

Donepezil-Induced Adverse Side Effects of Cardiac Rhythm: 2 Cases Report of Atrioventricular Block and Torsade de Pointes

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Abstract

Acetylcholinesterase inhibitors (AChIs) are widely used in the treatment of mild-to-moderate Alzheimer's disease (AD), but their cholinergic effects could generate adverse side effects in the cardiovascular system. This report presents the cases of 2 patients who experienced adverse side effects of cardiac rhythm with QT prolongation caused by Donepezil. Both of them improved to the original rhythm and shortened QT intervals after the discontinuation of Donepezil.

The present cases suggest that the cholinergic effects of Donepezil could induce adverse side effects on cardiac rhythm and careful consideration is needed for the patients treated by Donepezil.

Key words: acetylcholinesterase inhibitors (AChIs), Donepezil, QT prolongation, atrioventricular block, torsade de pointes

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Introduction

Acetylcholinesterase inhibitors (AChIs) are widely used in the treatment of mild-to-moderate Alzheimer's disease (AD) (1, 2). AChIs are well tolerated and the side effects are basically cholinergic dependent (3, 4). The cholinergic adverse effects, include gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea and anorexia) predominate. The patients receiving AChIs rarely develop serious disorders of the cardiovascular system such as syncope, bradycardia, atrioventricular block and QT prolongation (3). However, non-cardiac drugs can affect the cardiovascular system. QT prolongation may possibly lead to life-threatening ventricular arrhythmias (i.e: torsade de pointes, ventricular fibrillation). This report presents 2 cases in which patients experienced transient cardiac rhythm disorders, associated with Donepezil. The disorders disappeared after discontinuing Donepezil.

Case Report

Case 1

A 90-year-old man presented with accidental bradycardia. The patient had no history of the cardiovascular disease and syncope. The patient had been treated with Donepezil for Alzheimer's disease (AD) for many years. The daily dose of the drug was 5 mg, but it had been increased to 10 mg 3 days earlier because of his deteriorating mental state.

The patient was alert and asymptomatic, but not cooperative. His body temperature was 36.0°C; blood pressure was 158/49 mmHg; and heart rate was 36 beats/minute. The physical and neurological findings, chest x-ray, and laboratory screening test were unremarkable. A transthoracic echocardiography revealed normal left ventricular wall motion and ejection fraction. ECG demonstrated an advanced atrioventricular block (2:1 block) and a complete right bundle branch block with negative T-waves in leads I, II, aV_L and V2-6. Marked QT prolongation (QT 0.514 sec) was also observed (Fig. 1).

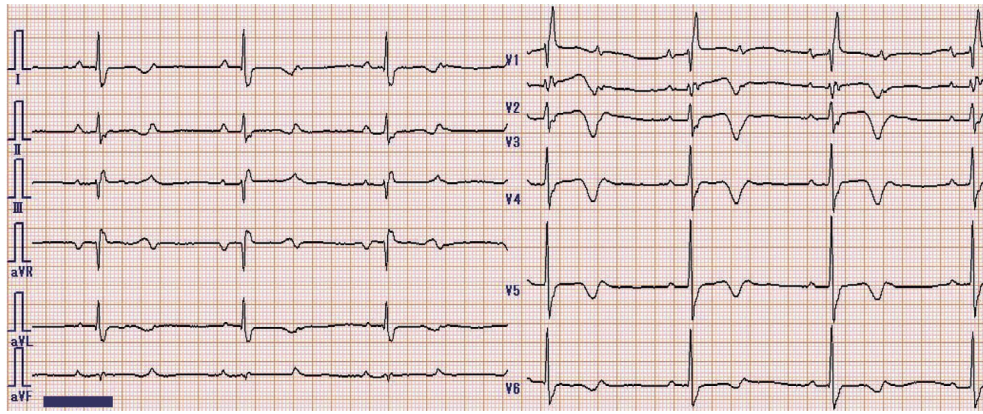


Figure 1. ECG showed 2:1 atrioventricular block and negative T-waves in leads I, II, aVL and V2-6 with QT prolongation (QT 0.514 sec).

