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Title page

Title:

ACE-inhibitor use and pneumonia risk in a general, essentially white population

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Abstract:

Objectives: To assess whether use of ACE-inhibitors is associated with a decreased risk of hospitalization for community-acquired pneumonia (CAP) in a general, essentially white population.

Patients and methods: Data were obtained from the Dutch PHARMO Record Linkage System. Cases were defined as patients with a first hospital admission for CAP. For each case, up to 4 population controls were matched by age and gender.

Main Results: The study population comprised 1,108 patients with a first hospital admission for CAP and 3,817 matched controls. After adjusting for several confounders, ACE-inhibitor use was not associated with a decreased incidence of pneumonia (adjusted OR 1.12; 95% CI 0.88 to 1.43). Additionally, no significant association was observed in patients with diabetes, patients with respiratory diseases, patients with heart failure, and patients with both of the last two conditions. Furthermore, adjustment of treatment effects on pneumonia risk using stratification on balancing score also showed no significant association between ACE-inhibitor use and pneumonia risk within the different strata (overall adjusted OR 1.09, 95% CI 0.87 to 1.36).

Conclusions: In contrast to previous findings in Asian populations, we were not able to confirm the beneficial effect of ACE-inhibitors on pneumonia risk in a general, essentially white population.

Key words:

angiotensin-converting enzyme inhibitor, angiotensin-converting enzyme insertion/deletion polymorphism, pneumonia

Introduction

Community-acquired pneumonia (CAP) is a major direct cause of death in the elderly with mortality rates varying from 5-20% [1, 2]. The increased incidence of CAP in the elderly is thought to be caused first by silent or manifest aspiration of oropharyngeal flora into the lungs and second by decreased function of the immune system [3, 4]. Angiotensin-converting enzyme (ACE) has a number of functions in the inflammatory/immune system. Along with its effects that cleave angiotensin I to angiotensin II, ACE also metabolizes the protussive peptides, substance P and bradykinin [5]. The decreased metabolism of these peptides by ACE inhibition could enhance the cough reflex and prevent aspiration. Besides this, ACE inhibition prevents the angiotensin II induced transcription of the proinflammatory nuclear factor-kappaB [6, 7]. Recent studies have demonstrated that ACE inhibitor use is associated with a reduced incidence of pneumonia, particularly in the elderly [8-12]. These studies were performed in subjects of Asian ethnicity with a history of stroke. Although these studies add to the body of evidence about the possible effects of these drugs on pneumonia risk, still little is known about the extent of the protective effect and whether or not it is present in the general population. The aim of this study was to assess whether use of ACE-inhibitors is associated with a decreased risk of hospitalization for community-acquired pneumonia (CAP) in a general, essentially white population.

Methods

Data source

The setting of the study was the PHARMO record linkage system (www.pharmo.nl). PHARMO includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of more than two million community-dwelling residents of more than forty population-defined areas in the Netherlands from 1985 onwards [13]. Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to receipt of prescription drugs.

The computerized drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Centre for Healthcare Information (LMR database), an institute that collates nationwide all hospital discharge records in the Netherlands since the 1960s into a standardized format. These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Patients

The study period consisted of the 6-year period between January 1, 1995 and December 31, 2000. Cases were selected according to the following criteria: adult (> 18 years old) and

hospitalized with a primary discharge diagnosis of CAP: pneumococcal pneumonia (ICD-9-M code 481), other bacterial pneumonia (ICD-9-M code 482), bronchopneumonia, organism unspecified (ICD-9-M code 485) or pneumonia, organism unspecified (ICD-9-M code 486). Besides this, patients with a signature of bacterial pneumonia (secondary discharge diagnosis) coupled with a primary pulmonary diagnosis (ICD-9-M codes 491-493 or 496) were selected. Deaths that were recorded during hospitalization also were selected as case. For each case, up to 4 population controls were matched by age and gender. Controls were patients present in the PHARMO database without a hospitalization for CAP. The date of admission was the index date. For all subjects pharmacy dispensing data were collected. Patients with no pharmacy dispensing history for the period minus 365 days till the index date were excluded.

Study design

A population based case-control study.

Exposure assessment

For each patient we identified all prescriptions for ACE-inhibitors and angiotensin-II antagonists (ATC code C09A to C09D) between entry into the cohort and the index date. The exposure time of ACE-inhibitor and angiotensin-II antagonist use was determined by calculation of the legend duration of treatment episodes. Treatment episodes were defined as series of subsequent prescriptions refills for these drugs. A new episode was assumed if an interval of 30 or more occurred between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient. Patients were classified as current users when the index date was between the start and the end date of a treatment episode. Patients were classified as past users when they were not using at the index date, but

had a history of use in the year before the index date. A patient was classified as new user when he received a first dispensing less than 14 days prior to the index date.

