WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 1, 1566-1571. Case Report ISSN 2277– 7105

CASE REPORT ON AMANTADINE WITHDRAWAL SYNDROME

Ajay Sairaj Asokan[1]*, Sandhiya Kannan[1], Bissy Babu Tressa[1], Jenipher Sweetlin Joseph[1], Infant Smily Alphonse[2], Subadhra Devi J.[3] and Venkatanarayanan R.[4]

[1]Pharm D Interns, RVS College of Pharmaceutical Sciences, Coimbatore-641402.

[2]Assistant Professor, Department of Pharmacy Practice, RVS College of Pharmaceutical Sciences, Coimbatore-641402.

[3]Assistant Professor and Head, Department of Pharmacy Practice, RVS College of Pharmaceutical Sciences, Coimbatore-641402.

[4]Principal, RVS College of Pharmaceutical Sciences, Coimbatore-641402.

Article Received on
17 Nov. 2021,

Revised on 07 Dec. 2021,
Accepted on 27 Dec. 2021

DOI: 10.20959/wjpr20221-22754

***Corresponding Author**
Ajay Sairaj Asokan
Pharm D Interns, RVS College of Pharmaceutical Sciences, Coimbatore-641402.

ABSTRACT

Amantadine is usually utilized in addition to dopaminergic substances like dopamine agonists or Levodopa in advanced Parkinson's disease (PD). However, adverse effects are common like hallucinations and delirium. Amantadine withdrawal syndrome (AWS) may be a rare adverse event that will present even in PD patients with cognitive impairment. Amantadine withdrawal could also be under-recognized by psychological state clinicians, which has the potential to steer to protracted hospital courses and suboptimal outcomes. Here, we report the case of a 76-year-old Parkinson's disease patient with previously known cognitive impairment. She presented with drug-withdrawal psychotic symptoms due to changes in her therapeutic regimen based on MMSE Score (newly introduced DOPAMINE PRECURSOR). Also, amantadine had been a part of her long-term medication for quite 2 years. The severity of her psychotic symptoms required L-Dopa monotherapy. After changing her medication, the patient developed severe delirium that resolved rapidly after i.v. amantadine infusion, suggesting an amantadine withdrawal syndrome. This case report highlights the necessity for a gradual withdrawal of amantadine albeit acute and severe psychotic symptoms are present.

KEYWORDS: Amantadine withdrawal syndrome, Parkinson's disease, Hallucination, MMSE score.

INTRODUCTION

Amantadine has been used for the treatment of Parkinson's disease (PD) patients since 1968.[1] In current treatment regimes, it is commonly used to reduce motor fluctuations, in particular dyskinesia. Even though a long-lasting antidyskinetic effect has long been debated, newert evidence has revealed its long-term effect.

Parkinson's disease (PD) is characterized by a wide range of motor and non-motor symptoms some of which remain refractory to conventional management and remain a key unmet need and challenge (LeWitt and Chaudhuri 2020). A finely balanced risk-benefit ratio is vital for optimal management when handling with dopamine replacement therapy for PD and brings its challenges to real-life use. Dopamine agonists (DA) remain a serious a part of the clinical armamentarium for drugs wont to manage PD, although, in recent years, considerable issues associated with "dopamine agonist phobia" (Rota et al. 2020) have emerged. In part, this is often driven by the heightened awareness of the damaging and medico legally relevant risk of impulse control disorder (ICD) and dysregulation behavioral syndromes emerging with the use of DA.[3] As a result, neurologists or health care professionals may sometimes reduce or discontinue a DA too quickly or abruptly in PD patients resulting in dangerous complications such as dopamine agonist withdrawal syndrome (DAWS), which may be life-threatening in extreme cases. The stop-page of oral DA abruptly also can occur in severely ill PD patients where the patient is unable to require drugs orally and has been recently highlighted in several patients being admitted.

The acute withdrawal of amantadine is known to result in an amantadine withdrawal syndrome in 14–25% of all patients, who may present aspects of acute delirium.[2] In contrast, amantadine withdrawal appears to be well tolerated, since delirium wasn't among the commonly reported adverse events during a study on patients undergoing amantadine withdrawal in 100-mg steps every 2 days. Here, we report a patient with PD developing severe delirium, persumably because of an acute amantadine withdrawal.

CASE REPORT

A 76-year-old female was presented in a tertiary care hospital with complaints of psychotic symptoms such as delirium, drowsiness, confusion, severe visual hallucinations, and abnormal behavior for the past 3 weeks. Moreover, she also had a history of generalized slowness in the movement for the past 1 week. She was a known case of Parkinsonism for the past 3 years, hypertension for 6 years, diabetes mellitus for 8 years, and bronchial asthma for

8 years. The patient's medication history was found out to be she is on Tab. Pacitane 4mg, Tab. Clonazepam 1mg, Tab. Quetiapine 50mg and Tab. Syndopa plus 125mg.