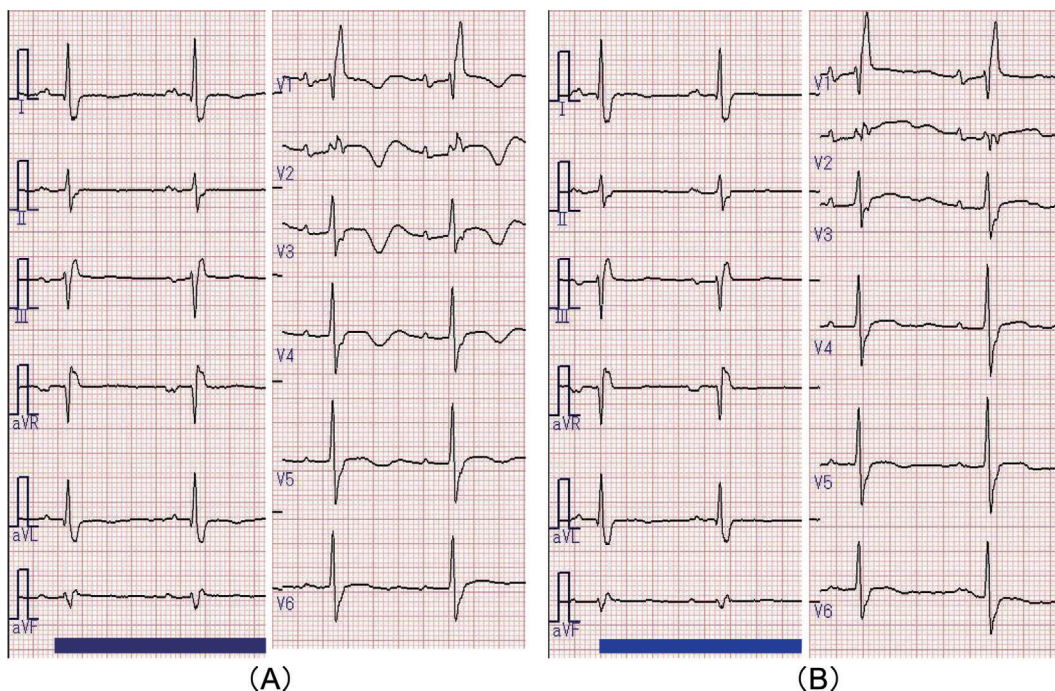


Figure 2. ECG showed sinus rhythm, but a 1st degree atrioventricular block (PQ 0.220 sec) and the negative T-waves in the same leads and QT prolongation (QT 0.536 sec; QTc 0.538) persisted (A). On the 5th day the negative T-waves disappeared and the QT interval decreased to QT 0.450 sec; QTc 0.456 (B).

We considered that the latest increase of Donepezil may have contributed to the atrioventricular block, and continuing the drug could worsen the arrhythmia. Therefore the daily Donepezil was discontinued and Orciprenaline at a dosage of 30 mg/daily, which has a β stimulating effect, was instead administered.

The following day, ECG showed sinus rhythm, but the 1st degree atrioventricular block (PQ 0.220 sec) and QT prolongation (QT 0.536 sec; QTc 0.538) remained. Orciprenaline was continued. The ECG on the 5th day showed that the QT interval was shortened to QT 0.450 sec and QTc 0.456 (Fig. 2). As a result, Orciprenaline was stopped, and he remained asymptomatic and no significant arrhythmia occurred thereafter for 2 months.

