Medication-induced rhabdomyolysis in a patient with bipolar disorder

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Ms. A, age 32, has a history of anxiety, bipolar disorder, and borderline personality disorder. She is undergoing treatment with lamotrigine 200 mg/d at bedtime, aripiprazole 5 mg/d, trazodone 100 mg/d at bedtime, clonazepam 0.5 mg twice a day, and hydroxyzine 25 mg twice a day. She presents to the emergency department with myalgia, left upper and lower extremity numbness, and weakness. These symptoms started at approximately 3 AM the same day. She denies fever, chills, shortness of breath, chest pain, abdominal pain, lightheadedness, or dizziness, as well as any history of similar symptoms.

Ms. A's vital signs are hemodynamically stable, but her pulse is 113 bpm. On examination, she appears anxious and has decreased sensation in her upper and lower extremities, with 3/5 strength on the left side. Her laboratory results indicate mild leukocytosis, hyponatremia (129 mmol/L; reference range 136 to 145 mmol/L), and elevations in serum creatinine (3.7 mg/dL; reference range 0.6 to 1.2 mg/dL), aspartate aminotransferase (654 U/L; reference range 10 to 42 U/L), alanine transaminase (234 U/L; reference range 10 to 60 U/L), and troponin (2.11 ng/mL; reference range 0 to 0.04 ng/mL). A urinalysis reveals darkly colored urine with large red blood cells.

Neurology and Cardiology consultations are requested to rule out stroke and acute coronary syndromes. A computed tomography scan of the head shows no acute intracranial findings. Her creatinine kinase (CK) level is elevated (>42,670 U/L; reference range 22 to 232 U/L), which prompts a search for causes of rhabdomyolysis, a breakdown of muscle tissue that releases muscle fiber contents into the blood. Ms. A reports no history of recent trauma or strenuous exercise. Infectious, endocrine, and other workups are negative. After a consult to Psychiatry, the treating clinicians suspect that the most likely cause for rhabdomyolysis is aripiprazole.

Ms. A is treated with IV isotonic fluids. Aripiprazole is stopped and her CK levels are closely monitored. CK levels continue to trend down, and by Day 6 of hospitalization her CK level is 1,648 U/L. Her transaminase levels also improve; these elevations are considered likely secondary to rhabdomyolysis. Because there is notable improvement in CK and transaminase levels after stopping aripiprazole, Ms. A is discharged and instructed to follow up with a psychiatrist for further management.

Aripiprazole and rhabdomyolysis

According to the National Institute of Mental Health, an estimated 2.8% of the US population has bipolar disorder and 0.24% to 0.64% has schizophrenia.[1,2] Antipsychotics are often used to treat these disorders. The prevalence of antipsychotic

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use in the general adult population is 1.6%.[3] The use of second-generation antipsychotics (SGAs) has increased over recent years with the availability of a variety of formulations, such as immediate-release injectable, long-acting injectable, and orally disintegrating tablets in addition to the customary oral tablets. SGAs can cause several adverse effects, including weight gain, hyperlipidemia, diabetes, QTc prolongation, extrapyramidal side effects, myocarditis, agranulocytosis, cataracts, and sexual adverse effects.[4]

Antipsychotic use is more commonly associated with serotonin syndrome and neuroleptic malignant syndrome than it is with rhabdomyolysis. Rhabdomyolysis as an adverse effect of antipsychotic use has not been well understood or reported. One study found the prevalence of rhabdomyolysis was approximately 10% among patients who received an antipsychotic medication.[5] There have been 4 case reports of clozapine use, 6 of olanzapine use, and 3 of aripiprazole use associated with rhabdomyolysis.[6-8] Therefore, this would be the fourth case report to describe aripiprazole-associated rhabdomyolysis.

Aripiprazole is FDA-approved for the treatment of schizophrenia. In this case report, we found that aripiprazole could have led to rhabdomyolysis. Aripiprazole is a quinoline derivative that acts by binding to the 5-HT1A and 5-HT2A receptors.[9,10] It acts as a partial agonist at 5-HT1A receptors, an antagonist at 5-HT2A receptors, and a partial agonist and stabilizer at the D2 receptor. By binding to the dopamine receptor in its G protein–coupled state, aripiprazole blocks the receptor in the presence of excessive dopamine.[11-13] The mechanism of how aripiprazole could cause rhabdomyolysis is unclear. One proposed mechanism is that it can increase the permeability of skeletal muscle by 5-HT2A antagonism. This leads to a decrease in glucose reuptake in the cell and increases the permeability of the cell membrane, leading to elevations in CK levels.[14] Another proposed mechanism is that dopamine blockade in the nigrostriatal pathway can result in muscle stiffness, rigidity, parkinsonian-like symptoms, and akathisia, which can result in elevated CK levels.[15] There are only 3 other published cases of aripiprazole-induced rhabdomyolysis; we hope this case report will add value to the available literature. More evidence is needed to establish the safety profile of aripiprazole.

Clinical Point

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