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Angiotensin-Converting Enzyme Inhibitor-Induced Cough Prevalence in Refractory Hypertensive Patients

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Abstract

Refractory Arterial Hypertension (RAH) is characterized by persistently high blood pressure values. Angiotensin Converting Enzyme (ACE) inhibitors in combination with other antihypertensive drugs are effective for RAH and have good clinical tolerance. According to the literature, the adverse effect of cough in patients using ACE inhibitors occurs in 5 to 20% of them. However, in clinical practice, the incidence appears to be higher, making it difficult the therapeutic adherence. This study aimed to evaluate the prevalence of cough induced by ACE inhibitors in patients with RAH as well as their clinical and laboratory characteristics. Cross-sectional study in a referral hospital in severe hypertensive cardiovascular disease. To assess the adverse effect cough in the use of ACE inhibitors, patients answered a questionnaire and blood pressure (BP) was measured on the day of the interview. 111 patients were analyzed and 67.6% were female (75). The average age was 62.8 ± 12 years. 100% (111) of the patients use or had used ACE inhibitors. The prevalence of cough was 64.9% (72). 62.2% (69) of patients were switched to angiotensin II receptor blocker as an ACE inhibitor substitute. 9.9% (11) of patients reported that the cough continued even after the discontinuation of ACE inhibitor. Patients used an average of 4.7 ± 1.1 antihypertensive medications. The average systolic blood pressure was 152.5 ± 28.4 mmHg and the average diastolic pressure was 88.5 ± 17.1 mmHg. We observed a high prevalence of cough associated with the use of ACE inhibitors in this population, different from that described in the literature. Despite the large number of antihypertensive drugs in use, the blood pressure was not controlled in most patients. It is possible that the non-use of ACE inhibitors may contribute to the low hypertensive control.

Keywords

Hypertension, ACE inhibitors, Cough, Side effect

Introduction

Systemic arterial hypertension (SAH) is one of the most common diseases in the world and is considered one of the main risk factor for cardiovascular diseases [1-3].

Refractory arterial hypertension (RAH) is defined as persistent blood pressure (BP) elevations above the recommended targets (> 140/90 mmHg or > 130/80 mmHg in patients with diabetes mellitus or established clinical nephropathy) despite the use of three antihypertensive drugs, one being a diuretic, or when using four or more antihypertensive drugs even with controlled BP [4,5].

While the prevalence of RAH is unknown, several cross-sectional studies have shown that is not uncommon [6]. Some studies suggest that the prevalence is around 4.5 to 15% of all hypertensive population [7-11].

According to the guidelines for pharmacological treatment of hypertension published by the World Health Organization and the International Society of Hypertension and the International Society of Hypertension, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers, and diuretics should be the first line treatment of hypertension. In adults, there is sufficient evidence to prove the effectiveness of ACE inhibitor in the treatment of SAH [12,13].

ACE inhibitors have fewer side effects in comparison to many β-blockers and diuretics [14]. However, among the side effects, dry cough is the most common and well known, making it difficult the medical adherence. ACE inhibitors promote an increase of the substance bradykinin and results in the side effect cough.

According to the literature, the incidence of ACE inhibitor-induced cough has been reported to be 5% - 20%. It is not dose dependent or related to the active ingredient of the drug. It is more common in women and in blacks, suggesting that the genotype is relevant [15-18]. Although this incidence is a literature's consensus, in medical practice what is observed is different. It is believed that, in hypertension clinics, over 20% of patients have their therapeutic plans modified (exchanging ACE inhibitor for other antihypertensive drug) complaining of constant coughing soon after the adoption of ACE inhibitors. With therapeutic change, patients generally report cough's improvement.

There is no article in the literature that studies the prevalence of cough due to ACE inhibitors in patients with RAH. The knowledge of the true prevalence will allow physicians better evaluate the adoption of this drug as first-line treatment of RAH. There will be then, with further studies, the possibility to suggest a better administration of ACE inhibitors during clinical performance.

