CASE REPORT

Collapse in the elderly: rivastigmine-induced heart block and a literature review of the pharmacology of acetylcholinesterase inhibitors used in Alzheimer's disease

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SUMMARY

Falls resulting in neck of femur fractures are common in the elderly. Often multiple comorbidities can make management and diagnosis of such a polyfactorial condition difficult, particularly with Alzheimer's dementia (AD). Indeed, poorly managed AD may contribute to falls. We present our management of an 87-year-old woman, on rivastigmine for AD, who presented with a collapse episode—attributed to rivastigmine—resulting in a neck of femur fracture. Furthermore, we perform a literature review of the pharmacology of acetylcholinesterase inhibitors and how their use in AD may contribute to bradyarrhythmias.

BACKGROUND

With an ever-ageing population, the prevalence of dementia is rising too. Indeed, the elderly (aged over 65 years) are at the greater risk of falling and sustaining injury, particularly neck of femur fractures; a risk heightened when suffering with dementia—Alzheimer's dementia (AD) being the most common. Currently, acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) are recommended as first-line treatment for individuals diagnosed with mild to moderate cognitive impairment secondary to AD.¹ These drugs are reported to have a safe side effect profile, with complaints commonly related to gastrointestinal symptoms: nausea, vomiting and sometimes diarrhoea; symptomatic cardiac dysrhythmias are uncommon.^{2,3}

Acetylcholinesterase (AChE) inhibitors prevent the cholinesterase enzyme breaking down acetylcholine, thereby amplifying and prolonging cholinergic response. This response results in an increase in acetylcholine binding to postsynaptic ACh receptors (nicotinic and muscarinic). On a cardiac level, muscarinic M2 receptors present in myocardial conduction tissue can result in a negatively chronotropic and dromotropic response causing first-degree heart block and, rarely, complete atrioventricular (AV) block.⁴

While case reports have suggested a link between AChE inhibitor use and bradycardia,^{5–7} a double-blind, multicentred randomised trial (n=2149) reported no changes on ECG parameters (heart

rate, PR, QTc and QRS interval) between rivastigmine and placebo groups over 26 weeks.⁸

We report our experience of a case of AChE inhibitor-induced dysrhythmia resulting in a fall with a subsequent neck of femur fracture and perform a brief literature review of the pharmacology of AChE inhibitor used in AD.

CASE PRESENTATION

An 87-year-old woman presented following an unwitnessed collapse with transient loss of consciousness; there was no prodrome of dizziness or palpitations. Of note, she had a diagnosis of AD and was on AChE inhibitors for 4 years: initially on donepezil but later switched to rivastigmine due to intolerable gastrointestinal side effects. Her heart rate before starting her rivastigmine transdermal patch was 93 bpm and her baseline ECG was normal. She was started on 4.6 mg/24 hours in October 2013 which was increased 3 months later to 9.5 mg/24 hours, the latter being the recommended daily effective dose. Her Montreal Cognitive Assessment Score was 22/30 and was unchanged since starting her rivastigmine. She subjectively felt that her cognition had remained stable on treatment and was keen to continue. She had no cardiac, neurological or other significant history. Interestingly, she had suffered a fall a year prior with a subsequent neck of femur fracture. At the time, her ECG showed a slightly prolonged PR interval of 210 ms with an overall heart rate of 64 bpm. This did not flag up any concerns at the time and she remained on her rivastigmine on discharge. From a functional perspective, she lived with her husband and managed her activities of daily living independently.

On presentation to the emergency department following her collapse, her blood pressure was 220/45 mm Hg with a heart rate of 47 bpm. An ECG demonstrated intermittent bradycardia with heart block (figure 1). On examination, her heart sounds were normal; neurological examination was unremarkable; her leg was shortened and externally rotated but neurovascularly intact. Imaging revealed an intracapsular neck of femur fracture. She was on no other medication which could have a negatively chronotropic effect on her heart rate.

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Figure 1 Pre-operative ECG.

Her blood work was unremarkable other than mildly elevated inflammatory markers attributed to her hip fracture.

INVESTIGATIONS

Echocardiogram: no structural abnormality with a good ejection fracture.

TREATMENT

A multidisciplinary team discussion with regards available treatment options was undertaken. This included drug cessation versus permanent pacemaker insertion to facilitate ongoing use of rivastigmine. Given her functional status and the clear benefit of AChE inhibitor treatment on her cognition, the consensus was that a permanent pacemaker insertion prior to surgical intervention for her hip fracture would be appropriate. As such, a dual chamber pacemaker was successfully inserted. Following a satisfactory pacemaker check (figure 2), she underwent a hemiarthroplasty a few hours after.

