INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Cardiac Safety of Donepezil in Elderly Patients with Alzheimer Disease

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Abstract

Objective Donepezil is a widely used cholinesterase inhibitor for the treatment of Alzheimer's disease (AD), however its cholinergic adverse side effects on the cardiovascular system are still unclear. In this study, we aimed to examine the adverse side effects caused by donepezil on cardiac rhythm and postural blood pressure changes in elderly patients with Alzheimer Disease.

Methods The ECG parameters including heart rate, PR, QT, QTc interval and QRS duration and postural blood pressure changes were recorded at the baseline and at each donepezil dose level (5 and 10 mg/d).

Patients Seventy-one consecutive patients who were referred by primary care centers to a Geriatric Clinic were enrolled and underwent comprehensive geriatric assessment.

Results Fifty-two subjects completed the study. There were no significant changes relative to the baseline in any of the ECG parameters or arterial blood pressure at any of the investigated dosages of donepezil.

Conclusion It was demonstrated that donepezil was not associated with increased negative chronotropic, arrhythmogenic or hypotensive effects for elderly patients with Alzheimer's disease.

Key words: Donepezil, cardiac safety, Alzheimer Disease, elderly, QT interval

(Intern Med 51: 575-578, 2012)
(DOI: 10.2169/internalmedicine.51.6671)

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly (1). Cholinesterase inhibitors (ChEIs) are currently considered to be the first line treatment for AD (2). Since the heart is rich in cholinesterase, its inhibition may adversely affect cardiac function, which, in turn, can cause risks, especially in elderly patients with cardiovascular disease. These cardiac adverse effects, including bradycardia, heart block and QT prolongation with or without a history of cardiac disease, can emerge as vagotonic effects due to ChEIs (3, 4). QT prolongation may lead to life-threatening ventricular arrhythmias (i.e., torsade de pointes and ventricular fibrillation) (5). Donepezil hydrochloride is a reversible, noncompetitive, piperidine-type ChEI which is widely used for the treatment of AD (2, 6). Although donepezil is generally considered to be well tolerated, cholinergic-dependent cardiac side effects of donepezil have been reported (5-8). When the increased prevalence of cardiac disease in the elderly is taken into account, the importance of donepezil, which induces these potential cardiac adverse events, is clear.

To date, donepezil-related cardiac adverse events have not been exhaustively studied in elderly patients with AD. Consequently, we conducted this study in this population to evaluate whether or not donepezil is associated with an increased risk of cardiac side effects.

Materials and Methods

Seventy-one patients, newly diagnosed with Alzheimer's disease, were enrolled in this study. Before participation, written informed consent was obtained from each partici-

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Received for publication October 5, 2011; Accepted for publication November 21, 2011
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Table 1. Demographics and Baseline Characteristics of Patients

Age (year)	74.9.±6.4*
Gender (Male/Female)	25/27
HT(%)	73.0
CAD (%)	40.3
MMSE	19.3 ± 5.3*
CDT	1.8 ±1.2*
IADLs	8.0 ± 5.6*
ADL(%)	87.5 ± 11.0*

*: Mean ± SD;

ADL: Activities of daily living (scored of 100). **CAD**: Coronary Artery Disease, **CDT**: Clock drawing test (scored of 4), **HT**: Hypertension, **IADL**: Instrumental activities of daily living (scored of 17), **MMSE**: Mini-Mental state examination (scored of 30)

pant, and legally authorized representatives according to the local guidelines. The investigation conforms to the Declaration of Helsinki.

Patients were diagnosed according to DSM-IV TR criteria for primary degenerative dementia of the Alzheimer type and the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria (9, 10) for probable AD. Patients who were initially treated with cardio stimulatory drugs, such as beta-adrenoceptor agonists, thyroxine, phosphodiesterase inhibitors, calcium sensitizers or atrioventricular node blocking drugs, such as beta blockers, calcium channel blockers, digoxin, and amiodarone were excluded from the study. In addition, the patients with pacemakers were also excluded from the study. There was no alteration in patients' medications during the study period.

