SHORT REPORT

Complete atrioventricular block and ventricular tachyarrhythmia associated with donepezil

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Donepezil is a reversible inhibitor of acetylcholinesterase. Its commonest adverse events are nausea, diarrhoea, malaise, dizziness, and insomnia. Symptomatic cardiac rhythm disturbances associated with the use of donepezil are extremely unusual. An 82 year old patient with Alzheimer's disease (AD) developed complete atrioventricular block and ventricular tachyarrhythmia 1 month after starting treatment with donepezil, and was admitted to the emergency department because of dizziness and syncope. Immediately after admission, a temporary ventricular pacing catheter was placed in the right ventricle. Rhythm was observed to return to a normal sinus rhythm on the fourth day after implantation. Treatment of AD with cholinesterase inhibitors carries a risk of cardiac disturbances. In addition to sinus bradycardia, it may lead to such major dysrhythmias as complete atrioventricular block and ventricular tachyarrhythmia, as in our case. In this report, we describe symptomatic complete atrioventricular block and ventricular tachyarrhythmia associated with the use of donepezil.

Donepezil is a reversible and specific inhibitor of acetylcholinesterase. The drug is highly selective for the central nervous system, and is becoming widely used in mild to moderate Alzheimer's disease (AD).¹

Donepezil is well tolerated; however, some side effects have been noted. The commonest adverse events are nausea, diarrhoea, malaise, dizziness, and insomnia. Symptomatic cardiac rhythm disturbances associated with the use of donepezil are extremely unusual.² To date, 16 cases of cardiac dysrhythmias related to donepezil use have been reported in the literature. Three of these were cases of complete atrioventricular block (table 1). We report a fourth case, in an elderly patient with AD.

CASE REPORT

An 82 year old man was admitted to the emergency department because of dizziness and syncope. The patient's history revealed use of 10 mg/day donepezil as treatment for AD for the previous 1 month. He had no history of any other drug use or additional cardiac disease. At examination on admission to the emergency department, blood pressure was 100/60 mmHg, and pulse rate was 35 beats/min. Neurological examination was normal.

A 12 lead electrocardiogram revealed complete atrioventricular block (fig 1A), and electrocardiographic monitoring revealed non-sustained ventricular beats (fig 1B). There was no orthostatic hypotension, and head up test results were normal. Echocardiogram results were also normal, and there was no evidence of structural heart disease. There was no alteration in cardiac rate with carotid sinus massage. Blood analysis and cardiac biochemical markers were normal. Immediately after initial evaluation, a temporary ventricular

pacing catheter was placed in the right ventricle, ventricular pacing was initiated, and the patient was transferred to the intensive care unit. During observation, rhythm was seen to return to a normal sinus rhythm on the fourth day of admission, and the temporary pacemaker was removed. The patient was discharged on the sixth day.

DISCUSSION

Donepezil is an acetylcholinesterase inhibitor under development for the treatment of mild to moderate AD. In humans, donepezil is slowly absorbed from the gastrointestinal tract. The compound has a terminal elimination half life of 50–70 h in young volunteers; in elderly volunteers, the half life of the compound is extended to over 100 h. Donepezil is extensively metabolised following oral administration. The parent compound is 93% bound to plasma proteins.³

Donepezil is centrally acting and highly specific for neural acetylcholinesterases. This specificity minimises peripheral adverse effects in therapeutic doses.⁴ These adverse effects are basically cholinergic dependent. The commonest adverse effects are nausea, diarrhoea, dizziness, and insomnia. Cardiac rhythm disturbances associated with the use of donepezil are unusual.²

In a wide ranging study of 1762 patients using donepezil, Nicholas *et al* reported drug related side effects of nausea, diarrhoea, malaise, dizziness, and insomnia, although no case with cardiac rhythm problems was reported.⁵

In a study carried out in 2005, Bordier *et al* examined patients with AD who were being treated with donepezil and experiencing syncope, and determined the cause of the syncope in 69% of patients. They found complete atrioventricular block in two cases, carotid sinus disease in three, sinus node dysfunction in two, severe orthostatic hypotension in two, and paroxysmal atrial fibrillation in one.⁶ In a study published in 2003, Bordier *et al* examined three cases

Table 1 Donepezil use related cardiac rhythm problems

Authors	Publication date	No. of cases	Rhythm disturbance
Bordier <i>et al</i> ⁶	2005	3	Carotid sinus syndrome
		2	Complete AV block
		2	Sinus node dysfunction
		2	Severe orthostatic hypotension
		1	Paroxysmal atrial fibrillation
Newby <i>et al</i> ⁸	2004	1	Carotid sinus syndrome
Brembilla <i>et al</i> ⁹	2004	1	Complete AV block
Bordier <i>et al</i> ⁷	2003	2	Bradyarrhythmia
Shepherd <i>et al</i> ⁴	1999	1	Symptomatic sinus bradycardia
Calvo-Romero <i>et al</i> ⁷	1999	1	Symptomatic sinus bradycardia

Abbreviation: AD, Alzheimer's disease

Figure 1 Electrocardiogram showed (A) complete atrioventricular block and (B) non-sustained ventricular beats.

treated with donepezil and experiencing syncope, and determined bradyarrhythmia in two of these. These authors also stated that pacemaker implantation rather than donepezil cessation seemed justified.⁷

Shepherd *et al* published a report of a case developing temporary bradycardia related to excessive donepezil dosage and successfully treated with atropine.⁴ Similarly, Calvo-Romero *et al* reported that sinus bradycardia may develop related to donepezil use. In that report, sinus bradycardia and left cardiac deficiency developed 3 weeks after donepezil administration, and the bradycardia quickly resolved when donepezil was halted.²

Newby *et al* diagnosed cardioinhibitory carotid sinus syndrome in a 69 year old woman using donepezil and experiencing syncope, and reported that they had to use a cardiac pacemaker in treating this case.⁸ Similar to our case, Brembilla *et al* reported that atrioventricular block could develop due to anticholinesterase therapy, but that this was temporary.⁹ McLaren *et al* reported that heart rate variability was significantly reduced following the administration of donepezil in the treatment of patients with dementia.¹⁰

In our case, non-sustained ventricular tachyarrhythmia attacks not previously reported in the literature, which could

have been fatal, were observed in our patient who used donepezil and who developed complete atrioventricular block. The patient was successfully treated by halting donepezil use and installing a temporary pacemaker.

In conclusion, although donepezil is widely used in the treatment of mild to moderate Alzheimer's disease, treatment of the disease with cholinesterase inhibitors carries a risk of cardiac disturbances. In addition to sinus bradycardia it may lead to significant and life threatening dysrhythmias such as complete atrioventricular block and ventricular tachyarrhythmia, as in our case.

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