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WHAT İS EFFECTİVENESS ON THE HEART OF DRUGS USED İN ALZHEİMER'S DİSEASE?

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ABSTRACT

Objective: The aim of this study was to retrospectively determine the Emergency or Cardiology department admission rates with cardiac complaints of the patients with Alzheimer's disease(AD) and establish whether these rates changed between the patients who used acetylcholinesterase inhibitors (AchEI) and those who did not. **Materials and Methods:** This single-centered retrospective study included 605 patients who were diagnosed with AD between January 2010 and 2018. The patient group was separated to two subgroups according to the use of AChEIs. **Results:** Comparison of these two subgroups in terms of baseline demographic and clinical characteristics demonstrated that there was no significant difference between them($p>0.05$). When these two groups were compared in terms of the ratio of myocardial infarction, angina pectoris, bradycardia, hypotension or serious arrhythmia identicated that there was no significant difference (respectively, $p=0.96$, $p=0.87$, $p=0.12$, $p=0.23$, $p=0.17$). Besides, there was no significant difference between two groups in terms of the ratio of cardiac causes of death,too($p=0.21$). **Conclusion:** In this study, it was shown that there was no significant difference between the ratio of cardiac death and Cardiology and/ or Emergency department admission with cardiac complaints between patients with AD using AChEIs and those not using.

KEYWORDS: Alzheimer's disease, acetylcholinesterase inhibitors, myocardial infarction, bradycardia, angina pectoris, mortality.

INTRODUCTION

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases and the most common form of senile dementia affecting about 45 million people worldwide.[1] It leads to the progressive mental, behavioral, and functional decline. Although there are still no effective drugs for AD, it was accepted that acetylcholinesterase inhibitors (AChEI) decelerate the disease progression in mild and moderate patients.[2] The AChEIs used in the clinic are three: donepezil, rivastigmine, and galantamine. It was shown in randomized-controlled studies, that these three molecules have similar efficacy in AD treatment.[3] This group of drugs acts by blocking the enzyme acetylcholinesterase and so reducing the degradation of acetylcholine.[4] Acetylcholine is a neurotransmitter and associated with memory function.

Though the target organ for is the brain, it is known that the heart is also plenty in cholinesterases and may be affected through vagotonic effects, whether this enzyme is inhibited.[5] Recently, some cholinergic cardiac side effects such as hypotension, bradycardia, heart block, and QT/QTc prolongation have been reported.[6] Due to these adverse effects associated with AChEIs, clinicians take care when prescribing, especially in elderly patients with AD. On the contrary, recently their cardioprotective effects have been revealed too.[7]

Therefore, our aim in this study was to retrospectively evaluate the patients diagnosed with AD in Cumhuriyet University Neurology Department between January 2010 and 2018, to determine the Emergency or Cardiology department admission rates with cardiac complaints and establish whether these rates changed between the patients who used AChEI and those who did not.

MATERIAL AND METHODS

The creation of the study population

This single-centered retrospective study included 605 patients who were diagnosed with AD between January 2010 and 2018 in Cumhuriyet University Neurology Department. The medical history, cranial magnetic resonance or computed tomography imaging findings showed no additional pathology (chronic subdural hematoma, intracranial mass…) except cerebral atrophy, normal results of laboratory tests to exclude additional diseases, the neurological examination findings and standardized mini mental test (SMMT) results of patients were used in order to determine the definitive diagnosis of AD. There were no restrictions regarding sex and age among the patients. The patients together with their

guardians provided informed written consents for the participation in the study.

At baseline, patients who had received the AChEI drug for at least 1 preceding month were included in the study. Additionally, the data of each patient on the use of AChEIs, memantine, antipsychotics, antidepressants, and anxiolytics were recorded if the patients had received these treatments for at least 10 consecutive days in the month preceding the assessment. Patients who discontinued AChEI drug for 30 days or more or changed the type of the AChEI during the period of this study were excluded from the study.

The patient group was separated to two subgroups according to the use of AChEIs. While the patients in the first group were using AChEI drugs, the patients in the second group were not.

All patients included in the study were analyzed in terms of parameters such as age, gender, years of education, type of AChEI (rivastigmine or donepezil), the use of antidepressants, anxiolytics, antipsychotics or memantine, prescribed drugs at baseline (antihypertensive and/or antidiabetic drugs), the presence of diabetes mellitus, hypertension or hyperlipidemia, tobacco(current tobacco user or having quit in the last 6 months) or statin use, the presence of myocardial infarction, angina pectoris, bradycardia, hypotension or serious arrhythmia and SMMT results.

