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Electrocardiographic Effects of Cholinesterase Inhibitors in Patients with Alzheimer's Disease

Alzheimer Hastalığı Tedavisinde Kullanılan Kolinesteraz İnhibitörlerinin Elektrokardiyografik Etkileri

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ABSTRACT

Aim: Cholinesterase inhibitors (ChEIs), such as donepezil and rivastigmine, are used safely in the treatment of Alzheimer's disease (AD). However, the effects of these drugs on the cardiac conduction system are not clear. In this study, we aimed to investigate the effect of donepezil and rivastigmine treatment on the cardiac conduction system in comparison with the controls, especially on the QTc interval.

Materials and Methods: We retrospectively enrolled 38 consecutive patients with AD, who were prescribed ChEIs for at least 3 months, and age, sex, and comorbidity-matched treatment-naive 37 control subjects. The electrocardiographic (ECG) parameters including heart rate, PR interval, QRS duration, QT interval, and QTc interval were recorded for each patient and control subject.

Results: A total of 24 patients were enrolled in the donepezil treatment group, 14 patients in the rivastigmine treatment group, and 37 patients in the control group. Donepezil treatment resulted in significant prolongation in PR interval, QT interval and QTc interval (p=0.027, p=0.001, p=0.023, respectively). Rivastigmine treatment resulted in significant prolongation only in QTc interval (p=0.018). There was no significant difference between the donepezil and rivastigmine treatment groups for all ECG parameters.

Conclusion: Donepezil and rivastigmine treatments significantly prolong QTc interval compared to controls in patients with AD. The donepezil treatment also prolongs PR and QT intervals. The donepezil and rivastigmine therapy had comparable effects on the cardiac conduction system.

Keywords: Alzheimer's disease, QTc prolongation, donepezil, rivastigmine

ÖZ

Amaç: Donepezil ve rivastigmin gibi kolinesteraz inhibitörleri Alzheimer hastalığının (AH) tedavisinde güvenle kullanılmaktadır. Ancak bu ilaçların kardiyak ileti sistemi üzerindeki etkileri net değildir. Bu çalışmada donepezil ve rivastigmin tedavisinin kontrol grubuna göre elektrokardiyografik (EKG) değişikliklerle ilişkili olup olmadığını araştırmayı ve özellikle QTc aralığı üzerindeki etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamıza AH tanısı almış ve en az 3 aydır kolinesteraz inhibitör tedavisi kullanan 38 hasta ve yaş, cinsiyet ve komorbiditeler açısından eşleştirilmiş, tedavi almayan 37 kontrol grubu retrospektif olarak dahil edildi. Tüm hastaların ve kontrol grubunun kalp hızı, PR intervali, QRS süresi, QT intervali ve QTc intervali gibi EKG parametreleri kaydedildi.

Bulgular: Toplamda 24 hasta donepezil tedavi grubuna, 14 hasta rivastigmin tedavi grubuna ve 37 hasta kontrol grubuna dahil edildi. Donepezil tedavisinin PR intervali, QT intervali ve QTc intervalini anlamlı olarak uzattığı saptandı (p=0,027, p=0,001, p=0,023, sırasıyla). Rivastigmin tedavisinin sadece QTc intervalini anlamlı olarak uzattığı saptandı (p=0,018). Tüm EKG parametreleri değerlendirildiğinde donepezil ile rivastigmin tedavisi arasında anlamlı bir fark saptanmadı.

Sonuç: AH tanısı almış hastalarda donepezil ve rivastigmin tedavisinin kontrollere kıyasla QTc intervalini anlamlı derecede uzattığı saptanmıştır. Donepezil tedavisi ayrıca PR ve QT intervalini de uzatmaktadır. Donepezil ve rivastigmin tedavisinin kardiyak ileti sistemi üzerindeki etkileri birbirine benzerdir.