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Objectives

The primary aim of this study was to estimate and analyze the prevalence of dry cough due to ACE inhibitors in patients with refractory arterial hypertension. The secondary objectives were to evaluate clinical and laboratory characteristics of refractory arterial hypertensive patients and to assess the prevalence of patients who discontinued ACE inhibitor due to its side effects.

Methods

Study design

This study was a cross-sectional observational analysis of patients referred to the Federal University of Bahia (UFBA) Severe Hypertensive Cardiovascular Disease Service at José Maria de Magalhães Netto clinic, that belongs to the Professor Edgard Santos University Hospital Complex (Complexo-HUPES), from November, 2012 to June, 2015. All patients participating in the study were invited and informed about the objectives and all the stages of the study. Those who agreed to participate signed the Informed Consent. This study was approved by the research team's institutional review board.

Study population

Patients were included in the study if they had a BP above 140/90 mmHg using three or more antihypertensive drugs, one being a diuretic, or were using four or more antihypertensive drugs despite the value of the BP. Patients were excluded of the study if they did not sign the Informed Consent, were not able to perform the necessary laboratory exams, never used ACE inhibitor as an antihypertensive drug and had any respiratory disease with cough as one of its symptoms. The patients then underwent a complete clinical and laboratory evaluation.

Patients were determined to have refractory hypertension based on their number of medications, BP measurement at the day of the visit and medication adherence. Adherent was determined by patient self-report. Those who were adherent to medications and filled the criteria of inclusion above were determined to have refractory hypertension.

A questionnaire was applied for each patient, which obtained qualitative variables (gender, race, acute myocardial infarction history, stroke history, cigarette smoking, alcohol consumption , diabetes mellitus, metabolic syndrome, Framingham score, antihypertensive drugs in use and the presence of side effects of these medications) and quantitative variables (age, body weight, height, body mass index, waist circumference, heart rate, time of hypertension, systolic and diastolic BP and routine laboratory data). Body mass index was calculated dividing the weight in kilograms by the square of the height in meters. The waist circumference was measured in the standing position at the mid-point between the lower ribs and the iliac crest. BP was the average of 2 measurements taken after the patient had been resting for at least 5 minutes. Routine laboratory data were total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, glycemia, plasma sodium, plasma potassium, plasma creatinine and urea. After the first interview, the patients were instructed to return to the clinic with the laboratory test results. All antihypertensive medications from each patient were registered from the medical records and prescriptions.

The metabolic syndrome evaluation was done according to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III-ATPIII) [19]. The presence of 3 of the following 5 criteria closed the diagnosis: waist circumference > 102 cm for men and > 88 cm for women; triglycerides ≥ 150 mg/dL; HDL-cholesterol < 40 mg/dL for men and < 50 mg/dL for women; BP ≥ 130x85 mmHg and fasting glucose ≥ 100 mg/dL.

To evaluate the presence of side effects due to ACE inhibitors and qualify them a questionnaire was applied. In this questionnaire the patient is asked if captopril or enalapril (in this population there was no use of other ACE-inhibitors) has been used; if there is any complaint regard those medications; if dry cough, dry throat and throat clearing were a complaint and if those symptoms continued after the drug was discontinued. For patients who still use ACE inhibitor the last question was ignored. Finally, patients were divided in 2 groups for a better characteristics analysis. The criteria for the division was the presence or not of cough. In this division gender and cough as a side effect from ACE inhibitor was taken into account.

Statistical analysis

Collected data were compiled into databases through Microsoft Excel® and were analyzed using the Statistical Package for the Social Sciences (SPSS), version 21.0 for MAC. Values are expressed as absolute frequencies, means ± standard deviation (SD) and percentage of incidence rates of events and/or procedures. Quantitative variables were analyzed by two-sample Student's t test or Mann-Whitney test, where appropriate. Categorical variables were analyzed using chi-square test. In this statistical analysis a P value ≤ 0.05 was taken as statistical significance. For a normal distribution check the Kolmogorov-Smirnov test was performed.

Results

Initially, a total of 151 refractory hypertensive patients were studied. However, 111 met the inclusion criteria and were included in the analysis. 40 patients were excluded because they never used ACE inhibitor or did not go back to the clinic with the laboratory tests results.