Diagnoses and treatments in the study at baseline and during the follow-up were identified by searching the hospital registration systems of the hospitals located in Sivas with the unique social securitynumber assigned to each Turkish citizen.

The missing information in our retrospective study was obtained via telephone interview with patients or their relatives.

Statistical analysis

The data of the study was measured by using the SPSS 22.0 program. The Kolmogorov– Smirnov test was used to determine whetherthe data were normally distributed. While the normally distributed continuous data were expressed as the mean± standard deviation, the non-normally distributed continuous data were expressed as median (min-max). The categorical data were indicated as percentage (%). While the independent T-test was used for the analysis of continuous data with normal distribution, the Mann–Whitney U-test was used for the analysis of continuous variables showing non-normal distribution. The comparision of the categorical datas was evaluated by the chi squared test. The statistical significance level was accepted as $p < 0.05$.

RESULTS

The patient group was separated to two subgroups according to the use of AChEIs as mentioned before. While the patients in the first group(n=402) were using AChEI drugs, the patients in the second group were not(n=203). Comparison of these two subgroups in terms of baseline demographic and clinical characteristics demonstrated that there was no significant difference in terms of age, gender, years of education, the presence of diabetes mellitus, hypertension or hyperlipidemia and tobacco or statin use (Table 1). The mean age of the first group was 72.64 ±6.7, while the second group was 73.01 ± 7.1 years. The comparison of the use of antidepressants, anxiolytics, antipsychotics or memantine showed that the patients in the first group took less anxiolytic and antipsychotic drugs (p=0.04, p=0.02) whereas the use of memantine was more in the second group (p<0.01). Besides, there were no significant differences between the two groups in terms of antidepressant medication and prescribed drugs at baseline (antihypertensive and/ or antidiabetic drugs). When the results of SMMT were examined, it was found that mean SMMT value in the second group was lower, but this was not statistically significant (p=0.12).

Table 1: The comparison of the baseline demographic and clinical characteristics of the first and second groups.

		First Group(n=402)	Second Group(n=203)	x^2	p
Age(mean±SD)(min–max)		72.64±6.7 (61- 93)	73.01±6.2 (66- 94)		0.29
Gender, n (%)**	**Female**	250 (62.2)	124(61.1)	0.58	0.91
	Male	152(37.8)	79(38.9)		
Years of education (median(min-max))		4(0-11)	6(0-17)		0.07
Type of AChEI, n (%)			-		-
Rivastigmine use		100(24.9)	-		
Donepezil use		302(75.1)	-		
Antidepressants use, n (%)**		201(50.0)	102(50.2)	1.12	0.62
Anxiolytics use, n (%)*		*60(14.9)*	*80(39.4)*	*0.26*	*0.04*
Antipsychotics use, n (%)*		*102(25.4)*	*92(45.3)*	*0.01*	*0.02*
Memantine use, n (%)*		*80(19.9)*	*190(93.6)*	*0.12*	*<0.01*
HT, n (%)**		127 (31.6)	63 (31.0)	2.71	0.78
DM, n (%)**		91 (22.6)	47 (23.2)	1.23	0.69
HL, n(%)**		55(13.6)	26(12.8)	2.12	0.09
Tobacco use, n (%)**		92 (22.8)	43 (19.3)	3.26	0.06
Statin use, n(%)**		62(15.4)	33(16.3)	0.56	0.28
Prescribed drugs at baseline, n(%)**					
Antihypertensive use		120(29.9)	61(30.0)	0.69	
Antidiabetic use		84(20.9)	45(22.2)	0.58	
SMMT(median(min-max))		17(3-23)	12(4-19)		0.08

Italic values are used to demonstrate the statistical significance. **: Chi square test used. Abbreviations: DM: diabetes mellitus, HL: hyperlipidemia, HT: hypertension, SD: stamdard deviation, SMMT: standardized mini mental test.

Comparison of these two groups in terms of the ratio of myocardial infarction, angina pectoris, bradycardia, hypotension or serious arrhythmia identicated that there was no significant difference between them (Table 2).

Table 2: The comparison of first and second groups in terms of the presence of myocardial infarction, angina pectoris, bradycardia, hypotension and serious arrhythmia.

	First Group (n=402)	Second Group (n=203)	x^2	p
Myocardial Infarction,n (%)**	15(3.7)	7(3.4)	2.97	0.96
Angina Pectoris, n (%)**	20(5.0)	11(5.4)	1.56	0.87
Bradycardia, n (%)**	55(13.7)	21(10.3)	1.17	0.12
Hypotension, n (%)**	61(15.2)	23(11.3)	0.94	0.23
Serious Arrhythmia, n (%)**	4(1.0)	3(1.5)	0.98	0.17

****: Chi square test used.

Also, in the follow-up period, 15% (n = 60) of the first group were ex while this percentage in the second group was 14% (n = 28)(p=0.28). As far as it was determined, 11.7% of these deaths were due to cardiac causes in the first group whereas this percentage was 14.3% in the second group(p=0.21)(Table 3). The detailed cardiac causes of death in the first and second groups were shown in Table 3 and there was no significant difference between two groups.

