Low dosage of aripiprazole induced neuroleptic malignant syndrome after interaction with other neuroleptic drugs

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ABSTRACT

Aripiprazole is a 2nd generation antipsychotic medication, atypical neuroleptic used for treatment of schizophrenia improving symptoms such as hallucinations, delusions, and disorganized thinking. A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. The disease is characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia. We report on a 63-year old woman with depression syndrome who developed neuroleptic malignant syndrome after twelve days of aripripazole 5 mg per day. Our case is added to the small number already described and suggests the need for caution when aripripazole is added to increase the effect of other antipsychotics.

Introduction

Aripiprazole is a 2nd generation antipsychotic medication, atypical neuroleptic used for treatment of schizophrenia improving symptoms such as hallucinations, delusions, and disorganized thinking. In some people, improvement in social isolation, reduced speech productivity and motivation also occur.[1] The mechanism of action of aripripazole is based on a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.[2] It is thought that its beneficial effect is due to its effects on dopamine and serotonin receptors. Its effects on these receptors are complex, involving stimulation of the receptors but to a lesser degree than the naturally occurring neurotransmitters (a process called partial agonism). Similarly, to other antipsychotics, aripiprazole has been related to fewer extrapyramidal side effects (restlessness, tremor, stiffness) or tardive dyskinesia (slow or jerky movements that one cannot control, often starting in the mouth with tongue rolling or chewing movements) that are thought to arise from a greater than 80% D2 receptor occupancy rate in the striatal area of the basal ganglia. A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole.[3,4] Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database.[5-8] The disease is characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia. The cause of NMS is unknown. Two major, though not necessarily competing, theories to explain NMS are a neuroleptic induced alteration of central neuroregulatory mechanisms. In fact, the clinical syndrome is thought to be secondary to decreased dopamine activity in the central nervous system either from blockade of dopamine D2-receptors or from decreased availability of dopamine itself. Blockade of dopamine neurotransmission in the nigrostriatum and hypothalamus results in muscular rigidity and altered thermoregulation, respectively. Sympathetic nervous system activation or dysfunction may play a significant role in the pathogenesis of NMS. Another theory is an abnormal reaction of predisposed skeletal muscle to assumption of neuroleptic medications. These latter drugs induce abnormal calcium availability in muscle cells of susceptible individuals and trigger muscle rigidity, rhabdomyolysis and hyperthermia.[3,4]

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Case Report

We report on a 63-year old female with depression syndrome who developed neuroleptic malignant syndrome after twelve days of aripiprazole 5 mg per day.

She had been admitted to our unit through the emergency department for slurred speech, generalized slowing of body movement, difficulty in walking with stiffness in arms and legs. There was no past history of illicit substance or alcohol abuse. The patient was in menopause but did not take any specific therapy for osteoporosis. There was no family history of movement disorders. The patient had enjoyed substantial wellbeing and unrelated diseases till four months ago when the depressive syndrome was diagnosed. Depressive disorder is a mental disorder characterized by episodes of all-encompassing low mood accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. However, depression can also create cognitive symptoms such as difficulty thinking clearly, concentration problems, and trouble making decisions. It can be problematic to differentiate between depression and dementia but there are salient features which help to tell them apart. For instance, people with depression might complain about their memory, but they often do well on mental status exams and other tests that evaluate cognitive function. On the other hand, those with dementia often deny any memory problems but do not do as well on mental status exams and similar tests. Also, a depressed person is less likely to show severe mood swings, whereas someone with dementia shows a wider range of emotions and sometimes makes inappropriate emotional responses (*e.g.* laughing while others are sad).

Initially, our patient began medication at home with olanzapine twice daily and triazolam as needed. After four weeks, the patient reports persistence of the symptomatology and, therefore, the therapy was modified. The new therapy was based on the assumption of the patient taking olanzapine 10 mg per day every evening, triazolam 0.25 mg 1 cp every night, alprazolam 0.25 mg 1 cp every morning, paroxetina 20 mg ½ cp after lunch. The patient during the therapy was regularly hydrated. During this period, the patient presented with symptomatology characterized by akathisia, insomnia, irritability. Therefore, the received therapy did not show effectiveness on the psychotic symptoms. The specialist switched from paroxetina to aripiprazole 5 mg per day with subsequent worsening of the previous clinical conditions after twelve days. During the first days of hospitalization, on physical examination, she was found to have bradykinesia and cogwheel rigidity. Her speech was initially slurred and she later became mute. Fever was also seen. There was a rise in her creatine phosphokinase level which increased to 1143 U/L. Further investigations underscored leukocytosis, a normal complete metabolic panel (normal renal and hepatic function), normal urine analysis and brain magnetic resonance imaging demonstrating only atrophic changes consistent with the patient's age. All medications were stopped. The patient received only intravenous hydration. In the following days, dysphagia[9] associated pneumonia appeared and it was necessary to give therapy with parenteral nutrition and intravenous antibiotics. After twenty days, the clinical condition of the patient showed improvement until complete resolution. Given this patient's medication history and clinical presentation, she would be classified as having moderate to severe NMS according to the scoring system proposed by Hynes and Vickar. Emergence of psychotic symptoms immediately following the addition of aripiprazole suggests a causative role of the drug in the onset of the present patient's syndrome. Furthermore, improvement in this patient's psychosis upon discontinuation of aripiprazole, as well as complete resolution of NMS following discontinuation, further supports that the compound was a causal agent. The most likely explanation for this phenomenon is aripiprazole's action as a dopamine partial agonist. Aripiprazole alleviates psychosis by interfering with dopamine transmission, but its agonist action at the D_2 receptor can intensify psychosis. Aripiprazole acts as a D_2 receptor antagonist in a hyperdopaminergic environment and as an agonist in a hypodopaminergic environment. In our case, the presence of olanzapina, which is a potent D_2 antagonist, led to a hypodopaminergic state. In the hypodopaminergic milieu, aripiprazole acted as an agonist and led to worsening of symptoms.[10] The activation of D_2 autoreceptors present on DA-releasing neurons due to aripiprazole causes the decrease in DA release. All this has been shown to decrease locomotor activity.[11] This hypothesis can be more strongly accepted for the present case in particular because withdrawal of aripiprazole led to improvement in psychotic symptoms. This report represents the first case that describes the risk of developing and worsening psychosis by low dose of aripiprazole. We recommend detailed history taking and monitoring for psychotic symptoms when using aripiprazole in the management of psychotic disease. Many factors present *in vivo*, such as neuroleptic metabolites, central dopaminergic blockade and risk factors for NMS should be taken into consideration in developing more precise pharmacological models to explore possible interactions between neuroleptics. Our case is added to the small number already described and suggests the need for caution when aripiprazole is added to increase the effect of other antipsychotics.

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