

Frequency of Angiotensin Converting Enzyme Inhibitor (ACEI) Induced Cough

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ABSTRACT

The objective was to assess the frequency of ACE inhibitor induced cough in our patients. The study was prospective open labeled one centre, in and out patients of cardiology department Sheikh Zayed Hospital, Lahore 2011. 200 patients using six different types of ACEI were used. Preference was given to patients to whom ACEI were prescribed for the first time. Patients with chronic respiratory diseases were excluded. Patients were followed up on fortnightly basis for three months. On each visit besides recording their blood pressure, they were not specifically inquired about occurrence of any cough. Patients themselves came with the complaint of cough. The dry cough frequency with different ACEI was 17%, ranging from almost 20% with Enalapril, 16.6% with Captopril, 10% with Lisinopril and Ramipril, 15% with Quinapril and Perindopril. The dry cough was moderate in the majority of our patients and they were not willing to continue their ACEI, although their blood pressure was well controlled with it. They were switched over to other group of anti hypertensive drugs. Incidence was almost same in males and females. ACEI have a relatively high frequency of dry cough and our patients don't want to take it if cough occurs.

Keywords: ACE inhibitors, dry cough.

INTRODUCTION

Captopril was the first ACE inhibitor to be introduced in early 1980's. Now days there are more than fifteen ACE inhibitors to be used all over the world. They are being prescribed for hypertension, congestive heart failure, left ventricular dysfunction and post myocardial infarction and diabetic nephropathy¹. Cough due to ACE inhibitors was first noted and described in 1985 by Sesko and Kanehoy in Annals of Internal Medicine². Cough may develop as early as one Week after the start of ACE inhibitors. It mostly begins with tickling sensation in the back of the throat. The cough is dry, non-productive, and unresponsive to antitussive agents. It may also be paroxysmal and may be during day time and may be worst at night. Associated adverse effects on the quality of life attributed to cough have included sleep disruption, vomiting, sore throat, voice

changes³ and stress urinary incontinence among postmenopausal type II diabetics⁴. Cough in a patient with a normal chest X-ray usually falls into one of the five categories: drug-induced (especially by ACE inhibitors), secondary to postnasal discharge, gastro esophageal reflux, or hyperactive airway diseases, and idiopathic but responsive to nebulized lidocaine⁵. Initially post marketing surveys reported an incidence of ACE inhibitors cough to be as low as 1-12% but a review of literature by Zafar Israeli and Hall estimated the incidence to range from 0.7-48%⁶.

The objective of this study was to determine the risk of coughing as an adverse reaction to ACE inhibitors in every day circumstances in a sample of Pakistani population. Cough has emerged as a class effect occurring with all ACE inhibitors⁷ and differences in the chemical, pharmacokinetic, or pharmacodynamic properties of individual ACE inhibitor influenced the incidence, onset, and

severity of this adverse event.

MATERIAL AND METHOD

It was a prospective, one centre, open labeled study. Two hundred patients, attending Out-Patients Department and admitted in wards of the Department of Cardiology Sheikh Zayed Hospital (SZH) Lahore were included. Major indications for using ACE inhibitors by them were hypertension; post myocardial infarction, LV failure dysfunction etc. In this study all age groups (mean age 56 years) and both genders (67% male and 33% of females) were included (Fig. 1). While registering patients, preference was given to the patients to whom ACE inhibitor was prescribed for the first time. Patients with concomitant respiratory diseases like bronchial asthma, chronic obstructive airway diseases (COAD), pulmonary tuberculosis, respiratory neoplasm and CRF were excluded. Patients were followed up on fortnightly basis for three months. On each visit besides recording their blood pressure they were not specifically inquired about occurrence of any cough.

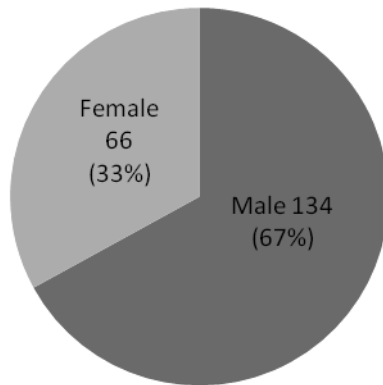


Fig. 1: Sex distribution.

RESULTS

A total of 200 patients were registered for the study. The ACE inhibitors used by these patients included Captopril (30 patients), Enalapril (100 patients), Lisinopril (10 patients), Ramipril (20 patients), Perindopril (20 patients) and Quinapril (20 patients) 134 were male patients and 66 were

females. Major indication for the use of ACE inhibitor was hypertension other indications included congestive heart failure, left ventricular dysfunction, acute myocardial infarction.

