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RESEARCH ARTICLE

FREQUENCY OF ANGIOTENSINE- CONVERTING ENZYME INHIBITORS INDUCED COUGH IN IRAQI PATIENTS

***Atta Gitti Allawi**

Senior Consultant Physician and Cardiologist, Wasit University, College of Medicine, Iraq

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ABSTRACT

Background: Angiotensine converting enzyme inhibitors (ACE-I) are commonly used drugs for treatment of hypertension and heart failure. Cough is most common side effect occurring in 0.7-35% according to various reports.
Objective: To estimate the incidence of ACE-I induced cough in IRAQI patients.
Method: 2800 Iraqi patients using different ACE-I drugs (captopril, Enalpril, Lisinipril and Ramipril) visiting hypertension and Out-patient –Clinic at ALKARAMA and AL-ZAHRA teaching hospitals at Wasit Governorate / IRAQ, these patients were interviewed for cough related to ACE-I use , patients having cough were underwent investigations to other causes of cough and re-evaluated 4-weeks after changing their medication.
Result: 925 patients have ACE-I induced cough (502 (54.27%) females Vs. 423(45.72%) males) so cough occur in 33% of total patients, more common in females , it occur most frequently with Enalipril users (44.75%) and least in Captopril group (25%).
Conclusion: ACE-I induced cough is common and underestimated problem in Iraq , genetics and environmental factors are playing important role in the determination of difference incidence around the world.

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INTRODUCTION

Angiotensine converting enzyme inhibitors (ACE-I) are commonly used drugs for treatment of hypertension and heart failure. It interferes with Renin Angiotensin System RAS), by inhibiting the enzyme that is responsible for the conversion of angiotensine I to angiotensine II ,however because ACE-I also inhibit Kinnase II this may lead to up regulate of Bradykinine which is playing a major role in cough production. (Longo *et al*., 2012) Cough is the most common side effect of ACE-I (Gabriel Khan, 2007; Ausillo, 2008), other side effects like skin rash, proteinuria, abnormal taste ,neutropenia and angioedema are rare. Cough occur in 0.7 — 35% of patients treated by ACE-I according to various reports from different countries. The cough is usually dried, irritant, bothering, and more troublesome at night. Women, black or Asian ethnicity have been reported to be at increasing risk of ACE-I induce cough (Ausillo, 2008; Mark, 2004) it may occur not necessarily shortly after starting of treatment but may occur months or even a year later. (Overlack, 1996)

****Corresponding author: Atta Gitti Allawi,***
Senior Consultant Physician and Cardiologist, Wasit University, College of Medicine, Iraq.

The mechanism of ACE-I induced cough is unrelated to inhibition of RAS because treatment with ARBs and renin inhibitor has not cause cough ,it is probably due to suppression of Kininas II activity which lead to accumulation of Kinins (like bradykinin and tachykinin) which stimulate vagal afferent nerve fibers. (Fox *et al*., 1996), Substance P, and prostaglandin (Overlack, 1996; Dicpinigaitis, 2006; Israili *et al*., 1992; Peter, 2006). The cough is not dose dependent (Dicpinigaitis, 2006), replacement by other ACE-I should not be tried, since the cough will almost recurs with re-introduction of same or other ACE—I (Overlack, 1996; Szmidt *et al*., 1999), however in special circumstances where ACE-I is mandatory we can use some agents to attenuate the cough induced by ACE-I inhibitors like inhaled sodium cromoglycate (Hargreaves and Benson, 1995) theophyline Cazolla *et al*., 1993, Sulnidac (McEwan *et al*., 1990), thromoxane receptor antagonist picotamide (Malini *et al*., 1997), indomethacine 15 Calcium Channel Blockers (Amlodipin or Nifedipine) 15, ferrous sulphate 16, Aspirin 17 and Baclofen 18. angioedema occur in 0.1—0.2% of patients receiving ACE-I the onset usually occur within hours or at most one week after starting of ACE –I. 8

Patients and method

We enrolled randomly 2800 (1424 female Vs. 1376 male) hypertensive patients on ACE inhibitors (Captopril, Lisinipril, Enalipril and Ramipril) consulted hypertension Unit or Out-patient Clinic at AL-ZAHRA and AL-KARAMA teaching hospitals in addition to our private Clinic at Wassit governorate/ Iraq during the period from January 2012 to February 2016,these patients from Wasit Governorate or different surrounding governorates. The age of these patients ranging from 22years to 86 years (mean 54). The enrolled patients were 715 on captopril therapy (311 female Vs. 404 male),, 1015 patients on lisinipril (480 female Vs. 535 male),,773 patients on enalipril (458 female Vs. 315 male) and 297 patients on Ramipril (175 female Vs. 122 male). (Table 1.)

