

CASE REPORT

NEUROLEPTIC MALIGNANT SYNDROME INDUCED BY ARIPIPRAZOLE - A CASE REPORT

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ABSTRACT: Neuroleptic malignant syndrome [NMS], although rare, is a well-documented life-threatening reaction to antipsychotic medications with mortality rate estimated as being up to 20%. NMS was traditionally attributed to potent dopamine antagonism of typical antipsychotics but cases of NMS have been reported for each of the newer atypical antipsychotics. Aripiprazole is one such atypical agent approved by FDA for treating schizophrenia in 2002 and acute bipolar mania in 2004. Aripiprazole is a dopamine D2 receptor partial agonist with partial agonist activity at 5-HT_{1A} receptor and antagonist activity at 5-HT_{2A} receptor. In comparison to other atypical it possesses unique mechanism of action that may limit development of hypodopaminergic state, however there are case reports of aripiprazole induced NMS, akathisia, rhabdomyolysis, parkinsonism and excessive somnolence in children. To add to this literature we report a case of 50 year old woman with multiple risk factors, developed NMS with low dose of aripiprazole.

INTRODUCTION: The neuroleptic malignant syndrome (NMS) is an idiopathic, life-threatening reaction to Antipsychotic medication, characterized principally by fever, muscle rigidity, altered consciousness, autonomic instability, laboratory findings such as elevated creatine phosphokinase (CPK), ¹ leukocytosis, raised liver enzymes. Serious complications are possible, including renal failure, thromboembolism, respiratory failure from chest wall rigidity, aspiration pneumonia, and arrhythmia². Different criteria's are proposed by different researchers for diagnosis of NMS but most commonly used are DSM-IV TR,³ and Levenson's,¹ criteria. Treatment consists of immediate discontinuation of the antipsychotics as well as D2 blocking agents, and most commonly used pharmacologic interventions are bromocriptine, and dantrolene.⁴ we report a case of 50 year old lady with multiple risk factors, developed NMS with low dose of single agent, aripiprazole.

CASE REPORT: Ms XY 50 yrs old lady initially presented to the hospital in November 2009 and was diagnosed to be suffering from undifferentiated schizophrenia and was treated with olanzapine 5mg/day. Later during the course of illness she exhibited depressive symptoms and fluoxetine 20 mg/day was added which was stopped after 6 months as her depressive symptoms remitted. Olanzapine was discontinued after 2 yrs of treatment as she developed Diabetes Mellitus. Later she was initiated on Trifluoperazine 15mg daily which had to be stopped within two weeks due to severe extra pyramidal symptoms [EPS]. Trihexyphenidyl, 2 mg/day was given for 4 weeks till her EPS subsided completely and tablet aripiprazole 2.5mg/day was started which was slowly increased to 5mg/day over next 4 weeks.

Within 4 weeks of starting with aripiprazole she developed EPS and at times she experienced acute dystonia. Trihexyphenidyl 2 mg/day was restarted in view of this but low grade of EPS

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persisted. It was also noticed that she was getting frequent urinary tract infection which was treated each time as per urine culture and sensitivity test in consultation with Nephrologists. She would at time show catatonic features which would ameliorate within couple of days with addition of oral Lorazepam 1-2 mg per day. She was investigated on couple of occasion for NMS with CPK levels and blood total counts, both of which were normal. She took aripiprazole 5mg daily till 12/10/2012 but within next two days it was increased to 10 mg/ day in view of her relapse of psychotic symptoms. The very next day there was an abrupt change in her mental state and worsening of her extra pyramidal symptoms.

On examination she was confused, exhibited marked rigidity in addition to her extra pyramidal symptoms. She was mute and there was drooling of saliva, mild dehydration was noted. Her temperature was 101.4°F and pulse was 104 per minute, respiratory breath rate was 20/min. Her blood pressure was 110/70 mm Hg and no fluctuations were recorded. She was uncomfortable and was in moderate distress.