Case 2

An 87-year-old woman, with a long-term history of hypertension, chronic atrial fibrillation and AD, was diagnosed to have bradycardia (heart rate 40 beats/minute) at another clinic. The ECG showed atrial fibrillation and negative T-waves in leads V1-2 and biphasic T-waves in leads V3-6 with QT prolongation (QT 0.570 sec; QTc 0.461). Because she experienced neither syncope nor heart failure, she was administered 100 mg/daily of Cilostazole in addition to her daily drugs (Amlodipine 5 mg, Spironolactone 25 mg, Warfarin 1 mg and Donepezil 5 mg). After a month, she was admitted to the department of orthopedics because of a thoracic vertebral fracture caused by sudden fall due to tran-

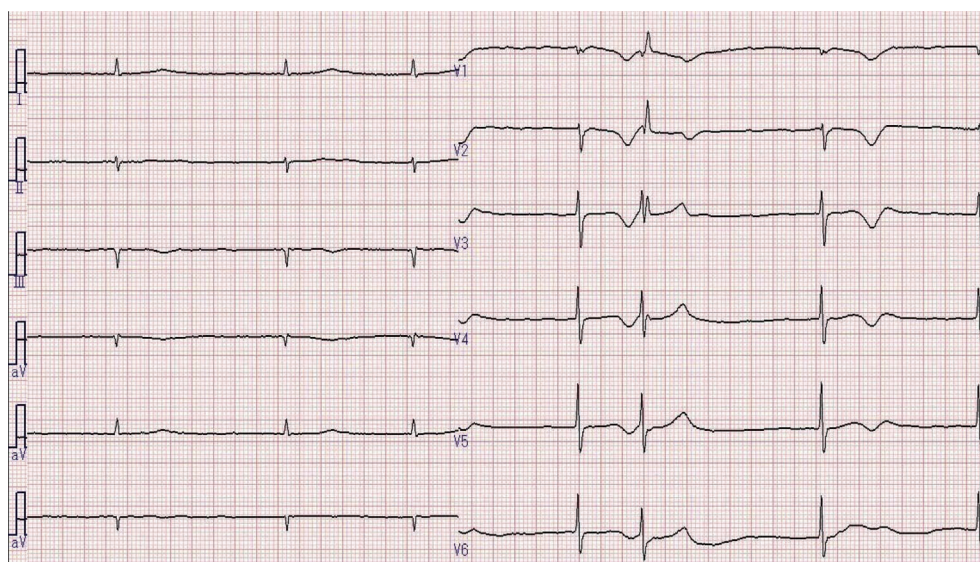


Figure 3. ECG showed atrial fibrillation and negative T-waves in leads V₁₋₂ and biphasic T-waves in leads V₃₋₆ with a longer QT prolongation (QT 0.720 sec; QTc 0.594) on admission.

