Olanzapine-Induced Neuroleptic Malignant Syndrome

Seyedhamze Hosseini, MD; Forouzan Elyasi, MD
Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Department of Psychiatry, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

Correspondence:
Forouzan Elyasi, MD;
Department of Psychiatry, Emam Khomeini General Hospital, Razi Avenue, Sari, Iran
Tel: +98 911 1551097
Fax: +98 11 33285109
Email: f.elyasi@mazums.ac.ir

Received: 20 September 2015
Revised: 07 November 2015
Accepted: 29 November 2015

Abstract
Neuroleptic malignant syndrome (NMS) is a rare but life-threatening idiosyncratic side effect resulting from neuroleptic drugs. NMS mainly occurs in patients treated with high-potency typical antipsychotics, but rarely caused by atypical antipsychotics. Although NMS is less common with atypical antipsychotic, but it seems that its incidence is rising due to increased administration of such drugs. We present the case of a 27-year-old man with a history of paranoid schizophrenia that showed signs consistent with NMS that occurred after treatment with olanzapine. The patient was adherent to treatment. He had decreased level of consciousness, muscle rigidity, diaphoresis, fever, drooling, urinary incontinence, and high blood pressure. This patient illustrates that NMS can occur due to treatment with atypical antipsychotic drugs like olanzapine, particularly in the presence of risk factors. This phenomenon is often unrecognized, underdiagnosed, or not treated properly. Physicians should be aware that NMS with extrapyramidal syndrome could occur with olanzapine at steady state doses without recent dosage adjustments or titration. It is essential that adequate and safe dose of medication is chosen and the patient is monitored by the signs and symptoms of this lethal syndrome.

Keywords ● Neuroleptic malignant syndrome ● Olanzapine ● Drug-related side effects

Introduction
Neuroleptic malignant syndrome (NMS) rare but life-threatening side effect of antipsychotic medications. However, despite its importance, the pathophysiology of NMS is not well known. It is suggested that the ability to create NMS by neuroleptics is associated with their ability to block dopamine in the nigrostriatal pathway, mesocortical pathway, and hypothalamic nucleus. Additionally, it may occur anytime following the consumption of dopamine antagonists. This disorder also occurs in patients with sudden discontinuation of dopamine agonist. Its incidence has been reported from 0.69 to 3.23 percent. According to various studies, the incidence of NMS has declined in recent years. The growing use of atypical antipsychotic has reduced the incidence of NMS and it is estimated that 0.01 to 0.02% of patients treated with antipsychotics will suffer from its fatal side effect. Although NMS is less common with atypical antipsychotic, but it seems that its incidence is increasing with the administration of these medications. Perhaps such increase is due to rising atypical forms of the disease caused by different
therapeutic mechanisms of modern medicine. There are several reports about NMS following atypical antipsychotic drugs such as risperidone, clozapine, olanzapine, and quetiapine.

Amanth et al. (2004) carried out a review study on NMS associated with atypical antipsychotic drugs. In MEDLINE database, they identified reviews on 68 patients (21 women and 47 men) suffering from NMS with atypical antipsychotic drugs, namely clozapine (n=21), risperidone (n=23), olanzapine (n=19), and quetiapine (n=5). Agrawal et al. (2013) reported a patient with bipolar disorder that showed NMS symptoms following the administration of intramuscular haloperidol. The medication was replaced with olanzapine, but NMS appeared again.

Herein, we report a case of NMS related to olanzapine therapy in a young male patient. The significance of this case stems from the scarcity of reports on NMS associated with olanzapine as well as similar presentations with traditional antipsychotic after one year of treatment.

Case Presentation

We present a 27-year-old man with a history of paranoid schizophrenia who showed signs consistent with NMS that occurred after one year of treatment with olanzapine (20 mg/day). The patient was adherent to treatment. Symptoms included fever, altered level of consciousness, changes in mental status, drooling, diaphoresis, urinary incontinence, sweating, development of tremors, lead pipe rigidity, tachycardia, and increased level of creatine phosphokinase. His level of consciousness according to the Glasgow coma score (GCS) was 11. The recorded vital signs were temperature of 38.2 °C, blood pressure 100/60 mmHg, heart rate 100 beats/min, and respiratory rate 11/min. On the second day, his blood pressure was 140/70 mmHg and temperature was 38.4 °C.