Assessment of potential confounders

Potential confounders in this study were drugs and 'medical signatures' as measured by the receipt of prescriptions drugs that have been associated with an increased or decreased risk of CAP [14-17]. The use of cardiovascular drugs (cardiac glycosides and diuretics) was used as marker for heart failure. Respiratory morbidity was measured by the use of inhaled glucocorticoids, beta-agonists or anticholinergic drugs. Furthermore we assessed diabetes through the use of oral antidiabetic agents and or insulin [18]. Identified confounding drugs were systemic glucocorticoids [19] and gastric acid suppressing drugs [20]. For all these drugs a patient was considered exposed if more than one dispensing did take place within a one year period prior to the index date.

Analysis

We approached data analysis in two ways. First, as measure of the association between ACE-inhibitor use and the occurrence of hospitalization for CAP, estimations of the relative risk through odds ratios (OR) were used. These were calculated using multivariable ~~te~~ conditional logistic regression. Statistical interaction terms were used to determine potential modification of the association by co-morbidities (heart failure, respiratory diseases or diabetes). Second, we applied the balancing score method to further determine potential modification of the effect of ACE-inhibition by overall pneumonia risk [21, 22]. This technique enables assessment of the association of ACE-inhibitor use with pneumonia occurrence in patients who have an equal probability of being a case. Logistic regression analysis was used to model for being a case. Variables considered for inclusion in this model included all prescription

drugs (except ACE-inhibitors and angiotensin II antagonists) evaluated as potential confounders in the study. The model was used to calculate the probability of being a case for each individual patient in the full data set (1.108 cases, 3.817 controls). Patients were stratified by quintiles of the distribution of their balancing score. The goodness of fit of the balancing score was evaluated by its ability to balance the covariates within each quintile group, using the logistic regression. Subsequently, the effect of ACE-inhibitor use on pneumonia risk was assessed within each quintile group. An overall effect was calculated using the Mantel-Haenszel statistic.

Results

A total of 1.108 patients with a primary diagnosis of CAP were identified and matched to 3.817 controls. Baseline characteristics are shown in Table 1. Both cases and controls had an average age of 67 years (± SE~~M~~ 0.51), and about 55% of the patients were male. The use of prescription drugs for both cases and controls is shown in Table 2. The prevalence of using ACE-inhibitors (current use) was higher among the cases (15.2%) than among controls (9.7%), yielding a crude OR of 1.65 (95% CI 1.36 to 1.99). Because only a very small number of patients (2.1%) were using Angiotensin-II antagonists this was not further analyzed. None of the patients could be classified as new user of ACE-inhibitors or angiotensin-II antagonists. After adjusting for respiratory diseases, heart failure, diabetes and the use of systemic corticosteroids and gastric acid suppressing drugs the OR decreased to 1.12 (95% CI 0.88 to 1.43). Considering different co-morbidities,as shown in Table 3, no significant association was observed in patients with diabetes (adjusted OR 1.02, 95% CI 0.59-1.77), patients with respiratory diseases (adjusted OR 0.97, 95% CI 0.59 to 1.60), patients with heart failure (adjusted OR 0.69, 95% CI 0.30 to 1.60) and patients with both of the last two conditions (adjusted OR 1.06, 95% CI 0.40 to 2.87).

The balancing score derivation model-which included the variables use of cardiac glycosides, diuretics, calcium channel blockers, oral corticosteroids, anticholinergic inhalation, beta-agonists, inhaled corticosteroids, gastric acid suppressing drugs, cancer medication and flu vaccination-was reliable as the odds ratios for component variables were all between 0.90 and 1.10 and none of the variables reached a significance level of 0.05 in any of the strata. In none of the balancing score strata ACE-inhibitor use was significantly associated with pneumonia risk (Table 4; overall adjusted OR 1.09, 95% CI 0.87 to 1.36).

Discussion

In our study, no significant association between use of ACE inhibitors and reduced risk of hospitalization for community-acquired pneumonia could be observed in a general, essentially white population. The initially observed overall higher use of ACE-inhibitors for the cases compared to controls could in our opinion be explained by cardiovascular morbidity as risk factor and indication for inpatient treatment of CAP [1, 16]. The fact that many of our patients used an ACE-inhibitor in combination with a diuretic and cardiac glycosides could mean they were suffering from congestive heart failure as well. Additionally, the use of respiratory drugs was also higher for the cases, confirming chronic pulmonary diseases as risk factor for community-acquired pneumonia [17]. The striking lower use of beta-blockers for the cases could, in our opinion, be explained as confounding by contra-indication. In the study period observed the use of beta-blockers was contra-indicated for both heart failure and patients with asthma or COPD (non-selective beta-blockers) [23].

