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Case Report

A Case Report of Severe Delirium after Amantadine Withdrawal

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Abstract
Amantadine is frequently used in addition to dopaminergic substances like dopamine agonists or L-Dopa in advanced Parkinson disease (PD). However, adverse effects like hallucinations limit its use. PD patients developing severe psychotic symptoms upon treatment with either dopaminergic substances and/or amantadine need to stop intake of any psychotropic substance. Here, we report the case of a 71-year-old PD patient without previously known cognitive impairment. He presented with drug-induced psychotic symptoms due to changes in his therapeutic regimen (increase in COMT inhibitors, newly introduced MAO B inhibitors). Also, amantadine had been part of his long-term medication for more than 2 years. The severity of his psychotic symptoms required a L-Dopa monotherapy. After changing his medication, the patient developed severe delirium that resolved rapidly after i.v. amantadine infusion, suggesting an amantadine withdrawal syndrome. Amantadine withdrawal syndrome is a rare adverse event that may present even in PD patients without cognitive impairment. This case report highlights the need for a gradual withdrawal of amantadine even if acute and severe psychotic symptoms are present. Moreover, this is the first report of a cognitively unimpaired patient developing an amantadine withdrawal syndrome.

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Introduction

Amantadine has been used for the treatment of Parkinson disease (PD) patients since 1968 [1]. In current treatment regimes, it is commonly used to reduce motor fluctuations, in particular dyskinesia [2]. Even though a long-lasting antidyskinetic effect has long been debated [3], more recent evidence has revealed its long-term effect [4]. Thus, its antidyskinetic properties and the postulated positive effects on non-motor symptoms like apathy [4] still make amantadine an important oral therapeutic in advanced PD. However, neuropsychiatric adverse effects like insomnia, confusion, and hallucinations often limit its use. This is of particular importance for PD patients with risk factors for psychosis like high age, long disease duration, dementia, and co-medication with cholinergic or dopaminergic drugs or dopamine-enhancing compounds like catechyl-O-methyl-transferase (COMT) inhibitors [5].

PD patients developing severe psychotic symptoms upon dopaminergic treatment often need to stop any psychotropic substance immediately, since the improvident use of neuroleptics to treat psychotic symptoms in PD is hindered by the fact that only clozapine is known to efficaciously treat psychotic symptoms in PD without worsening motor symptoms [6]. In addition, the treatment of psychotic symptoms often requires the combined use of clozapine and benzodiazepines, which, however, bears the potential risk of respiratory failure [7].

The acute withdrawal of dopamine agonists (DA) is known to result in DA withdrawal syndrome in 14–25% of all patients, who may present aspects of acute delirium [8–10]. In contrast, amantadine withdrawal appears to be well tolerated, since delirium was not among the commonly reported adverse events in a study on patients undergoing amantadine withdrawal in 100-mg steps every 2 days [4]. Here, we report a patient with PD developing severe delirium, most likely due to an acute amantadine withdrawal.

Case Description

A 71-year-old patient with a 13-year history of PD (Hoehn and Yahr stage IV) presented to our emergency room with psychotic symptoms including drowsiness, confusion, and severe visual hallucinations, starting 3 days prior to admission. Moreover, the patient showed severe gait impairment with recurrent falls and intermittent dyskinesia. He had been discharged from a local hospital 7 days prior, where his daily L-Dopa dose had been increased from 500 to 625 mg/day, and his entacapone dosage from 800 to 1,000 mg/day. In addition, rasagiline treatment (1 mg/day) had been initiated. Furthermore, treatment with 3-mg/day transdermal rotigotine had been discontinued 3 weeks before admission. The daily dose of amantadine (200 mg/day) was unchanged.

The patient's wife reported that amantadine had been part of the patient's medication for more than 2 years. On previous assessments, there had been no signs of cognitive impairment (previous Mini-Mental State Test, performed 24 days prior to admission to our hospital: 30/30), nor did the patient's wife report any disoriented behavior or memory deficits during the last weeks or months.