Anahtar Kelimeler: Alzheimer hastalığı, QTc uzaması, donepezil, rivastigmin

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INTRODUCTION

Cardiovascular diseases and cognitive impairment often coexist in elderly patient populations. Alzheimer's disease (AD) is the most frequent cause of dementia in these elderly patients[1]. AD causes progressive deterioration in cognitive functions. The primary therapeutic target for the treatment is the cholinesterase enzyme[2]. Cholinesterase enzyme inhibitors (ChEIs), including donepezil and rivastigmine, are the first-line treatment options that have a positive effect on promoting the cognitive functions of AD patients[3].

The effects of ChEIs are not limited to the central nervous system. ChEIs also affect intrinsic cardiac neurons in mammalian hearts which modulate the chronotropic and dromotrophic functions of the heart[4]. The donepezil treatment significantly reduces heart rate[5] and it has also been demonstrated that there is a strong link between donepezil treatment and QTc prolongation and risk of Torsades de pointes (TdP) but data on rivastigmine are scarce so it is challenging to clarify the effect of rivastigmine on QTc prolongation[6]. On the other hand, recent studies have shown the cardioprotective effects of ChEIs. A retrospective database study has demonstrated that therapy with ChEIs has significantly decreased the risk of cardiac pacemaker implantation[7].

The potential electrocardiographic (ECG) effects of each ChEIs were evaluated in the literature[6,8]. However, the comparison between donepezil and rivastigmine therapy on ECG parameters with respect to controls was not extensively studied. Thus, we aimed to investigate the effects of donepezil and rivastigmine treatment on ECG parameters including heart rate, PR interval, QRS duration, QT, and QTc interval in comparison with control subjects and between each treatment group.

MATERIALS AND METHODS

We retrospectively enrolled 38 consecutive patients who had been diagnosed with AD according to the National Institute on Aging-Alzheimer Association criteria between November 2021 and September 2022[9]. Thirty-seven age, sex, and comorbidity-matched control subjects were also recruited for the study. We included patients aged 55-85 years, who had a 12-lead ECG as a part of any outpatient clinic visit while taking cholinesterase inhibitors for at least 3 months. All patients were compliant in taking their medication and reached steady state of donepezil 10 mg and rivastigmine 13.3 mg. The route of administration for donepezil included oral tablets and transdermal patches for rivastigmine. Patients with atrial fibrillation, heart failure, and pacemaker implantation, having a history of catheter ablation for any arrhythmia, thyroid abnormality, and chronic renal disease requiring dialysis were excluded from this study. Patients who were treated with antiarrhythmic medications (except beta blockers) and drugs that affected QT interval were also excluded. All data were collected from institutional electronic medical records.

Baseline patient characteristics and comorbidities were recorded. The current use of blood pressure-lowering medication was defined as hypertension and the current use of medication for diabetes was defined as diabetes mellitus. Hyperlipidemia was defined as the current use of cholesterol-lowering therapy. The presence of coronary artery disease was defined as prior history of myocardial infarction or coronary artery revascularization. Ischemic cerebrovascular disease was defined as having a history of minor stroke caused by a small or big blood vessel pathology. Among laboratory data, baseline hemoglobin, thyroid function tests, serum creatinine, estimated glomerular filtration rate, and serum electrolytes including sodium, potassium, and calcium levels were noted. A resting 12-lead ECG was recorded from all patients by using 25 mm/sec paper speed and standardized at 0.1 mV/mm. ECG parameters including heart rate, PR interval, QRS duration, QT interval, and QTc interval were calculated automatically by the ECG apparatus and reviewed by a cardiologist. QTc was corrected for heart rate using the Bazett's formula (QTc=QT/ÖRR)[10].

This study was approved by the Dokuz Eylül University Local Ethics Committee (approval no: 2021/27-01, date: 06.10.2021).

Statistical Analysis

A standard statistical software program [Statistical Package for the Social Sciences (SPSS) version 26; SPSS, Inc., Chicago, IL] was used. The Kolmogorov-Smirnov test was used to check continuous variables for normality. The categorical variables were represented as numbers and percentages and continuous variables were represented as the mean±standard deviation and median (interquartile range). If results were asymmetrically distributed, nonparametric tests were used. Comparisons between the three groups were performed using the Kruskal-Wallis test for non-normally distributed data, the one-way ANOVA test for normally distributed data, and the chi-square test for categorical variables. Multivariate analysis of variance test was used to examine ECG parameters including PR interval, QT duration, and QTc. A p-value <0.05 was considered to be statistically significant.

