPN +HF + NPY	1(1.0%)
	HPN +HF	10(9.8%)
	HPN + NPY	20(19.6%)
	HF + NPY	12(11.8%)
	NPY alone	2(2.0%)
Types of ACEIs	Enalapril	100(98.0%)
	Captopril	2(2.0%)
Dose of enalapril	2.5mg daily	16(16.0%)
	5mg bid	26(26.0%)
	10mg bid	7(7.0%)
	15mg bid	2(2%)
	25mg daily	1(1%)
	5mg daily	33(33%)
	2.5mg bid	10(10%)
	10mg daily	5(5%)
Dose of captopril	25mg daly	1(50%)
	12.5mg bid	1(50%)
Occurrence of cough	Yes	30(29.4%)
	No	72(7O.6%)
Characteristics of cough	Dry and nonproductive and without chest pain	11 (36.7%)
	Productive associated with chest pain	19 (63.3%)
Onset of cough	Before starting treatment	10 (33.3%)
	After 1 weak of treatment	7(23.4%)
	After 1 month of treatment	3(10.0%)
	After 2 months of treatment	10 (33.3%)
Duration of cough	<2wks	14(46.6%)
	2wks-1month	8(26.7%)
	1mon-2month	2(6.7%)
	2mon-3month	3(10.0%)
	>3month	3(10.0%)

HPN=Hypertension HF=Heart failure NPY= Nephropathy

Table 3: Multivariate binary logistic regression analysis of factors associated with cough among patients treated with ACE inhibitors.

Variables		Cough	Multivariate	
			P-value	OR(95%CI)
Sex	Female	14(46.7%)	0.861	1.145(0.253,5.168)
	Male	16(53.3%)		1
Age	18-39	3(10.3%)	0.326	4.018(0.251, 64.326)
	40-60	18(62.1%)	0.300	0.436(0.091, 2.095)
	>60	8(27.6%)		1
Educational status	Illiterate	13(43.3%)	0.615	1.932(0.148, 25.155)
	Primary	9(30%)	0.483	2.373(0.212,26.533)
	Secondary	3(10%)	1.932	2.373(0.113, 33.079)
	College/University	5(16.7%)		1
Ethnicity	Tigray	29(96.7%)	0.518	2.573(0.147, 45.156)
	Amhara	1(3.3%)		1
Marital status	Married	24(80%)	0.339	2.565(0.371, 17.711)
	Divorsed	6(20%)		1
Place of residence	Rural	9(30%)	0.365	2.094(0.423, 10.372)
	City	21(70%)		1
Indication	HPN alone	11(36.7%)	0.329	7.276(0.136, 389.670)
	HF alone	4(13.3%)	0.498	3.868(0.077,193.633)
	HPN +HF + NPY	5(16.7%)	0.932	0.839(0.015, 47.141)
	HPN +HF	8(26.7%)	0.367	0.367(0.110,390.641)
	HPN + NPY	1(3.3%)		-
	HF + NPY	1(3.3%)		1
Dose of enalapril	2.5mg daily	5(16.7%)	0.450	0.233(0.005, 10.250)
	2.5mg bid	4(13.3%)	0.237	0.082(0.001, 5.176)
	5mg daily	8(26.7%)	0.274	0.133(0.004, 4.941)
	5mg bid	8(26.7%)	0.224	0.111(0.003, 3.844)
	10mg daily	1(3.3%)		-
	10 mg bid	3(10%)	0.173	0.044(0.000, 3.927)
	15mg bid	1(3.3%)		1
Duration of ACEI treatment	3wks-1month	1(3.3%)	0.737	0.448(0.004, 48.185)
	1month-6month	7(23.3%)	0.003	36.408(3.362, 394.324)
	6month-1year	4(13.3%)	0.004	46.917(3.301, 666.798)
	1year-2years	4(13.3%)	0.027	19.067(1.404, 258.912)
	2years-3years	5(16.7%)	0.060	12.493(0.903, 172.881)
	>3years	9(30%)		1

