Prevalence of Captopril-induced Cough in Mosul Hypertensive

Wahda B Al-Youzbaki MBChB, MSc, PhD

Isam H Mahmood BSc, MSc, PhD

Abstract

Objective: To study the prevalence of Captopril- induced cough in local population of Mosul (Iraq) and also to characterize those patients who developed cough.

Design: Case-Control Study.

Setting & Period: The Medical Consultant Public Clinic in Mosul for the period from the 1st of February to the 1st of May of 2006.

Patients & Methods: One hundred thirteen hypertensive patients who received the angiotensin converting enzyme inhibitor captopril through the pharmacist of public clinic in Mosul were interviewed and their age, sex, dose of the drug, duration of use and the incidence of cough and the time of occurrence were recorded on an already prepared questionnaire form and compared with the information about 175 neither hypertensive patients nor receiving captopril.

Results: The incidence of captopril-induced cough in Mosul hypertensive was **31.8 %** compared with 6 % of the control (significant difference, P=0.000). This incidence was not related significantly to age, sex, dose nor the duration of treatment with captopril.

Conclusion: The prevalence of captopril-induced cough found in Mosul hypertensive patients (31.8 %) was approximate that of Japanese patients (38 %), slightly lower than that reported in Basrah patients in Iraq (40.5 %) and that reported in Chinese patients (46 %) but higher than that found in Greek (6.58 %).

Key words: Captopril, Cough, Hypertensive

Introduction

Captopril, is an angiotensin converting enzyme (ACE) inhibitor , was first reported in 1977 and was approved for human use in severe hypertension in late July 1980[1]. Currently, it is widely used for the treatment of many disorders including hypertension, heart failure, left ventricular dysfunction after myocardial infarction[2,3] and diabetic nephropathy [3,4] (Microalbuminurea greater than 30 mg / day) in insulin-dependent diabetes mellitus[3].

The uses of captopril in medicine is associated with a number of adverse effects including angioneurotic edema, cough, hypotension, taste disturbances, hyperkalemia, neutropenia, rashes, proteinurea, hepatic failure and pancreatitis[2,3,5].

Treatment with angiotensin converting enzyme inhibitors has been associated with the development of cough in up to 20 % of hypertensive patients [2, 6]. The cough is reported to be persistent, paroxysmal and non productive; it causes irritation of the throat and may be accompanied by voice changes [7].

The mechanism of cough induced by ACE inhibitors is not completely understood and may be related to bronchial hyperactivity and/or an accumulation of kinins [8]. The result of the study of Fox [9] in conscious guinea pigs indicated that bradykinin, (normally degraded by ACE)-evoked sensitization of airway sensory nerves may underlie the pathogenesis of ACE inhibitor cough. While just [10] showed that cough may be due to mechanism seems related to stimulation of lung afferent c fibers, perhaps by prostaglandin E_2. It may also be related to decrease breakdown of substance P, the neurochemical mediator of the cough reflex released in response to stimulation of c fibers and metabolized by ACE.

The present study was carried out to evaluate the prevalence of cough among hypertensive patients treated with captopril and to determine the possible correlated factors including age, sex, dose of drug and duration of treatment in Mosul city.

Patients & Methods

To evaluate the prevalence of cough in hypertensive patients receiving captopril, interviews were carried out with 113 patients in Mosul, who were taking captopril therapy for treatment of hypertension and 175 non hypertensive individuals matched for sex and age and receiving other drugs except captopril (controls).

All cases and controls had no record of respiratory infection, influenza, tuberculosis, asthma, chronic bronchitis, emphysema, congestive heart failure, sinusitis or laryngitis during the study period.

The patients were interviewed according to a questionnaires designed for this study which included in addition to personal details, captopril dose, duration of treatment, time of occurrence of cough and other diseases or drugs used. The most certain method for verifying that cough induced by captopril, was the disappearance of cough after stopping captopril therapy.

Statistical methods was done by using unpaired t-test and χ^2 test at significance level of $P < 0.05$.

Results

The main characteristics of the patients appeared in Table (1). All patients used captopril for controlling hypertension in doses ranged from 25 mg to 150 mg daily in duration of treatment ranged from 3 days to 5 years. The patients included 57 males, age range was from 28 to 75 years and 56 females, age range was from 27 to 70 years and the controls included 85 males, age range was from 27 to 73 years and 90 females, age range was from 28 to 68 years.