Table 1. Distribution of patients according to gender and type of ACEI

drug	Total number	female	male	%
captopril	715	311	404	25.54
lisinipril	1015	480	535	36.25
enalipril	773	458	315	27.60
ramipril	297	175	122	10.60
total	2800	1424	1376	100%

These patients were interview and evaluated for having cough for more than one month after using ACE inhibitors, all later group investigated by Chest X-ray and ECG, while Echocardiography and pulmonary function test were done in appropriate patients according to the individual case to exclude heart failure, bronchial asthma, COPD or other lung diseases can causing cough. In all these patients we changes their medication from ACEI to angiotesine receptor blockers(ARBs) and to be re-evaluated 4 weeks later.

Patients that fulfill all the following criteria were consider to have cough induced by ACEI and including in our study.

1. Cough of more than one month.
2. Normal Chest –x-ray
3. No evidence of bronchial asthma, COPD, or cardiac failure (clinically or by investigations).
4. Disappearance or significant improvement after discontinuation of offending drug.

RESULTS

Of 2800 patients enrolled in the study ,we found 936 patients having cough suppose to be due to ACE—I, after 4- weeks of stopping their therapy and using alternative therapy ,we received only 925 patients, while 11 patients became out of the study due to loss of contact with them due to various causes. Those 925 (502 female vs. 423 male) in whom the cough was disappear or significantly improved after changing their therapy consider to have ACE—I induced cough ,so the frequency of cough induced by ACE-I in our study is 33% (or even higher if escaped patients were involved in the study), this result is compatible with various similar published studies (ranging from 0.7 to 35% in various papers),however it is in the higher side of the range. The highest prevalence according to available published literatures is among Chinese according to Woo KS, *et al* study in which they found 46% of Chinese patients on ACE-I having cough 19, while it is 29.2% in Indian patients according to Singh *et al*., 20. And frequency of 30.4% in Singapore according to Ng LP, *et al* report 21. Frequency of 27% in Nigeria according to Adiquine, *et al*. 22. Efstratopoulos, *et al*. reported the frequency of 6.58% in Greek [23], while most western medical text books mention the range of 10-15 %. 1,3 The women have higher incidence than men (502 female 54.27% Vs. 423 male 45.72%) ,table 2.,this result is compatible with most published papers like (Mark, Israili, Singh, Adigun, Efstrat Semple, Yesil) (Mark, 2004; Israili *et al*., 1992; Sing *et al*., 1998; Adigun *et al*., 2001; Efstratopoulos *et al*., 1993; Semple, 1995; Yesil *et al*., 1994) while disagreed by other studies - Woo. KS *et al*, (Wood, *et al*., 19, 26)-in which they found no sex difference.

Table 2. Gender distribution of cough in various individual drug of ACE-I

drug	Total number	female	male
captopril	179	107	72
lisinipril	317	188	129
enalpril	315	152	163
ramipril	114	55	59
	925	502 (54.27%)	423 (45.72%)

There is different drug incidence within the group of ACE-I in our study, with highest result in Enalipril group (40.75%)and lowest incidence in Captopril group (25%),this result is agreed by Singh NP, *et al* , Yesil .S *et al* 20,25 but it is disagreed by Overlack A. and Wood R 5,26

Tables 3,4,5,6, Show the frequency of cough in Captopril, Lisinipril, Enalipril and Ramipril respectively

drug	Total number enrolled	Total number having cough	female	male	%
captopril	715	179	107	72	25

drug	Total number enrolled	Total number having cough	female	male	%
lisinipril	1015	317	188	129	31.23

drug	Total number enrolled	Total number having cough	female	male	%
enalipril	773	315	152	163	40.75

drug	Total number enrolled	Total number having cough	female	male	%
ramipril	297	114	55	59	38.38

DISCUSSION

In our study we found ACE-I induce cough is common in Iraqi patients and it is more than average or in upper range of published papers, this can be due to both genetics and environmental factors. Genetic cause could be due to genetic variation in metabolism of ACE-I , this can explain the high incidence of ACE-I induced cough in Asian patients (China, Singapore and India) and to lesser extend in Africans

patients (Nigeria) in comparison with the relatively low frequency of ACE-I induced cough in Caucasians (European and other Western countries),this supported by study done by Tseng DS, *et al*[27] in which they found the high incidence of ACE-I induced cough in Chinese - Americans sharing the same environment. The high prevalence of ACE-I induced cough among black patients clearly rise the possibility of interracial and ethnical differences and consequently the significance of genetic factor. On the other hand the role of environmental factor supported by many facts like the clear difference in the incidence of ACE-I induced cough between Western and East countries, which have difference Climate, air pollutions, habits and other environmental factors so it is more common in Asian patients than Europeans patients. Environmental factors also supported by the observation that most of our patients having cough due to ACE-I feel dramatic improvement in their symptom when travel for few weeks trip to Europe. The more frequent occurrence of ACE-I cough in women is difficult to explained, it could be due by gender variation in ACE-I metabolism and this need further studies. The clear difference in cough incidence between various drugs within ACE-I group can be explained by individual drug metabolism and pharmacological property.

Conclusion

Cough induced by ACE-I is common problem in Iraqi patients, it occur in 33% of patients using ACE-I, it is more common in females , and there is individual drug variation within ACE-I group with highest incidence in patients using Enalpril and lowest in patients using Captopril.

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