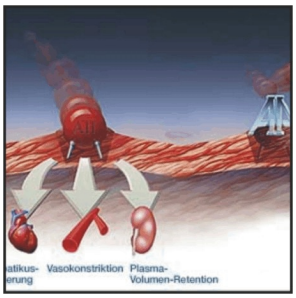
ORIGINAL PROF-924

INCIDENCE OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR INDUCED COUGH



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ABSTRACT... dramir2005@hotmail.com **Objective:** The objective of our study was to assess the incidence of ACE inhibitor induced cough in our population. **Study Design:** Mainly prospective, multicenter, open labeled study of 500 patients. **Setting:** Department of Medicine of Combined Military Hospital (CMH) Lahore and PNS SHIFA (Naval Hospital) Karachi. Period February 2000 to February 2001. **Material and Method:** 500 Patients using eight different types of ACE inhibitors were selected and an especially designed Performa was completed. In this study preference was given to patients to whom ACE inhibitors were prescribed for the first time. Patients with concomitant respiratory diseases like chronic bronchitis, chronic obstructive airway disease and pulmonary tuberculosis were excluded. Patients were followed up on fortnightly basis for six to eight months. On each visit besides recording their blood pressure they were specifically inquired about occurrence of any cough. They were also requested to complete the cough questionnaire. **Results:** A dry cough incidence with different ACE inhibitors was 12.8%, ranging from 6.8% with Captopril to 17.3% with Enalapril. The dry cough was mild in the majority of our patients and they were willing to continue their ACE inhibitor, because their blood pressure was well controlled with it. Only a small percentage 3.6% discontinued ACE inhibitor due to severe bothersome, irritating cough. They switched over to other group of antihypertensives mostly Angiotensin II antagonists. Incidence of cough was slightly more in females (14.3%) as compared to males (12.0%). **Conclusion:** Although ACE inhibitors have a low incidence of adverse effects, a dry cough was class effect occurring with all ACE inhibitors.

INTRODUCTION

In the early 1980's the first ACE inhibitor Captopril was introduced .Now there are more than fifteen ACE inhibitors. They are being prescribed widely for hypertension, congestive heart failure, ventricular dysfunction and post myocardial infarction and diabetic nephropathy[1]. ACE inhibitors induced cough was first described in 1985 by Sesko & Kanehoy in Annals of Internal Medicine[2]. 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 worst at night. Associated adverse effects on the quality of life

attributed to cough have included sleep disruption, vomiting, sore throat, voice changes[3] and stress urinary incontinence among postmenopausal type II diabetics[4]. Refractory cough in a patient with a normal chest X-ray usually falls into one of five categories: drug-induced (especially by ACE inhibitors), secondary to postnasal discharge, gastroesophageal reflux, or hyperactive airway disease, and idiopathic but responsive to nebulized lidocaine[5]. Initially post marketing surveys reported an incidence of ACE inhibitors cough to be as low as 0% to12% but a review of literature by Zafar Israeli & Hall estimated the incidence to range from 0.7%to 48%[6].

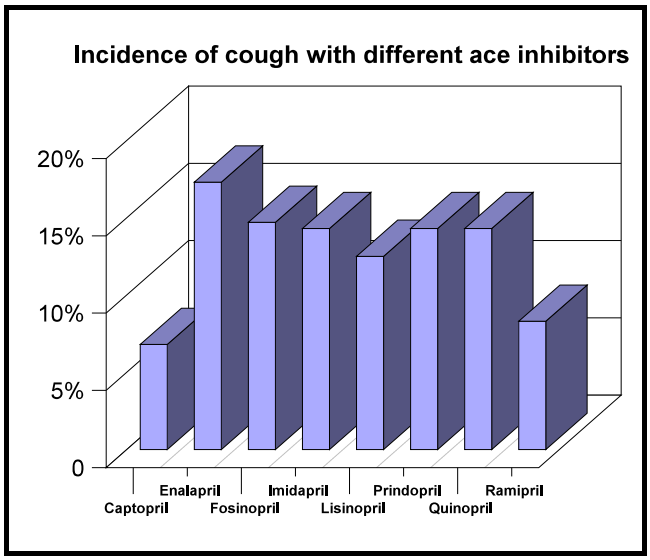
The objective of this study was to determine the risk of coughing as an adverse reaction to ACE inhibitors in every day circumstances in a sample of Pakistani population. Cough has emerged as a class effect occurring with all ACE inhibitors[7] and differences in the chemical, pharmacokinetic or pharmacodynamic properties of individual ACE inhibitor influenced the incidence, onset and severity of this adverse event. A comparison of cough profile of different ACE inhibitors was carried out.

MATERIAL AND METHOD

Mainly prospective, multicenter, open labeled study. Five hundred patients, attending out patients department (OPD) and admitted in wards of the Department of Medicine of Combined Military Hospital (CMH) Lahore and PNS SHIFA (Naval Hospital) Karachi were registered for the study from February 2000 to February 2001. Major indications for using ACE inhibitors by them were hypertension, post myocardial infarction and diabetic nephropathy etc. In this study all age groups (mean age 56 years) and both sexes (33% of females) were included. While registering patients, preference was given to the patients to whom ACE inhibitor was prescribed for the first time. Patients with concomitant respiratory disease like bronchial asthma, chronic obstructive airway disease (COAD), Pulmonary tuberculosis and respiratory neoplasm were excluded. ACE inhibitors were selected and an especially designed Performa was completed. Patients were followed up on fortnightly basis for six to eight months. On each visit besides recording their blood pressure they were specifically inquired about occurrence of any cough. They were also requested to complete the cough questionnaire.