RESULTS

The study population was divided into three groups: The donepezil treatment group, the rivastigmine treatment group, and control group. A total of 24 patients were in the donepezil treatment group, 14 patients were in the rivastigmine treatment group, and 37 patients were in the control group. Table 1 represents the clinical and laboratory characteristic of the treatment and control groups. There were no significant

differences in age, sex, comorbidities, baseline laboratory parameters, and beta-blocker usage among the three groups (Table 1).

Among ECG parameters, PR interval, QT interval and QTc interval were significantly different among three groups (p=0.03, p=0.001, p=0.005, respectively) whereas heart rate and QRS duration were not different between three groups (p=0.12, p=0.19, respectively) (Figure 1, Table 2).

Pairwise comparisons revealed that the PR interval was significantly different between the donepezil treatment group and control group (p=0.027). There were no significant differences between the rivastigmine treatment group and control group and between the donepezil and rivastigmine treatment groups (p=0.43, p=0.64, respectively) (Table 3). For QT interval, the analysis revealed a significant difference between the donepezil treatment group and control group (p=0.001) whereas there was no significant difference between the rivastigmine treatment group and control group and between the donepezil and rivastigmine treatment groups (p=0.57, p=0.12, respectively) (Table 3). For QTc interval, significant differences emerged for the donepezil treatment group and control group and between the rivastigmine treatment group and control group (p=0.023, p=0.018, respectively). There was no significant difference between the donepezil and rivastigmine treatment groups for QTc (p=0.87) (Table 3).

DISCUSSION

Our study demonstrates that among ECG parameters, no significant difference was observed in heart rate and QRS duration among the three groups. The PR interval and QT interval were significantly prolonged only in the donepezil treatment group, whereas QTc interval was significantly longer in both donepezil and rivastigmine treatment groups. Regarding all ECG parameters, no significant difference was detected between the donepezil and rivastigmine treatment groups.

The previous reports suggest that ChEIs are associated with cardiovascular side effects, including bradycardia, complete atrioventricular block, and TdP[11-14]. As increased levels of acetylcholine in the heart enhance vagal tone, it is evident that ChEIs may decrease heart rate[15]. However, in concordance with our results, Isik et al.[16] demonstrated that none of the ChEIs including donepezil, rivastigmine, and galantamine was associated with an increased risk of bradycardia. The discrepancies between these results may have been related to several factors. First, comorbidities of patients including ischemic heart disease differ among these studies. Second, serum electrolytes, especially potassium and calcium, may affect heart rate[17] and not all studies report serum electrolyte levels that may affect their results. Finally, concomitant use of other medications may have been responsible for these discordant ChEIs-associated ECG changes.

The QT interval corresponds from the beginning of ventricular depolarization to the end of ventricular repolarization and QTc prolongation is associated with an increased risk of ventricular arrhythmias[18], TdP, and sudden death[19]. When acetylcholinesterase receptors are inhibited in the heart, intracellular calcium concentrations increase. As a result, phase 2 of the cardiac action potential prolongs and increases the subsequent risk of ventricular arrhythmias[20]. Reports

Table 1. Baseline clinical and laboratory characteristics of the treatment and control groups