Laboratory findings include CPK level 2855 IU/L, Hb 11gm/dl, total leucocytes 10500/mm³. Her urea, creatinine, serum electrolytes, and liver function tests were within normal limits. Her urine analysis showed numerous pus cells. Abdominal ultrasound showed thick urinary bladder wall.

Her brain tomography demonstrated mild atrophic change. Plain MRI of the brain revealed sub centric hyper intensities in both frontal and occipital white matter, corona radiate and in periventricular region, suggestive of non-specific etiology. Rest of the brain parenchyma was normal. No acute vascular event was reported on consultation with radiologist. Her ECG was unremarkable. From the patient's medical history and presentation, the diagnosis of NMS was made based on DSM-IV TR and Levensons criteria for diagnosing NMS. Ms XY received IV hydration, Paracetamol oral medication. Her aripiprazole was stopped immediately and she was started on bromocriptine 1.25 mg/day, clonazepam 2 mg/day. Her trihexyphenidyl was continued as 2 mg/day. Also she was started on antibiotics for urinary tract infection [UTI] along with urine alkalinizer awaiting urine culture and sensitivity report. She was treated in psychiatric unit in liaison with general medicine department.

Next day her temperature recorded was normal and she started to improve, aside from mild EPS. Her recovery was uneventful. Her CPK level was 25 IU/L within a week. She continued same dose of bromocriptine for 10 days and clonazepam was reduced and stopped over 4 weeks along with trihexyphenidyl.

She did not exhibit any psychotic features until a month and remained hospitalized for supervision of re-emergence of psychotic feature. Later she began developing catatonic symptoms hence she was been started on olanzapine 2.5mg/day and Lorazepam 2mg/day and thereafter has been maintaining fairly well without much symptoms.

DISCUSSION: Atypical neuroleptic agents have been shown to be highly effective and in general, safe, obtaining widespread use in medicine. However, it is imperative to note that all antipsychotics have been reported as having the ability to induce NMS, including rare reports of NMS caused by clozapine, olanzapine, and risperidone.⁵ This case presents occurrence NMS induced by one of the newest atypical antipsychotic, aripiprazole.

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NMS is an idiosyncratic reaction and cannot be predicted, but there are some identified risk factors. Young age, male gender, dehydration, agitation, rapid dose escalation, and intra-muscular administration increase the risk.^{2, 6} Prior history of NMS increases the risk for future episodes. There is some evidence for an association between NMS and concurrent lithium treatment, poorly controlled extra pyramidal symptoms, patients with affective disorders, iron deficiency, poor nutrition, environmental heat load, catatonia, and those drugs that are more potent dopamine-2 (D2) antagonists.^{4, 7}

Our patient had majority of risk factor like rapid escalation of the dose, associated UTI, mild persisting EPS, atrophic brain changes, dehydration, all these factors may have contributed to development of NMS although she was receiving single agent small dose of aripiprazole which is considered comparatively safer than other atypical antipsychotics. In comparison to the other atypical, it possesses a unique mechanism of action that may limit the development of hypo dopaminergic states. Determining neuroleptic malignant syndrome risk with aripiprazole is difficult; two cases were reported in the premarketing sample.⁸ one animal study showed diminished catalepsy with chronic aripiprazole use, in contrast to persistent catalepsy with haloperidol.⁹ Adverse effects are probably underrepresented. Clinical deterioration and adverse effects were reported after starting, switching to, or combining aripiprazole with other antipsychotics or serotonergic agents (Trazodone, sertraline, or venlafaxine).^{10, 11}

CONCLUSION: All Patients who are on neuroleptic medication and especially with risk factors for developing NMS should be monitored carefully to prevent life threatening complication of NMS.

In our case patient recovered promptly due to early diagnoses and prompt treatment with dopamine agonist bromocriptine, withdrawal of antipsychotic and good supportive care.

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