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Incidence of angiotensin-converting enzyme inhibitor-induced cough in a Malaysian public primary care clinic: A retrospective cohort study

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Abstract

Introduction: The incidence of angiotensin-converting enzyme inhibitors (ACEi)-induced cough has been reported between 5% and 30% but is unknown in Malaysia. This study aimed to determine the incidence of ACEi-induced cough and its associated factors in a public primary care clinic in Malaysia.
Methods: A retrospective review of electronic medical records of patients who were initiated ACEi between January 1, 2015, and December 31, 2015, and reviewed until July 31, 2016. A total of 1,091 patients were newly prescribed ACEi, and 394 patients were eligible for this study. We excluded patients who defaulted follow-ups with no further clinic visits before July 31, 2016, were transferred to the clinic without the recorded date of ACEi initiation, were transferred to other clinics during the study period, were followed up at other clinics and attended the study clinic for a short period, or were given only a stat dose of ACEi.
Results: Among the 394 patients initiated on ACEi, 225 (57.1%) were male, 369 (93.7%) were Malay, 376 (95.4%) had hypertension, and 192 (48.7%) had diabetes. The incidence of ACEi-induced cough was 24.1%, and 42 (10.7%) patients developed cough on the day of therapy initiation. There was no association between age, gender, ethnicity, type of ACEi, and cough.
Conclusion: Approximately one quarter of patients developed cough after ACEi initiation, and approximately half of them developed cough within 1 week of ACEi initiation. Doctors should consider early follow-up for patients initiated on ACEi therapy to ensure adherence, quality of life, and minimise unnecessary treatment.

Introduction

Angiotensin-converting enzyme inhibitors (ACEi) are effective in the treatment of hypertension, left ventricular systolic dysfunction, post-myocardial infarction, renal failure, and diabetic nephropathy.[1] They inhibit angiotensin II formation and block the breakdown of bradykinin, leading to vasodilation and reduced arterial pressure, preload, and afterload.[2] ACEi are recommended as one of the first lines of therapy for newly diagnosed uncomplicated hypertension, and are the first agent of choice for patients with hypertension and diabetes, according to guidelines.[3] In Malaysia, perindopril is the most commonly prescribed ACEi, followed by enalapril.[4]

Despite the benefits of ACEi, dry cough is a troublesome side effect.[1,5] The mechanism of how these drugs induce cough remains unclear, but it likely involves the degradation of the protussive mediators bradykinin and substance P (a prostaglandin-like substance), leading to accumulation in the upper respiratory tract.[1,5,6] The accumulation of these substances causes irritation of the throat and is believed to induce the dry cough, which leads to non-adherence and withdrawal from therapy. ACEi-induced cough has been shown to occur within days to months (5–180 days) after initiation of therapy.[7]

The incidence of ACEi-induced cough has been shown to range between 5% and 30% in America, Israel, and Singapore.[8,9,10] This wide range in the incidence of ACEi-induced cough could be a result of differences in age,[11] gender,[8,11] ethnicity,[10,12,13] and genetics.[14, 15]

As ACEi-induced cough is one of the differential diagnoses of chronic cough,[16] it is important for physicians to recognise this phenomenon to avoid unnecessary investigation and treatment in patients treated

with ACEi.[17] Malaysia is a multi-ethnic country. Approximately 30% and 20% of the population aged 18 years and older have hypertension and diabetes, respectively.[18] A recent local paper that studied 13,784 medical records from 20 public primary care clinics found that 54.8% of patients with hypertension were taking ACEi, and 67.3% of hypertensive diabetic patients with proteinuria had been prescribed ACEi or angiotensin receptor blockers.[19] Despite ACEi being widely prescribed, there is a lack of research on the incidence of ACEi-induced cough. This study aimed to determine the incidence of ACEi-induced cough and its associated factors in a public primary care clinic in Malaysia.

Methods

Study design

A retrospective review was conducted on data from the electronic medical records of patients who attended a public primary healthcare clinic in Malaysia. The study centre was a public primary care clinic in Putrajaya, Malaysia that had a daily attendance of about 1,000 patients; it was chosen as the study centre as it had an electronic record system that enabled the retrieval of records.