The mean age was 62.8 years, 67.6% were women and 50.5% were black. Most of the population was overweight, had metabolic syndrome and had a high Framingham risk score. Most did not consume alcoholic beverages, did not have cigarettes smoking habits and did not have diabetes mellitus. Baseline characteristics of the analyzed patients are presented in table 1.

The average values of total cholesterol, triglycerides, LDL-c, plasma sodium, plasma potassium, plasma creatinine and urea are within normal values. The average blood glucose value is increased. Table 2 shows the laboratory results studied in those patients.

Most patients had a BP outside the control range (≥ 140 × 90 mmHg). However diastolic BP remained controlled in the majority of the population as shown in table 3.

When responding to the questionnaire about ACE inhibitors, 72 (64.9%) patients reported side effects at the beginning of the treatment

Table 1: Baseline characteristics.

Characteristics	No. of patients (N = 111)
Woman	75 (67.6%)
Age in years, mean	62.8 12
Black race	56 (50.5%)
Body weight, mean (Kg)	72.2 14.8
Height, mean (meters)	1.59 0.1
BMI, mean (Kg/m²)	28.18 4.72
History of MI	23 (20.7%)
History of stroke	26 (23.4%)
High Framingham score	71 (64%)
Alcohol consumption	10 (9%)
Current smoker	3 (2.7%)
Past smoker	43 (38.7%)
Diabetes Mellitus	39 (35.1%)
Metabolic syndrome	62 (55.9%)
Time of SAH, mean (years)	21.7 ± 12.9
Number of BP drugs, mean	4.7 ± 1.1
Baseline systolic BP, mean	152.5 ± 28.4
Baseline diastolic BP, mean	88.5 ± 17.1

Data are expressed as number of patients (percentage) or mean ± SD. BMI: Body Mass Index; MI: Myocardial Infarction; SAH: Systemic Arterial Hypertension; BP: Blood Pressure.

Table 2: Laboratory results.

Characteristics	No. of patients (N = 111)
TC, mean (mg/dL)	185.5 46.8
HDL-c, mean (mg/dL)	49.1 13.4
LDL-c, mean (mg/dL)	108.1 34.7
TG, mean (mg/dL)	136.1 80.4
Serum glucose, mean (mg/dL)	110.7 ± 28.6
Na^+, mean (mmol/L)	140.9 3.8
K^+, mean (mmol/L)	4.4 0.5
Cr, mean (mg/dL)	1.1 0.4
Ur, mean (mg/dL)	40.8 17.2

Data are expressed as mean ± SD. TC: total cholesterol; HDL-c: High-Density Lipoprotein-cholesterol; LDL-c: Low-Density Lipoprotein-cholesterol; TG: Triglycerides; Na+: Plasma Sodium; K+: Plasma Potassium; Cr: Plasma Creatinine; Ur: Plasma Urea.

Table 3: BP values (N = 111).

BP	Controlled	Not controlled
SBP	46 (41.4%)	65 (58.6%)
DBP	71 (64%)	40 (36%)
BP	44 (39.6%)	67 (60.4%)

Data are expressed as number of patients (percentage). SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BP: Blood Pressure.

Table 4: ACE inhibitor questionnaire.

Characteristics	No. of patients (N = 111)
Reported side effects	72 (64.9%)
Reported dry cough	68 (61.3%)
Reported throat clearing	61 (55%)
Reported dry throat	59 (53.2%)
Presence of symptoms after discontinuation of ACE inhibitor	11 (9.9%)
Still use ACE inhibitor	38 (34.2%)
Switched to ARB	69 (62.2%)

Data are expressed as number of patients (percentage). ACE: Angiotensin-Converting Enzyme; ARB: Angiotensin Receptor Blocker.

Table 5: Baseline characteristics comparing patients who reported cough and patients who did not reported.