HPN=Hypertension HF=Heart failure NPY= Nephropathy

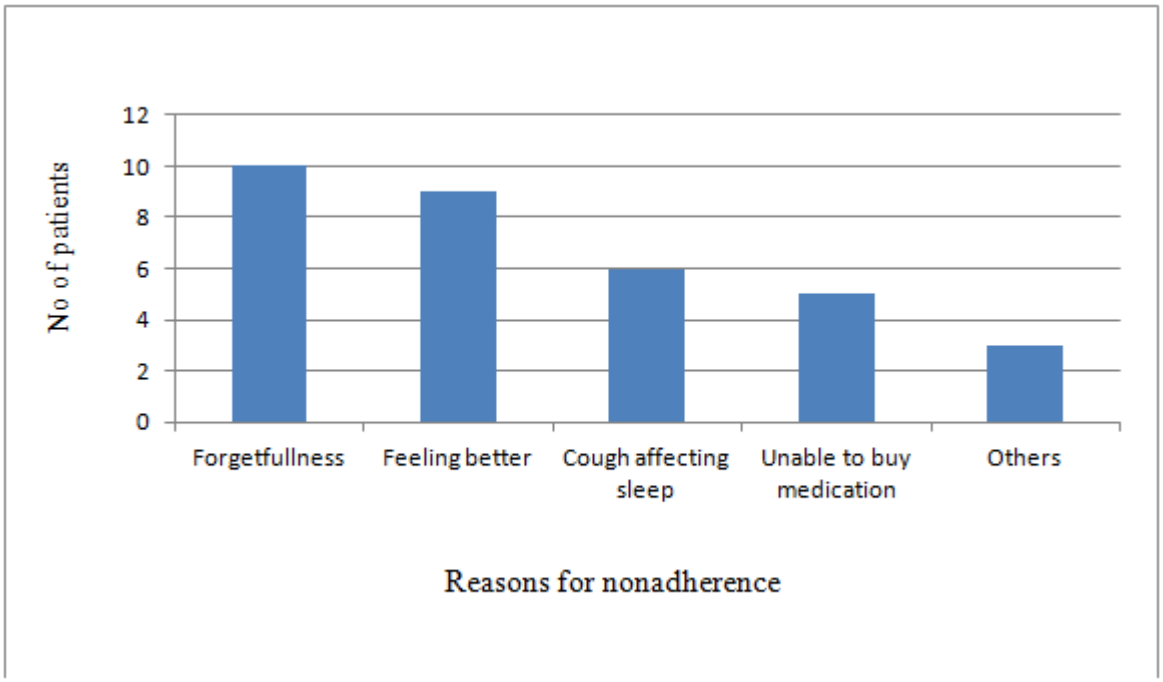

Figure 1: Reasons for non-adherence among patients taking ACE inhibitors

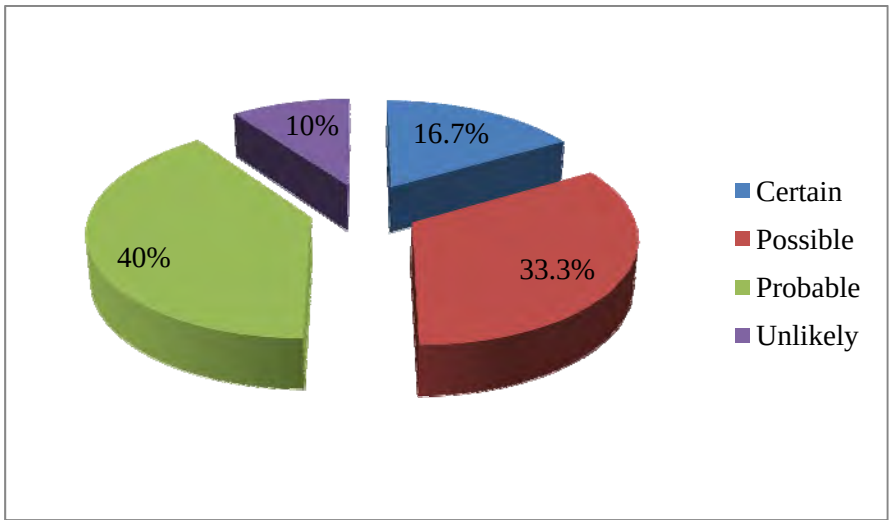

Figure 2: Causality classification of cough associated with ACE inhibitors