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Donepezil Associated Bradyarrhythmia in a Patient with Dementia with Lewy Bodies (DLB)

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Abstract

Dementia with Lewy bodies (DLB) is a neurodegenerative condition that results in loss of mesopontine cholinergic neurons and sympathetic deinnervation. While acetylcholinesterase inhibitors (ChE-Is) have been shown to improve cognitive and behavioral deficits in DLB, these patients may be more susceptible to bradyarrhythmic side effects from this class of drugs due to the autonomic insufficiency associated with the disease. We present a patient who experienced a dose-dependent, symptomatic sinus bradyarrhythmia with donepezil doses at and greater than 5 mg. Due to underlying autonomic dysfunction, patients with DLB may be at increased risk of bradyarrhythmia resulting from treatment with ChE-Is.

Dementia with Lewy bodies (DLB) is a neurodegenerative condition characterized by parkinsonism, hallucinations, and cognitive fluctuations[1]. DLB is associated with a selective reduction of mesopontine cholinergic neurons in the nucleus basalis[2]. Consequently, patients treated with acetylcholinesterase inhibitors (ChE-Is) may experience significant improvements in cognition, and behavior.

Donepezil is a specific, reversible ChE-I that has been approved by the Food and Drug Administration (FDA) for the treatment of Alzheimer's Disease (AD). Donepezil and other ChE-Is have been reported to be beneficial in treating the cognitive and behavioral symptoms of DLB, though they are not FDA approved for this indication [2]. Improvements in verbal and spatial working memory, episodic memory, attention, verbal initiation and executive

function have been noted in subjects four weeks to one year post-baseline, [2] while behavioral benefits include a reduction of hallucinations, delusions, and apathy[3]. Although donepezil preferentially inhibits acetylcholinesterase in the central nervous system, peripheral side effects such as nausea (5–19%), and diarrhea (8–15%) have been described. Symptomatic cardiac arrhythmias are relatively rare. Nevertheless, as cholinergic agonists, ChE-Is have the potential to exert vagotonic effects on the sinoatrial (SA) and atrioventricular (AV) nodes, resulting in bradyarrhythmias. Autonomic failure is a well-recognized consequence of DLB. Patients may experience bradyarrhythmias and orthostatic hypotension due to autonomic dysfunction. Consequently, the DLB population may be particularly susceptible to the bradyarrhythmic side effects of ChE-Is. We describe a case of a patient with DLB who experienced recurrent episodes of sinus bradycardia with donepezil doses between 5 and 10 mg per day.

Case Report

A 72-year-old right-handed man presented with three years of progressive memory loss, executive and visuospatial dysfunction and two years of decreased facial expressivity, falls and a shuffling gait. He endorsed visual misperceptions but denied hallucinations. He had a twelve-year history of purposeful movements during sleep suggestive of REM sleep behavior. He experienced difficulty visually locating objects and was forced to restrict his driving due to his impaired navigational skills. His past medical history was unremarkable, and in particular he had no history of syncope, palpitations, arrhythmia or other heart disease. His medications included trazodone 50 mg at bedtime, vitamin B complex, multivitamin, fish oil, primrose oil, phosphatidylcholine, flaxseed oil and the homeopathic agent zincum metallicum. On examination, he was noted to have borderline orthostatic hypotension, with supine blood pressure 142/69 and pulse 61, standing blood pressure 122/72, and pulse 72. His neurological examination was remarkable for mild-to-moderate parkinsonism. Neuropsychological testing revealed a Mini Mental State Exam (MMSE) score of 26/30, impaired verbal memory (recalled 3/9 items after 10 minutes on the California Verbal Learning Test), and impaired executive function (On Modified Trails, he lost track of the task, completing 7 lines with 3 errors in 120 seconds). His visuospatial function was fully intact. The patient was diagnosed with DLB and prescribed donepezil, titrating up to 10 mg daily. A baseline ECG was normal prior to initiating treatment (ECG 1a).

At a follow-up appointment, the patient reported feeling “foggy” and the dose of donepezil was decreased to 5 mg daily. The patient and family reported considerable improvement in cognition on this dose. Eight months later, the patient complained of palpitations and was noted on cardiac examination to have an irregular rhythm. ECG showed sinus bradycardia at 56 with short-long sequelae most compatible with sinoatrial exit block (ECG 1b). The patient discontinued donepezil with resolution of both palpitations and arrhythmia. One month later, the patient elected to restart donepezil at 5 mg daily, and he tolerated this dose until it was increased to 7.5 mg daily due to further cognitive decline. On this dose he was found to have an asymptomatic irregular heart rate with pauses. ECG showed an irregular sinus bradycardia at 43–46 (ECG 1c). Donepezil was decreased to 5 mg, and the patient tolerated this dose without further bradyarrhythmias.

