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Angiotensin converting enzyme inhibitors related cough and associated medications

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ABSTRACT

Objectives: Angiotensin-converting enzyme inhibitors (ACEi) are among the main anti-hypertensive medications. While they are generally well tolerated, dry cough is one of their important side effects, with a frequency of up to 10 percent. Medications that are associated with increased ACEi-related cough frequency are not well described. We wanted to evaluate medications that might have an effect on ACEi-related cough.

Method: This study was designed as a post-hoc analysis of our previously published study. Patients who were on ACEi were identified, and demographics, comorbidities, laboratory data, and medications were retrieved via electronic medical records. Patients who reported cough and whose cough ceased after ACEi withdrawal were defined as having an "ACEi-related cough." Patients were grouped according to their ACEi-related cough presence.

Results: One hundred and twenty-one patients were included in the study, of whom 14 experienced ACEi-related coughs. All medications except for low dose acetylsalicylic acid (ASA) and calcium channel blockers (CCB) were similar between the groups. Low dose ASA use was significantly higher among patients who experienced ACEi-related cough (50% vs. 16.8%, p=0.04). On the other hand, CCB use was associated with lower ACEi-related cough (7.7% vs. 35.5%, p=0.03). Medications other than ASA and CCB, demographics, comorbidities, and laboratory data were similar across the groups.

Discussion: ACEi-related cough risk is higher among patients on low dose ASA and lower among patients on CCB. Further studies are needed to demonstrate if there is a "safe" acetylsalicylic acid dose that is not associated with ACEi-related cough.

Keywords: hypertension, angiotensin converting enzyme inhibitors, acetylsalicylic acid, calcium channel blockers, cough

Hypertension is a significant contributor to cardiovascular risk, alongside conditions like coronary artery disease. Its management involves implementing lifestyle modifications and utilizing medicines. Several prominent categories of drugs used to treat hypertension, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), are commonly included in the treatment plans of many individuals with high blood pressure.[1,2] In addition to treating hypertension, ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) are often prescribed for patients with albuminuric diabetic renal disease and heart failure with reduced ejection fraction.[3,4] The latest hyperten-

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sion guidelines recommend the use of dual combination therapy, namely the addition of either an ACE inhibitor or an ARB to either calcium channel blockers or thiazide diuretics. Although ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) are typically well tolerated, ACEi is linked to a dry cough that requires discontinuation of the medication and a switch to ARB in 5 to 10 percent of patients, with other reports indicating rates as high as 30 percent.[5,6] According to reports, this condition is less prevalent in people with hypertension but more prevalent in patients with coronary artery disease and diabetes mellitus.[6] The precise mechanism behind ACEi-related cough is not well understood. However, the most probable explanation for the dry cough is that ACEi inhibits the breakdown of bradykinin and substance P, resulting in the constriction of airway smooth muscles and subsequent coughing.[7] Various factors have been suggested and defined to elucidate the reasons why certain patients develop a cough as a result of ACE inhibitor (ACEi) use while others do not. These factors encompass lung congestion caused by heart failure, varying levels of bronchial activity, heightened sensitivity of airway sensory nerve fibers to bradykinin, a reduced ability to break down bradykinin, and genetic variations in the bradykinin gene.[6] In addition to ACE inhibitors, various medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), beta-blockers, and acetylsalicylic acid (ASA), have the potential to trigger bronchospasm and result in coughing.[8] A study with ASA has shown that ASA has a bimodal effect on ACEi-related cough: While intermediate doses can lower ACE-related cough, low ASA doses have no effect.[9]

This study aimed to examine the impact of medications that are known to cause dry cough when used alone (such as ASA, beta-blockers, NSAIDs, etc.) or medications commonly used in hypertensive patients taking ACE inhibitors but not directly linked to dry cough when used alone (such as metformin, calcium channel blockers, proton pump inhibitors, etc.) on ACE inhibitor-induced cough.

METHODS

Design

This study was designed as a post-hoc analysis of our previously published study on hypertensive patients. Our previous study's aim was to evaluate the renal side effects of ACEi and ARBs via machine learning algorithms. During that study, some patients who were already on ACEi therapy were detected to report a chronic cough that had ceased after ACEi withdrawal, and we defined this cough as an "ACEi-related cough." In this study, we acquired the clinical characteristics of the patients who were on ACEi, and we grouped them as patients who experienced ACEi-related cough ("Cough" group) and patients who did not experience ACEi-related cough ("No Cough" group).

