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ANGIOTENSIN CONVERTING ENZYME- INHIBITORS ASSOCIATED COUGH: A PROSPECTIVE EVALUATION IN HYPERTENSIVES

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Keywords: Prevalence, cough, ACE-inhibitor, hypertension

Abstract

Background/Objective: To determine the prevalence of ACE-Is induced cough among Nigerian hypertensives and evaluate any association with patients' age or sex.

Methods: A prospective case-control study.One hundred and sixty-eight hypertensive patients on angiotensin converting enzyme-inhibitors (ACE-Is; captopril and lisinopril) were matched in age and sex with controls that were on anti-hypertensives that excluded ACE-Is (nifedipine, aldomet and moduretic). Both groups of patients were followed up on either drug as a monotherapy over an average of 9 months.

Results: The prevalence of ACE-Is induced cough was 20.2%, while that of the alternative group was 0.6%. There was a significant statistical difference between ACE-Is and the alternatives medications-induced cough: OR=42.37(95%CI; 6.11-843.32), P< 0.0001.There was however, no significant statistical difference between captopril and lisinopril-induced cough, OR=1.30 (95%CI;0. 6-2.81), P value=0.587 and no significant age or sex differences were observed in the occurrence of cough; OR=0.97 (95%CI; 0.52-1.81), P value= 0.95 and OR=0.79(95%CI; 0.27-2.28), P value=0.808 respectively.

Conclusion: Cough complicating ACE-Is therapy is not uncommon; however, it has no link with the patients' age or sex.

Mots-clés : Prédominance, toux, ACE -inhibiteur, hypertension

Résumé

Fond/Objectif : Pour déterminer la prédominance de la toux induite de ACE-Is parmi des hypertensifs nigérians et évaluer n'importe quelle association avec l'âge ou le sexe des malades.

La méthode : une étude éventuelle de cas commande.cent et soixante-huit de malades hypertensifssur inhibiteurs de l'enzyme de conversion de l'angiotensine (ACE-Is : captopril et lisinopril) ont été égalé en l'âge et en sexe avec les contrôles qui étaient sur anti-hypertensifs excluant l'ACE-Is (nifédipine, aldomet et modulatoire). Les deux groupes de malades ont été observés sur la drogue comme une monothérapie par-dessus une moyenne de 9 mois.

Résultats : la prédominance de la toux induite d'ACE-Is était 20,2 %, pendant que celle du groupe alternatif était 0,6 %. Il y avait une différence statistique significative entre l'ACE-Is et la toux induite médications alternatives : OR=42.37 (95%CI; 6.11-843.32), P <0.0001. Il y avait pourtant, aucune différence statistique significative entre captopril et la toux induite lisinopril, OR=1.30 (95%CI; 0. 6-2.81), P valeur=0,587 et aucun âge significatif ou différences sexuelles n'a été observé dans l'occurrence de toux; OR=0.97 (95%CI; 0.52-1.81), P valeur = 0.95 et OR=0.79 (95%CI; 0.27-2.28), P valeur=0.808 respectivement.

La conclusion : la Toux compliquant de la thérapie d'ACE-Is n'est pas rare ; cependant, il n'a pas de lien avec l'âge ou le sexe des malades.

Introduction

Angiontensin converting enzyme inhibitors (ACE-Is) are anti-hypertensive agents that reduce peripheral resistance by acting as vasodilators.[1] They have beneficial effects on left ventricular dysfunction, and they reduce proteinuria associated with kidney disease.[2] Therefore they are prescribed in the management of systemic hypertension, heart failure, myocardial infarction and diabetic nephropathy.[3] However, ACE-Is have cough as one of its drawbacks. This has been described as dry and irritating[4] cough that could be paroxysmal or persistent in nature.[5] It has been reported in patients receiving captopril,[6] enalapril,[7] lisinopril,[8] ramipril[9] and cilazapril.[10] The incidence of this cough varied widely, depending, probably on the method of each study. It ranged from as low as 0.2 –18.6 %[6,7,11] in some reports to as high as 20- 41.8% in others.[5,8,10] Some of these studies also reported female preponderance[7,8] while some found it to be commoner in the older ones[12,13]and some reported racial predilection.[13,14] Others did not find any association with the patients' age or sex.[14-16] We are therefore set to determine the prevalence of ACE-Is induced cough in some of our hypertensive patients, and to know if there is any link with the patients' age or sex.

