Memantine-induced bradycardia – a rare adverse reaction

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Behavioural and psychological symptoms of dementia, such as aggression or agitation are very frequent in Alzheimer’s disease with most guidelines recommending memantine as first-line pharmacological treatment. Here, the authors describe a patient who developed bradycardia when prescribed memantine and the subsequent changes required to her medication management to avoid further cardiac adverse reactions.

In the last three decades the aging population has increased globally and continues to do so. As a result of this phenomenon the incidence of dementia, mainly Alzheimer’s disease (AD), is also increasing and there is therefore a need to provide efficient treatment options for patients who suffer from AD.

The most common type of dementia is AD, which accounts for 60% to 80% of all cases. Patients with AD are characterised by their progressively deteriorating cognitive and functional skills. Vascular dementia (VD) and dementia with Lewy bodies (DLB) are less common types of dementia and affect around 150,000 and 100,000 people in the UK, respectively. When two or more types of dementia coexist, then the patient suffers from mixed type dementia. In the most common form of mixed type dementia, the abnormal protein deposits associated with Alzheimer’s disease coexist with blood vessel problems linked to VD.

Some reports show that when AD is diagnosed early and treated then the rates of cognitive and functional impairment can be reduced. Acetylcholinesterase inhibitors (AChEIs) – such as donepezil, rivastigmine, and galantamine – have been the first-line pharmacological treatment for AD since 1997.

In more than 80 countries, memantine has been used for treating patients with AD (mainly moderate to severe AD) for more than 10 years, and its efficacy and safety profile have been described in numerous clinical trials and meta-analyses. Memantine can be used as a monotherapy or in combination with AChEIs. In randomised, placebo-controlled trials; both AChEIs and memantine were shown to improve cognition, behaviour and daily functioning.

Behavioural and psychological symptoms of dementia (BPSD), such as aggression or agitation are very frequent in AD. They are associated with disability and suffering for both patients and their caregivers. BPSD remains often challenging in clinical setting because of the frequent and severe side effects of the psychotropic drugs when used in this indication. Evidence-based data confirm that antipsychotics and antidepressants are efficient for the treatment of BPSD but have a poor tolerance profile and their use is problematic (atypical antipsychotics significantly increase the risk of strokes). Most guidelines now recommend memantine as first-line pharmacological treatment for BPSD.

Despite the evidence that the early initiation and commitment to treatment is significant in alleviating the clinical symptoms of AD, a considerable number of patients who suffer from AD, do not receive any medication for the condition. However, some studies have indicated that when AD is not treated with medication then the outcomes are poor.

Memantine – mechanism of action

A focal procedure in memory and learning is long-term potentiation (LTP). LTP is mediated by the neurotransmitter glutamate via the N-methyl-D-aspartate (NMDA) receptors. These receptors are located in many areas throughout the brain. However, the most densely populated areas are the dendrites of pyramidal cells in the hippocampus and cortex (areas that have a role to play in memory, cognition and learning). Normally, the glutamate that is released by the neurons is metabolised or taken up by adjacent cells. When these pathways are disrupted, the accumulated glutamate overexcites the NMDA receptor and induces pathology that is characteristic of neurodegenerative diseases.

NMDA antagonists differ in affinity and in the site of action, and are looked to as neuroprotective agents. Most of them are competitive antagonists and patients sometimes cannot tolerate them because of their adverse reactions, including hallucinations and schizophrenia-like symptoms, which happen because they hinder physiological functions of the NMDA receptors. NMDA receptors play a key role in memory, cognition and learning and any drug that has the NMDA receptor as a target of action must secure this pattern of physiological function in order to be therapeutically useful.
Memantine is a fast-binding antagonist. However, it dissociates from the receptor swiftly and in a concentration-independent manner. As a result, the dose can affect the binding affinity of memantine without affecting its removal from the site of action, thus enabling increased efficacy with limited adverse reactions. In contrast with the other antagonists, memantine is a fast-binding antagonist and therefore it has less effect on physiological mechanisms.

**Presentation**

A 79-year-old widowed lady, already diagnosed with mixed-type dementia (abnormal protein deposits associated with AD coexisted with blood vessel problems linked to VD in her MRI scan) was admitted to our old age psychiatry acute ward due to rapid deterioration of her mental state. She used to reside in a residential home and over the previous six months prior to admission she had become increasingly aggressive/agitated and severely forgetful. She was also seen on several occasions reacting to external stimuli and frequently had paranoid ideas about her food being poisoned or that her belongings were stolen.

On admission we were unable to assess her cognitive status with an Addenbrooke’s Cognitive Examination-III (ACE-III) test because of her advanced dementia (she could not understand the questions of the test). There were no particular abnormalities revealed by the physical examination. The patient had no history of heart disease, and on admission her baseline ECG and blood tests were normal. She was not receiving any regular medication for physical health issues and was not receiving any psychotropic medication either.

The patient was initially started on olanzapine 5mg twice daily, but olanzapine was found to have an inadequate antipsychotic effect and therefore it was discontinued and subsequently the patient was started on quetiapine. Quetiapine was effective in eliminating the paranoid ideas, but some minor aggression/agitation persisted. Two and a half months after admission she was started on memantine tablets 5mg initially, increased seven days later to 10mg at night. As stated previously, memantine is used in moderate to severe stages of AD and is also beneficial for patients who suffer from AD and also exhibit aggression/agitation.