Clinical Data

- The following clinical data were acquired for the analysis:
- Demographics: Age and sex
- Comorbidities: diabetes mellitus (DM), coronary artery disease (CAD), heart failure (HF), chronic kidney disease (CKD), pulmonary disease, active malignancy, connective tissue disorders
- Medications: thiazide diuretics, calcium channel blockers (CCB), beta blockers, loop diuretics, insulin, metformin, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, statins, and acetylsalicylic acid (ASA)
- Laboratory Values: Urea, glomerular filtration rate (GFR), creatinine, uric acid, sodium, potassium, calcium, glucose, low-density lipoprotein (LDL), triglyceride, and albumin

Statistics

For descriptive statistics, continuous variables were presented as "mean (±standard deviation)" or "median (interquartile range)" according to their distribution pattern. Categorical variables were presented as "numbers (percentages)". For comparison of continuous variables' between-group differences, the student's t-test or Mann-Whitney U test was used according to the variables' distribution patterns. Pearson's chi-squared test ($\chi 2$ test) (or Fisher's exact test when needed) was used for comparison of categorical variables' between-group differences. Two-sided significance testing was performed to calculate p-values, and p-values less than 0.05 were considered significant. All analyses were conducted using IBM SPSS Software version 23.0 (SPSS Inc., Chicago, IL), licensed to the institution where the study was carried out.

Ethics

Patients were assigned an anonymous identification number to protect confidentiality. The processing of the data did not require informed consent, and

written informed consent was not obtained due to the study's retrospective design. The study complies with the principles outlined in the Declaration of Helsinki, and this study was approved by the Hacettepe University Institutional Review Board (Project number GO22/734).

RESULTS

One hundred and twenty-one patients who were on ACEi therapy were included in the study. Of those, 14 (11.5%) experienced an ACEi-related cough, while 107 (88.5%) did not. The median age was 62, and there was a slight female dominance that did not show a difference between the groups.

The two most common comorbidities were diabetes mellitus and coronary artery disease, with frequencies of 42.1% and 33.9%, respectively. Coronary artery disease, the primary indication for acetylsalicylic acid use, was almost identical in the no-cough and cough groups (33.6% vs. 35.7%, p=1). Diabetes mellitus and heart failure frequencies, which were associated with higher ACEi-related cough risk, were similar between the two groups (41.1% vs. 50%, p=0.52, and 4.7% vs. 7.1%, p=0.53, respectively). Although pulmonary disorders were more common among patients who experienced ACEi-related cough (6.5% vs. 21.4%),

Table 1. Characteristics of patients grouped by their cough status

	TOTAL n = 121	NO COUGH n = 107	COUGH n = 14	p
Demographics				
Age	62 (14)	62 (15)	58 (10)	.13
Female sex	72 (59%)	65 (60.7%)	7 (50%)	.44
Comorbidities				
Diabetes mellitus	51 (42.1%)	44 (41.1%)	7 (50%)	.52
Coronary artery disease	41 (33.9%)	36 (33.6%)	5 (35.7%)	1
Heart failure	6 (5%)	5 (4.7%)	1 (7.1%)	.53
Chronic kidney disease	6 (5%)	6 (5.6%)	0	1
Pulmonary disease	10 (8.3%)	7 (6.5%)	3 (21.4%)	.09
Active malignancy	2 (1.7%)	1 (.9%)	1 (7.1%)	.21
Connective tissue disorders	8 (6.6 %)	6 (5.6%)	2 (14.3%)	.23
Medications				
Thiazide diuretics	47 (39.2%)	40 (37.4%)	7 (40%)	.25
Calcium channel blockers	39 (32.5%)	38 (35.5%)	1 (7.7%)	**0.03**
Beta blockers	42 (34.7%)	39 (36.4%)	3 (21.4)	.37
Loop diuretics				
Insulin	16 (13.3%)	14 (13.1%)	2 (15.4%)	.68
Metformin	43 (35.5%)	37 (34.6%)	6 (42.9%)	.56
Nonsteroidal anti-inflammatory drugs	15 (12.5%)	13 (12.1%)	2 (15.4%)	.66
Proton pump inhibitors	31 (25.8%)	28 (26.2%)	3 (23.1%)	1
Acetylsalicylic acid	25 (20.7%)	18 (16.8%)	7 (50%)	**.004**
Statins	21 (17.4%)	16 (15%)	5 (35.7%)	.067
Laboratory Values				
Urea	30 (14)	30 (15)	32 (13)	.97
Glomerular filtration rate	93 (21)	91 (22)	101 (18)	**.017**
Creatinine	.80 (.27)	.80 (.29)	.74 (.19)	.63
Uric acid	5.6 (1.8)	5.4 (1.8)	5.9 (2.3)	.68
Sodium	139 (3)	139 (3)	138 (3)	.5
Potassium	4.2 (.5)	4.2 (.5)	4 (.7)	.06
Calcium	9.6 (.7)	9.6 (.7)	9.4 (.8)	.19
Glucose	108 (25)	108 (23)	106 (33)	.93
Low density lipoprotein	113 (56)	113 (58)	114 (44)	.70
Triglyceride	150 (103)	151 (104)	131 (103)	.82
Albumin	4.3 (.5)	4.3 (.5)	4.1 (.8)	.30