Persistent cough was reported in 36 patients (31.8%) used captopril which call for the discontinuation of therapy in 15 patients and in 11 individuals (6 %) of the controls, the difference was significant (p = 0.000). Cough appeared in the 36 patients at different intervals after starting treatment with captopril ranged from 3 days to 3 years and disappeared 3-7 days after discontinuation of captopril therapy.

The mean age of the 36 patients with cough (50.94 ± 11.20 years) was statistically non significant from that of the patients without cough (n=77, mean 53.58 ± 11.55 years) (p=>0.2). In relation to sex, cough appeared in 19 males and 17 females and the difference was not statistically significant (p = 0.807).

The mean dose of the 36 patients (61.80 ± 27.31 mg / day) with cough was statistically not significant from that of the patients without cough (63.31 ± 35.94 mg / day) (p > 0.4).

Concerning smoking, 4 patients in the patients group are smokers (no cough) and 7 individuals in the control group are smokers (1 with cough).

Table 1. Main Characteristics of Patients

No. patients		Sex	Age	Dose	Duration of treatment
Total 113 Male = 57 Female = 56	With cough (n=36)	Male = 19 Female= 17	Range = 30-75 years Mean± SD = 50.94±11.20 years	Range=25-100 mg/d Mean± SD = 61.8±27.31 mg/day	Range = 3 days to 3 years
	Without cough (n=77)	Male = 38 Female= 39	Range=28-75 years Mean± SD = 53.58±11.55 years	Range = 25-150 mg/day Mean ± SD = 63-31±35.94 mg/d	Range =1 month to 3 years

Discussion

Dry cough is one of the most common side effects of ACE inhibitors [11] which, on occasion, requires termination of therapy [12]. The reported prevalence of cough with ACE inhibitors therapy has varied from 0.2 to 25%, depending upon methods of data collection, analysis and symptom reporting [12], being higher in small studies and smaller in retrospective studies with large number of patients [13].

The prevalence of cough induced by captopril in Iraqi population of Mosul was 31.8 %, which approximates the Japanese figure of 38 % for enalapril [14], but relatively lower than that of Iraqi population in Basrah of 40.5 % [15] and that of Chinese figure of 46 % for captopril and 41.4 % for enalapril [12], but higher than that of Greek figure of 6.58 % [13].

The occurrence of cough in captopril used hypertensive of this study was not related significantly to age, sex, dose of captopril, duration of treatment nor to smoking status. These results were in agreement with the study of Jawad [15] which was done in Basrah, Iraq and found that neither the dose nor the duration of captopril treatment seemed to have an effect on the occurrence of cough but in contrast to our results, Jawad's study [15] found that female to male ratio was 2.08 in the coughed group compared to 1.08 in the control group.

Our results are also in agreement with the results reported by Lefebvre *et al*., [16] who showed that cough due to captopril was not statistically related to sex or age and with that reported by Woo and Nicholls [12] who stated that the complication of cough was not related significantly to age, sex, underlying disease, drug dosage nor to smoking status in captopril treated Chinese patients.

Our results are in contrast with those reported by Capella [17] who stated that cough represented 37% of the reports of side effects of captopril. There was a remarkable female predominance among patients with cough developed at very low doses (15 mg).

In this study in the majority of patients who developed cough, it was dry, irritating and appeared

at different intervals after starting captopril therapy, ranged from 3 days to 3 years and call for the discontinuation of therapy in 15 patients. Just [10] reported that a tickling, dry, not productive and persistent cough occurs during therapy with ACE inhibitors. Onset usually occurs during the first week of therapy and lasts as long as the drug is taken while Jawad [15] found that in the majority of patients, cough was dry and irritating. Only 3 patients described the cough as productive. In 57.5 % of patients, cough occurred within one month after starting captopril treatment, and in 90 %, the cough occurred within three months. The cough seemed to occur more at night.

The current study indicated that cough is a common side effect of treatment with captopril in Mosul hypertensive, although in most patients cessation of therapy is not required. The frequency of cough is not related to age, sex, and duration of treatment or dose of captopril.

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***Department of Pharmacology, College of Medicine, Mosul, Iraq**