Characteristics	Dry cough (n = 68)	No dry cough (n = 43)	P value*
Woman	47 (69.1%)	28 (65.1%)	0.66
Age in years, mean	62.2 12.2	62.7 ± 11.9	0.82
Black race	36 (52.9%)	20 (46.5%)	0.04
Body weight, mean (Kg)	72.9 ± 12.9	70.8 ± 17.4	0.44
Height, mean (meters)	1.59 0.10	1.60 ± 0.11	0.48
BMI, mean (Kg/m^2)	28.7 3.8	27.4 ± 5.9	0.64
History of MI	16 (23.5%)	7 (16.3%)	0.36
History of Stroke	13 (19.1%)	13 (30.2%)	0.18
High Framingham score	37 (54.4%)	34 (79.1%)	0.03
Alcohol consumption	6 (8.8%)	4 (9.3%)	0.93
Current smoker	3 (4.4%)	0 (0%)	0.16
Past smoker	29 (42.6%)	14 (32.6%)	0.29
Diabetes Mellitus	20 (29.4%)	19 (44.2%)	0.11
Metabolic syndrome	40 (58.8%)	22 (51.2%)	0.43
Time of SAH, mean (years)	22.3 ± 12.4	20.7 ± 13.7	0.62
Number of BP drugs, mean	4.8 ± 1.7	4.5 ± 1.1	0.27
Baseline systolic BP, mean	148.3 ± 27.4	159.3 ± 28.9	0.33
Baseline diastolic BP, mean	88.3 ± 16.6	88.9 ± 18.1	0.36

**Chi-square test and t test. Data are expressed as number of patients (percentage) or mean ± SD. BMI: Body Mass Index; MI: Myocardial Infarction; SAH: Systemic Arterial Hypertension; BP: Blood Pressure.*

with ACE inhibitor. Most of them reported dry cough, throat clearing and dry throat, 68 (61.3%), 61 (55%) and 59 (53.2%) patients, respectively. 38 (34.2%) patients continued using ACE inhibitors and 69 (62.2%) patients were switched to angiotensin receptor blocker (ARB). 11 (9.9%) patients still reported those symptoms even after discontinuation of ACE inhibitor (Table 4).

Table 6: Laboratory results compared on both groups (dry cough and no dry cough).

Characteristics	Dry cough (n=68)	No dry cough (n=43)	P value*
TC, mean (mg/dL)	184.7 42.1	186.9 ± 53.9	0.31
HDL-c, mean (mg/dL	48.8 13.1	49.6 ± 14.1	0.51
LDL-c, mean (mg/dL)	109.9 36.1	105.1 ± 32.7	0.39
TG, mean (mg/dL)	134.9 60.1	137.9 ± 105.7	0.33
Serum glucose, mean (mg/dL)	106.2 ± 24.4	117.9 ± 33.3	0.78
Na^+, mean (mmol/L)	141.1 4.2	140.5 ± 3.1	0.12
K^+, mean (mmol/L)	4.4 0.6	4.4 ± 0.5	0.37
Cr, mean (mg/dL)	1.1 0.4	1.1 ± 0.5	0.11
Ur, mean (mg/dL)	38.9 14.4	43.7 ± 20.8	0.11

**T test. Data are expressed as mean ± SD. TC: Total Cholesterol; HDL-c: High-Density Lipoprotein-cholesterol; LDL-c: Low-Density Lipoprotein-cholesterol; TG: Triglycerides; Na+: Plasma Sodium; K+: Plasma Potassium; Cr: Plasma Creatinine; Ur: Plasma Urea.*

In table 5, patients were divided into 2 groups: those who had dry cough and those who did not have dry cough. The female population represented the majority in both groups, with a greater percentage in the group who reported cough (p = 0.66). Age was similar in both groups.

The prevalence of alcoholism was 9% in the general population, being similar between the 2 groups (p = 0.93). The presence of diabetes mellitus was higher in patients who had no cough (p = 0.11). The average body mass index in both groups was high, however there was no difference in values between the groups (p = 0.64). The mean systolic blood pressure and diastolic blood pressure did not differ between the groups, with p values of 0.33 and 0.36 respectively. The number of antihypertensive drugs used in both groups was similar (p = 0.27). In the group that reported cough, 58.8% had metabolic syndrome compared to 51.2% in the group that did not reported cough (p = 0.43). There were more current smokers in the group of patients with cough (p = 0.16).

