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SHORT COMMUNICATION

The Effects of Antitussive Treatment of ACE Inhibitor-Induced Cough on Therapy Compliance: A Prescription Sequence Symmetry Analysis

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Abstract
Background A common adverse effect of angiotensin-converting enzyme inhibitors (ACEI) is a persistent dry cough. Physicians and pharmacists who fail to recognise dry cough to be ACEI related may prescribe antitussives, instead of recommended ACEI substitution.
Objective The aim of this study was to determine the influence of antitussive treatment of ACEI-induced cough on ACEI therapy compliance.
Methods Prescription data from community pharmacies between 2000 and 2012 were retrieved from the IADB.nl database (InterAction Database) in The Netherlands. A prescription sequence symmetry analysis was used to determine whether antitussive agents were prescribed more often following ACEI initiation (cases) than the other way around (controls). ACEI therapy compliance was assessed using the proportion of days covered (PDC) method; patients with a PDC of at least 80 % were considered compliant. Compliance was compared between patients receiving antitussives for ACEI-induced cough and patients receiving antitussives for other reasons and patients who did not receive antitussives.
Results A total of 1,898 starters of ACEI and antitussives within a half-year time span were included. A significant excess of patients received antitussives after ACEI initiation compared with before ACEI initiation (1,269 cases vs. 629 controls), yielding a sequence ratio of 2.0 (95 % CI 1.8–2.2). The estimated proportion of patients with ACEI-induced cough receiving antitussives decreased over time: from 20.4 % in 2000–2004 to 8.0 % in 2008–2012. ACEI therapy compliance in patients receiving antitussives due to ACEI initiation was 52.4 %, significantly lower than compliance in control patients receiving antitussives for cough unrelated to ACEI (75.5 %, $P < 0.001$) and control patients who did not receive antitussives (75.2 %, $P < 0.001$).
Conclusions Many patients receive antitussives after ACEI initiation. This suggests that ACEI-induced cough is often either not recognized as being ACEI related or is symptomatically treated. Such prescription behaviour may decrease ACEI therapy compliance.

1 Introduction

Angiotensin-converting enzyme inhibitors (ACEI) inhibit the renin–angiotensin–aldosterone system (RAAS) and are prescribed for various cardiovascular and renal diseases [1–3]. Although ACEI are not associated with long-term adverse outcomes, a common acute adverse drug effect is a persistent dry cough, the frequency of which ranges from 5 % to 20 % [4, 5]. This adverse effect usually develops within a few weeks after ACEI initiation, is not dose-dependent, and is more common in women, non-smokers and Asians [5–8]. After ACEI discontinuation, the adverse effect will usually abate within a few days [9, 10]. If the cough is not mild enough to tolerate, substitution of ACEI with alternative RAAS blocking agents, namely angiotensin II antagonists, is recommended [9, 11].

Despite the fact that the adverse drug effect and recommended course of action are well known, misdiagnosis is common [12]. A previous study from our group reported that ACEI-induced cough is treated with antitussives (e.g.

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noscapine or codeine) in around 15 % of all cases [13]. There are several reasons why antitussive treatment of ACEI-induced cough, instead of substituting alternative antihypertensives, constitutes irrational pharmacotherapy:

1. Antitussives are not effective for this adverse drug effect [5, 14].
2. Patients are unnecessarily exposed to the adverse drug effects of antitussives, which include fatigue and nausea. This furthers the so-called 'prescribing cascade', in which adverse drug reactions are misinterpreted as new medical conditions and treated with more drugs. Such 'prescribing cascades' should be avoided [15, 16].
3. An association has been reported between ACEI-induced cough and increased risk of angio-oedema [8], which is a potentially fatal affliction. There is a lack of available evidence on this matter, however.
4. Antitussive treatment of ACEI-induced cough may adversely affect ACEI therapy compliance.

The influence of antitussive treatment of ACEI-induced cough on therapy compliance has not been studied before. We hypothesised that there would be a decreased compliance, as self-initiated therapy modification of hypertension treatment is common in patients with medication problems [17]. The aim of this study was to test our hypothesis in a large, observational prescription database.