The study population included all patients who were initiated on ACEi at the study centre from January 1, 2015, to December 31, 2015. To define this study population, the records of patients taking ACEi were generated on the electronic medical records using keywords (drug names, dispensing date, patient name, and identification number) from January 1, 2014, to July 31, 2016. If a patient's record was present in both 2014 and 2015, it would be excluded as it meant that the patient had been initiated on ACEi in 2014; if a patient's record was present only in 2015, it meant that the patient had been initiated on ACEi in 2015 and was included in our study population. Generated records included periods in 2016 to account for the possibility of ACEi-induced cough that occurred within 6 months of therapy initiation. Perindopril, perindopril/indapamide (Coversyl Plus), enalapril, and captopril were the selected drug names, as these were the only ACEi available at the study centre during the studied period.

The following records were excluded: 1) patients who defaulted follow-ups with no further clinic visits before July 31, 2016; 2) patients who were transferred to the clinic without the recorded date of ACEi initiation; 3) patients who were transferred to other clinics during the study period; 4) patients who were followed up at other clinics and attended the study clinic for a short period; and 5) patients who were given only a stat dose of ACEi. These patients were excluded as the adverse effects from ACEi could not be determined.

Baseline clinical and demographic data were collected, and each record was independently reviewed by two researchers.

Operational definition

We adapted the World Health Organisation Uppsala Monitoring Centre causality assessment system[20] to define ACEi-induced cough: 1) temporal relationship of cough to initiation of treatment ('Did the cough appear after the ACEi was administered?'), 2) absence of drugs or diseases that can cause cough ('Are there alternate causes [other than ACEi] that could solely have caused the cough?'), 3) discontinuation effect ('Did the cough improve when the ACEi was discontinued?'), and 4) re-introducing effect ('Did the cough reappear when ACEi was readministered?'). We then categorised the certainty of causality of ACEi-induced cough into four categories: 'certain of causality' (all criteria were fulfilled), 'probable of causality' (all criteria were fulfilled, except reintroducing effects), 'possible of causality' (all criteria fulfilled, except discontinuation and reintroducing effects), and 'unlikely of causality' (none of the criteria were fulfilled). Operationally, ACEi-induced cough was defined as all cases that were of certain, probable, and possible causality. Patients who developed cough and had documented asthma, chronic obstructive pulmonary disease, gastroesophageal reflux disease, upper respiratory tract infection, or smoking were categorised as 'unlikely of causality' for ACEi-induced cough.

Statistical methods

Statistical analyses were performed using Statistical Package for the Social Sciences version 22 (SPSS-22). The chi-square test was used for evaluating associations between categorical variables, while the independent t-test was used for continuous variables. Statistical significance was considered if $p < 0.05$.

Ethical consideration

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health

Malaysia (MREC approval reference number: [5] KKM/NIHSEC/P17-1170).

Results

A total of 1,091 patients were initiated on ACEi in 2015. Only 394 patients were eligible for this study, and 697 were excluded for the following reasons: 192 defaulted follow-ups with no further clinic visits before July 31, 2016; 383 were transferred to the clinic without the recorded date of ACEi initiation; 39 were transferred to another centre; 75 were followed up at other clinics and attended the study clinic for medication temporarily; and 8 were given only a stat dose of ACEi.

Table 1 shows the sociodemographic profile of the study population. Of the 394 patients, 93.7% were Malay, 57.1% were male, 95.4% had hypertension, and 48.7% had diabetes. A total of 386 (98.0%) patients were initiated on perindopril, 6 patients on perindopril/indapamide (Coversyl Plus), 1 patient on captopril, and 1 patient on enalapril.

Table 1. Sociodemographic profile of the study population (n=394).

Variable	No. (%)
Gender	
Male	225 (57.1)
Female	169 (42.9)
Ethnicity	
Malay	369 (93.7)
Indian	11 (2.8)
Chinese	10 (2.5)
Others	4 (1.0)
Comorbidity*	
Hypertension	376 (95.4)
Diabetes Mellitus	192 (48.7)
Chronic Kidney Disease	13 (3.3)
Ischemic Heart Disease	8 (2.0)
Heart Failure	4 (1.0)
Stroke	4 (1.0)

* Some patients had multiple comorbidities.

The incidence of ACEi-induced cough was 24.1% (n=95), of which 92 patients discontinued the drug, and 3 patients continued with therapy despite the cough. Of the 394 patients on ACEi, 107 (27.2%) discontinued the drug; in addition to the 92 patients who discontinued due to ACEi-induced cough, 15 discontinued for other reasons, such as pregnancy, dizziness, allergic reaction, and erectile dysfunction. Among the 95 patients who had ACEi-induced cough, 47 (49.5%) were male, 90 (94.7%) were Malay, 2 (2.1%) were Chinese, 94 (98.9%) had hypertension, 40 (42.1%) had diabetes, and 94 (98.9%) had been initiated on perindopril.