Out of the data presented only race and a high Framingham score showed a relationship with the appearance of dry cough with a p value of 0.03 and 0.05 respectively. Finally, laboratory parameters examined in this study are described in table 6. It can be observed that fasting blood glucose was higher in the group that did not report cough (p = 0.78). Triglycerides also showed higher values in this group (p = 0.33).

Discussion

Because ACE inhibitors are first-line treatment for refractory hypertension, lack of therapeutic adhesion due to the side effect dry cough can greatly impair the treatment. Therefore, relationship between dry and ACE inhibitor has been extensively studied. This present work was a cross-sectional study and aimed to estimate and analyze the prevalence of dry cough due ACE inhibitor in patients with RAH.

In this study it was found, through the ACE inhibitors questionnaire, that 61.3% of patients reported dry cough as a side effect of the drug. This value was higher than the ones found in the literature. In the study by Sato A, et al. (2015) [18], conducted in a prospective way to verify cough's frequency and characteristics during treatment with ACE inhibitor, it was found an incidence of 20%. In the study by Ng L, et al. (2014) [20], held in Singapore, with the aim to analyze the impact discontinuation of ACE inhibitor due to cough, the incidence was 30.4%. However, the relationship between race and drug tolerance must not be underestimated [20]. The difference in the incidence of cough found in our study may suggest a lower tolerance to ACE inhibitor in patients with RAH contributing to greater difficulty in controlling BP. However, more studies are needed to elucidate these issues.

In relation to the other side effects studied, more than half of the population reported throat clearing and dry throat. In the study by Ye WW on the prevalence of persistent cough during long-term

treatment with enalapril, the prevalence for voice changes was 14% and for sore throat was 10% [21]. The difference of incidence may also be attributed to a lower tolerance to ACE inhibitor in patients with RAH.

Studies have shown that the discontinuation of ACE inhibitor due to cough ranged between 2.4% and 30.4% [17,18,20]. However, in this study it was found that the substitution of ACE inhibitor for ARB occurred in 62.2% of patients. This large difference can be explained by the higher incidence of cough I this study. One should take into consideration that it was not asked or studied the cause of ACE inhibitor discontinuation.

When analyzing the number of antihypertensive drugs and BP control, it can be noticed that BP of the vast majority of the population is not controlled but the systolic blood pressure is controlled even with the average use of 4.7 antihypertensive drugs. This result is similar with what has been described by Lloyd-Jones, et al. (2000) [22] and Cushman, et al. (2002) [23], which also showed a significant control of DBP and a weak control of SBP and BP. Historically, a correlation was made between SBP with arteriosclerosis process, with consequent loss of elasticity in the arterial system, common in the human being's natural aging process [2], and recommended that a more drastic therapeutic actions should be taken only if there is an elevation of DBP. However, it has been shown that a high SBP is much more common in the population [23] and may be a better predictor for cardiovascular disease than a high DBP [22]. This acknowledges is important to know especially in our population that presents with additional risk factor for isolated systolic hypertension, such as obesity and advanced age.

Patients with cough were mostly of black race, compared with the group of patients who did not have cough ($p = 0.04$). In the literature there is clear evidence of a higher incidence and severity of hypertension in blacks compared with the white population. The studies of Rivero-Becerra J, et al. (2004) [24], Lackland DT (2014) [25] and Saunders E (1991) [26] are examples of some of these evidences [24-26]. Bicket DP (2002) [15] found that the side effect cough due to ACE inhibitors is more common in blacks than in whites. The study by Elliott WJ (1996) [17] found that the prevalence of the side effect cough that required discontinuation of ACE inhibitors was 9.6% among blacks compared with 2.4% among other ethnicities.