Table 3: The comparison of first and second groups in terms of death causes.

Causes Of Death	First Group(n=60)	Second Group(n=28)	x^2	p
Unknown, n (%)**	20(33.3)	9(32.1)	3.22	0.89
Dehydration, n (%)**	1(1.7)	1(3.6)	0.12	0.06
Foreign body aspiration, n (%)**	3(5.0)	1(3.6)	0.26	0.12
Infection, n (%)**	6(10.0)	3(10.7)	2.58	0.67
Advanced dementia, n (%)**	10(16.7)	4(14.3)	1.32	0.29
Malnutrition, n (%)**	10(16.7)	4(14.3)	1.31	0.28
Bone fracture, n (%)**	3(5.0)	3(10.7)	0.02	0.06
Cardiac causes, n (%)**	7(11.7)	3(14.3)	2.65	0.21
Myocardial infarction, n (%)**	5(8.3)	2(7.2)	3.52	0.96
Congestive heart failure, n (%)**	1(1.7)	1(3.6)	1.12	0.09
Serious arrhythmia, n (%)**	1(1.7)	0(0.0)	1.87	0.08

****: Chi square test used.**

DISCUSSION

In this study, we revelaed that there was no significant difference between the ratio of cardiac death and Cardiology and/ or Emergency department admission with cardiac complaints between patients with AD using AChEI drugs and those not using.

AChEIs, which were presented in the mid-1990s for the treatment of AD, are the first- line treatment for patients with mild to moderate AD (3). They are widely used and well tolerated, but have side effects too. Though their most common side effects are associated with the gastrointestinal tract, vagotonic side effects could also be of interest with cardiovascular system. It was showed that AChEI treatment was associated with minor but important elevation in the bradycardia, hypotension, cardiac arrhythmia, and syncope risks. Conversely, the evidences indicating cardioprotective effects of AChEIs in patients with AD have shown an increase recently.[7,8]

The retrospective cohort study of 7073 patients with AD from the Swedish Dementia Registry was assessed by Nordström et al.[8] Of these patients, 5159 patients received AChEIs at least once. The analysis of this study showed that patients who had used AChEIs at least once had a 34% lower risk for the composite outcome of myocardial infarction or death during the follow-up than those who had not. In our study, in contrast to this study, there was no significant difference in the rate of myocardial infarction or cardiac causes of death between patients treated with AChEI drugs and patients non-treated with AChEIs.

The meta-analysis of 22 longitudinal studies done by Isik et al. indicated that AchEI treatment was associated with increased risk of bradycardia and hypertension.[9] Besides, this study also revealed that the use of AChEIs was associated with a 37% lower risk of cardiovascular events. According to them; first, similar to parasympathetic activity through vagal stimulation or

exercise, AChEIs might have a protective role against heart failure and CV diseases. A number of previous studies found that parasympathetic activity has direct positive effects at the ventricular level independent of its sinüs node effects.[8] Greater cholinergic activity has also benefits by affecting CV events through other potential mechanisms, including antiinflammatory pathways, modulation of nitric oxide signaling, regulation of redox states, improvement in mitochondrial biogenesis and function, and potential calcium regulation.[8] AChEIs might also protect cardiomyocytes against acute hypoxia and ischemia by increasing cholinergic activity in the heart. Second, it was reported that cholinesterase inhibition reduced levels of thrombomodulin, a marker of endothelial activation, and b-thromboglobulin, a marker of platelet activation. Thus, AChEIs might prevent vascular endothelial damage and play a cytoprotective role in endothelial function.[8] In contrast to this study, there was no increase in the rate of bradycardia or in the rate of cardiac events in patients using AChEI drugs in our study.

Ku et al showed that the patients treated with AChEI drugs had lower mortality rates and long-term AChEI treatment could further decrease the mortality risk.[10] Unfortunately, no comprehensive evaluation of the duration of AChEI drugs use has been made in our study.

There were various limitations of our study. First of all, it was single-centered study, the patient number was relatively small to reflect the population. The design of our study also retrospective. This situation made it difficult to evaluate some parameters in detail. As mentioned before, comprehensive evaluation of the duration of AChEI treatment use was not made. Therefore, there is a need for more extensive and prospective studies in the future.

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