OUTCOME AND FOLLOW-UP

Following her pacemaker insertion and hemiarthroplasty, she made a quick and uneventful recovery postoperatively. She was followed up at 3 months in our outpatient clinic and has remained well without any further syncopal episodes.

DISCUSSION

Rivastigmine is one of three AChE inhibitors licensed for AD. It is also indicated for use in patients diagnosed with dementia associated with Parkinson's disease and Lewy body dementia.

Of the three available acetylcholinesterase inhibitors, rivastigmine appears to be more selective towards the G1 isoform of AChE, found more predominantly in the cerebral cortex,

whereas the G4 isoform is more prevalent in peripheral skeletal muscle.⁹ As such, it is thought that this may explain the favourable side effect profile and the reduced incidence of adverse cardiac events.¹⁰

This was confirmed further in a recent systematic review of 142 studies consisting of 110 randomised trials, 21, non-randomised trials and 11 cohort studies which sought to examine the comparative effectiveness and safety of cognitive enhancers (donepezil, oral rivastigmine and galantamine) for treatment of AD. One of the primary endpoints considered was the risk of serious adverse events reported including falls and bradycardia. The conclusion from the review was that there was no increase in adverse events noted across all the cognitive enhancers considered.³

Conversely, we looked at the conclusions from a population-based study carried out by Park-Wyllie *et al*, which examined the association between use of acetyl cholinesterase inhibitors and hospitalisation for bradycardia.¹¹ They found that initiation of acetylcholinesterase inhibitor therapy was associated with a more than doubling of the risk of hospitalisation for bradycardia. They went on to describe that resumption of the offending drug following discharge was also common, suggesting that the potential cardiovascular toxicity of cholinesterase inhibitors is underappreciated by clinicians.

Furthermore, we identified a number of sporadic case reports of adverse cardiac events in patients on acetylcholinesterase inhibitors. One of such cases was a report of an 82-year-old woman presenting with a third-degree AV block while on rivastigmine and metoprolol. Interestingly, her telemetry normalised after discontinuing both medications.¹²

Another short case series of two patients have been described where a rivastigmine transdermal patch was thought to induce complete AV blockade.⁹

Existing evidence showing a causal association between acetylcholinesterase inhibitor therapy and significant bradycardia remains inconclusive. This may in part be because the eligibility criteria in most clinical studies often excludes the most fragile patients who are likely to have multimorbidity and polypharmacy and as such makes it difficult to make a strong association of adverse cardiac effects with use of these medications particularly in this patient cohort.

Learning points

- ▶ Less common side effects of acetylcholinesterase (AChE) inhibitors include cardiac bradycardia. These are difficult to detect given their low incidence, but clinicians should be aware of warning signs: bradycardia, syncope and dizziness.
- ▶ An ECG should be performed before commencing AChE inhibitors for Alzheimer's disease to ensure there is no undiagnosed heart block.
- ▶ Patients should be educated and encouraged to self-report symptoms of syncope or presyncope when on AChE inhibitors to allow for further detailed assessments.
- ▶ A multidisciplinary team approach may well be required, particularly when optimisation for surgery is required.
- ▶ Permanent pacemaker insertion may be considered over drug cessation where a clear benefit of treatment with AChE inhibitors with regards a positive effect on cognition and level of function has been established.

Figure 2 Postpacemaker insertion ECG.

Further research is therefore required to provide more evidence of a causal association between treatment with AChE inhibitors and cardiac arrhythmias.

Our case provides important lessons: a presentation with a syncopal episode attributed to rivastigmine induced AV block. This serious event should be considered by physicians attending to individuals treated with AChE inhibitors presenting with bradycardia, syncope and dizziness as it may be difficult to detect due to its low incidence. Our case was further complicated with the fall resulting in a neck of femur fracture, a pathology associated with considerable morbidity and mortality; and the precipitating cause may easily have been missed without a multidisciplinary approach which allowed for rapid optimisation prior to surgical fixation.

In conclusion, AChE inhibitors may result in some uncommon but serious adverse cardiac effects. These, in the ever-ageing population, can be further complicated with secondary injuries requiring rapid surgical treatment. A multidisciplinary approach should be employed to best optimise individuals in such circumstances.

Contributors OA identified the case as an excellent learning opportunity and conceived the idea to write it up as a case report. OA discussed this with the patient and her next of kin and obtained the required patient consent. She also wrote the initial draft and did part of the background literature review. FMIqbal edited the first draft and also made a significant contribution to the literature search and review. He also made significant revisions and delivered an amended draft. EC was the supervising consultant involved in the patient's management and provided critical revision of the manuscript. All named authors contributed towards the final approval of the version to be published.

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