2 Methods

To test our hypothesis, we compared ACEI-treated patients who received antitussives for ACEI-induced cough (cases) with ACEI-treated patients who received antitussives for other reasons (controls-1); and with a second control group composed of ACEI-treated patients who never received antitussives (controls-2).

Drug-dispensing data between 2000 and 2012 were retrieved from the IADB.nl database (InterAction Database). This database holds prescription records of over 500,000 individuals, containing basic patient characteristics (anonymous identifier, sex and date of birth) and information on drug name, dosage and dispensing date [18, 19]. Over the counter (OTC) drugs are not included. As patient commitment to their pharmacy is high in The Netherlands [20] complete medication histories could be retrieved.

Incident users of both ACEI and antitussives within a half-year time span were identified; there was no minimum duration of use for either drug. A prescription sequence symmetry analysis was used to determine whether antitussive agents were prescribed more often following ACEI initiation (cases) as compared with antitussives followed by ACEI (controls-1) [21]. Because of the within-person design, the sequence ratio is robust towards confounders that are stable over time, but sensitive to trends over time. The outcome was therefore adjusted for time trends in drug use [21]. The rationale, advantages and limitations of the prescription sequence analysis and the adjustment for time trends in drug use are discussed in detail elsewhere [21]. Because available data spanned 12 years, three separate analyses were performed covering 4-year periods to identify possible time trends: from the beginning of 2000 to the end of 2003; from the beginning of 2004 to the end of 2007; and from the beginning of 2008 to the end of 2011.

Therapy compliance (adherence) is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [22]. The proportion of days covered (PDC) method was used, calculated as the number of days the patient had access to the ACEI in 1 year, divided by 365 [23]. In case of overlapping prescriptions, the second prescription was shifted forward to account for drug stockpiling. Based on empirical studies on compliance and health outcomes [24–27] a threshold of 80 % was used to dichotomize between compliant and non-compliant patients. Patients who switched to angiotensin II antagonists were excluded, as were patients who received only one ACEI prescription or those who could not be followed in the database for 1 year (censored). Thus, compliance was assessed in patients on chronic ACEI therapy.

Because cough is a very common disorder, there will be patients in the cases group who received antitussives for complaints not related to the ACEI therapy. Differences in compliance were therefore adjusted for antitussives prescribed for unrelated respiratory problems, by determining the *excess* of non-compliant patients in cases (those receiving antitussives after ACEI initiation) relative to controls (those having received antitussives before ACE initiation) [21]. This was based on the assumption that the rate of cough unrelated to ACEI therapy was similar in both patient groups. A further control group was formed from ACEI-treated patients who never received antitussives (controls-2). Differences in compliance were tested using the Chi-squared test. Statistical analyses were performed using Microsoft Excel, version 2010 (Microsoft Corporation, Redmond, WA, USA).

3 Results

A total of 47,802 incident users of ACEI therapy were identified. Of these, 1,943 patients initiated ACEI and antitussives (mainly codeine and noscapine) within a half-year time span. Forty-five patients (2.3 %) started both therapies on the same day and were excluded. In the remaining 1,898

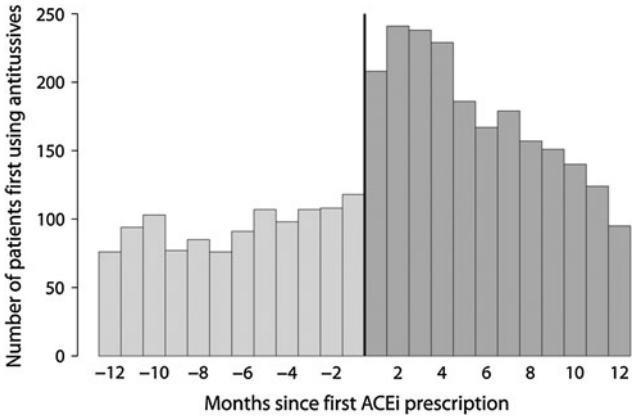

Fig. 1 Prescription asymmetry in the initiation of ACEIs and antitussives. For the analyses, only patients from month −6 to month +6 were selected. *ACEIs* angiotensin-converting enzyme inhibitors

