Significance of syncope in patients with Alzheimer’s disease treated with cholinesterase inhibitors

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We describe three cases of patients with Alzheimer’s disease who presented with cardiac syncope soon after initiation of a cholinesterase inhibitor therapy (donepezil). Bradycardia was documented in two patients, considered probable in one, and was presumed related to the cholinergic therapy. Pacemaker implantation seemed justified rather than donepezil cessation. Moreover, it permitted an increase in donepezil dosage.

Introduction

Alzheimer’s disease is a common worldwide public health problem but few therapies delay its progression[1–4]. Cholinesterase inhibitors are used to treat Alzheimer’s disease but their cholinergic side-effects may result in discontinuation of therapy[5,6]. Symptomatic cardiac conduction disorders are considered unusual with cholinesterase inhibitors in therapeutic doses. Bradycardia, dizziness, syncope and seizure are rarely described and their relationship to therapy is unclear[7–10]. We report our experience with three patients with Alzheimer’s disease who presented with cardiac syncope after starting donepezil. We defined dizziness as a sensation of light-headedness or postural instability, and syncope as sudden and complete loss of consciousness. The diagnosis of Alzheimer’s disease was established by a neurologist according to the Diagnostic and Statistical Manual of Mental Disorders (Third Edition, revised) criteria.

Case 1

An 80-year-old man with a 2-year history of Alzheimer’s disease was hospitalized following two episodes of syncope on the same day. There was no previous history of syncope. He had been taking donepezil 5 mg day⁻¹ for 1 year and experienced dizziness since the onset of therapy. His past history consisted of hypertension treated with lisinopril and nicardipine, paroxysmal atrial fibrillation treated with propafenone 600 mg day⁻¹ and glaucoma treated with timolol eye drops. All these medications had been taken for more than 10 years. The physical findings and ECG are described in Table 1. Carotid sinus massage was associated with no symptom and no change in blood pressure. The results of other investigations are shown in Table 2. The patient was...
discharged without a diagnosis and the drug regimen was continued. One week later, the patient was readmitted with another episode of syncope. An electrophysiological study revealed no inducible atrial or ventricular tachycardia but the corrected sinus node recovery time was 700 ms and the HV interval was 60 ms. Though these criteria were weak, a pacemaker was finally implanted because of recurrent, unexplained syncope despite extensive evaluation. A DDD pacemaker was implanted and all the medications were continued. At 1 month and 23 months after pacemaker implantation no dizziness or syncope was reported by the patient or his wife. Donepezil was increased to 10 mg day\(^{-1}\) after 1 month without any symptom.

### Case 2

An 83-year-old man with Alzheimer’s disease was referred for evaluation of a first syncopal episode resulting in severe facial trauma. There was no significant past history. He was being treated with trimetazidine 60 mg day\(^{-1}\), domperidone 30 mg day\(^{-1}\) and donepezil 5 mg day\(^{-1}\). The latter was begun 2 weeks before syncope. The clinical and ECG characteristics are presented in Table 1.

Echocardiography and brain CT were performed on the first day by the emergency team (Table 2), followed by no further testing since we had clearly identified the cause of syncope. In fact, on the second day, 2:1 atrioventricular (AV) block was recorded during continuous ECG monitoring, eventually progressing to spontaneous complete AV block the next day. ECG monitoring showed no ventricular escape rhythm, and cardio-pulmonary resuscitation was performed for 20 min before the start of reliable percutaneous temporary cardiac pacing. A VDD pacemaker was implanted. One month after discharge, the patient remained asymptomatic and donepezil dose was increased to 10 mg day\(^{-1}\). The patient was still asymptomatic 28 months after pacemaker implantation.

### Case 3

An 87-year-old woman with Alzheimer’s disease was admitted because of syncope and persistent sinus bradycardia at 45 bpm. She had a past history of hypertension and depression but no syncope. She had been on propranolol 40 mg day\(^{-1}\) for 4 years for idiopathic tremor of the right arm, and clomipramine 10 mg day\(^{-1}\), oxazepam 30 mg day\(^{-1}\) and domperidone 30 mg day\(^{-1}\). Donepezil (5 mg day\(^{-1}\)) had been started 19 days before syncope. Table 1 shows the results of physical examination and ECG data. Light carotid sinus massage caused sudden loss of consciousness 12 s after the onset of sinus arrest without escape rhythm, followed by convulsions. Since the effect of carotid sinus massage was reproducible by a second manoeuvre, we considered that no other examination was warranted (Table 2). After implantation of a DDD pacemaker the patient has remained asymptomatic for 22 months, without any change in her medications except for donepezil increased to 10 mg day\(^{-1}\) 1 month after the implant.

