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Memantine associated with parkinsonism in a patient with Alzheimer's disease: A case study and the review of the literature

Parkinsonizem povzročen z memantinom pri bolniku z Alzheimerjevo boleznijo: Študija primera in pregled literature

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Abstract: The positive effect of memantine on parkinsonism has been reported widely, but there have not been reports in the literature of parkinsonism, tremor and bradykinesis, induced by memantine, in an Alzheimer's patient, who did not have Parkinson's disease or a history of antipsychotic agents. In this case study, we report parkinsonism, tremor and night bradykinesis induced by memantine use (5 mg daily) in a 83-year-old Slovenian female patient. After memantine discontinuation, suggested by a clinical pharmacist specialist, and switching to donepezil 5 mg, the adverse drug reactions disappeared the next day. This case study may serve to help clinicians and clinical pharmacists distinguish memantine-induced parkinsonism from more serious conditions.

Keywords: parkinsonism, adverse event, literature review, Alzheimer's disease, clinical pharmacy.

Povzetek: Pozitivni učinki memantina na parkinsonizem so pogosto opisani, a parkinsonizem, tremor, bradikinezija povzročeni z memantinom, brez zgodovine zdravljenja z antipsihotiki, pri bolniku z Alzheimerjevo boleznijo v literaturi še niso bili opisani. V tej študiji primera prikazujemo z memantinom (5 mg dnevno) povzročen parkinsonizem, tremor in bradikinezijo pri 83-letni slovenski bolnici. Po ukinitvi zdravljenja z memantinom in uvedbo donepezila 5 mg dnevno, svetovano s strani kliničnega farmacevta specialista, so se neželeni učinki umaknili naslednji dan. Ta študija primera lahko služi kot pomoč zdravnikom in kliničnim farmacevtom v razlikovanju z memantinom povzročenega parkinsonizma od bolj resnih stanj.

Ključne besede: parkinsonizem, neželeni dogodek, pregled literature, Alzheimerjeva bolezen, klinična farmacija.

1. Introduction

With the aging population and its rapidly increasing prevalence, Alzheimer's disease (AD) has become an important public health concern in both developed and developing countries. Memantine is a non-competitive low-affinity antagonist of the N-methyl-D-aspartate (NMDA) receptor with a half-life of 70 hours. Memantine also has no impact on CYP450 metabolism and is not metabolized by CYP450. Its major route of elimination is unchanged with kidneys. Addressing the issue of interpatient variability in treatment response might be of significant importance for the vulnerable population taking anti-dementia drugs. (1) Memantine is beneficial for AD patients with regards to cognition and the Clinical Global Impression. Usually memantine is not discontinued due to its adverse effects. (2) In addition, memantine is also being investigated as a treatment option for a number of different conditions and although there are reports of a number of psychiatric and neurological adverse effects, it is considered to be a generally well-tolerated drug. However, there are two case reports of AD patients repeatedly losing consciousness after a long-term memantine treatment. The adverse effects were resolved after memantine discontinuation. This report indicates the need for increased caution and careful weighing of benefits and risks of prolonged treatment with memantine in patients with AD. (3)

A PubMed search was conducted using the terms memantine, AD and adverse effects to identify randomized controlled trials and case reports, that evaluated the adverse effect for this patient. The positive effect of memantine on parkinsonism has been reported widely, but there have not been reports in the literature of parkinsonism, tremor and bradykinesia, induced by memantine, in an Alzheimer's patient, who did not have Parkinson's disease or a history of antipsychotic agents. This present paper describes the first case of memantine related parkinsonism, tremor and night bradykinesia with a prompt resolution upon the recognition and discontinuation of memantine.

2. Results and discussion

An 83-year-old Caucasian Slovenian female was admitted to a psychiatric department in July 2013 because of severe AD (Parkinson's disease and dementia with Lewy bodies were excluded previously when AD was diagnosed in January 2013).

In her medical history, she denied using alcohol, herbal products and smoking. The patient reported no known drug allergies. Her medications before hospitalization included lisinopril 10 mg daily, donepezil 10 mg daily and escitalopram 10 mg daily and she reported good adherence to medication. The patient had no history of antipsychotic treatment. She did not report previous syncope, palpitations, dyspnea, loss of consciousness, sleep disorders or seizures. Visual hallucinations also did not occur. Baseline laboratory results collected on admission showed a normal platelet count, serum creatinine, normal liver enzymes, and liver function tests. Her score on the Mini -Mental State Exam was 15/30, therefore patient was switched from donepezil to memantine 5 mg daily and titration up to 10 mg daily after 7 days was suggested. On the fourth day of treatment with memantine, the patient developed generalized parkinsonism with resting and postural tremor (without resting tremor) and night bradykinesia without behavioral deviations. The patient also started complaining of slowness of movement, only being able to make small steps when walking, difficulty from sitting, disturbance of speech (slurred speech), and the development of a mask-like facial expression. All other vital signs were normal and serum creatinine was not elevated. The patient could no longer walk without staff support. On the next morning these symptoms continued and the patient was therefore sent to a clinical pharmacist. Her medication list included lisinopril 10 mg daily, memantine 5 mg daily and escitalopram 10 mg daily without any herbal products.