	Donepezil (n=24)	Rivastigmine (n=14)	Controls (n=37)	p value
Age (years)†	76 (73-79)	73 (65-81)	72 (68-75)	0.11‡
Women, n (%)	9 (37.5)	7 (50)	15 (40.5)	0.74§
Hypertension, n (%)	16 (66.7)	9 (64.3)	25 (67.6)	0.97§
Diabetes, n (%)	8 (33.3)	8 (57.1)	14 (37.8)	0.33§
Hyperlipidemia, n (%)	11 (45.8)	6 (42.9)	16 (43.2)	0.97§
CAD, n (%)	10 (41.7)	3 (21.4)	10 (27)	0.34§
ICVD, n (%)	6 (25)	2 (14.3)	5 (13.5)	0.48§
Hemoglobin (gr/dL)*	13.3±1.7	12.6±1.4	13.2±1.4	0.43¶
Creatinine (mg/dL)†	0.94 (0.87-1.1)	0.83 (0.73-1.1)	0.9 (0.8-1)	0.66‡
eGFR*	71.1±17.6	71±18.9	73±17.5	0.88¶
Serum sodium (mmol/L)†	141 (138-142)	141 (139-142)	141 (139-142)	0.91‡
Serum potassium (mmol/L)*	4.4±0.4	4.3±0.5	4.4±0.4	0.97¶
Serum calcium (mmol/L)†	9.6 (9.4-9.9)	9.6 (9.1-10)	9.7 (9.2-9.9)	0.94‡
TSH [m(IU)/L]†	1.1 (0.85-1.9)	1.35 (0.98-1.7)	1.4 (0.9-2)	0.82‡
Beta blocker, n (%)	6 (25)	5 (35.7)	9 (24.3)	0.69§

*Mean±standard deviation, †Median (interquartile range), ‡Kruskal-Wallis test, §Chi-square test, ¶One-way ANOVA test.
CAD: Coronary artery disease, ICVD: Ischemic cerebrovascular disease, eGFR: Estimated glomerular filtration rate, TSH: Thyroid stimulating hormone

