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Angiotensin Converting Enzyme Inhibitors and Cognitive and Functional Decline in Patients with Alzheimer's Disease: An Observational Study

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We previously reported that angiotensin converting enzyme inhibitors (ACEIs) decrease the rate of cognitive decline in elderly patients with hypertension, but their impact on patients with Alzheimer's disease (AD) is not known. A total of 62 elderly patients with AD were enrolled, and 52 completed the study for 6 months. Mini-Mental Status Examination (MMSE), Clock Draw Test (CDT), working memory (Digit Ordering), Instrumental Activities of Daily Living (IADL) scale, and the Screen for Caregiver Burden (SCB) were collected at baseline, 3 months, and 6 months. AD patients receiving ACEI (N = 15) demonstrated a slower rate of decline in digit forward (P = .003) and IADL scale (P = .003) and an improved measure of caregiver burden (P = .04) but not MMSE (P =.15) or CDT (P =.9) compared with those not receiving ACEI after adjusting for other risk factors. This study suggests that use of ACEI in AD patients is associated with slower rate of AD progression. A randomized clinical trial is needed to confirm our finding.

Keywords: Alzheimer's disease; angiotensin converting enzyme inhibitor; hypertension

Introduction

Observational studies have demonstrated that elevated blood pressure may predispose patients to develop Alzheimer's disease (AD), the most common form of dementia.[1-4] Although blood pressure decreases in the period immediately preceding the onset of dementia or AD,[5] hypertension in patients with existing AD leads to an increase in the rate of cognitive decline. In an analysis of data from 700 patients diagnosed with mild AD who had been randomly assigned to the placebo arm of a clinical trial, higher blood pressure was associated with an increased rate of cognitive decline over a 6-month period (odds ratio = 1.6, 95% confidence interval 1.0-2.7).[6] A similar effect was noted in African American patients with AD independent of other risk factors, such as stroke or low education levels.[7]

The renin–angiotensin system plays a critical role in hypertension pathogenesis and may play a role in AD pathogenesis and progression.[8] For example, patients with AD demonstrate elevated levels of angiotensin converting enzyme in the hippocampus, frontal cortex, and caudate nucleus.[9] Polymorphisms in the genes regulating the renin–angiotensin system seem to also be associated with risk for AD.[10] In addition, angiotensin II and its receptors are located in neurons

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inside the blood–brain barrier and in the cerebrovascular endothelial cells and circumventricular organs.[11] In animal experiments, angiotensin II has been associated with poor conditioned learning, and the use of angiotensin converting enzyme inhibitor (ACEI)[12] has been found to facilitate learning.

Human studies have also confirmed this observation.[13] In the Perindopril Protection Against Recurrent Stroke Study, ACEI reduced the risk of incident cognitive impairment in individuals with a previous history of stroke.[14] ACEI were also associated with decreased disability and preserved function in the same study.[15] The likely role played by the renin–angiotensin system in AD and the demonstrated benefits of ACEI in preserving cognitive function in other populations raise the question of whether ACEI can modulate disease progression in patients with AD. This is further corroborated by a recent study in patients with amnestic mild cognitive impairment, where those receiving ACEI showed a lower risk for further cognitive decline.[16] If similar protective effects can be demonstrated in AD patients, then new therapeutic options for this debilitating condition may be available.

The specific hypothesis tested in this study is that ACEI may affect the progression of cognitive and functional manifestations of AD. We have previously reported that in a different sample of patients followed at a geriatric practice, use of antihypertensives in general and ACEI in particular were associated with lower rate of cognitive decline.[17] That study did not assess function or caregiver burden.

Our objective hence was to further investigate if treatment with an ACEI is associated with slower cognitive decline in a cohort of patients with AD. Because AD affects all aspects of daily life of patients and their caregivers, we were also interested in the impact of ACEI on functional measures and caregiver burden in the same population.

Methods

This is an observational, prospective, and longitudinal study of patients with mild to moderate AD with repeated measures. Participants were followed for 6 months and were evaluated at baseline, 3 months, and 6 months. Recruitment started in July 2004 and continued through June 2005.

The inclusion criteria were the following: (1) age 55 years or older, (2) available caregiver or guardian to provide informed consent and study information on participants' cognitive and functional status, (3) ability to perform the study procedures and to present to the study center, and (4) a diagnosis of probable or possible AD based on the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA).[18] The exclusion criteria were the following: (1) inability to perform cognitive assessment at baseline due to medical or psychiatric illnesses, language difficulty, or other barriers; (2) delirium; (3) severe hypertension at screening (blood pressure >200/110 mmHg); (4) recent (past 6 months) myocardial infarction, stroke, coronary artery bypass grafting or major surgery; (5) uncontrolled atrial fibrillation (heart rate >100); or (6) seizures in the past 6 months. Participants who were receiving antidepressants were enrolled if they have been on a stable dose for the past 6 months.