When comparing the average age and hypertension time between the 2 groups of patients with and without cough it can be seen that there was no statistical significance between them ($p = 0.82$ and 0.62 respectively). Similarly, the comparison of laboratory date, such as total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, serum glucose, serum sodium, serum potassium, serum creatinine and serum urea, between these 2 groups of patients shows that there was no statistical significance between them ($p = 0.31$; 0.51; 0.39; 0.33; 0.78; 0.12; 0.37; 0.11; 0.11, respectively). These results seem to show that none of these factors has a direct influence on the incidence of side effect cough.

The presence of alcoholics, smokers and history of acute myocardial infarction and stroke was low in the general population and no statistical significance was found between the 2 groups, demonstrating a homogeneity pattern analyzing these factors and probably, individually, are not risk factors for the occurrence of cough due to ACE inhibitors.

In both groups the number of antihypertensive drugs and the average DBP were similar. The average SBP in the group of patients without cough was higher. Despite these results, there was no statistically significant difference between the 2 groups in any of the mentioned factors. It is worth noting that most of the patients were using 4 to 5 antihypertensive drugs. As this is a population with severe hypertension, mostly with long-time diagnosis, possible the pressure values and the number of medications in use did not influence the incidence of cough.

When the BMI in compared, it is clear there is a similarity between the 2 groups and there was no statistical significance ($p = 0.64$). In the group with cough the average BMI was 28.7 and in the group without cough the average BMI was 27.4. Mancia G, et al. (2014) [27] conducted a randomized, double-blind, placebo-controlled study that was conducted in 100 centers in 7 European countries. 1039 patients were studied. The study showed that the group taking 20 mg of enalapril had a BMI of 30.12 ± 5.2 and the incidence of cough was 3.6%. The BMI value is close to the value found in our work and, despite the absence of dosage of the drugs, the incidence of cough was much higher than in the study of Mancia G, et al. (2014) [27]. The BMI values should not have contributed to the onset of coughing.

Despite the higher incidence of Diabetes Mellitus in the group without cough and a higher incidence of Metabolic Syndrome in the group of patients with cough, there was no statistical significance in the comparison of any of these factor ($p = 0.11$ and 0.43 respectively).

There are many potential limitations of this study inherent in its format. Because it is a cross-sectional study, it may have some biases and cannot evaluate causal and temporal relationships between the studied factors. In addition, there was some difficulty performing Ambulatory Blood Pressure Monitoring in all patients. Therefore, we cannot verify if the patients have truly refractory hypertension or have white-coat hypertension, characterizing pseudo hypertension. It was found, in the study performed by la Sierra, et al. (2011) [28], that 37.5% of patients considered having refractory hypertension may be under the white-coat effect, with normal BP levels after Ambulatory Blood Pressure Monitoring. However, because this study has a population treated at a referral center for severe hypertensive cardiovascular disease, and mostly accompanied by a long period already, it is expected that much of the sample actually fill the criteria for refractory hypertension.

In summary, the present study found that the prevalence of the side effect cough due to ACE inhibitors in the studied population was higher than the ones found in the literature for hypertensive patients. Also, refractory hypertensive patients who had cough showed a higher incidence of high Framingham score than the patients who did not have cough as well as in the first group there was more black patients than the second. Finally, a large number of patients switched the ACE inhibitor for an ARB.

Based on this discussion, physicians should better evaluate the adoption of ACE inhibitors as first-line treatment of RAH. There is a possibility that the use of other first line drugs for hypertension would result in a better medical adherence and BP control.

Perspectives

There are no studies addressing the relationship between RAH and side effect cough due to ACE inhibitor, justifying the importance of this work. The characterization of the population with refractory hypertension and the knowledge of cough's incidence is important to avoid non adherence, which may contribute to the worsening of the overall picture of these patients. For these reason reasons, further clinical research is needed to better understand this relationship, as this study showed a high prevalence of cough due to ACE inhibitors, higher than the ones found in the literature for patients with SAH.

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Conflicts of Interest

There are no conflicts of interest.

Ethical Statement

This study in an addition of the "Clinical and Metabolic Assessment in Refractory Arterial Hypertension" and was already

planned within their specific objectives. The project was approved by the Research Ethics Committee of Hospital Ana Nery under number 138371, on 05/11/2012. All patients signed the Informed Consent.

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