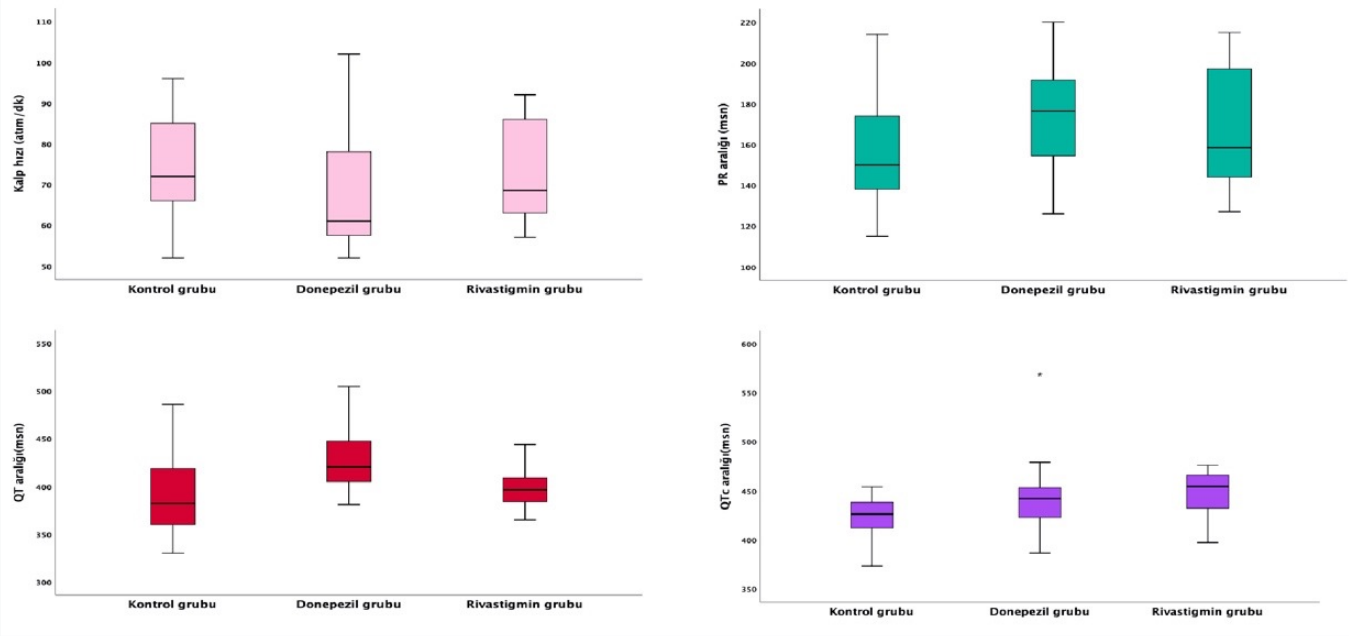

Figure 1. Comparisons of ECG parameters between groups

ECG: Electrocardiography

Table 2. Effects of donepezil and rivastigmine treatment on ECG parameters

	Donepezil (n=24)	Rivastigmine (n=14)	Controls (n=37)	p value
Heart rate (bpm)*	67±14	72±12	74±12	0.12¶
PR interval (msec)*	175±26	167±28	157±26	**0.03¶**
QRS duration (msec)†	98 (92-105)	88 (86-95)	98 (86-106)	0.19†
QT interval (msec)*	422±39	399±21	389±34	**0.001¶**
QTc interval (msec)*	443±38	447±22	423±19	**0.005¶**

*Mean±standard deviation, †Median (interquartile range), †Kruskal-Wallis test, ¶One-Way ANOVA test, ECG: Electrocardiographic

Statistically significant values are shown in bold type

Table 3. Comparisons of ECG parameters between the donepezil group and controls, the rivastigmine group and controls, and the donepezil and rivastigmine groups

	Donepezil vs. control p value	Rivastigmine vs. control p value	Donepezil vs. rivastigmine p value
PR interval (msec)	**0.027****	0.43**	0.64**
QT interval (msec)	**0.001****	0.57**	0.12**
QTc interval (msec)	**0.023****	**0.018****	0.87**

**MANOVA test. Statistically significant values are shown in bold type.

MANOVA: Multivariate analysis of variance

on the effects of ChEIs on QT interval prolongation and QTc are scarce. To date, most studies examining the effects of donepezil treatment on QT interval and QTc found that therapy with donepezil was associated with an increased risk of QT interval and QTc prolongation[6,14,21], whereas some studies found no associations[8,16]. We demonstrated that therapy with both donepezil and rivastigmine significantly increased the QTc interval in comparison with control subjects. It has been shown that drug-associated QT prolongation and the risk of TdP are aggravated by the presence of at least one risk factor including female gender, presence of cardiac disease, electrolyte imbalances, overdosing, drug-drug interactions, and familial history of long QT syndrome[22]. For our present report and other clinical studies, it may be difficult to determine the alternative cause for this adverse effect as most cases and clinical studies included patients with at least one other risk factor for QT prolongation.

Besides, our study showed that donepezil and rivastigmine had similar effects on the cardiac conduction system. This result of the present study is in accordance with a previous study that demonstrated similar effects on ECG parameters of all three ChEIs including donepezil, rivastigmine, and galantamine[16].

Study Limitations

Our study has several limitations. First, this is a retrospective study in a single center with a relatively small number of patients. Second, as this is a retrospective study, we could

not examine the confounding factors that might prolong QTc interval including active infections, hypomagnesemia, metabolic problems, and other QTc-prolonging drugs. Finally, a 24-hour Holter monitoring would allow a more reliable evaluation of cardiac conduction abnormalities in patients taking QTc-prolonging agents.

CONCLUSION

In conclusion, donepezil and rivastigmine treatment significantly prolongs QTc interval compared to controls in patients with AD. The donepezil treatment also prolongs PR and QT intervals. The donepezil and rivastigmine therapy had comparable effects on the cardiac conduction system. Elderly patients are more susceptible to drug-induced arrhythmias because of age-related prolongation of the QT interval and repolarization dispersion. The risk of arrhythmias could be minimized with a multidisciplinary approach both for the initiation of ChEI therapies and the follow-up of AD patients.

Ethics

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Dokuz Eylül University Faculty of Medicine (decision no: 2021/27-01, date no: 06.10.2021).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: A.Ç., D.Ö., Design: A.Ç., D.Ö., Data Collection or Processing: A.Ç., D.Ö., Analysis or Interpretation: A.Ç., D.Ö., Literature Search: A.Ç., D.Ö., Writing: A.Ç.

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