When considering the reduction of CAP risk by the use of ACE-inhibitors, there are several reasons to explain the difference between our findings and the Asian studies mentioned before [8, 10, 11]. One major difference with the study of Okaishi et al. is that we included patients with CAP admitted to a hospital, instead of nosocomial pneumonia in an inpatient ward. Besides this, they only included 55 cases and almost 80 percent of all cases (47% for controls) in this study were suffering from dementia and in bedridden state. It is unclear in what way pneumonia risk could be affected by these underlying chronic conditions. Previous studies have shown an increased pneumonia risk among patients in bedridden state, it is presumable that ACE-inhibitors can be protective in this specified patient group but that its protective effect is absent in a larger general population. In comparison with our study, Ohkubo et al. only included patients with a history of stroke or transient ischemic attack. In this randomized

trial a subject was considered as case if pneumonia was reported by the patient during a routine follow-up with the researcher. The high percentage of fatal pneumonia in their study (115 fatal and 155 nonfatal) is remarkable. In our study only 7.4% of all pneumonias was fatal, a percentage that corresponds well with literature giving mortality rates between 5 and 20% [1, 2]. Given this information, this could mean an underestimation of nonfatal pneumonias in their study population. Another difference previously mentioned is the ethnicity. Okaishi used Asian subjects exclusively and Ohkubo has a high percentage (39%) of Asian subjects as well. Although Ohkubo et al. studied a more ambulatory population of patients with a history of stroke, they were not able to associate ACE-inhibitor use with reduced pneumonia risk in their non-Asian participants. Something which seems to be confirmed in the present study. One possible explanation for this is the higher prevalence of the I allele and II genotype in Asian participants. The ACE I/D polymorphism accounts for 47% of the total variance of serum ACE, with lowest ACE levels in the II genotype [24].

As mentioned before, induction of the cough reflex is one possible explanation for the protective effect of ACE-inhibitors on pneumonia risk. The mechanisms by which ACE-inhibitors induce cough are thought to be inhibition of ACE and with this the metabolism of bradykinin and substance P, both inflammatory peptides which sensitize airway sensory nerves and enhance the cough reflex [5]. Considering that patients with the II genotype already have lowest ACE activity, administration of an ACE-inhibitor in these patients could increase bradykinin levels possibly above a cough threshold. Something which seems to be confirmed by the study of Ye et al. showing that the cough induced by ACE-inhibitors was related to I allele and II genotype and that ACE-levels were significantly lower in patients with ACE-inhibitor induced cough [25]. Besides this, ACE-inhibitor related cough has been reported to be more prevalent in individuals of Asian ethnicity [26]. As the prevalence of the

II genotype in the white and African populations is low compared with the Asian (18% vs. 39%) [24], this provides a possible explanation why we were not able to associate ACE-inhibitor use with a reduced pneumonia risk in a general, essentially white population. However, in the recent study of Ohkubo et al. [10] this hypothesis could not be confirmed possibly indicating that other unknown factors could be involved.

Strength of our study is that we were able to include a large number of patients, that the study was population based and that we had good data quality regarding exposure assessment. Besides this, we used different methods to adjust for potential confounding. In both models no association between ACE-inhibitor use and pneumonia risk could be observed. The application of the balancing score method to stratify patients in our case-control study provided additional information that ACE-inhibitor use was not associated with hospitalization for community-acquired pneumonia in both low and high risk patients.

A limitation of our study is that we only selected cases of CAP who got hospitalized. Considering that not all community-acquired pneumonia is treated as inpatient and that only the cases at risk for worse outcome get hospitalized this means we cannot conclude whether or not ACE inhibitors can be protective in low risk patients. Another limitation is that we included pneumonia based on ICD-9 codes [27]. In our study over 70% of the patients had a diagnosis of pneumonia of unspecified organism recorded. It is known from literature that the etiology of the infectious agent in many pneumonia cases remains unknown [28]. This could imply that for example some nonpneumonic exacerbations of COPD could be incorrectly recorded as pneumonia. But other studies using advanced analytical techniques report percentages with known etiology up to 87% [29, 30], indicating that the fact no organism was specified using conventional techniques does not imply no pathogen was involved. Concerning adjusting for confounding in our study, we corrected for as many confounders as

possible. However, we realize that there are additional risk factor that could not be controlled for [15-17]. In our study we used “medical signatures” by the receipt of prescription drugs to adjust for confounding through co-morbidities. For this reason we were not able to adjust for other additional risk factors (e.g. current smoking, low body mass index, excessive use of alcohol, hypertension or stroke) while these medical conditions do not share a specific pharmacological treatment which we could uniquely measure. An additional limitation is that patients with no pharmacy dispensing history for the period minus 365 days till the index date were excluded. This could imply selection bias through exclusion of CAP patients without antecedent pharmologic treatment. We expect, however, due to the high age of patients with pneumonia and the fact that many patients at least receive antibiotics for their pneumonia the number of patients hospitalized for CAP without ever prescription drug use to be negligible.

