A case of Neuroleptic malignant syndrome associated with olanzapine and responsive to bromocryptine

Mrugank BP*, Hareesha RP*, Deepanjali M*, Mangala L*, Sibasish D*

National Institute of Pharmaceutical Education and Research (NIPER), Department of Pharmacy Practice, M.Pharm (Student)
National Institute of Pharmaceutical Education and Research (NIPER), Department of Pharmacy Practice, M.Pharm (Student)
Gauhati Medical College and Hospital (GMCH), Department of Psychiatry, Assistant Professor.
Gauhati Medical College and Hospital (GMCH), Department of Pharmacology, Prof and Head; Chief academic co-ordinator, NIPER-Ghy.
Gauhati Medical College and Hospital (GMCH), Department of Pharmacology, MD (Student)

ABSTRACT

Neuroleptic malignant syndrome (NMS) is the most serious of acute neurological side effects produced by antipsychotic medication, characterized by hyperthermia, rigidity, altered consciousness and autonomic dysfunction, the prevalence of which varies from 0.4-1.4%. NMS is usually seen in treatment with high potency typical antipsychotics and very rarely with atypical antipsychotics. However, NMS cases have been reported with risperidone, clozapine, olanzapine and quetiapine. The presentations of NMS have often varied, and we report atypicality in presentation of NMS due to olanzapine use.

Key words: Atypical antipsychotics, neuroleptic malignant syndrome, olanzapine, bromocryptine

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an uncommon but serious complication of neuroleptic medications. It was first described in 1967 as "akinetic hypertonic syndrome." NMS is a potentially fatal adverse event associated with the use of antipsychotics. The incidence of NMS in patients with psychiatric disorders treated with antipsychotics is 0.4% to 1.4% per year.\cite{1, 2} The mortality is 10%-30%.\cite{3} Most frequent signs and symptoms of NMS include fever, muscle rigidity, autonomic dysfunction (e.g., tachycardia, labile blood pressure, tachypnea), and mental status changes, including delirium. The most consistently abnormal laboratory finding is elevated serum Creatine Phosphokinase (CPK) and leucocytosis. The diagnosis of NMS is made clinically, and several criteria exist for diagnosing the condition. A variety of medical conditions
may present with features similar to NMS. Due to the antidopaminergic properties of medications that cause NMS and the condition's response to dopamine-agonists such as bromocryptine, the pathophysiology of NMS is believed to be related to central dopaminergic receptor-blockade. Blockade of dopamine neurotransmission in the nigrostriatum and hypothalamus results in muscular rigidity and altered thermoregulation, respectively. Sympathetic nervous system activation or dysfunction may also play a significant role in the pathogenesis of NMS.

Typical antipsychotic agents are most frequently reported as contributing to NMS in the literature, although NMS may also occur in association with atypical antipsychotic medications, as well. NMS is most frequently reported during treatment of schizophrenia, mood disorders, mental retardation, and substance-induced conditions, although it may occur in the absence of primary psychiatric illness.

Olanzapine is new generation thienobenzodiazepin antipsychotic having multiple receptor activity. It has effect on muscarinic, alpha-adrenergic, potent antiserotonergic (5HT2 and 5HT6) and antidopaminergic (D1-D5) receptors. Because of this unique characteristic, the incidence of side effects of olanzapine such as NMS and extrapyramidal symptoms is extremely low.

**Material and Method:**
A 62-year-old man developed NMS with classical features of NMS including muscular rigidity and fever on olanzapine (Atypical Antipsychotic). Patient came with a history of weakness, slowness of activity, inability to walk, tremulousness, reduced sleep increased irritability, slurring of speech and on further evaluation patient gave a history of intake of 7.5 mg olanzapine per day for last 22 days for treatment of paranoid schizophrenia outside before he was admitted to Dept. of Psychiatry, Gauhati Medical College and Hospital. He also gave a history of intake of other neuroleptic medications including long acting inj. of Fluphenazine Decanoate (Typical Antipsychotic) for the last 20 yrs which was stopped prior to administration of Olanzapine.

On general examination temperature was raised, 104 °F. Blood pressure was raised up to 190 / 90 mmHg and pulse rate were raised up to 98 / min. severe dehydration and diaphoresis were present. On examination of central nervous system the patient was found to be conscious but drowsy, disoriented to time and place, oriented to person, comprehension was poor, speech was slurred, bilateral plantar reflex was extensor, and severe muscular rigidity was present. In other systemic examinations, no abnormality was detected.