Exogenous variables that can influence the blood pressure including food intake, exercise, smoking, and the ingestion of caffeine avoided in the 60 minutes before evaluation, and both blood pressure measurement and ECGs were recorded at the same time which was scheduled to correspond with the Tmax of donepezil (approximately 4 hours after dose administration). After patients sited quietly for five minutes in a quiet and warm setting, their blood pressure measurements were taken in the supine, sitting and upright position by a mercury sphygmomanometers with a proper-sized cuff (11).

All patients were examined with a comprehensive geriatric assessment (12) and a 12-lead surface ECG measurement was recorded by using 25 mm/sec paper speed and standardized at 0.1 mV/mm after the patient had rested for at least 10 minutes in the supine position.

The patients with AD were treated with a flexible 4 weekly donepezil tablet (Aricept®, Pfizer, Istanbul, Turkey) dosage titration regimen up to 10 mg/day. ECG parameters and blood pressure measurements were recorded at the baseline and 4 weeks after each dose of the donepezil (5 mg, and 10 mg) was given.

ECG parameters, including heart rate, PR, QT and QTc interval and QRS duration were calculated automatically by the apparatus. The QT interval was corrected for the heart rate by using Bazett's formula (QTc=QT/square root of RR) (13) and more than 450 msec was defined as QTc prolongation (14).

Statistical analysis

Power and sample size calculation: To detect an increase in QTc interval at alpha=0.05, and power=0.95, the minimal sample size required was 19 patients (Power and sample size calculator, version 3.0, Vanderbilt University, Nashville, TN, USA).

Statistical analyses were performed by using the SPSS software, version 11.5 (SPSS Inc., Chicago IL). Demographics and baseline characteristics were reported as the number (n) and percentage (%) for nominal variables and as the mean ± SD for continuous variables. The Kolmogorov-Smirnov Test was used to determine the distribution characteristics of the variables. Because the differences and its SD among the groups did not show normal distribution, all of the comparisons were tested for statistical significance by using the Wilcoxon test. The differences were considered to be significant at $p<0.05$.

Results

A total of 71 patients were enrolled in the study, but only 52 of them completed the study. The number of patients who dropped out was 19; 6 patients had donepezil intolerance due to refractory nausea, vomiting and diarrhea, 5 patients due to initiation of treatment with cardio stimulatory drugs and 8 patients were lost to follow-up. Therefore, we studied 25 male and 27 female elderly subjects with newly diagnosed AD. The demographics and baseline characteristics of the patients are given in Table 1.

There were no changes, in any of the ECG parameters when compared with the baseline during the 2 donepezil treatment periods of four weeks at each dose (Table 2). The arterial blood pressure of the patients in supine, sitting and upright positions remained unchanged according to the baseline (Table 3) ($p>0.05$ for each comparison). All comparisons were analyzed excluding the dropouts. The data of dropouts were not considered and thus, could not affect the results, even though the mean values of all available data for the dropouts were similar to those who continued.

Discussion

In this study, it was demonstrated that each dose of donepezil has no significant effect on the ECG parameters and arterial blood pressure of elderly patients with AD.

It is known that QT interval prolongation was associated

Table 2. ECG Parameters at Each Donepezil Dosage Titration and Comparisons*

	Baseline	5 mg/day	10 mg/day	p **
HR (beat/min)	76.16 ± 13.64	74.47 ± 11.38	72.72 ± 13.06	*NS*
PR (msec)	168.21 ± 22.26	167.39 ± 27.50	169.42 ± 30.92	*NS*
QRS (msec)	92.81 ± 22.47	93.51 ± 15.90	91.51 ± 23.19	*NS*
QT (msec)	375.85 ± 44.19	376.55 ± 42.51	385.48 ± 32.27	*NS*
QTc (msec)	421.44 ± 30.02	415.68 ± 29.66	420.03 ± 27.68	*NS*

*: Mean ± SD; **: p>0.05

HR: heart rate, **PR**: PR interval **QRS**: QRS duration, **QT**: QT interval, **QTc**: corrected QT interval.