Table 2 shows the duration of ACEi therapy before the development of cough. Among the 95 patients who had ACEi-induced cough, 44.2% developed cough on the same day of initiation, 52.6% developed within 1 week, 69.4% within 1 month, and 25.3% within 1–6 months. We did not find any significant associations between age, gender, ethnicity, type of ACEi, and incidence of ACEi-induced cough.

Table 2. Duration of ACEi therapy before the development of cough.

Duration	No. (%) (n=95)*
On the same day (0–1 day)	42 (44.2)
1–6 days	8 (8.4)
7–30 days	16 (16.8)
1–6 months	24 (25.3)
>6 months	5 (5.3)
Total	95 (100.0)

* Total number of patients with ACEi-induced cough.

Discussion

We found the incidence of ACEi-induced cough to be 24.1%. This value was consistent with values reported in other studies, which ranged from 5% to 20%,[8,9] but was lower than in other Asian countries, where 30% to 44% of patients were reported to have ACEi-induced cough.[10,13] The reasons for this variation could be due to ethnicity[10,12,13] or genetics.[14, 15]

Our study population was mostly of the Malay ethnic group, in which the incidence of ACEi-induced cough had not been previously reported. A study in Singapore on mainly ethnically Chinese patients had reported that 30.4% had ACEi-induced cough.[10] Studies on American and Hong Kong Chinese patients found that 34% and 44% developed ACEi-induced cough, respectively, while the general American population reported an incidence of 13%.[12,13] Furthermore, we did not find any association between ethnicity and incidence of ACEi-induced cough. Previous studies had shown that females were more susceptible to ACEi-induced cough[8,11] and this was related to pharmacokinetic, pharmacodynamic, or pharmacogenetic differences.[11] We did not find any significant association between gender and ACEi-induced cough. We cannot conclude whether there were associations between ethnicity, gender, and incidence of ACEi-induced cough, as our study cohorts of Chinese and female patients were small. Future prospective studies are needed to determine possible associations between these two factors and ACEi-induced cough.

Among the 394 patients initiated on ACEi, 42 (10.7%) developed cough on the day of therapy initiation and 50 (12.7%) developed cough within 1 week of therapy initiation. Cough may occur within hours of the first dose of medication, or its onset can be delayed for weeks or up to 6 months after the initiation of therapy.[7] Therefore, it is desirable to conduct a follow-up for patients initiated on ACEi 1 week after initiation, to identify possible cough development that may affect compliance. The decision to discontinue ACEi therapy could then be decided cooperatively by the patient and doctor, taking into consideration the indications and benefits of the therapy and the patient's tolerance to cough.

This study was limited by record review of indications and reasons for discontinuing ACEi therapy, which may have led to bias. Approximately two thirds of the patients were excluded due to challenges during follow-ups and data retrieval; this could be attributed to the lack of continuity of care in the current primary care system, where patients are free to attend any clinic of their choice for care. A prospective study would mitigate the possible bias due to the number of records being excluded. We defined patients who had documented diseases that could cause cough as 'unlikely of causality' for ACEi-induced cough, which could have underestimated the incidence of ACEi-induced cough. The samples were from a single public primary care clinic and may not have been representative of the entire population of Malaysia. However, these findings have provided insight into the estimated incidence of ACEi-induced cough in a majority Malay ethnicity group, where this data is lacking. Future prospective studies should be conducted in more primary care clinics in areas with a higher proportion of other ethnic groups and in private primary care clinics to improve the generalisability of the results.

We found the incidence of ACEi-induced cough to be 24.1% in a majority Malay population, and approximately half of the patients developed cough within 1 week of ACEi initiation. Early review of patients 1 week after ACEi initiation would ensure adherence and minimise unnecessary treatment for ACEi-induced cough.[17]

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Conflicts of interest

The authors have no conflicts of interest to declare.

How does this paper make a difference in general practice?

- There are no published local data on ACEi-induced cough, despite hypertension and diabetes being the most common non-communicable diseases in Malaysia, and ACEi being widely prescribed in general practice.
- There are no data on ACEi-induced cough among the Malay ethnic group, who this paper addresses, especially in Southeast Asian countries.
- We found that approximately one quarter of patients developed cough after ACEi initiation, and approximately half of them developed cough within 1 week of ACEi therapy initiation. Doctors should consider early follow-up for patients initiated on ACEi therapy to ensure adherence, quality of life, and minimise unnecessary treatment.