A provisional diagnosis of Olanzapine induced NMS was made with, clinical features of severe muscle rigidity, bradykinesia, pyrexia, vasomotor disturbances like altered blood pressure and pulse rate, tremors at rest on limbs, altered sensorium and disorientation, dehydration and diaphoresis and, incontinence. Biochemical analysis revealed increase in white blood cells (WBCs) count 14,800 U/L (Normal: 10,000 U/L) and Creatine Phosphokinase (CPK) 2491 U/L (Normal: < 174 U/L). Liver function test (LFT), Serum ammonia, Serum creatinine, and random blood sugar (RBS), cerebrospinal fluid analysis were found to be within normal limits. The NMS rating was found to be 46. Thus a confirmatory diagnosis of olanzapine induced NMS was made.

Supportive care therapy was initiated with intra venous normal saline to control dehydration along with lorazepam 2.5 mg per orally once daily. The patient did not show improvement of the symptoms till day 13 of lorazepam treatment so from day 14 lorazepam was withdrawn and started with oral bromocryptine 5 mg. The dose of bromocryptine was decreased to 2.5 mg the
very next day because of improvement in muscular rigidity, tremor and decrease in body
temperature. The NMS rating score which was 46 before initiation of bromocryptine therapy,
reduced to 15 on the second day and 10 on the third day, on re-evaluation of the patient.
Consequently, the patient improved completely on day 20 with total 15 mg dose of
bromocryptine. No rechallenge was carried out with olanzapine in this case. He was discharged
in a stable condition after 2 days on observation.

**DISCUSSION**

The pharmacokinetics of olanzapine is linear and dose-proportional within the approved dosage
range. Its mean half-life in healthy individuals is 33 hours, ranging from 21 to 54 hours. The
mean apparent plasma clearance is 26 L/h, ranging from 12 to 47 L/h. Smokers and men have a
higher clearance of olanzapine than women and nonsmokers. After administering olanzapine,
approximately 60% of the radioactivity was excreted in urine and 30% in faeces. Olanzapine is
predominantly bound to albumin (90%) and alpha 1-acid glycoprotein (77%).

In a case report by Levenson, a 62 years old man has fulfilled the major and minor criteria of
neuroleptic malignant syndrome. Addonizio et al reviewed 18 cases of the neuroleptic malignant
syndrome occurring in patients older than 60 years.\[^7\]

Incidence of neuroleptic malignant syndrome induced by olanzapine, which is an atypical
antipsychotic, is extremely rare. In our literature research, only 20 cases of NMS induced by
olanzapine have been reported so far.\[^8\] Considering this fact, the above case of NMS induced by
olanzapine treatment is of interest. John et al. have reported that in first 2 weeks, the occurrence
rate of NMS is 80 %. In our case the patient manifested NMS on the 22\(^{nd}\) day of the olanzapine
therapy.

Hyperthermia, muscle rigidity, autonomic instability, delirium and increased CPK values and
leucocytosis are the main feature of NMS. Levenson\[^9\] has reported that 52 of 53 cases studied
had hyperthermia. Hyperthermia (\(>104 ^\circ\)F) in our case lasted for 13 days even with lorazepam
therapy for NMS. This raise in body temperature could not be correlated to any other disease.
Although benzodiazepines are the preferred drug for the treatment of NMS, lorazepam was
ineffective in our case. The raised temperature returned to normal only on the 14\(^{th}\) day after
initiation of bromocryptine therapy.

Neuroleptic malignant syndrome is a potentially fatal complication. Death usually occurs as a
result of cardiovascular collapse, renal or respiratory insufficiency and dysarrythmias. In this
case, with the early diagnosis and appropriate treatment, none of the complications occurred.
Levinson and Simpson point out, those patients with severe extrapyramidal symptoms, with or
without fever, are at risk for potentially lethal complications from neuroleptic-induced dopamine
blockade. They suggest the use of bromocriptine as appropriate treatment drug based on the
dopamine-blockade theory.\[^10\] In this case, most of the symptoms presented by the patient
disappeared completely within 5 days of starting bromocryptine therapy. The patient showed no
extrapyramidal symptoms on the 20\(^{th}\) day and subsequently after 2 days of observation; he was
discharged from the hospital.

**CONCLUSION**

The patients with NMS should admit to emergency services. In differential diagnosis of the
patients referred to emergency services with the complaints of muscle rigidity, high fever,
unconsciousness and antipsychotic drug use in history, NMS should also be considered. Although it is rare, practitioners need to be aware of that NMS may occur after Olanzapine treatment. With early diagnosis and appropriate treatment, NMS that may cause death should be managed successfully.

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REFERENCES