Reporting of cough on every fortnightly visit the percentage of cough with Captopril was 16.6%, Enalapril 20%, Perindopril and Quinapril 15% each, Lisinopril 10% and Ramipril 10% (Table 1). Overall incidence of dry cough was 17% with six different ACE inhibitors. In most cases the ACE inhibitors induced cough was moderate and was bothersome. All patients don't want to continue with ACEI.

Table 1: Percentage of cough in patients taking ACEI.

ACEI	No. of patients	No. Having cough	Cough (%)
Captopril	30	05	16.6
Enalapril	100	20	20
Lisinopril	10	01	10
Ramipril	20	02	10
Perindopril	20	03	15
Quinapril	20	03	15

DISCUSSION

Cough is one of the commonest symptoms of lung disease and is a frequent problem encountered in general practice as well as in hospital practice. Patient with a normal chest X-ray and complaining of cough usually falls in to one of the five categories: drug-induced (especially by ACE inhibitors and other drugs), secondary to postnasal discharge, gastroesophageal reflux, or hyperactive airway disease, and idiopathic but responsive to nebulized lidocaine⁵. Iatrogenic agents can induce an isolated cough, particularly ACE inhibitors, beta-blockers and inhaled agents that cause 75% of the reported cases of iatrogenic cough⁸. Physician has to keep in mind that bronchospasm, cough, or bronchiolitis of unknown origin, may have an iatrogenic cause. Accurate assessment of frequency of ACE inhibitor associated cough is particularly challenging. In the present study the cough incidence was measured at each visit by a self-administered symptom. The results of our study support the hypothesis that dry irritating cough is a class effect occurring with all ACE inhibitors. Our

results are quite comparable to other studies^{9,10,11}.

Three large studies are so important and worth to be mentioned. First one is the Clinical Altace Real-World Efficacy (CARE Study) compiled by Kaplan-NM⁹. This post marketing surveillance study was undertaken to confirm the efficacy and safety of the ACE inhibitor Ramipril and to extend the findings of controlled clinical trials into real-world conditions. A total of 11,100 patients with mild-to-moderate hypertension treated by primary care physicians were enrolled in this 8-week, open-label study. Ramipril was usually initiated at a dosage of 2.5mg once daily and titrated to achieve target blood pressure. Adverse events were generally mild; cough (3.0%) was the most frequent. If we compare the results of our study, we registered 20 patients using Ramipril. Our frequency of cough was 10% and all patients withdrew medication. Although compared to CARE study this incidence is quite high but they might have under estimated, because study was carried out just for 8 weeks and that too as a post marketing survey.

Second study is Staril study conducted by Edwards-C, Blowers-DA and Pover-GM¹⁰ Fosinopril national survey: a post-marketing surveillance study of Fosinopril (Staril) in general practice in the UK was a open, noncomparative study, involved 12,067 hypertensive patients assessed at baseline and after two and six months of treatment; 10,791 patients provided valuable data with 5.2 months average treatment. Adverse events were reported in 24% of patients, the most common being mild-to-moderate cough (6.05%).

The third one of the largest study was Perindopril post marketing surveillance: a 12-month study in 47,351 hypertensive patients of France¹¹. Aims of the study were to gain information on serious adverse events in a large number of patients exposed to Perindopril. Results were as under, withdrawals due to adverse events occurred in 6.1% of female and 3.2% of male patients. The reported incidence of cough was 11.3% in women and 7.8% in men, this being compatible with the best estimates of the true incidence of cough during ACE-inhibitor therapy. This is a model study in which a very large population participated and that too with a sufficient follow up period. So, its results should be given due value.

In our Study 20 patients were on Prindopril and 15% reported cough. In the above-mentioned study the incidence of cough is 11.3% and 7.8% for females and males respectively; which is relatively closer to our study. In this study they also observed that incidence of cough was more in females as compared to males, our study also showed same gender related difference.

CONCLUSION

ACE inhibitors are being used frequently and increasingly to treat hypertension and congestive heart failure and other conditions discussed as above. In general ACE inhibitors are extremely well tolerated and have a low incidence of adverse effects; a dry cough is the most common adverse effect. Overall incidence of ACE inhibitor induced cough in our study was 17% but ranging from 20% with Enalapril and 10% with Lisinopril. In other words we can say that 1.7 out of 10 patients using ACE inhibitor complained of cough, almost all of them were not tolerating it well and almost every patients withdrew medication. In our studies although the patients had moderate cough but all of them could not tolerate and therefore we have to withdraw ACEI as per request of the patients and we have to switch over to other medication for hypertension. We should not impose the patients to continue ACEI because other alternative drugs are available for hypertension and for other medical conditions in which we usually prescribe ACEI.

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