### Discussion

Peripheral cholinergic adverse effects of cholinesterase inhibitors include nausea, vomiting, diarrhoea, dizziness, syncope and even seizure that may lead to discontinuation of treatment\(^{[5,9,10–13]}\). Cholinergic-dependent side-effects on cardiac rhythm are related to vagal tone stimulation\(^{[14]}\). Theoretically, sinus bradycardia, sino-atrial block, worsening of sinus node disease and AV block can be induced\(^{[7,8,15]}\). These abnormalities

<table>
<thead>
<tr>
<th>BP (mmHg)</th>
<th>Orthostatic hypotension</th>
<th>Rhythm/HR (bpm)</th>
<th>PR interval (ms)</th>
<th>QRS complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>154/85</td>
<td>No</td>
<td>Sinus/56</td>
<td>220</td>
</tr>
<tr>
<td>Patient 2</td>
<td>159/86</td>
<td>No</td>
<td>Sinus/60</td>
<td>200</td>
</tr>
<tr>
<td>Patient 3</td>
<td>125/77</td>
<td>No</td>
<td>Sinus/51</td>
<td>180</td>
</tr>
</tbody>
</table>

BBB, bundle branch block; BP, blood pressure; HR, heart rate.

<table>
<thead>
<tr>
<th>Routine laboratory studies</th>
<th>TSH</th>
<th>Holter ECG 48 h</th>
<th>Echocardiography</th>
<th>Echo-Doppler of supra-aortic vessels</th>
<th>Head-up tilt test</th>
<th>EEG</th>
<th>Brain CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
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<tr>
<td>Patient 2</td>
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<tr>
<td>Patient 3</td>
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n, Normal; TSH, thyroid stimulating hormone; –, not performed.
resolve with atropine and stopping the medication. The effect of cholinesterase inhibition on vagal tone has been used with edrophonium as a provocative agent for inducing syncope during tilt-table testing.

In patients 2 and 3, bradyarrhythmias observed during hospitalization strongly suggested a relationship with the episodes of syncope that had occurred out of the hospital. The absence of recurrence of syncope after pacemaker insertion during a follow-up of over 18 months in each patient may be further evidence of this causal relationship. Circumstantial evidence strongly implicates the role of donepezil in the development of syncope in 2 patients and dizziness (and eventual syncope) in another because the symptoms occurred soon after the initiation of therapy.

Atropine (1 mg) was administered to patient 1 during electrophysiological study without any significant change in measured data. But at baseline these data were slightly abnormal. For patient 2, the over-riding factor was prolonged resuscitation. In the third case, a second carotid massage after atropine was not performed for fear of possible further convulsions if atropine was not effective.

Two patients had been treated with antiarrhythmic drug therapy for a long time before donepezil was started but they probably contributed little to the symptomatic bradycardia induced by donepezil. In patient 1, the symptoms were probably secondary to sick sinus syndrome aggravated by donepezil, and the response to pacing was dramatic in the relief of dizziness. In patient 2, significant conduction system disease with right bundle branch block and left anterior hemiblock associated with the duration of the arrest suggested infra-His disease as the primary problem rather than a drug effect which would be expected at the AV nodal level. Nevertheless, aggravation of conduction system disease by donepezil was rather consistent. Patient 3 suffered from sick sinus syndrome and marked carotid sinus hypersensitivity (not an uncommon association with sick sinus syndrome) unmasked by donepezil.

The documentation of severe bradycardia as a putative adverse effect of an anticholinesterase led us to recommend the implantation of a pacemaker rather than discontinuation of drug therapy. Though we recognized that permanent pacing to manage an adverse effect from another therapy may be controversial, we made this choice because cholinergic therapy is the only therapeutic option known to slow the progression of this disease. Nevertheless, pacing is the primary problem rather than a drug effect which would be expected at the AV nodal level. Nevertheless, aggravation of conduction system disease by donepezil was rather consistent. Patient 3 suffered from sick sinus syndrome and marked carotid sinus hypersensitivity (not an uncommon association with sick sinus syndrome) unmasked by donepezil.

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In conclusion, dizziness and syncope are uncommon features of Alzheimer’s disease even when treated with donepezil and, although our findings only give an inference as to the cause, these symptoms require investigation for a cardiac aetiology. If the aetiology is shown to be cardiac and secondary to donepezil or strongly suspected (an implantable loop recorder may also be needed), pacemaker implantation may be justified instead of drug cessation. Furthermore, a pacemaker permits an increase in donepezil dosage. A prospective and large study is needed for screening patients prior to commencement of cholinergic therapy to determine whether risk factors may be identified for severe bradycardia under this therapy.

References