A drug-induced psychosis was suspected, triggered by the increased entacapone dosage and the newly added rasagiline treatment. Besides discontinuing entacapone and rasagiline, amantadine was also withdrawn due to the severity of the psychotic symptoms. Antipsychotic therapy with clozapine was initiated (12.5 mg/day) upon admission. As a consequence, the patient's orientation stabilized for 3 days before he started to develop progressive delir-

ium with severe psychomotor hyperactivity on day 3. Clozapine was increased to 25 mg on day 8, 50 mg on day 10, and 75 mg on day 12. Lorazepam (2 mg/day) was added on day 8.

No underlying cause (i.e., an infection, dehydration, or renal failure) was identified; however, his condition worsened to a point at which oral L-Dopa treatment became impossible because he was unable to swallow adequately and did not tolerate a nasogastric tube. Thus, amantadine sulfate i.v. (200 mg) was reapplied to treat progressive bradykinesia. After the first injection of amantadine sulfate, he regained consciousness and orientation the next few hours. Therefore, an amantadine withdrawal syndrome (AWS) was suspected, and amantadine sulfate was continued at 150 mg/day orally. His medical condition stabilized, and L-Dopa treatment was reinstated. The patient was amnestic for the time of the delirium, but he did not experience any long-term psychotic symptoms. He was discharged with 600 mg of L-Dopa and 150 mg of amantadine sulfate daily 26 days after admission.

Conclusions

Reports about delirium after amantadine withdrawal date back to 1987 [11] and, to the best of our knowledge, this adverse event has last been reported in 1998 by Factor et al. [12] who described 3 demented PD patients developing delirium secondary to amantadine withdrawal after long-term (4–18 years) treatment. In light of that report, 4 additional cases were described [13], suggesting the potential risk to develop AWS, which is in line with the present report. The sequence in which the symptoms appeared in this case and the rapid end of delirium upon amantadine sulfate treatment make an alternative diagnosis unlikely.

DA withdrawal syndrome may be an alternative explanation for the observed delirium. However, the onset of DA withdrawal symptoms in patients who rapidly taper or discontinue DAs may appear as early as after the initial dose reduction or only after complete withdrawal [14]. Latencies between DA withdrawal and symptom onset are not described in the literature, and in the case described here, rotigotine was withdrawn 3 weeks prior to the onset of delirium.

Consistent with previous cases, our patient had advanced PD and had been treated with amantadine for several years. Therefore, disease duration and long-term amantadine treatment may be risk factors to develop AWS. In contrast to previously described patients, no cognitive impairment was present. Since no deficits on MMSE testing were detected 24 days prior to admission, and since the patient's wife did not report any signs of disorientation prior to the onset of hallucinations, it is very unlikely that the patient had developed a rapidly progressing form of dementia or suffered from a prodromal form of dementia. Thus, this case report suggests that AWS may occur in patients without previous cognitive deficits.

Amantadine is currently the drug with the most potent antidyskinetic effect in the treatment of advanced PD [15, 16]. Recently, safinamide has been introduced for dyskinetic patients. A dual mechanism of action, with MAO B-inhibitory effects in addition to antiglutamatergic effects, has been described for this compound. Neuropsychiatric side effects appear to be rare using this substance [17]. However, its antidyskinetic effects were only significant in patients with severe dyskinesia. Amantadine extended release may be another therapeutic alternative to reduce dyskinesia. However, the spectrum of adverse events was similar to immediate release forms of amantadine [18]. Therefore, despite the fact that advanced PD patients have an increased risk to develop psychotic symptoms [5], amantadine is still frequently used even in these patients, since it is often the sole option for the treatment in older patients (>70 years) who do not qualify for invasive therapies to alleviate fluctuations.

Taken this into account, reports about AWS are very rare, and, thus, AWS may be considered a rare complication of amantadine withdrawal. Since a rapid recovery after reintroducing amantadine has been a common feature in all reported cases, reinstalling amantadine early could be a putative strategy in the differential diagnosis of delirium in these patients. Moreover, a gradual withdrawal even in the emergency situation of acute and severe psychotic symptoms should be the primary choice in order to prevent AWS.

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Statement of Ethics

The patient gave written informed consent to publish this report.

Disclosure Statement

The authors declare no competing interests.

Authors Contribution

F.M.: case report conception and writing of the manuscript. D.M.: case report conception and writing of the manuscript. J.W.: manuscript review and critique. M.U.: manuscript review and critique. All authors have read and approved the final manuscript.

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