Participants were recruited from a geriatric primary care practice and a memory disorders clinic. In addition, announcements were made at local communities, such as retirement communities, assisted living facilities, and senior centers. The Institutional Review Board at Palmetto Health approved this study. Prior to enrollment, all potential participants and their guardians or caregivers were asked to provide informed consent.

All participants were confirmed for the diagnosis of probable or possible AD at baseline. The diagnosis process included obtaining information from the participant, proxy (guardian or caregiver), and medical records. We screened 116 patients with dementia, 62 of whom satisfied the NINCDS–ADRDA criteria for the diagnosis of probable or possible AD, 42 did not, and the remaining refused to cooperate.

Data collected from consenting participants included demographics (age, gender, and self-reported race and ethnicity), family history of dementia or AD and hypertension, and social elements (marital, socioeconomic, employment status, educational attainment, living setting, alcohol consumption, and smoking status). A social engagement measure was collected because it has been linked to cognitive function in AD by using the Social Disengagement Index.[19] Medical history and comorbidity were obtained from the patient's medical record and interview at each visit and the Charlson Comorbidity Index was derived from the collected information.[20] Weight in kilograms (kg) and standing height in meters were also measured at each visit.

Information on all currently prescribed and over-the-counter medications that the participants were using, including information on ACEI, was collected during each visit by a combination of medical record review and medication bottles inspection. Medications information included the corresponding therapeutic class, the dosage, and the route and frequency of administration. Combination drugs were entered as 2 separate drugs. We collected medication data during each visit, and there was no change in the use of ACEI or acetylcholinesterase inhibitors during the study period.

Functional status was measured using the standardized scale of the Lawton and Brody Instrumental Activities of Daily Living Scale (IADL).[21] Caregiver burden was assessed using the Screen for Caregiver Burden (SCB).[22] Trained personnel assessed cognitive function in a quiet room at baseline and subsequent visits. The assessment was supervised by a psychologist (AA). General cognitive abilities were measured by the Mini-Mental Status Examination (MMSE)[23] and Clock Draw Test (CDT).[24] In addition, we assessed working memory function using Digit Ordering,[25] Digit Forward,[26] and Digit Backward.[26] We used these 3 tasks because they varied in their executive function requirements to assess working memory: Digit Forward was used to assess the storage function of working memory with low executive demands, Digit Backward was used to assess simultaneous storage and processing with medium executive demands, and Digit Ordering was used to assess simultaneous storage and processing with high executive demands. Blood pressure measurements were performed using a standardized procedure according to the American Heart Association guidelines: Blood pressure was taken in a quiet room after the patient had rested for 5 minutes. All study personnel were certified on the American Heart Association guidelines. Quality control measures included careful training of personnel in standardized measurement techniques, testing using a dual stethoscope, and blood pressure measurement observations. Systolic blood pressure was defined as the pressure corresponding to the first Korotkoff sounds (K1) and the diastolic as the pressure corresponding to the last Korotkoff sound (K5). Blood pressure was measured and recorded in both arms at the screening visit and the arm with the higher blood pressure (dominant arm) was used throughout the study. At each visit, 3 measurements in the dominant arm were obtained 5 minutes apart, and we used the average of the 3 readings in our analysis.

Statistical Design

The dependent variable were cognitive test scores, IADL and SCB, and the independent variable was ACEI use. Analysis was performed using mixed models (Proc Mixed) for repeated measures.[27] This procedure is used in unbalanced data; incorporates longitudinal change in covariates such as blood pressure, BMI, age, and drug exposure; and is minimally affected by missing data.[28] Modeling for each outcome measure was performed and covariance structure was selected based on the best-fit model. We provide the results of 2 models; the first model was developed using a stepwise forward/backward approach, and the second model included covariates that had a *P* value of less than 0.5 when compared between the 2 groups. Covariates compared between the 2 groups included baseline test score, blood pressure, BMI, age, gender, race, education level, alcohol consumption, smoking status, use of cholinesetrase inhibitors, and family history of dementia or AD. Results presented as change in the least square means from baseline to 6 months obtained from the multivariate mixed models. *P* values were obtained from the mixed models for the repeated measures of 3 visits. Because of multiple testing, we used the Bonferroni correction, a significantly conservative approach, adjusting for testing 7 hypotheses (0.05/7) with a *P* value of less than .007 being significant.

Results

We screened 116 potential participants with dementia. Of those screened, 62 were enrolled (41 were ineligible because of their diagnosis of other dementias or severity of their disease, and 13 refused to participate). Of the 62 enrolled, 1 died, 2 developed breast cancer, and 7 moved. There was no difference in age, gender, race, education, and baseline cognitive assessments between those who completed (N = 52) and those who did not (N = 10) complete the 3 visits. Of the 62, 24% were receiving ACEI at baseline, 24% at visit 2, and 19% at visit 3.

