

Lesson of the month 1: Prolonged QT syndrome due to donepezil: a reversible cause of falls?

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ABSTRACT

Prolonged QT syndrome precipitates cardiac arrhythmias such as torsades de pointes (TdP) resulting in cardiogenic syncope or sudden death. We report a case of prolonged QT syndrome caused by donepezil which resulted in a fall and hip fracture. In this case female sex, advanced age and diuretic use may have increased the risk of recurrent syncope and potential underlying TdP. Cessation of donepezil resulted in normalisation of the QT interval. This case highlights a lesser known side effect of this dementia drug. It also reminds us of the importance of taking a thorough drug history while considering potential drug toxicity/interactions as part of the comprehensive geriatric assessment.

KEYWORDS: Donepezil, falls, QT interval, torsades de pointes, syncope

Case presentation

An 83 year old Caucasian female presented to the emergency department with hip pain after an unwitnessed syncopal episode. She denied any prodromal symptoms and there was no post-ictal phase, tongue biting or incontinence. A fractured neck of the femur was diagnosed and she was transferred to the orthopaedic trauma ward. Her past medical history included early Alzheimer's dementia, hypertension and recurrent falls (although she had not previously sought medical attention for this problem). Her admission medications were bendroflumethiazide 2.5 mg, simvastatin 20 mg and donepezil 10 mg. She lived alone and was independent with activities of daily living (ADLs).

On admission the patient's electrocardiogram (ECG) demonstrated normal sinus rhythm with a prolonged corrected QT interval (QTc) of 638 ms (the upper limit of normal for females is 460 ms).¹ Blood tests, including electrolytes, were all within normal limits and there was no postural blood pressure deficit. The patient was reviewed by the orthogeriatrics team for falls and bone health assessment, and medical optimisation prior to surgery. Given her history of syncope without prodromal symptoms, we suspected that this patient had fallen as a result of cardiogenic syncope

relating to prolonged QT syndrome. Donepezil was withdrawn as the potentially causative medication. The 12 lead ECG was repeated at days 2 and 10, and the QTc had returned to normal (436 ms) by day 10. Subsequent echocardiogram and 24 h ECG were normal. Following surgical intervention for the fracture, and input from the multi-disciplinary team, the patient was transferred to a community rehabilitation facility.

Discussion

The QT interval is the measurement between the start of the QRS complex and the end of the T wave, and it represents the duration of ventricular repolarisation.¹ There are multiple factors that affect the duration of the QT interval including sex, heart rate and underlying heart rhythm. In clinical practice it is most relevant to correct QT for heart rate; Bazett's formula ($QTc = QT/\sqrt{RR}$) is most widely used. Drug interactions can lead to a cumulative effect on QT interval although this has an unpredictable effect in causing TdP and is affected by many risk factors.² In this case the only causative medication was donepezil, although female sex, advanced age and use of diuretics were risk factors for TdP with prolonged QT.

Donepezil is a reversible inhibitor of acetylcholinesterase for use in mild to moderate dementia in Alzheimer's disease. It has multiple known cardiac side-effects including dizziness, syncope, bradycardia, atrioventricular block, and sinoatrial block.³ In recent years, cases of donepezil-induced QT prolongation and TdP have been reported but this is not widely known and it is not a listed side effect in the British National Formulary.^{3–7} The list of drugs known to cause prolonged QT syndrome is long and frequently growing. The website CredibleMeds.org, published in conjunction with the US Food and Drug Administration, is a regularly updated list of drugs with a risk of QT interval prolongation and cardiac arrhythmias. Indeed, donepezil is listed as a 'known risk of TdP' on this resource.⁸

People living with dementia have an increased risk of falls. This is related to multiple factors including impaired gait, balance and orthostatic hypotension coupled with changes in cognition, attention and behaviour.⁷ Furthermore people living with dementia are more likely to suffer the serious consequences of falls and less likely to recover from their injuries.⁹ A recent Cochrane review of the use of donepezil in Alzheimer's disease has found only modest benefit in terms of cognition and ability to perform ADLs with no improvement in quality of life. Concern was also raised about the rate of adverse effects with donepezil

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which increased with higher doses.¹⁰ With this in mind, clinicians should consider the cardiac side effects and measure a baseline QT interval prior to commencing therapy.

Key points

- > Donepezil causes QT prolongation but this is not widely known.
- > Growing evidence is emerging of the significant potential harms related to donepezil with only modest benefit.
- > Clinicians should start this drug with caution after careful consideration of the cardiac side effects and risk of falls.
- > Prior to starting donepezil, a 12 lead ECG should be performed to document baseline heart rhythm and QTc and risk factors for TdP should be considered.
- > Patients should be informed of the potential for cardiac arrhythmias and falls when starting donepezil. ■

Consent

Consent was obtained to publish the clinical details in this article.

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