On admission, the patient was in an altered sensorium with resting tremor, no eye-opening to pain, localization to a painful stimulus, and stiffness in all four limbs. The patient was admitted to the neurology department due to her vulgurous mental health and all her medications were continued for the patient to analyze her condition, In addition, conservative management was also given for her co-morbidity conditions. Patients' laboratory investigations were normal except for the sodium electrolyte (129 mEq/L) which was decreased. However, CT, MRI, and lumbar puncture reports were shows no abnormalities.

During the hospitalization on the neurology ward, the patient became increasingly disoriented, paranoid, and agitated, several times pulling out her intravenous catheter, and requiring physical restraints to maintain safety. Metabolic and neurological workup failed to reveal a mechanism for the ongoing mental status changes and the patient was transferred to the psychiatry ward for further management. At the time she was oriented to all spheres but with mild cognitive impairment, as indicated by a score of 20 of 30 on the Mini-mental State Examination (MMSE).

Later during the admission patient's son reported that amantadine had been part of the patient's medication for more than 1 year. On previous assessments, there had been no signs of cognitive impairment (previous Mini-Mental State Test, performed 3 weeks before admission to the hospital: 30/30). Thus Tab. Amantadine 200mg was withdrawn from the prescription and Tab. Syndopa plus (Levodopa 100mg + carbidopa 25mg) was added.

The admitting team noted that the worsening of the motor symptoms correlated with a recent withdrawal in the outpatient dose of amantadine 200 mg BD. No underlying cause (i.e., an infection, dehydration, or renal failure) was identified. Thus, amantadine sulfate i.v. (200 mg) was reapplied to treat the progressive conditions. After the first injection of amantadine sulfate, she regained her mental status within the next few hours. Therefore, an amantadine withdrawal syndrome (AWS) was suspected, and amantadine sulfate was continued at 150 mg/day orally along with her currently used medications. In addition to that Tab. Tolvaptan was added for her hyponatremia condition. She was discharged home at his cognitive baseline (MMSE score of 29) with the same medication along with her antihypertensive drugs and insulin.

SYNOPSIS OF FINDING IN CASE		
Admission Examinations	**Laboratory Reports**	**Discharge Medication**
Mental status: Fully oriented, depressed, paranoid, and suicidal thought content **Neurological:** Parkinson's disease motor symptoms (chin tremor, grade 2 rigidity in all 4 limbs, hypomimia, bradykinesia, resting tremor right hand > left hand) **General physical examination:** Vital signs normal Otherwise unremarkable	**CBC**: normal **Troponin**: negative **CXR**: normal **CK**: normal **ELECTROLYTES** Sodium- 128mEq/L **CT (head):** no acute intracranial process **Blood/urine/stool cultures, HIV, RPR**: negative **CSF:** wnl **MRI:** normal	**Tab. Syndopa plus 125mg Od** **Tab. Tolvaptan 15mg Od** **Tab. Amantadine 100mg Bid** **Tab. Clonazepam 1mg Od** **Tab. NPH insulin 10 units Bid** **Inh. Forcort 200mg Bid** **Tab. Quetiapine 50mg Od** **Tab. Amlodipine 10mg Bid** **Tab. Pacitane 4mg Bid**

CBC indicates complete blood count; **CK,** creatinine kinase; **CXR,** chest x-ray; **CT,** computerized tomography; **HI,** human immunodeficiency virus; **RPR,** rapid plasma regain; **CSF,** cerebral spinal fluid; **MRI,** magnetic resonance imaging; **Od,** once daily; **Bid,** twice daily

DISCUSSION

In this present case, the patients experienced psychotic symptoms such as delirium, drowsiness, confusion, severe visual hallucinations, and abnormal behavior which is similar to the study conducted by Factor et al., that patients who, after long-term therapy with amantadine experienced an acute delirium with confusion, disorientation, agitation, and paranoia on withdrawal.[1]

Reports about delirium after amantadine withdrawal date back to 1987 and, to the simple of our knowledge, this adverse event has last been reported in 1998 by Factor et al. 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, suggesting the potential risk to develop AWS, which is in line with the present report. The Mini-Mental State Examination (MMSE) is a widely used tool for assessing cognitive mental status which can be administered in less than 10 minutes. Though it cannot be used for creating formal diagnosis, the MMSE has been used as a first step in detecting

cognitive impairment. In this study, the same MMSE scoring was used to analyze the patient's mental state.[2]

