



## ACE INHIBITORS; COMPARISON OF ACE INHIBITORS (PERINDOPRIL, RAMIPRIL & LISINOPRIL) INDUCED COUGH.

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**ABSTRACT:** Persistent dry cough is commonest undesirable effect of the angiotensin converting enzyme inhibitors. The mechanism of cough due to ACE inhibitors is uncertain, but most likely is due to the cough mediators as substance P agents & bradykinin which are degraded by ACE inhibitors. **Objective:** To compare the incidence of cough in hypertensives which were prescribed lisinopril, perindopril & ramipril. **Study Design:** Mainly cross sectional prospective multicenter, open labeled study of 100 patients. **Place & Duration of Study:** Department of Medicine of University Medical Diagnostic Centre & District Head Quarter Hospital Sargodha, period January 2016 to June 2016. **Methodology:** 100 Patients using three types of ACE inhibitors were selected and an especially designed performa was completed. In our study we gave preference to those patients who were prescribed ACE inhibitors for the first time. The patients were instructed (at the baseline visit) to inform during the succeeding visit about the onset of any adverse drug reactions like cough, hypotension, headache, dizziness, fatigue, nausea, angioedema. Patients were not informed that incidence of cough was the main seek of the study, so there was no chance for Hawthorne effect. **Results:** The incidence of ACE inhibitor induced cough has been reported to as: perindopril was 5.4 %, ramipril 6.89 % & lisinopril 8.82 %. Overall incidence of dry cough was 7.0 % with three different ACE inhibitors. The onset of cough after taking ACE inhibitors ranges from within days of the first dose to months after starting the therapy. Cough usually resolves within 1 to 4 weeks after the cessation of treatment. **Conclusion:** Chronic dry cough is a general consequence of angiotensin converting enzyme inhibitors. The cough is also associated with irritating & tickling sensations in throat.

**Key words:** Comparison. ACE inhibitors. Cough.

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### INTRODUCTION

The first angiotensin converting enzyme inhibitor was introduced in 1981. In treatment of different diseases affecting the quality of life (congestive cardiac failure, hypertension, ventricular dysfunction, acute coronary syndrome and diabetic nephropathy), ACE inhibitors have brought an innovative change and their affectivity in endothelial problems have also been proved. In patients having co morbidities like hypertension with diabetes, the use of ACE inhibitors prevent the worsening of renal activity and reduces albuminuria.<sup>1</sup>

ACE inhibitors act as vasodilators and reduce peripheral vascular resistance to treat hypertension.<sup>2</sup> These anti hypertensive's in combination with diuretics and digoxin have

proved their efficacy in treating complicated situations such as CCF in diabetics with hypertension patients.<sup>3</sup> In 1985 Sesko & Kanehoy first described ACE inhibitors induced cough in Annals Internal Medicine.<sup>4</sup> Even as the benefits of ACE inhibitors are documented, coughing is their commonest side effect, occasionally entailing cessation of therapy.<sup>5</sup> Cough can start even within a week of starting the medication.<sup>6</sup> Other side effects which influence the quality of life due to cough have included sore throat, vomiting, voice changes, sleep disturbance and urinary stress incontinence in type II diabetics.<sup>7</sup> According to post marketing surveys which were carried out in 1980s, the incidence of ACE inhibitors induced cough was 0% to 12% but Zafar Israeli & Hall reviewed the literature & reported the incidence to range from 0.7% to 48% in their medical trials.<sup>8</sup>

The study purpose was to conclude that cough is troublesome effect of ACE inhibitors in Pakistani population. Three different ACE inhibitors were used and a comparison of induced cough was done.

## METHODOLOGY

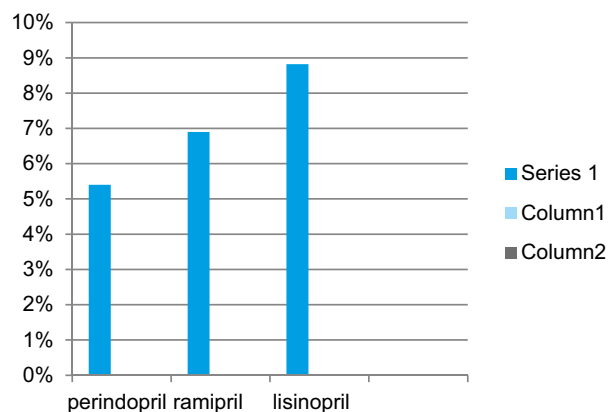
Study was conducted on 100 well oriented & cooperative hypertensive patients (age 20-75 years) presented in outpatient department (OPD) and admitted in teaching Medical unit of DHQ Hospital Sargodha. Patients having respiratory illnesses like asthma, COPD, pulmonary Koch's, allergic bronchopulmonary aspergilosis, intrinsic lung disease (CFA), bronchiectasis and lung malignancy while seriously ill patients were excluded from the study.

Every eligible patient was assessed for the competency of the diagnosis of hypertension as described below. The qualifying patients were assessed for cough due to prescribed ACE inhibitors. The qualifying hypertensives were asked to present again on specified dates for the assessment of adverse effects. Diagnostic criteria for hypertension was.