In summary, we conclude that ACE-inhibitor use does not reduce risk of hospitalization for CAP in the general, essentially white population. Further steps to elucidate the possible effects of ACE-inhibitors on community-acquired pneumonia may include more detailed information of ACE genotype, ACE gene expression profiles and (inflammatory) biomarkers to ascertain CAP disease severity.

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Table 1. Patient characteristics of both cases and controls

Characteristic	Cases n=1.108		Controls n=3.817	
Age (years)				
< 40	99	(8.9)	396	(10.3)
40-49	91	(8.2)	352	(9.2)
50-59	116	(10.5)	461	(12.1)
60-69	190	(17.1)	637	(16.7)
70-79	353	(31.9)	1048	(27.5)
80-89	218	(19.7)	798	(20.9)
≥ 90	41	(3.7)	125	(3.3)
Gender				
Male	650	(58.7)	1998	(52.3)
Female	458	(41.3)	1819	(47.7)
CAP discharge diagnosis				
Primary diagnosis of CAP	1100	(99,3)		
Pneumococcal pneumonia	84	(7.6)		
Other bacterial pneumonia	90	(8.1)		
Bronchopneumonia, organism unspecified	140	(12.6)		
Pneumonia, organism unspecified	794	(71.7)		
Co-morbidities				
Heart failure	126	(11.4)	108	(2.8)
Respiratory diseases	454	(41.0)	333	(8.7)
Diabetes	134	(12.1)	259	(6.8)

Table 2. **Univariate odds ratios (OR) of hospitalisation for community acquired pneumonia and use of medication in the year before the index date**

Characteristic	Cases (n=1.108)		Controls (n=3.817)		Crude OR (95% CI)
	No.	(%)	No.	(%)	
Cardiac glycosides	124	(11.2)	156	(4.1)	2.92 (2.26-3.77)
ACE-inhibitors	168	(15.2)	370	(9.7)	1.65 (1.36-1.99)
Ca-channel blockers	179	(16.2)	346	(9.1)	1.82 (1.49-2.24)
Beta-blockers	155	(14.0)	575	(15.1)	0.87 (0.72-1.06)
Diuretics	392	(35.4)	638	(16.7)	3.16 (2.66-3.75)
Oral corticosteroids	176	(15.9)	58	(1.5)	11.41 (8.27-15.76)
Anticholinergic inhalation	258	(23.3)	134	(3.5)	8.43 (6.58-10.80)
Beta-agonists inhalation	324	(29.2)	183	(4.8)	7.69 (6.21-9.53)
Inhaled corticosteroids	347	(31.3)	196	(5.1)	8.07 (6.52-9.98)
H2-antagonists	93	(8.4)	172	(4.5)	1.95 (1.49-2.55)
Proton pump inhibitor	144	(13.0)	226	(5.9)	2.33 (1.85-2.92)
Flu vaccination	244	(22.0)	560	(14.7)	2.52 (1.94-3.28)

OR: odds ratio; CI: confidence interval

Table 3. Associations between hospitalisation for CAP and the use of ACE-inhibitors in all patients and different subgroups

Characteristic	Crude OR (95% CI)	Adjusted OR (95% CI)
All patients		
current use	1.65 (1.36-1.99)	1.12 (0.88-1.43)*
past use	2.09 (1.39-3.13)	1.43 (0.89-2.31)*
Patients with diabetes		
current use	1.10 (0.69-1.75)	1.02 (0.59-1.77)**
Patients with respiratory diseases		
current use	0.98 (0.61-1.52)	0.97 (0.59-1.60)**
Patients with heart failure		
current use	0.81 (0.39-1.80)	0.69 (0.30-1.60)**
Patients with both respiratory diseases and heart failure		
current use	1.05 (0.40-2.75)	1.06 (0.40-2.87)**

OR: odds ratio; CI:confidence interval

*adjusted for diabetes, respiratory diseases, heart failure, use of systemic corticosteroids and gastric acid suppressing drugs

**adjusted for the use of systemic corticosteroids and gastric acid suppressing drugs

Table 4. Adjusted treatment effects on pneumonia risk using stratification on propensity **balancing score**

	n	**Odds ratio**	**95% Conf. Interval**	
total sample	4.925	1.09#	0.87	1.36
1st quintile group	982	1.48	0.68	3.22
2nd quintile group	986	1.22	0.63	2.39
3rd quintile group	694	1.66	0.82	3.37
4th quintile group	1.278	0.90	0.56	1.45
5th quintile group	985	1.03	0.75	1.42

calculated using the Mantel-Haenszel statistic. Strata vary in size because a large group of patients with similar balancing score near the third quintile cut-off were entirely allocated to the fourth quintile group.