Amantadine is used in the treatment of early-stage PD and for levodopa-induced dyskinesia (LID). The reasons for reducing or discontinuing amantadine might be associated with unremitting and troublesome peripheral edema as well as neuropsychiatric side effects, QTc prolongation, sleep disturbances, and livedo reticularis and corneal edema. When amantadine is discontinued in PD patients presenting with LID, an increase in dyskinesia can be expected, as shown in the AMANDYSK study from Ory-Magne and co-workers (Ory-Magne et al. 2014) and in a study on the long-term antidyskinetic effect of amantadine from Wolf and co-workers (Wolf et al. 2010).[7,8] found that amantadine (with an average dose of 294mg) was abruptly discontinued (not recommended by us) without inducing any noteworthy adverse events, apart from one case in which there was an increase in LID.[6] However, in this case, the patient had her prescription altered, which caused psychotic symptoms due to sudden withdrawal syndrome of amantadine, which has been already reported in previous study by Fryml LD.et.al due to withdrawal syndrome, Therefore, the patient recovered when amantadine was started during the 2nd of hospital admission at the high dose of 200mg BD IV, and her MMSE score was analyzed and found to be 29 of 30. Later the dose of amantadine was tapered during the discharge and patient counseling was given to improve the quality of life of the patient.

CONCLUSION

Amantadine withdrawal syndrome is a rare finding in medical practice. However in this case the patient has withdrawn from amantadine after analyzing her MMSE score 30 of 30. During the hospitalization, it was ruled out and she was administered with inj. Amantadine 200mg BD IV. Later she recovered from her psychotic symptoms. Since a rapid recovery after reintroducing amantadine has been found out in this case, reinstalling amantadine early could be a putative strategy in the differential diagnosis of delirium in patients. Reaction to medication change in PD varies from patient to patient and depends on the progression of the disease.

Moreover, a gradual withdrawal even in the emergency situation of acute and severe psychotic symptoms should be the primary choice to prevent amantadine withdrawal syndrome. In this we searched for available evidence to guide PD medication management when tapering or discontinuing becomes necessary because of side effects. Further research is

required to enhance medication management when PD medication has got to be reduced to maintain a proper quality of life of the patients.

ABBREVIATIONS

AWS- Amantadine Withdrawal Syndrome, MMSE- Mini-Mental State Examination, DAWS- Dopamine Agonist Withdrawal syndrome, PD- Parkinson's Disease, LID- levodopa-induced dyskinesia, ECT- electroconvulsive therapy, NMS- Neuroleptic Malignant Syndrome.

REFERENCE

1. Schwab RS, England AC, Poskanzer DC, Young RR: Amantadine in the treatment of Parkinson's disease. JAMA, 1969; 208: 1168–1170.
2. Marxreiter F, Winkler J, Uhl M, Madžar D: A Case Report of Severe Delirium after Amantadine Withdrawal. Case Rep Neurol, 2017; 9: 44-48. DOI: 10.1159/000460814
3. Fryml LD, Williams KR, Pelic CG, Fox J, Sahlem G, Robert S, Revuelta GJ, Short EB. The Role of Amantadine Withdrawal in 3 Cases of Treatment-Refractory Altered Mental Status. J Psychiatr Pract, 2017; 23(3): 191-199. DOI: 10.1097/PRA.0000000000000237. PMID: 28492457.
4. Factor SA, Molho ES, Brown DL. Acute delirium after withdrawal of amantadine in Parkinson's disease. Neurology, 1998; 50(5): 1456-8. DOI: 10.1212/wnl.50.5.1456. PMID: 9596005.
5. Pezzotti, P., Scalmana, S., Mastromattei, A. et al. The accuracy of the MMSE in detecting cognitive impairment when administered by general practitioners: A prospective observational study. BMC Fam Pract, 2008; 9: 29. https://doi.org/10.1186/1471-2296-9-29
6. Koschel, J., Ray Chaudhuri, K., Tönges, L. *et al.* Implications of dopaminergic medication withdrawal in Parkinson's disease. *J Neural Transm*, 2021. https://doi.org/10.1007/s00702-021-02389-x
7. Wolf E, Seppi K, Katzenschlager R, Hochschorner G, Ransmayr G, Schwingenschuh P, Ott E et al Long-term antidyskinetic efficacy of amantadine in parkinson's disease. Mov Disord, 2010; 25(10): 1357–1363. https://doi.org/10.1002/mds.23034
8. Ory-Magne F, Corvol J-C, Azulay J-P, Bonnet A-M, Brefel-Courbon C, Damier P, Dellapina E et al Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial. Neurology, 2014; 82(4): 300–307. https://doi.org/10.1212/WNL.0000000000000050.