patients, the mean age at ACEI initiation was 64.4 ± 13.5 years; 58.3 % were female. There was prescription *asymmetry* in the initiation of ACEI and antitussives, as shown in Fig. 1. A total of 1,269 patients started ACEI therapy first and antitussives second, whereas 629 patients started antitussive therapy first, yielding a sequence ratio of 2.0 (95 % CI 1.8–2.2). The results were not significantly influenced by time trends in prescribing. Thus, patients initiating ACEI therapy were twice as likely to be prescribed antitussives compared with patients who did not receive ACEI therapy. The duration of antitussive treatment was a bit longer in cases compared with controls, although this difference was not statistically significant (cases: median 13 days, mean 29 days; controls: median 10 days, mean 22 days; $P = 0.08$).

The sequence ratio analysis was repeated in 4-year periods (Table 1). There was a decrease in the likelihood of being prescribed antitussives following ACEI initiation over time. The percentage of ACEI-induced cough treated with antitussives also decreased over time, although a considerable amount of mistreatment was found in all time periods.

For the analysis of ACEI compliance, 34 % of patients were excluded: 20 % because they switched to an angiotensin II antagonist, 9 % because they were censored within 1 year and 5 % who received only one ACEI prescription. Corrected for non-ACEI-related antitussive prescriptions, compliance in chronic users who received antitussives due to ACEI was 52.4 %, whereas it was 75.5 % in the control-1 group ($P < 0.001$) [Table 2]. Patients receiving antitussives due to ACEI were more likely to be non-compliant, odds ratio 2.8 (95 % CI 2.2–3.6). Therapy compliance in the control-2 group of ACEI users who never received antitussives was 75.2 %. This was not different from control-1 ($P = 0.818$), but significantly higher than compliance in patients with antitussive treatment due to ACEI ($P < 0.001$) [Fig. 2].

4 Discussion

A significant and clinically relevant excess of patients receive antitussive agents in the first half-year after ACEI initiation compared with the 6 months before ACEI initiation. In these cases, dry cough is either not recognized by health-care professionals as being ACEI related or is symptomatically treated with antitussives. Interestingly, the risk for patients receiving antitussives after ACEI initiation decreased over time. This might be due to increased knowledge of the adverse drug effect by health-care professionals over time, or due to reluctance in earlier years to substitute ACEI with the newer angiotensin II antagonists. It may also be caused by increased use of OTC antitussives, which could not be measured in our study. Still, even in the most recent time period (between 2008 and 2012), there remained a significantly increased risk of misdiagnosis and mistreatment of ACEI-induced cough. The recommended course of action for troublesome ACEI-induced cough is substitution with other RAAS blocking agents such as angiotensin II antagonists, for which the frequency of cough is much lower [28].

Table 1 Difference in antitussive treatment of ACEI-induced cough over time

Time period	Total ACEI users	Sequence order[a]	Sequence rate (95 % CI)	Estimated % mistreated cough[b]
Overall (2000–2012)	47,802	1,269/629	2.0 (1.8–2.2)	13.4
2000–2004	13,972	512/227	2.3 (1.9–2.6)	20.4
2004–2008	17,368	448/225	2.0 (1.8–2.4)	12.8
2008–2012	16,462	309/177	1.7 (1.5–2.1)	8.0

ACEI angiotensin-converting enzyme inhibitor

[a] The sequence order is the number of patients who received antitussives after ACEI initiation divided by the number of patients who received antitussives before ACEI initiation; the outcome of this division is shown in the 'Sequence rate' column

[b] The estimated frequency of antitussive treatment of ACEI-related cough is the difference between the sequence orders, divided by the total number of ACEI-related cough cases (assumed at a prevalence of 10 % of all ACEI users) [13]

Table 2 Compliance with ACEI therapy, unadjusted and adjusted for unrelated antitussive prescriptions in the cases