Materials and Method

Consecutive patients with systemic hypertension were recruited from the clinics over a two and half year period. Each of them was randomized into ACE-I or alternative group by a blind slot after seeking and obtaining their informed consent. The two groups were matched in age (within ±5years age range) [17 and] sex. Each patient was informed of the possibility of a dry cough developing during the course of drug therapy. The medication was to be discontinued if the cough disturbs the patient's routine chores or prevented sleep. The types of ACE-Is and the alternatives used in each group after randomization was determined by cost and local availability. The alternative was medication other than ACE-Is, either of which (ACE-I or the alternative) was used as monotherapy. At each clinic visit each patient was questioned about dry cough and time of it onset. Patients' biodata, type and dosage of ACE-I or alternative prescribed were recorded in questionnaires. Hypertensive patients with condition that can cause cough such as heart failure, respiratory tract infection, COPD or asthma were excluded. Systemic hypertension was defined as a systolic blood pressure of greater than 140mmHg and/ or a diastolic blood pressure of greater than 90mmHg measured twice at two separate clinic visits.[18]

The frequencies and percentages of all the variables were generated. The mean and standard deviation (SD) were determined by analysis of variance (ANOVA). Test of significance was conducted by chi- square technique among; (1) intergroup (captopril and lisinopril). (2) ACE-I and the alternative.

Results

One hundred and sixty-eight patients (89 males and 79 females) aged 31- 73years (mean of 45±22.9 years) were on ACE-Is. Table 1. Ninety-two (54.8%) were on captopril 12.5mg-50mg/day, while 76 (45.2%) were on lisinopril 5mg-20mg/day. Table II. The age range of patients in the alternative group was 35-78 years with a mean of 47.36±7.4years. Fifty-eight (35%) of them were on nifedipine 20-60mg/day, 43(25%) on aldomet 500mg-1500mg/day and 67(40%) were on moduretic 1 tablet/ day. Table 2. Duration of patients' follow-up in the clinics ranged from 5.7months to 17.3months with an average of about 9 months. Thirty-four (20.2%) patients on ACE-Is; 19(11.3%) on captopril and 15(9%) on lisinopril, developed a dry cough, while a female patient (0.6%) on aldomet reported a spontaneous cough. Table 1. The time of onset of this cough ranged from 5-180days of initiating therapy, with an average of 37.7± 8.5days. The dosage of the drugs was not reduced in any of the patients but medication was discontinued in 3 (8%) of them and the cough disappeared within 10 days. There was no significant statistical difference between captopril and lisinopril; X^2=0.26, OR=1.30 (95%CI; 0. 6-2.81), P value=0.587. There was also no significant sex difference observed; X^2=0.06, OR=0.79(95%CI; 0.27-2.28), P=0.808. The mean age of 34 patients on ACE-Is that developed cough was not significantly higher than that of their controls that did not develop cough; (53.72+5.8 vs. 47.36±7.4 years). X^2=0.01, OR=0.97 (95%CI; 0.52-1.81) P value= 0.95, There was, however, a significant statistical difference in cough induction between the ACE-Is and the other medications; X^2=32.66, OR=42.37(95%CI 6.11-843.32), P< 0.0001.

Table 1: Prevalence of cough in patients treated with ACE-Is and alternative medications

Variable	ACE-I	Control
TNP	168	168
Male	89(53)	93(55)
Female	79(47)	75(45)
Age ±SD	45±22.9	47.36±7.4
NDC	34(20.2)	1(0.6)
Male	16(9.5)	-
Female	18(10.8)	1(0.6)
Age ±SD	53.72+5.8	41.