Neurologic examination showed an increase of muscle tone in four limbs and bilateral tremor of upper limbs. The level of creatine kinase was 30,445 IU/L, creatine phosphokinase 4,145.5 MB, and lactate dehydrogenase (LDH) 2,599. The results of cerebrospinal fluid were normal. The hemoglobin level was 15.9 g/dl, leukocyte count of 14,300/mm3, and platelet count of 43,000/mm3. Neutrophils were 82% and lymphocytes 18%. ESR was 18 at the end of the first hour. SGPT and SGPT were 123 U/L and 138 U/L, respectively. The kidney function, analysis of cerebrospinal fluid, and serum electrolyte levels were normal.

Early differential diagnoses were seizure, aspiration, stroke, and infection. These diagnoses were ruled out and NMS was considered after which olanzapine was discontinued. The Naranjo probability scale indicated a possible relationship between the development of NMS and olanzapine. Bromocriptine began (dose of 2.5 mg per 8 hours) through gastric feeding tube and was increased to 5 mg every 8 hours. The patient received traditional treatment for NMS, such as intravenous fluids and supportive care. An infusion of NaCl 0.45% with sodium bicarbonate was administered. Creatine kinase (CK) level fell and dropped to 403 IU/L on day 13 (normal level: 15-300) and by day 15 it was within the normal range.

Informed consent was given by the patient for the publication of this case report.

Discussion

Briefly, the patient had decreased level of consciousness, intense muscle rigidity, fever, drooling, diaphoresis, urinary incontinence, sweating, and increased blood pressure. NMS was detected according to the DSM-V. Clinical features of this syndrome include high fever, extrapyramidal symptoms, and dysfunction in autonomic system such as unstable blood pressure, cardiac arrhythmia, dyspnea, sweating and urinary incontinence. However, fever and muscle rigidity are the most recognized signs in various studies. Our patient showed these signs and his other criteria were high too.

As mentioned, patients with NMS may present different symptoms. NMS is more commonly seen in treatments with typical antipsychotic drugs. It seems that NMS can occur during treatment with atypical antipsychotics such as olanzapine. This syndrome is uncommon with atypical antipsychotic drugs like olanzapine. Physicians should be vigilant in identifying which patients are more prone to develop NMS. Several factors such as male gender, agitation, physical exhaustion, dehydration, and neurological defects are associated with an increased risk of NMS. Our patient had predisposing factors for this syndrome. Male patients are at twice the greater risk of this syndrome than females. The majority of patients are in the age range of 20-50 years.

In our case, there were anomalies in clinical findings and laboratory tests (such as CPK: 40000 IU/L) after exposure to the causative agent. These symptoms could not be clarified by other diseases or medications and discontinuation of the drug resulted in significant clinical improvement.

We assessed the causality of this side effect with WHO-UMC causality assessment system.
and Naranjo assessment scale. According to typical clinical features and laboratory abnormal findings in NMS, there was no need to rechallenge with the drug. According to the WHO-UMC causality assessment system, side effects were probably related to olanzapine. In terms of Naranjo assessment scale, the probability score was 8.

Symptoms following atypical antipsychotics include fewer extrapyramidal symptoms, reduced creatine kinase elevations, reduced muscle rigidity, and frequent mild fever. Occasionally, for instance, rigidity can be seen in the extremities instead of general muscular rigidity. The study by Hassan and Buckley showed that clinical findings following typical and atypical antipsychotic drugs are the same, but increased CPK has been observed more by typical antipsychotic. However, CPK increased significantly in our patient.

Our report indicates that even with olanzapine treatment in the therapeutic range, a high-risk NMS is curable even after one year. Therefore, it is essential that adequate and safe dose of medication is chosen and the patient is monitored by the signs and symptoms of this lethal syndrome.