References

1. Wong J, Patel RA, Kowey PR. The clinical use of angiotensin-converting enzyme inhibitors. *Prog Cardiovasc Dis*. 2004;47(2):116–130. doi:10.1016/j.pcad.2004.04.003
2. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-converting enzyme inhibitors in hypertension: to use or not to use? *J Am Coll Cardiol*. 2018;71(13):1474–1482. doi:10.1016/j.jacc.2018.01.058
3. Ministry of Health Malaysia. *Malaysia Clinical Practice Guideline: Management of Hypertension*. 5th ed. MOH; 2018:42. Accessed March 17, 2021. https://www.moh.gov.my/index.php/pages/view/133
4. Chok CFM, Ahmad Shanizza AI. Malaysian Statistics on Medicines 2015-2016. Kuala Lumpur: Pharmaceutical Services Programme, Ministry of Health Malaysia; 2020. Pg 42
5. Omboni S, Borghi C. Zofenopril and incidence of cough: a review of published and unpublished data. *Ther Clin Risk Manag*. 2011;7:459–471. doi:10.2147/TCRM.S25976
6. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(supp 1):169S–173S. d doi:10.1378/chest.129.1_suppl.169S
7. Salami AK, Katibi IA. Angiotensin-converting enzyme inhibitor-associated cough: a prospective evaluation in hypertensives. *Ann Afr Med*. 2005;4(3):118–21.
8. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann Intern Med*. 1992;117(3):234–242. doi:10.7326/0003-4819-117-3-234
9. Ravid D, Lishner M, Lang R, Ravid M. Angiotensin-converting enzyme inhibitors and cough: a prospective evaluation in hypertension and in congestive heart failure. *J Clin Pharmacol*. 1994;34(11):1116–1120. doi:10.1002/j.1552-4604.1994.tb01989.x
10. Ng LP, Goh PS. Incidence of discontinuation of angiotensin-converting enzyme inhibitors due to cough, in a primary healthcare centre in Singapore. *Singapore Med J*. 2014;55(3):146–149. doi:10.11622/smedj.2014034
11. Alharbi FF, Kholod AAV, Souverein PC, et al. The impact of age and sex on the reporting of cough and angioedema with renin-angiotensin system inhibitors: a case/noncase study in VigiBase. *Fundam Clin Pharmacol*. 2017;31(6):676–684. doi:10.1111/fcp.12313
12. Tseng DS, Kwong J, Rezvani F, Coates AO. Angiotensin-converting enzyme-related cough among Chinese-Americans. *Am J Med*. 2010;123(2):183.e11–183.e1.83E15. doi:10.1016/j.amjmed.2009.06.032
13. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. *Br J Clin Pharmacol*. 1995;40(2):141–144.
14. Nishio K, Kashiki S, Tachibana H, Kobayashi Y. Angiotensin-converting enzyme and bradykinin gene polymorphisms and cough: a meta-analysis. *World J Cardiol*. 2011;3(10):329–336. doi:10.4330/wjc.v3.i10.329
15. Mukae S, Aoki S, Itoh S, Iwata T, Ueda H, Katagiri T. Bradykinin B(2) receptor gene polymorphism is associated with angiotensin-converting enzyme inhibitor-related cough. *Hypertension*. 2000;36(1):127–131. doi:10.1161/01.hyp.36.1.127
16. Holmes RL, Fadden CT. Evaluation of the patient with chronic cough. *Am Fam Physician*. 2004;69(9):2159–2166.
17. Sebastian JL, McKinney WP, Kaufman J, Young MJ. Angiotensin-converting enzyme inhibitors and cough. Prevalence in an outpatient medical clinic population. *Chest*. 1991;99(1):36–39. doi:10.1378/chest.99.1.36
18. Institute for Public Health 2020. National Health and Morbidity Survey (NHMS) 2019: Non-communicable diseases, healthcare demand, and health literacy–Key Findings. National Institute of Health, Ministry of Health Malaysia; 2020. Pg 10.
19. Teh XR, Lim MT, Tong SF, Husin M, Khamis N, Sivasampu S. Quality of hypertension management in public primary care clinics in Malaysia: an update. *PLoS One*. 2020 Aug 11;15(8):e0237083. doi:10.1371/journal.pone.0237083
20. Zaki SA. Adverse drug reaction and causality assessment scales. *Lung India*. 2011;28(2):152–153. doi:10.4103/0970-2113.