Table 2: Distribution of ACE-I and Alternative medication by sex

Variable	Medication				
	ACE-I		Alternative		
	Captopril	Lisinopril	Nifedipine	Aldomet	Moduretic
Total	92(54.8)	76(45.2)	58(35)	43(25)	67(40)
Male	58(34.5)	31(18.4)	36(21)	18(11)	39(23)
Female	34(20.2)	45(26.8)	22(13)	25(15)	28(17)
NDC	19(11.3)	15(9)	-	1(0.6)	-
Male	10(5.9)	6(3.6)	-	-	-
Female	9(5.4)	9(5.4)	-	1(0.6)	-

ACE-I = Angiotensin converting enzyme-inhibitor; NDC= Number that developed cough

Discussion

ACE-Is are useful as single drug therapy for many patients with hypertension, hypertensive and diabetic nephropathy.[3,19] There has been conflicting results[20] on the effectiveness of ACE-I monotherapy in controlling blood pressure among hypertensive Nigerians; it was ineffective as a sole drug in some studies[21,22] others found it effective in mild to moderate hypertension[23] and even in severe and resistant hypertension.[24] The blood pressure of each patient in this study was controlled and maintained with ACE-I or alternative drug monotherapy. This effectiveness is derived from the inhibition of angiotensin converting enzyme[5] (ACE), the enzyme involved in the conversion of angiotensin I to angiotensin II (a potent vasoconstrictor). However, the link of ACE-Is with a dry, non-productive cough could be puzzling[12] since the rennin- angiotensin system does not appear to have any important function in the lung.[6] The frequency of this cough in our study was 20.2% and there was no significant difference in the prevalence of cough induced by captopril (11.3%) and lisinopril (9%). Sex involvement was about equal; occurring in 9.5% of males and 10.8% of females respectively. The age difference between those with ACE-I induced cough and the controls was also not statistically significant (53.7± 5.8 years vs. 47.4±7.4 years, P-value=0.95). ACE-I was discontinued in 3(8%) patients; 2 on captopril and 1 on lisinopril because of persistent cough that disturb their sleep, however, it was tolerated in others.

ACE-Is are pro-drugs that are converted to active form after oral administration[1] with little significant differences between them. One of these is the presence or absence of sulphydryl group[1] that is known to affect the time of onset and the duration of action of individual drug. However, the specific mechanism of cough in some patients receiving this class of drugs is not fully understood. A number of studies[4, 5, 19, 25] have related it to the effects of the drugs on the kininogen-kinin (bradykinin) system. Immunochemistry has shown nerves containing substance P[26] and neurokinin A[27] in human lung. Most of such neurons arise from the vagus nerve and present beneath the respiratory epithelium of the tracheal and the major bronchi[12]. ACE is known to be identical with bradykininase or kininase II[12] that degrades kinins (bradykinin and tachykinin). ACE-I may therefore reduce the degradation of bradykinin leading to local accumulation in the lungs. This may activate pro-inflammatory peptides (e.g. substance P, neuropeptide Y) [5, 28] in the airways with consequent stimulation of vagal afferents[4] that subserve cough reflex, particularly the unmyelinated or the C fibres[4] and the rapidly adapting receptors in the airway. [29] Prostaglandin and histamine that are released in the respiratory tract due to the same effect of bradykinin can also cause cough reflex hypersensitivity.[4,5] These putative mechanisms of ACE-I induced cough may explain the increase in frequency of cough seen in those group of patients on it (20.2%) far above that of their control subjects (0.6%). The cough may improve spontaneously[14,15,16,19] in some patients as observed in our patients or with agents that inhibit prostaglandin synthesis.[9,29] Improvements have also been reported with calcium channel blockers[30] and theophyllines.[31]

In conclusion, dry cough, complicating therapy with ACE-I as a class of drugs is not uncommon. It is however, unrelated to patients' age or sex.

References

1. Martindale: The extra pharmacopoeia. The Royal pharmaceutical society of Great Britain. 1997; 821-824
2. Anonymous. Cough caused by ACE inhibitors. Drug Ther Bull 1994;32: 55-56
3. Howes LG, Christie N. Angiotensin receptor antagonist and ACE inhibitors. Austr Fam Physician 1998;27:914-917
4. Semple PF. Putative mechanism of cough after treatment with angiotensin converting enzyme inhibitor. J Hypertens 1995;(suppl) 3: S17-S21
5. Kalberg BE. Cough and inhibition of the rennin-angiotensin system. J Hypertens 1993;11(suppl):S49-S52
6. Coulter DM, Edward IR. Cough associated with captopril and enalapril. Br Med J 1987;294:1521-1523
7. Berkin KE, Ball SG. Cough and angiotensin converting enzyme inhibition. BMJ