Category	Systolic BP(mmHg)	Diastolic BP (mmHg)
Optimal	Less than 120	Less than 80
Normal	below 130	Less than 85
Pre hypertension	131-139	85-89
Hypertension Stage 1	140-159	90-99
Stage 2	160-179	100-109
Stage 3	More than 180	More than 110

## RESULTS

To conduct this study the number of enrolled patients was 100. Three different ACE inhibitors were prescribed to them included ramipril (29), lisinopril (34) and perindopril in (37 patients). Among these 57% were males and 43% were female patients. Main indication for ACE inhibitors use was high blood pressure, Other indications included diabetic nephropathy, congestive cardiac failure, LVH, acute myocardial infarction and ventricular dysfunction



On basis of evaluation perform the cough incidence with perindopri was 5.4 %, ramipril 6.89 % and lisinoprii 8.82 %. In general the dry cough occurrence was 7 % due to these blood pressure lowering agents. Percentage of cough was 9.4% in females and 6.6 % in males. In most patients cough due to ACE inhibitors was meek and not incommodious. While cough was so troublesome in some patients that it lead to cessation of therapy.

## DISCUSSION

ACE inhibitors are useful as solitary drug therapy for many patients with hypertension, hypertensive & diabetic nephropathy. There had been contradictory results on the efficacy of ACE inhibitors monotherapy in controlling blood pressure among patients; it was ineffective as sole drug in some studies, others found it effective for mild to moderate hypertension & even in severe & resistant hypertension.<sup>9</sup> In this study blood pressure of every patient was controlled & maintained by ACE inhibitors. This efficiency is resulting from the inhibition of angiotensin converting enzyme.<sup>10</sup> The text is full of articles regarding angotensin converting enzyme inhibitors induced cough and range of its frequency is 5% - 35%, on the whole the literature favours the fact that females are more prone to ACE inhibitors related cough as compare to males. The cough is in fact not dose related, as small or high doses can lead to similar problems.<sup>8,11</sup>

Cough is usually troublesome, dry and without wheez, starting in early stage of treatment and may be delayed to months after the commencement

of treatment. Generally cough resolves within a week after termination of medication, but it may persist for as 4-5 weeks.<sup>6,12</sup>

During current clinical trial a self-administered complaint evaluation survey was carried out at every visit to calculate the cough incidence. The evaluation Performa for this study was tailored from assessment questionnaires of previous mucolytic and antitussive surveys. Estimation of symptoms occurring in these hypertensive patients gave a precise gauge of ACE inhibitors related cough.

Outcome of this study sustain the premise that arid grating cough is a well-known effect caused by ACE inhibitors. These results are relatively analogous to one study conducted in Ireland by Brugett's-JJ & Arima-H in which patients were clinically judged for perindopril induced cough by using multivariate logistic regression analysis. Randomized clinical trials were done in 27,492 patients and analysis of results revealed a low incidence of cough (about 4%). This type of cough has strong association with advanced age, female gender & simultaneous use of statins. However, cough incidence was not related to ethnic differences.<sup>13</sup>

Regarding ramipril our study results also resemble with one study conducted by Katarzyna Wyskida & Edyta jura – Szoltys in 2010. In this study the enrolled number of patients taking ramipril was 10,380. Among these 50.8% were males and 49.2% females. A total of 869 patients (8.3%) presented with the complain of dry cough in their routine visits and it occurred usually  $14 \pm 8$  days (from 1 to 8 weeks) following ramipril therapy.<sup>14</sup>

One big population based study done by Kaplan-NM is the CARE study. The aim of study was to verify the security and effectiveness of ramipril and to get the outcomes of clinical trials. The initial dose of ramipril was 2.5mg once daily and was titrated to gain normal blood oressure. In this study huge number (11,100) of American hypertensive patients were assessed for ramipril induced adverse effects and during 8 weeks of

observational time period the dry cough was reported only in 3.0% of patients. To evaluate our results, we selected 29 patients taking ramipril, the percentage of cough Incidence was 6.89 % which was relatively high as compare to CARE study. The results were not comparable and this incidence of CARE study might have underestimated due to short time span of only few weeks.<sup>15</sup>

Our results regarding Lisinopril also are comparable to one study which showed a high rate of withdrawal of ACE inhibitor therapy due to raised incidence of cough among black as compare to nonblack patients (9.5% : 2.3%). Lisinopril induced undesirable effects were noted as, cough most frequent (1.5 % - 10%), raised level of creatinine (7%) and rihinitis (up to 1%). Other very unusual effects were eosinophilic pulmonary disease, bronchospasm, rhino sinusitis and fibrosing alveolitis.<sup>16</sup>

The outcomes of our study support the hypothesis that all ACE inhibitors can cause dry annoying and troublesome cough.

## CONCLUSION

ACE inhibitors should be considered as entirely or partly causative, In a patient with persistent cough. Patients suffering from congestive cardiac failure, diabetic nephropathy and hypertension are being treated with ACE inhibitors which usually have a low incidence of adverse effects and are exceedingly well tolerated.

On the whole frequency of cough due to ACE inhibitors was 8% in this study which is a bothersome consequence of these medicines but it is tolerable as compare to those serious side effects which occur with other alternative anti hypertensive agents. Therefore if the cough is not inconvenient then the use of ACE inhibitors may be carried on. So it is very important for treating physician to diagnose if it is ACE inhibitor induced cough otherwise patient may be considered to undergo expensive and needless assessments, investigations and consultations. The subsequent use of antibacterials, bronchodilators,


theophylline, anticholinergics and cough suppressants may add the cost of treatment. So the end of therapy is the only evenly effective cure for cough due to ACE inhibitors.

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## AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Amar Nazir	Writing, References	
2	Dr. Fida Muhammad Sheikh	Tables formeting	
3	Dr. Shahzad Aslam	Data analysis	
4	Dr. Uzma Javaid	Introduction	