	No. of compliant patients (%)	No. of non-compliant patients (%)	Odds ratio (95 % CI)
Unadjusted results			
Cases[a]	534 (64.1)	299 (35.9)	1.7 (1.3–2.3)
Controls-1[a]	299 (75.5)	103 (24.5)	
Adjusted results[b]			
Cases	216 (52.4)	196 (47.6)	2.8 (2.2–3.6)
Controls-1	636 (75.5)	206 (24.5)	

ACEI angiotensin-converting enzyme inhibitor

[a] Cases were patients receiving antitussives for ACEI-related cough; controls-1 were patients receiving antitussives for cough unrelated to ACEI

[b] Adjusted results were derived by calculating the *excess* of compliant and non-compliant patients in cases relative to controls [21]

Antitussive treatment of ACEI-induced cough is ineffective [5, 14], contributes to an unnecessary prescribing cascade [15, 16] and may be associated with an increased risk of angio-oedema [8]. Our present study adds to this list the novel finding that antitussive treatment of ACEI-induced cough decreases ACEI therapy compliance. Therapy compliance in patients receiving antitussives due to ACEI was 52.4 %, compared with 75.2 % in the control groups (controls-1 and controls-2 combined). Non-compliance with ACEI is known to be associated with increased hospitalizations in patients with hypertension [27] and increased mortality in patients with diabetes mellitus and ischaemic heart diseases [24–26].

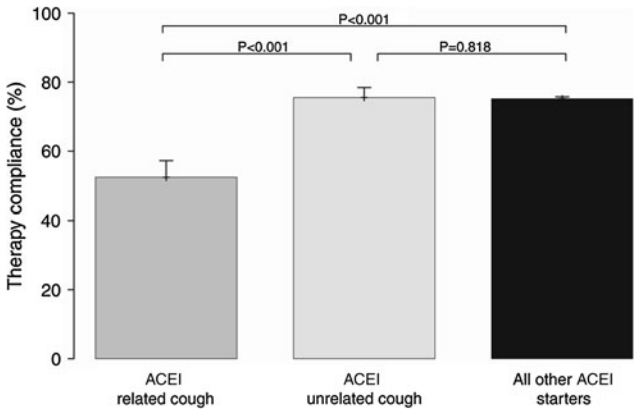

Fig. 2 Reduced compliance with ACEI therapy was seen in patients receiving antitussives for ACEI-related cough (cases, *left bar*) compared with patients receiving antitussives for cough unrelated to ACEI (controls-1, *middle bar*) and patients who did not receive antitussives (controls-2, *right bar*). For ease of interpretation, prescription of antitussive treatment was described as 'cough' in the label text. *ACEI* angiotensin-converting enzyme inhibitor

Compliance was assessed in patients on chronic ACEI therapy; censored patients or those switching to angiotensin II antagonists were excluded. Therefore, our findings apply to patients receiving antitussives due to ACEI-related cough in whom ACEI therapy is not discontinued. The threshold to define compliant patients in this study was 80 %, following previous studies [24–27]; varying this threshold to 70 % or 90 % did not substantially change the results (data not shown).

A limitation of our study is the fact that OTC antitussives were not included in our database. This might have led to underestimation of the frequency of antitussive treatment of cough if patients attempted to manage the adverse drug effect without consulting health-care providers. It might also have overestimated the results if patients who initiated ACEI therapy afterwards more frequently visited health-care providers for unrelated respiratory problems. However, this limitation is not expected to have influenced differences in therapy compliance. It is possible that patients with ACEI-related cough did not switch to angiotensin II antagonists but to other antihypertensives. When we accounted for this possibility in our analysis, the difference in compliance remained (56.3 % in cases vs. 77.1 % in the control groups, $P < 0.001$). Differences in compliance were adjusted to account for the fact that some cases may have received antitussives for complaints not related to the ACEI therapy. This adjustment rests on the assumption that the rate of cough unrelated to ACEI therapy is similar in both cases and controls; for completeness, both uncorrected and corrected results are shown.

5 Conclusion

We confirmed that patients with ACEI-induced cough are often treated with antitussives. We found that this prescription behaviour decreased therapy compliance with ACEI therapy by a large extent.

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