At baseline, there was no difference between those on ACEI and. those who were not on ACEI (Table 1). Of those not on ACEI, 43% were hypertensive. However, there was no difference in baseline systolic ($P = .06$) or diastolic ($P = .34$) blood pressure or use of other antihypertensives. As shown in Table 1, there was also no difference in baseline scores on

Table 1. Baseline Characteristics of the Study Sample by Antihypertensive Use

	Not on ACEI	On ACEI	*P* Value[a]
N	47	15	NA
Mean age ± SE (years)	83.8 ± 0.9	80.7 ± 2.0	.1237
Gender (% women)	79	67	.3424
Ethnicity			.9545
% White	87	87	
% African American	13	13	
Education			.9924
% High school or less	53	53	
% Some college and beyond	47	47	
Alcohol consumption			.7097
Daily	4	0	
1-6 Times per week	30	33	
Never	66	67	
Tobacco			.3398
% Never	66	60	
% Former	26	40	
% Current	8	0	
% Family history of Alzheimer's disease	53	46	.2534
Mean BMI ± SE	27.9 ± 0.8	26.9 ± 0.7	.4886
Mean SBP ± SE (mmHg)	133.1 ± 2.5	142.4 ± 3.8	.0635
Mean DBP ± SE (mmHg)	68.7 ± 1.4	71.5 ± 3.2	.3729
% Hypertensive	43	100	.0379
% Participants on other antihypertensives			
Diuretics	40	47	.6697
β Blockers	13	20	.4886
CCB	13	7	.5158
ARB	6	0	.3158
Number of antihypertensives	1.7 ± 0.2	1.8 ± 0.2	.8265
Acetylcholinesterase inhibitors	63	80	.2434
Geriatric Depression Scale score (short)	4.8 ± 0.6	4.5 ± 0.8	.7984
Social Disengagement Scale	2.4 ± 0.1	2.3 ± 0.2	.5229
Digit Ordering score	7.2 ± 1.0	5.4 ± 1.5	.3146
Digit Forward score	7.4 ± 0.4	6.6 ± 0.8	.332
Digit Backward score	3.5 ± 0.4	2.2 ± 0.6	.1070
MMSE	20.4 ± 0.8	21.5 ± 1.5	.4862
Clock Drawing score	3.3 ± 0.3	2.9 ± 0.6	.6231
IADL	4.9 ± 0.6	7.3 ± 0.9	.0525
Screen for caregiver burden	14.9 ± 1.8	17.4 ± 3.7	.5229

Abbreviations: SE, standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; ARB, angiotensin receptor blockers; MMSE, Mini-Mental Status Examination; IADL, Instrumental Activity of Daily Living.

[a] *P* value was obtained from the *t*-test (continuous variable) or χ^2 (discrete variable) to compare the 2 groups.

cognitive tests, IADL, or SCB. There was no difference in exposure to acetylcholinesterase inhibitors.

AD participants treated with ACEI demonstrated slower rate of decline in the score of the digit forward test compared with those not receiving ACEI ($P = .007$) (Table 2). This remained true in both models after adjusting for multiple covariates (Table 2). In addition, there was a trend for a slower decline on the MMSE and the digit ordering test, although this did not reach statistical significance ($P = .15$). There was also no difference on other cognitive tests including the CDT and the Digit Backward.

Participants with AD who were receiving ACEI also demonstrated an improvement in IADL compared with those not receiving ACEI who showed a progressive decline over the study follow-up period ($P = .005$). This difference remained significant after adjusting for hypertension, age, blood pressure levels, and use of acetylcholinesterase inhibitors ($P = .003$). Caregiver stress showed a similar trend despite covariate

Table 2. Longitudinal Change in the Selected Outcomes at 6 Months Compared With Baseline in Those Treated With an ACEI-Based Regimen Versus Those Who Were Not[a]