RESULTS

A total of 500 patients were registered for the study. The ACE inhibitors used by these patients included captopril (132 patients), enalapril (167 patients), fosinopril (34 patients), lisinopril (40 patients), perindopril (35 patients), ramipril (36 patients) and imidapril and quinapril (28 patients each). 333 were male patients and 167 were females. Major indication for the use of ACE inhibitor was hypertension (n=340) other indications included congestive heart failure, early ventricular dysfunction, left ventricular hypertrophy, early stage acute myocardial infarction and diabetic nephropathy.



Cough Profile Based on questionnaires and spontaneous reporting of cough on every fortnightly visit the percentage of cough with captopril was 6.8%, enalapril 17.3%, fosinopril 14.7%, imidapril, perindopril and quinapril 14.3%, lisinopril 12.5% and ramipril 8.3%. Overall incidence of dry cough was 12.8% with eight different ACE inhibitors.

In most cases the ACE inhibitors induced cough was

mild and cough was not bothersome. However in small percentage of patients the cough was moderate to severe and was troublesome enough to lead them to withdrawal of ACE inhibitors. A total of 18 patients withdrew their ACE inhibitor, which is 3.6% of total patients. Largest withdrawal was with lisinopril 2 out of 40 (5%) patients and 7 out of 167 (4.2%) patients using enalapril. Just a single patient using ramipril (1 out of 36, 2.7%) withdrew treatment.

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. Refractory cough in a patient with a normal chest X-ray usually falls in to one of five categories: drug-induced (especially by ACE inhibitors), secondary to postnasal discharge, gastroesophageal reflux, or hyperactive airway disease, and idiopathic but responsive to nebulized lidocaine[5]. Iatrogenic agents can induce an isolated cough, particularly ACE inhibitors, beta-blockers and inhaled agents that cause 75% of the reported cases of iatrogenic cough[8]. The 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 symptoms assessment questionnaire. The questionnaire for our study was adapted from questionnaires previously validated in antitussive and mucolytic studies. These self-administered symptoms assessment questionnaires provided an accurate measure of the cough profile associated with different ACE inhibitors.

The results of our study add to a growing body of data in support of the hypothesis that dry irritating cough is a class effect occurring with all ACE inhibitors. Our results are quite comparable to one study carried out in a large military medical center of USA. The study was carried out by Wirebaugh-SR et al of Wilford Hall Medical Center, Lackland Air Force Base USA[9]. The medical charts of 227 patients for whom lisinopril was prescribed from June 1991 to June 1992 were reviewed for appropriateness of prescribing and occurrence of any adverse drug reactions. The most common adverse drug reactions detected were cough (7%). In our study 40 patients were on lisinopril, 5 patients (12.5%) reported of cough and 2 patients (5%) withdrew lisinopril.

Three large population based studies are worth mentioning. First one is the Clinical Altace Real-World Efficacy (CARE Study) compiled by Kaplan-NM[10]. The 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 2.5 mg 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 36 patients using ramipril. Incidence of cough was 8.3%and just 1 patient 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-GM[11] Fosinopril national survey: a post-marketing surveillance study of fosinopril (Staril) in general practice in the UK was a open, non-comparative 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%). In our study 34 patients used fosinopril, 14.7% patients reported of dry irritating cough. Here also the incidence is more than that of STARIL study, but withdrawal rate is just 2.9%, which means that in most cases the cough was mild and not troublesome.

The third one of the largest study was Perindopril post marketing surveillance: a 12-month study in 47,351

hypertensive patients of France[12]. 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 5 out of 35(14.3%) patients complained of cough. In the above-mentioned study the incidence of cough is 11.3% &7.8 % for females &males respectively; which is close 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. In one study conducted by Seedat et al in India[13], among 50 Indian patients using perindopril, 42 %(n=21) complained of cough during a 1 – year comparison trial against atenolol (cough noted in 14%). Onset ranged from 1 day to 10 months, with drug withdrawal in 4.

The incidence of drug-related cough was significantly higher with enalapril (18%) than with irbesartan (0%) in a comparative trial conducted by Chiou-KR et al[14] in 116 Taiwanese patients, which is quite close to our study (enalapril induced cough in 17.3% patients).

CONCLUSION

ACE inhibitors are being used increasingly to treat hypertension and congestive heart failure. 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 12.8%. In other words we can say that 1 out of 8 patients using ACE inhibitor complained of cough, most of them tolerating it well and just one fourth of effected patients, accounting very small percentage (3.6%) of total withdrew medications. Cough as a side effect of ACE inhibitor therapy may be tolerated well as compared to more serious adverse effects of alternate and often previously tried antihypertensive therapies. So if the cough is mild and not bothersome, patient may be advised to continue the ACE inhibitors and they should not be switched over to angiotensin receptor antagonists because ACE inhibitors are widely available and are cost effective as compared to angiotensin receptor antagonists. Contrary to the aforementioned if the clinician is unable to recognize that the cough may be related to ACE inhibitor therapy, the patient may be subjected to extensive and unnecessary evaluations, diagnostic tests, and consultations. Empiric treatment of the cough with antitussive agents, bronchodilators, or antibiotics may also add to the cost. A short-term trial of withdrawal of ACE inhibitor or substitution of a different type of antihypertensive agent is an inexpensive, easy way to determine if the ACE inhibitor is the cause of cough.

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When I look into the future; it is so bright, it burns my eyes.

Oprah Vinfrey