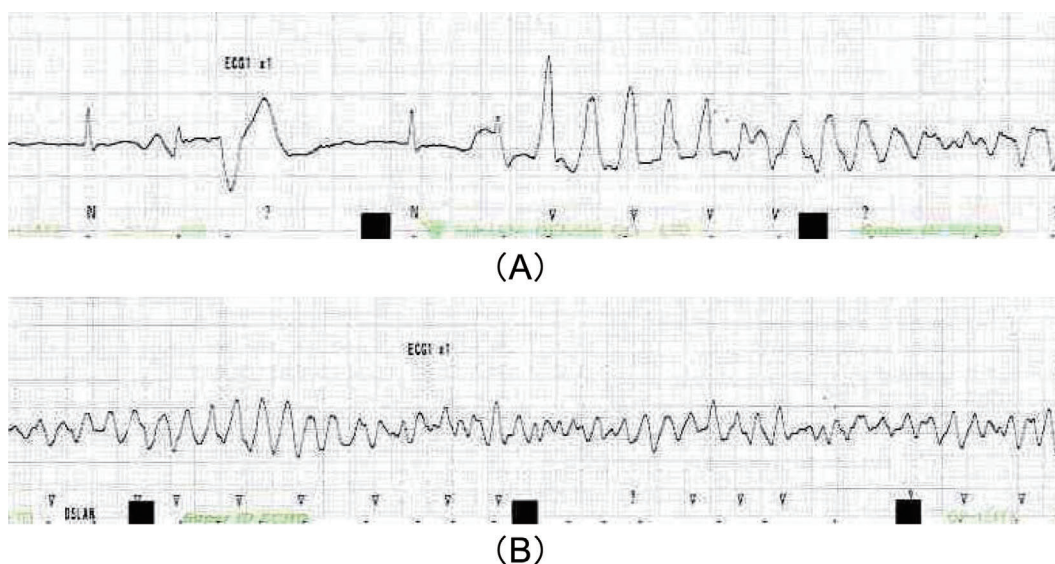


Figure 4. ECG monitor recording showing Torsade de Pointes followed by R on T (A). Leading to ventricular fibrillation (B). This arrhythmia was observed for about 3 minutes and thereafter recovered without medication.

sient syncope.

On admission she had become alert and complained of back pain. Her body temperature was 36.4°C; blood pressure was 115/63 mmHg; and heart rate was 40 beats/minute. The physical and neurological findings, radiologic examinations, including a computed tomography of the brain, and laboratory screening test were unremarkable. A transthoracic echocardiography revealed normal left ventricular wall motion and ejection fraction. ECG demonstrated atrial fibrillation and the T-wave morphology in the aforementioned leads with QT prolongation (QT 0.720 sec; QTc 0.594; Fig. 3).

Ten hours after hospitalization, she suddenly complained of vomiting and nausea. Thirty minutes before that event, the continuous ECG monitoring had revealed torsade de pointes followed by R on T and leading to ventricular fibril-

lation (Fig. 4). This arrhythmia was sustained for about 3 minutes and recovered to the original rhythm without medication. She was therefore assumed to have fallen because of Adams-Stokes syndrome due to torsade de pointes. Orciprenaline 30 mg/daily was administered in order to prevent the progression of the bradycardia. Furthermore, Donepezil was discontinued on the 5th day. Her heart rate slightly increased to 55 beats/minute, and no adverse ventricular arrhythmia was seen. ECG on the 18th day showed disappearance of the negative part of the T-waves in leads V₃₋₆ and significantly shortened QT intervals (QT 0.490 sec; QTc 0.446; Fig. 5). She was discharged on the 37th day, under the administration of Orciprenaline 30 mg/daily and her usual medications, without the administration of Donepezil.

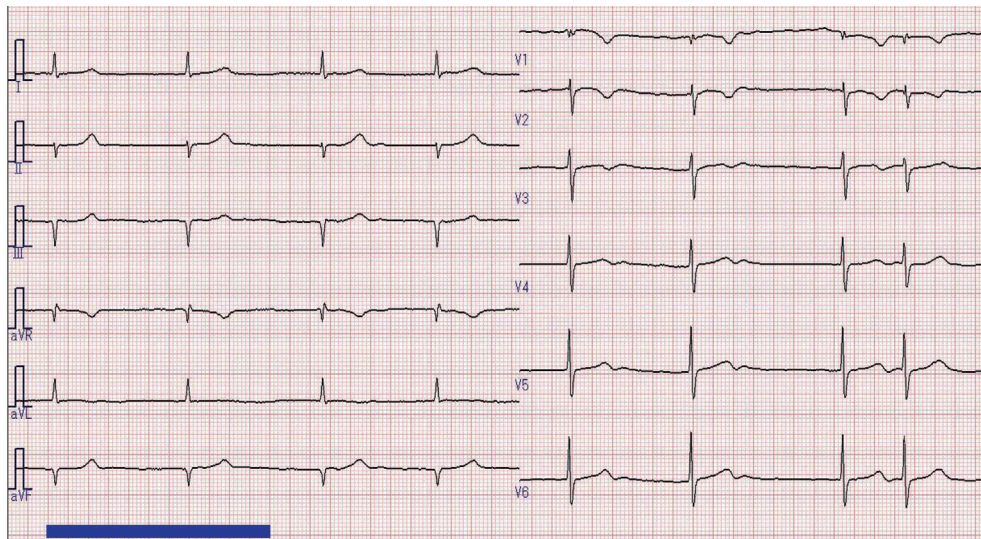


Figure 5. ECG on the 18th day showed disappearance of negative part of the T-waves in leads V₃₋₆ and shortened QT intervals (QT 0.490 sec; QTc 446).