The clinical pharmacy service recommended stopping the memantine immediately and switching to donepezil 5 mg daily. The physician accepted these recommendations and cognitive and psychiatric symptoms did not worsen when memantine was immediately discontinued and an adverse medication withdrawal event was not observed. Day after drug discontinuation, the patient recovered progressively with less severe adverse effects and completely recovered in 3 days. On the seventh day after the drugs were switched, the patient left the hospital with 5 mg of donepezil daily without any symptoms of parkinsonism. An adverse effect was determined by a clinical pharmacist with the Naranjo probability scale and was possibly associated with memantine use (4 points). (4)

Such a case has not been described in the literature. Essential tremor is one of the most common and most disabling movement disorders among adults. Memantine is a potentially useful drug for treating essential tremor, particularly given its neuroprotective efficacy. (5) In a systematic review of 889 studies, Young and colleagues found memantine had significant benefits for AD patients in terms of cognition and the Clinical Global Impression. There were no significant benefits for AD patients in terms of mental state or activities in daily life. Memantine did not significantly affect discontinuation, caused by serious adverse events, but did increase the risk for somnolence, weight gain, confusion, hypertension, nervous system disorders, and risk for falls. (2) There have not been reports of memantine causing parkinsonism, tremor and night bradykinesia without associated polypharmacy, and of the adverse effect ceasing after replacing memantine with donepezil. We also do not believe that any

pharmacokinetic and/or pharmacodynamic drug–drug interaction could had occurred, which would have led to this adverse effect. The relationship between the patient's symptoms with the initiation, discontinuation and half-life of the memantine suggests that the drug had a causal effect. No other medication was changed regarding dosage in this time.

Tremor, dyskinesias, movement disorders, and akathisia have been attributed to escitalopram, which was continued in this patient. (6) Memantine has no impact on CYP450 metabolism and is not metabolized by CYP450, therefore it is not expected that memantine would alter (increase) escitalopram plasma levels (i.e. parkinsonism due to increased plasma levels of escitalopram because of pharmacokinetic interaction with memantine). (1) In addition, memantine is an inhibitor of the cationic renal transporter, and it is not known if escitalopram is a substrate of this transporter. (1) Although we believe that these hypotheses are not a likely reason for the observed effects, this cannot be excluded unless escitalopram plasma levels are measured before and after memantine. The antidepressant escitalopram is metabolized by the cytochrome-P450 (CYP) enzymes CYP 2D6, 2C19 and 3A4. The genetic polymorphisms in CYP2C19 may influence escitalopram serum concentrations, which may lead to a small additive effect in this case. (7) Consequently, small additive effect of escitalopram cannot be excluded, although drug-drug pharmacokinetic interaction between memantine and escitalopram had not occured. However, with use of the Naranjo scale, this adverse effect was not associated with escitalopram use (0 points). The patient also recovered immediately after drug discontinuation, so we do not believe that this adverse effect was an adverse effect of escitalopram or of a drug-drug interaction.

One limitation of our case report is that we did not rechallenge the patient with memantine and show that adverse effects would recur. Obviously, drug rechallenge would have established a stronger causal relationship between memantine and adverse effects for this patient (2 points on Naranjo scale), but we felt it would be unethical to do so and risk serious adverse effects, especially when alternative drug was readily available. We would recommend a rechallenge with memantine only in cases where no other options are available, such as in a case of a patient with multiple drug allergies. These examples show that the response of health care professionals to adverse effects varies among different cases, but both the conservative approach (drug discontinuation) and the approach with drug reinitiation may contribute to patient safety. The decision for an approach depends primarily on the risk of an adverse effect and the availability of alternative drugs. The withdrawal of the donepezil therapy may have also possibly contributed to the patient's symptoms (2 points on Naranjo scale). When donepezil therapy was reinitiated after memantine discontinuation, the symptoms improved. Therefore, the possiblity of an adverse drug withdrawal event should have also been considered (2 points for donepezil on Naranjo scale).

Memantine is an adamantane derivative just as amantadine, which has U.S. Food and Drug Administration approval for use both as an antiviral and an antiparkinsonian drug. Additionally, its effectiveness as an antiparkinsonian drug is undetermined, with a 2003 Cochrane Review concluding that there was insufficient evidence in support or against its efficacy and safety in the treatment of idiopathic Parkinson's disease. (8)

This case serves to illustrate how clinical pharmacy can help ensure a satisfactory clinical outcome and prevent a potentially life threatening adverse drug reaction. Along with similar case studies, it highlights the importance of collaboration between the field of clinical pharmacy and psychiatry in successfully managing adverse psychotropic drug reactions. (9, 10, 11, 12) As shown in this case report and in many others, the diagnosis of an adverse drug reaction is often tentative. Physicians and clinical pharmacists treating patients with a psychiatric disorder must carefully weigh the risk of developing these potential problems against the possibility of relapse of the disorder, should the medication be discontinued.

3. Conclusions

In conclusion, even though memantine is known to be a well-tolerated and safe drug, physicians and clinical pharmacists should be aware of the possible risk of parkinsonism associated with memantine. Substituting memantine with donepezil reversed this adverse effect and eliminated it. This specific adverse effect has not been previously reported in the medical literature. In this report, we identified a case with evidence for memantine-induced adverse effects with a single agent responsible rather than a pharmacokinetic and/or pharmacodynamic drug–drug interaction. It is our hope that this report will help alert clinicians and pharmacists to the possibility of memantine related parkinsonism, tremor and night bradykinesia and serve as the impetus for further published case reports and clinical studies.

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