1988; 296: 1279-1280
8. Nicholls MG, Gilchrist NL. Sulindac and cough induced by converting enzyme inhibitors. Lancet 1987; I :872
9. Macweran JR. Change in cough reflex after treatment with enalapril and captopril. Br Med J 1989;299:13-16
10. Lernhardt EB, Ziegler MG. Cough caused by cilazapril. Am J Med Sci 1988;296:199-200
11. Robert CG, Leonard SL, Harold SL. Prevalence of cough during angiotensin converting enzyme inhibitor therapy. Am J Med 1988;85:887-889
12. Alyn HM, Rachel L, Morris JB et al. Angiotensin converting enzyme and cough. Lancet 1987;14:1116-1118
13. Adigun AQ, Ajayi AA. Angiotensin converting enzyme inhibitor induced cough in Nigerians. West Afr J Med 2001;20:46-47
14. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol1995;40:141-144
15. Wood R. Bronchospasm and cough as adverse reactions to the ACE inhibitors captopril, enalapril and lisinopril. A controlled retrospective cohort study. Br J Clin Pharmacol 1995;39:265-270
16. Ravid D, Lishner M, Lang R et al. Angiotensin converting enzyme inhibitor and cough: a prospective evaluation in hypertension and in congestive heart failure. J Clin Pharmacol 1994; 34:1116-1120. 17
17. Feinstein AR. Principle of medical statistics. Chapman and Hall, Boston, 2002; 576-578
18. WHO. International society of hypertension. Guidelines for the management of hypertension. J Hypertens 1999;17:151-183
19. Reisin l, Schneesweis A. Spontaneous disappearance of cough induced by angiotensin converting enzyme inhibitor (captopril or enalapril). Am J Cardiol 1992;70:398-399
20. Kadiri S. Management of hypertension with special emphasis on Nigeria. Niger Clin Rev 2001;5:5-8
21. Ajayi AA, Oyewo EA, Ladipo GOA, Akinsola A. Enalapril and hydrochlorothiazide in hypertensive Africans. Eur J Clin Pharmacol 1989;36:229-234
22. Ikeme AC. The management of hypertension in Nigerians. Nigerian Medical Practitioner 1993;25:62-68
23. Abengowe CU, Ezedinachi ENU, Balogun MO. An open trial of lisinopril (ZESTRIL^{TM}) in mild to moderate hypertension in Nigeria. West Afr J Med 1997;16:218-222
24. Ositelu SB, Odutola TA, Onuzo OBC, Mabadeje AFB. Captopril in severe and drug resistant hypertension. Nigerian Medical Practitioner 1986;11:108-111
25. Triffilief A, Da-Silva A, Gies JP. Kinins and respiratory tract disease. Eur Respir J 1993;6:576-587
26. Lundberg JM, Horkfelt T, Martling CR et al. Substance P immunoreactive sensory nerves in the lower respiratory tract of various mammals including man. Cell Tissue Res 1984;235:251-261
27. Martling CR, Theodorsson-Norheim E, Lunberg JM. Occurrence and effects of multiple tachykinins; substance P, neurokinin A, neuropeptide K in lower human airways. Life Sci 1987;40:1633-1643
28. Cascaeril M, Bull H, Munford R et al. Carboxyl-terminal tripeptidyl hydrolysis of substance P by purified rabbit lung angiotensin converting enzyme and potentiation of substance P activity in vivo by captopril and MK 422. Mol Pharmacol 1983; 25:287-293
29. Lowry R, Higginbotham T, Johnson T et al. Inhibition of artificially induced cough in man by bronchodilator. Br J Clin Pharmacol 1987;24: 503-510
30. Fogari R. Effects of nifedipine and indomethacin on cough induced by angiotensin converting enzymes inhibitors: a double blind, randomized, cross over study. J Cardiovasc Pharmacol 1992;19:670-673
31. Cazzola M, Matera MG, Liccardi G et al. Theophylline in the inhibition of angiotensin converting enzyme induced cough. Respiration 1993;60:212-215