Discussion

The disorders of recognition in Alzheimer's disease (AD) are caused by a decreased function of the central cholinergic nervous system (5). Donepezil is a drug which has inhibitory effects on acetylcholinesterase which can improve cognitive function in AD and it is widely used in the treatment of mild-to-moderate AD (1, 2). Donepezil mainly works at the level of the central nervous system, and causes few peripheral side effects (6, 7). Although its cholinergically-dependent gastrointestinal effects are well recognized, Donepezil requires careful administration for patients with sinus node dysfunction or conduction disturbance because of its cholinergic effects. Morganroth et al reported that about 30% and 10% of the patients treated with AChIs in Alzheimer's disease had cardiovascular disorders and heart rate/rhythm disorders, respectively (8). However, drug-induced bradycardia has rarely been reported and essentially occurs only when the drug is administered in excessive doses. Therefore, the direct relationship between the routine use of AChIs and bradyarrhythmia remains controversial and life-threatening ventricular arrhythmia had also rarely been reported (6, 9).

Both bradycardia and QT prolongation were observed in the current cases (case 1: HR36 beats/minute and QT0.514 sec, case 2: HR40 beats/minute and QT0.536 sec; QTc 0.538). Donepezil had not been used at either in excessive doses or in combination with other drugs that might effect of QT prolongation. Fortunately, the symptoms improved after discontinuation of Donepezil. Some reports have shown that the serum potassium level is important to QT prolongation (10, 11). However, the serum potassium concentration of both patients was 4.4 mEq/L. In both cases it was unclear whether or not they had conduction disturbances of the heart before Donepezil medication, because we did not have any

past ECG taken during without Donepezil medication. Therefore, we concluded that the observed changes had been induced by Donepezil. But there was possibility that Donepezil worsened their potential conduction disturbances of the heart, because they were extremely old aged. Bordier et al examined patients with AD who were being treated with Donepezil and experienced syncope, and found a complete atrioventricular block in two cases (12). On the other hand, Fisher et al demonstrated a case with QT prolongation and recurrent syncope after restarting Galantamine (AChIs) (13). According to an analysis by the Australian Adverse Drug Reaction Advisory Committee (ADRAC), no cases of torsade de pointes associated with AChIs were reported, and the rate of reported adverse effects of Donepezil is 2 times lower than the rates for other AChIs (i.e., Galantamine and Rivastigmine) (13). These side effects may occur more frequently than in previous reports, because the patients with AD are often unable to describe symptoms and they could be asymptomatic cases such as those seen in the current report.

The QT interval is often prolonged by class Ia antiarrhythmic drugs. These drugs inhibit the function of the rapidly activating delayed rectifier potassium current (I_{Kr}), coded by the HERG (human ether-a-go-go related gene), which is most frequently affected by drugs inducing QT prolongation (14-17). These QT prolongations are thought to be a marker of the fatal ventricular arrhythmia (i.e., torsade de pointes, ventricular fibrillation) as in the present latter case (18-20). QT intervals on the surface ECG show the repolarization in the M cell zone with the longest action potential duration in the myocardium. Some possible factors inducing specific gene mutations and selective action potential prolongation in this zone may lead to a proarrhythmic state precipitating the onset of QT prolongation and torsade de pointes (21, 22). This indicates that there are individual specificities and differences in the sensitivity to the drug,

and gene abnormalities are assumed behind these differences (23, 24). Therefore, the drug effects blocking I_{Kr} could accelerate such subclinical genetic features of the ion channels and thereby lead to the development of QT prolongation.

In conclusion, Donepezil has been widely used in the treatment of AD and it is well tolerated. However, the po-

tential adverse and life-threatening cardiac effects of Donepezil should be carefully followed by ECG, because they are caused by various factors such as diverse underlying drugs, organic heart disease, metabolic abnormalities and genetic features.

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