This patient demonstrated repeated sensitivity to donepezil doses equal to or greater than 5 mg/day, with ECG evidence of bradyarrhythmia that resolved each time the dose of donepezil was decreased. Factors likely contributing to this clinical phenomenon include underlying DLB dysautonomia, as well as the vagotonic effects of donepezil.

Autonomic failure is recognized as one of the major clinical features of DLB[1]. Patients frequently experience symptoms of sympathetic dysfunction including orthostatic hypotension, urinary incontinence, and erectile dysfunction [1]. Bradycardia and carotid sinus

hypersensitivity are common consequences of cardiac deinnervation in this population. Cardiac sympathetic deinnervation has been demonstrated by single photon computed tomography (SPECT), with DLB patients showing reduced myocardial I-meta-iodobenzylguanidine (MIBG) uptake compared to controls[4].

Compared to AD patients, individuals with DLB may be more susceptible to the bradyarrhythmic side effects of ChE-Is. These drugs exert vagotonic effects on the SA and AV nodes, and animal models have shown that donepezil, galantamine, and rivastigmine all slow spontaneous cardiac neuronal activity[5]. Symptomatic bradycardia with excessive doses of donepezil was reported in a 79 year-old patient with AD mistakenly administered a 50 mg dose [6]. There are several case studies describing sinus bradycardia and AV block with therapeutic doses of donepezil[7,8]

Prospective studies of anti-cholinesterase associated bradyarrhythmia have mostly been confined to the AD population. Bordier and colleagues prospectively studied the susceptibility of AD patients to bradycardia and syncope induced by donepezil. The drug was administered at 5 mg/day for one month and was increased to 10 mg/day for the following seven months [9]. Forty-three percent of subjects enrolled in the study were already taking negatively chronotropic or dromotropic drugs. The investigators found a mild drop in heart rate and mild increase in PR interval among patients *not* taking chronotropic agents, though both values remained in the normal range. There was no relationship between donepezil and syncope [9]. There are few reports in the literature specifically addressing the cardiac side effects of ChE-Is in patients with DLB. A review of safety data for rivastigmine revealed no statistically significant changes in heart rate, blood pressure, or adverse cardiac events amongst DLB patients enrolled in a clinical trial[10].

This case illustrates potential adverse consequences that may result when administering ChE-Is to a patient with DLB. The addition of vagotonic agents to an underlying sympathetic deinnervation may place patients at risk for bradyarrhythmia. Though this adverse effect has rarely been found in limited prospective trials of ChE-Is in DLB, clinicians should exercise increased caution when prescribing ChE-Is in this disorder. DLB patients should be screened for symptomatic bradyarrhythmia prior to and during treatment with ChE-Is, and these drugs should be suspected when treated patients develop cardiac symptoms. While DLB patients may warrant pacemaker implantation for cardiac sympathetic deinnervation, patients on ChE-Is should first be evaluated upon withdrawal of the drug in order to prevent an unnecessary procedure. However, our experience suggests that patients with DLB may show clear cognitive improvement on ChE-Is, and selected patients may choose to undergo pacemaker placement in order to safely continue taking these medications.

In summary, our case demonstrates that reversible symptomatic bradyarrhythmia can occur in a DLB patient with no cardiac history while taking a moderate dose of donepezil. The absence of prior cardiac arrhythmia, the dose-dependent bradyarrhythmia with donepezil, and the resolution of symptoms upon withdrawal of the medication suggest that this clinical observation was most likely an adverse effect of the drug. Further studies are needed to evaluate whether DLB patients are at increased risk of experiencing this adverse effect of ChE-Is. Furthermore, increased awareness of the cardiovascular side effects of ChE-Is should foster better communication between neurologists, primary care physicians and cardiologists in order to optimize patient care.

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Figure 1.

ECG Results: (1a) Baseline ECG obtained prior to initiation of donepezil. (1b) ECG obtained while patient taking donepezil 5 mg. Findings are consistent with sinoatrial exit block. (1c) ECG obtained while patient taking donepezil 7.5 mg. There is an irregular sinus bradyarrhythmia.