The patient did not experience any immediate side effects with memantine. However, after less than a month of receiving the drug it was noticed that her morning (08:00) pulse rate had started to decrease significantly. Although the patient usually had a pulse rate of 67–80 beats per minute, the 20th day after memantine was introduced her morning pulse rate was reported to be 37 beats per minute, dropping further the following two days to 36 beats per minute and 34 beats per minute, respectively. Her blood pressure remained within normal limits, ECG showed sinus bradycardia with normal conduction times (PQ interval = 123ms, QT interval = 440ms) and the patient was asymptomatic. The evening pulse rate was within normal range.

Laboratory tests showed normal blood glucose, kidney function tests, serum electrolytes and liver function tests. Mild anaemia (hematocrit 37.9%, reference range 39–55%) was also noted.

We had a discussion with the medical team and assumed that one of the medications given to her at night was probably the cause of the morning bradycardia. The patient was receiving 50mg of quetiapine and 10mg of memantine at night, alongside sertraline 150mg and quetiapine 50mg at 09:00, and lorazepam 0.5mg at 14:00. Quetiapine had been initiated two months previously and was found to have a good antipsychotic effect on this patient, so we did not want to stop it. Taking into consideration that memantine was the only newly introduced medication we decided to discontinue it.

Once memantine was discontinued the patient’s morning pulse rate started to increase two days after discontinuation and came back to normal levels four days after memantine cessation. The patient did not experience any further incidents of bradycardia thereafter, and she continued receiving all her other medications, such as quetiapine, sertraline and lorazepam. The patient also had a cardiology assessment a few weeks later, with a cardiac echocardiogram and a Holter monitoring, and no abnormalities were detected.

**Discussion**

The target dose for memantine in patients with AD is 20mg once daily and the dosage is usually increased at weekly increments of 5mg. Memantine undergoes both renal and hepatic elimination. Patients who have impaired renal or liver function, should be prescribed lower doses of memantine.

In general, patients tolerate memantine well, and very few patients who receive it discontinue therapy compared with those who receive placebo. Memantine has an acceptable safety profile, with side effects reported in around 2% of patients and at a greater frequency (not statistically significant) than in placebo-treated patients during clinical trials. Reported side effects include pain, fatigue, dizziness, hypertension, constipation, headache, back pain, vomiting, somnolence, confusion, coughing, hallucination, agitation, urinary incontinence, bronchitis,
diarrhea, urinary tract infections, influenza-like symptoms, abnormal gait, peripheral oedema, anxiety, depression, anorexia, arthralgia and nausea.18

Clinicians should be cautious when combining memantine with other NMDA antagonists such as ketamine, amantadine and dextromethorphan. Sometimes when patients are given memantine they may experience initial sedation and/or confusion, but this phenomenon tends to be mild and temporary in most of the patients who experience it.19 Following oral administration, memantine is well absorbed by the gastrointestinal tract and its absorption is not affected by the presence of food. It reaches maximum plasma concentration after a single dose in 3–7 hours, and its plasma half-life is around 60–80 hours.20

Memantine is not approved for people who suffer from VD, but two double blind studies have shown possible outcomes for people who suffer from VD.21 The drug also seems to improve global clinical status and behavioural symptoms of patients with mild to moderate DLB, and might be an option for treatment of these patients. Large-scale studies are now required to confirm preliminary findings.22

Some studies indicate that quetiapine and other antipsychotics can rarely cause bradycardia with or without QT interval prolongation.23 In this case, we think that memantine and not quetiapine was the cause of bradycardia, because the patient had been taking quetiapine for almost two months without any side effects and memantine was the only newly introduced medication. The fact that the patient did not experience any further episodes of bradycardia after memantine cessation, despite continuing to receive quetiapine, accompanied by the fact that the patient had no physical health issues and the cardiology assessment was normal, strongly indicates that memantine was the cause of bradycardia. However, we cannot absolutely exclude the possibility that quetiapine had a role to play in this phenomenon.

Our review of the literature identified only one report of bradycardia induced by memantine, coming from the French Pharmacovigilance Database. This report indicates that memantine can produce some rare cardiac adverse reactions, such as orthostatic hypotension with falls, electrocardiogram perturbations, fainting, malaise with arterial hypotension, arterial hypotension and acute renal failure, fatal heart failure, sudden death and bradycardia. The mechanism of cardiac adverse reactions with memantine remains unexplained and the cardiovascular properties of memantine seem to be complex and remain unclear.24

Memantine is reported to cause fewer cardiovascular side effects when compared with AChEIs.25 The latter is known to cause bradycardia through its peripheral muscarinic effect.26 Prescription of memantine is increasing significantly as the regular release tablets have been off-patent since mid 2015 and hence the acquisition costs have reduced.

**Conclusion**

We recommend that doctors remain watchful for signs or symptoms of unusual adverse reactions that occur in elderly patients who receive memantine. Patients who have a history of cardiac conditions such as heart failure, arrhythmias and conduction irregularities may be more prone to cardiac adverse reactions, while they receive memantine (mainly when at higher dosages), and therefore should be observed for any cardiac adverse reactions, including bradycardia.

Moreover, patients who discontinued a particular treatment because of adverse events or inadequate response are likely to benefit from switching to other therapies.27

**Declaration of interests**

No conflicts of interest were declared.

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