**Conclusion**

In this report, we described a young male patient with NMS caused by olanzapine treatment. This case underlines the need for vigilance regarding the side effects of taking atypical antipsychotic. Neuroleptic malignant syndrome can occur with atypical antipsychotic drugs such as olanzapine, particularly when risk factors are present. We should pay attention to this rare but life-threatening event associated with fatal complications. This phenomenon is often unrecognized, underdiagnosed, or even not treated properly. It is important to realize that an early detection and treatment of this disorder is vital. Clinicians should be aware that NMS with EPS could occur with olanzapine at steady state doses without recent dosage adjustments or titration.

**Conflict of Interest:** None declared.

**References**

1. Sadock BJ, Sadock VA. Kaplan and Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry. Philadelphia: Lippincott Williams & Wilkins; 2015. p. 925-6.
2. Khaldi S, Kornreich C, Choubani Z, Gourevitch R. Neuroleptic malignant syndrome and atypical antipsychotics: A brief review, Encephale. 2008;34:618-24. doi: 10.1016/j.encep.2007.11.007. PubMed PMID: 19081460.
3. Gelenberg AJ, Bellinghausen B, Wojcik JD, Falk WE, Farhadi AM. Patients with neuroleptic malignant syndrome histories: What happens when they are rehospitalized? J Clin Psychiatry. 1999;50:178-80. PubMed PMID: 2565897.
4. Buckley PF, Hasan S. Atypical neuroleptic malignant syndrome and atypical antipsychotics. Am J Psychiatry. 1998;155:1633. PubMed PMID: 9812143.
5. Abay E, Kose R. Amisulpride-induced neuroleptic malignant syndrome. J Neuropsychiatry Clin Neurosci. 2007;19:488-9. doi: 10.1176/jnp.2007.19.4.488. PubMed PMID: 18070872.
6. Stubner S, Rustenbeck E, Grohmann R, Wagner G, Engel R, Neundorfer G, et al. Severe and uncommon involuntary movement disorders due to psychotropic drugs. Pharmacopsychiatry. 2004;37 Suppl 1:S54-64. doi: 10.1055/s-2004-815511. PubMed PMID: 15052515.
7. Choi-Kain LW, Pope HG. "Atypical" neuroleptic malignant syndrome and the spectrum of malignant cerebrotoxic syndromes. Harv Rev Psychiatry. 2007;15:181-6. doi: 10.1080/10673220701551110. PubMed PMID: 17687712.
8. Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malignant syndrome: A review. Psychiatr Serv. 1998;49:1163-72. doi: 10.1176/ps.49.9.1163. PubMed PMID: 9735957.
9. Nielsen J, Bruhn AM. Atypical neuroleptic malignant syndrome caused by olanzapine. Acta Psychiatr Scand. 2005;112:238-40; discussion 40. doi: 10.1111/j.1600-0447.2005.00578.x. PubMed PMID: 16095481.
10. Patra BN, Khandelwal SK, Sood M. Olanzapine induced neuroleptic malignant syndrome. Indian J Pharmacol. 2013;45:98-9. doi: 10.4103/0253-7613.106448. PubMed PMID: 23543750; PubMed Central PMCID: PMC3608309.
11. Sing KJ, Ramaekers GM, Van Harten PN. Neuroleptic malignant syndrome and quetiapine. Am J Psychiatry. 2002;159:149-50. doi: 10.1176/appi.ajp.159.1.149. PubMed PMID: 11772710.
12. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs.
13. Tripathi P, Agrawal H, Goyal P, Kar SK. Olanzapine-induced neuroleptic malignant syndrome in a patient with bipolar affective disorder: Does quetiapine holds the solution? Ind Psychiatry J. 2013;22:159-60. doi: 10.4103/0972-6748.132934. PubMed PMID: 25013321; PubMed Central PMCID: PMC4085812.

14. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45. PubMed PMID: 7249508.

15. Hasan S, Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: A review and critique. Am J Psychiatry. 1998;155:1113-6. doi: 10.1176/ajp.155.8.1113. PubMed PMID: 9699705.