this difference did not reach statistical significance (p=0.09). All other comorbidity frequencies were also similar between the groups (p>0.05).

Regarding biochemical characteristics, two groups did not differ except for the GFR. GFR was slightly higher in ACEi-related cough patients compared to the non-cough group (101 vs. 91, p = 0.017).

The most common medications were thiazide diuretics, metformin, and beta blockers (39.2%, 35.5%, and 34.7%, respectively). Calcium channel blockers (CCB) were used by 39 patients (32.5%) in total, and CCB use was significantly more common among patients who did not experience ACEi-related cough (35.5% vs. 7.7%, one-sided p=0.03). Acetylsalicylic acid (ASA) was used by 25 patients (20.7%), and ASA use was significantly more common among patients who experienced ACEi-related cough (50% vs. 16.8%, p=0.004). All medication uses other than ASA and CCB were similar across the groups (p>0.05). Table 1 illustrates in detail the clinical characteristics of patients according to their ACEi-related cough status.

DISCUSSION

This study illustrated that acetylsalicylic acid and calcium channel blockers are associated with higher and lower angiotensin-converting enzyme inhibitor-related cough, respectively. A dry and persistent cough is a well-described side effect of ACEi. Although all ACEi can produce dry coughs, perindopril is associated with lower ACEi-related coughs, due in part to its higher tissue potency.[10,11] Alongside ACEi, several medications, some of which may be used concomitantly with ACEi, also have an effect on cough. While many of them may increase cough incidence (e.g., beta blockers), some have the potential to reduce cough (e.g., calcium channel blockers).[8] It has been shown that the addition of calcium channel blockers reduces cough compared to ACEi monotherapy.[12] Possible mechanisms include inhibition of prostaglandin synthesis and decreased central transmission of cough reflexes.[6] Regarding ASA, a previous study was able to demonstrate that intermediate-dose ASA could suppress ACEi-related coughs while low-dose ASA could not suppress them. Our findings illustrate that low-dose ASA is associated with an even higher ACEi-related cough compared to a lack of ASA. To the best of our knowledge, this is the first study to demonstrate the association between ASA use and higher ACEi-related associations. Prostaglandins (PG) have been proposed to play a major role in ACEi-related cough. It is known that ASA irreversibly inhibits cyclooxygenase, the first enzyme in PG synthesis, converting arachidonic acid to PG-H2.[9] This mechanism can explain the intermediate dose of ASA's suppressing effect on ACEi-related cough but cannot elucidate the dose-dependent observation.

We acknowledge the limitations of our study. Firstly, this study was a retrospective analysis and prone to many limitations of retrospective studies. Secondly, the number of patients in both the total and cough groups was small; therefore, differences that are slightly above the p value of 0.05 (e.g., statin use, pulmonary disease presence) might be due to the small sample size. Thirdly, we did not take into account the CCB and ACEi types and doses; hence, we do not know whether different doses and types are associated with different cough frequencies. Lastly, these patients were receiving ACEi for hypertension but not for heart failure with reduced ejection fraction or albuminuric diabetic renal disease, so the findings might not be generalizable for indications other than hypertension.

In conclusion, clinicians should be aware of the fact that ACEi-related coughs are more common among patients who are on ASA. CCB can be more suitable than thiazides when added to ACEi due to the lower ACEi-related cough with CCB. Further studies on large patient numbers and different patient backgrounds are needed to clarify the association between acetylsalicylic acid use and ACEi-related cough.

CONCLUSION

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Hacettepe University. (Decision number: 2022/12-29, date: 5.7.2022).

Authors' Contribution

Study Conception: ATG; Study Design: ATG, MÖ;

Supervision; ATG, MÖ; Funding: ATG, MÖ; Materials: ATG, MÖ; Data Collection and/or Processing: ATG, MÖ; Analysis and/or Data Interpretation: ATG, MÖ; Literature Review: İD; Critical Review: ATG, MÖ; Manuscript preparing: ATG, MÖ.

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