Table 3. Arterial Blood Pressure Measurements at Each Donepezil Dosage Titration and Comparisons*

		Baseline	5 mg	10 mg	p **
SBP (mmHg)	Supine	127±16	125±13	128±17	*NS*
	Sitting	126±16	123±13	124±17	*NS*
	Upright	126±15	118±11	121±19	*NS*
DBP (mmHg)	Supine	78±9	79±11	78±10	*NS*
	Sitting	76±9	78±12	78±9	*NS*
	Upright	75±8	75±10	75±10	*NS*

*: Mean ± SD; **:p>0.05

SBP: Systolic blood pressure **DBP**: Diastolic blood pressure

with a higher risk of cardiac morbidity and mortality in patients with or without coronary heart disease (15), and age-associated degenerative changes in the conduction system increases the risk of arrhythmia (16). In addition, cholinesterase (ChE) is distributed abundantly in the heart and its inhibition may affect cardiac function, especially in elderly patients. Inhibition of ChE increases the concentration of acetylcholine (ACh) by preventing degradation (3). High levels of ACh have affected GABAergic and glycinergic inhibitory receptors via triggering vagal neurotransmission and thus, may develop the cardioinhibitory effect (17). Therefore, this potentially high risk of elderly patients should be kept in mind when they are treated with ChEIs, which may also have an effect on the cardiac conduction system. In our previous study, it was reported that galantamine, another ChEI, did not affect the ECG parameters. Moreover, arterial blood pressure compared with the baseline in the elderly patients with AD and the usual dosage of galantamine seemed to be well tolerated in these elderly patients (18). However, until now, it has not been clearly shown whether or not donepezil has an effect on the cardiac conduction system in elderly patients with AD.

In the previous studies, it was demonstrated that a significant drop in heart rate and rise in the PR interval was not seen in patients who were treated with donepezil (19-23). Whereas, Bordier et al reported that a donepezil-induced decrease in heart rate and increase in PR interval were observed in patients with AD, who were not treated with chronotropic or dromotropic drugs (24). However, none of these studies gave detailed information on the adverse effects of donepezil on the cardiac conduction system, such as QT prolongation (19-24). Moreover, it was also reported that bradycardia, complete atrioventricular block and QT prolongation were seen in patients taking donepezil (24-28). Therefore, there has been significant anxiety among prescribers regarding the potential for cardiac adverse effects associated with ChEIs, such as donepezil in elderly patients with AD (29). The present results showed that donepezil therapy for each dose has no significant effect on the ECG parameters including heart rate, PR, QT and QTc interval and QRS duration in elderly patients with AD compared to the baseline. When the age-associated degenerative changes in the conduction system, including loss of pacemaker and conducting cells and myocardial fibrosis, which increased the risk of arrhythmia (16), are taken into account, it is obvious how important it is not to have negative chronotropic, arrhythmogenic and hypotensive effects for elderly patients, who are taking donepezil. In addition, we think that comorbidities and medications may have been responsible for donepezil-induced QT and PR prolongation encountered in previous studies. Furthermore, it was also shown that donepezil has no effect on postural changes of arterial blood pressure in these patients. Due to the high density of butyrylcholine esterase in the heart (30), it might be the result of the selectivity of donepezil against acetylcholine esterase but not butyrylcholine esterase.

As it would not be ethical to treat patients with a placebo following the diagnosis of AD, comparisons between the pre-medication values (the baseline) and medication values of the same patients were made. There was no placebo group. Furthermore, the duration may be a limitation of the study as these results include only 2 months of treatment with donepezil. Although a small sample group of 52, it must be pointed out that this was a selected sample group of elderly patients with AD.

Finally, it was demonstrated that donepezil has neither negative chronotropic and arrhythmogenic effects nor hypotensive effects on the elderly patients with AD. However, when physicians prescribe donepezil, they should be aware of the comorbidities, especially cardiac conduction disease and medications of the patients.

The authors state that they have no Conflict of Interest (COI).

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