	Unadjusted			Model 1[b]			Model 2[c]		
Outcome	Not on ACEI (N = 47)	On ACEI (N = 15)	*P*[d]	Not on ACEI (N = 47)	On ACEI (N = 15)	*P*[d]	Not on ACEI (N = 47)	On ACEI (N = 15)	*P*[d]
Mini-Mental Status Examination	1.1 ± 0.6	2.5 ± 1.2	.54	–0.7 ± 0.3	2.4 ± 1.2	.29	1.1 ± 0.7	2.6 ± 1.2	.15
Clock Drawing Score	–0.7 ± 0.3	–0.9 ± 0.5	.89	–0.7 ± 0.3	–0.7 ± 0.5	.98	–0.7 ± 0.3	–0.8 ± 0.5	.98
Digit Ordering Score	–0.3 ± 0.7	0.7 ± 1.4	.53	0.2 ± 0.7	0.3 ± 1.3	.63	0.2 ± 0.7	1.1 ± 1.3	.66
Digit Forward Score	0.6 ± 0.3	2.0 ± 0.6	.007	0.5 ± 0.3	2.0 ± 0.5	.002	0.4 ± 0.3	1.9 ± 0.5	.003
Digit Backward Score	1.1 ± 0.4	0.4 ± 0.7	.58	1.1 ± 0.4	0.5 ± 0.6	.48	0.9 ± 0.4	0.4 ± 0.7	.52
Instrumental Activity of Daily Living	–0.2 ± 0.4	0.7 ± 0.7	.005	–0.5 ± 0.3	0.6 ± 0.6	.001	–0.5 ± 0.4	0.5 ± 0.6	.003
Caregiver stress	–0.6 ± 1.9	7.7 ± 3.5	.09	0.3 ± 1.8	9.1 ± 3.1	.03	1.1 ± 1.8	9.3 ± 3.0	.04

Abbreviation: ACEI, angiotensin converting enzyme inhibitor.

[a] Numbers are the least squares mean difference between baseline and 6 months obtained from the mixed models for the repeated measures (negative signs indicate a decline).

[b] Model 1 includes age, hypertension, baseline cognitive score, and acetylcholinesterase inhibitors use.

[c] Model 2 includes age, gender, systolic blood pressure, baseline cognitive score, acetylcholinesterase inhibitors use, smoking, BMI, family history of dementia, and hypertension diagnosis.

[d] *P* values are obtained from the same models and represent testing the hypothesis that there is a significant difference between the 2 groups. Significant *P* values based on *F*.

adjustments, the statistical significance was less robust ($P = .03$ and .04 in models 1 and 2, respectively).

Discussion

This study suggests that patients with AD who were receiving ACEI demonstrated a slower rate of decline in working memory and daily function compared with patients who were not receiving ACEI. This is likely to be independent of blood pressure or hypertension diagnosis.

This observational study adds more evidence for the positive effect of ACEI on the brain and aging. A prior trial by Ohrui et al[29] has shown that all ACEIs penetrating the blood–brain barrier have a positive effect on MMSE scores. We did not identify a significant effect on MMSE, but the trend was similar. We did identify an effect on the storage function of working memory, which has not been reported previously. Working memory is an important and understudied manifestation of AD.[25]

Our study demonstrated that ACEI may be associated with an improved functional capacity in patients with AD. This has not been previously reported. In addition to cognitive effects, other observational studies have demonstrated that in those without AD, ACEI use is associated with improved lean muscle mass, lower extremity muscle strength, and gait speed.[30,31] In the Women's Health and Aging Study, ACEI use was associated with improvement in lower extremity muscle strength in elderly women.[32]

The mechanism by which ACEI can provide this effect in patients with AD is not well-known. This could be mediated by their effect on cerebral blood flow,[33] their pleiotropic effects on the musculoskeletal system and nervous system, or their effect on inflammation and oxygen radicals.[34,35] ACEIs have also been shown to decrease the progression of white matter hyperintensities, which has been linked to further cognitive and functional declines.[14]A prior in vitro study has suggested that ACE may decrease levels of Aβ protein.[36] This raised concerns about the effect of ACEI on cognitive function. More recently, in vivo animal studies failed to show a role of ACE in Aβ protein.[37] Our study also suggests that ACEIs do not show a detrimental effect on AD progression. In addition, a recent observational study in the United Kingdom showed a protective effect of ACEI on the global deterioration scale in patients with AD.[38]

Prior studies have suggested a U-shaped association between blood pressure and cognitive function.[39] In this study, our association between ACEI and outcomes remained significant even after adjusting for blood pressure or hypertension. This suggests that this observation may not be mediated by the lowering

blood pressure effect of ACEI. On the other hand, between 60% and 80% of the participants were receiving acetylcholinesterase inhibitors, which affects AD progression and may have an effect on blood pressure.[40] Our models were adjusted for the use of acetylcholinesterase.

A major limitation of our study is bias by indication. Although our baseline assessment did not reveal a difference between those on and those not on ACEI, our results should be interpreted with this bias in mind. This study is a first step to identifying additional treatment options to patients with AD. We recommend a larger study sample to further confirm our results.

Another limitation is the possibility of type 1 error considering the relatively small sample size and the number of outcomes tested. We have used a conservative multiple-testing procedure to correct for this limitation. Furthermore, the same personnel collected medication and outcome data and hence they were not blinded to group assignments.

Conclusions

Use of ACEI in AD patients may be associated with slower rate of progression in both cognitive and functional aspects of this disease. A randomized clinical trial is needed to confirm our finding.

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