

### Paliperidone-Induced Rhabdomyolysis: A Case Report

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Dear Editor,

Rhabdomyolysis is a clinical and biochemical syndrome that occurs as a result of skeletal muscle destruction and the release of various cellular components into the bloodstream. Rhabdomyolysis can cause serious complications. It can be triggered by various causes, the most common being mechanical, such as direct muscle trauma, intense physical exercise, toxins, use of medications and drugs, infections, and genetic causes. Although antipsychotic agents are not among the drugs that often cause rhabdomyolysis, several cases have been reported in which a direct link has been established between rhabdomyolysis and the use of both typical and atypical antipsychotics. In these cases, rhabdomyolysis usually occurs as a symptom of neuroleptic malignant syndrome (NMS), although it sometimes occurs in isolation. The mechanism by which antipsychotics produce this rare side effect is not known with certainty and more studies are needed. However, the possible involvement of certain pathways and receptors has been postulated.

We report the case of a female patient who developed rhabdomyolysis after starting treatment with oral paliperidone. We briefly reviewed cases of rhabdomyolysis that have occurred in association with the use of antipsychotics and in the absence of NMS.

#### Introduction

Rhabdomyolysis is the destruction of skeletal muscle and release into the bloodstream of various cellular components, including creatine phosphokinase (CPK) and myoglobin.<sup>1,2</sup>

The clinical presentation of rhabdomyolysis varies, usually debuting with fever, nausea, vomiting, and muscle weakness. It can lead to serious complications, particularly heart failure or cardiac arrhythmias, and acute renal failure. Characteristic signs are choloria, elevation of serum CPK, and myoglobinuria.<sup>2,3</sup>

The main causes of rhabdomyolysis are direct muscle damage, intense physical exercise, certain drugs (some of them commonly used, such as statins), toxins, infections, and genetic defects. In psychiatric patients, rhabdomyolysis usually occurs in association with use of the intramuscular route of administration, mechanical restraints, acute dystonia, or in the context of an episode of psychomotor agitation. The mere occurrence of an acute psychotic episode seems to predispose to rhabdomyolysis, probably due to specific muscle dysfunction present in psychotic patients, especially patients with schizophrenia.<sup>1,4</sup> The concomitant use of electroconvulsive therapy (ECT) and the occurrence of tardive dyskinesia, polydipsia, and hyponatremia could act as precipitating factors of antipsychotic-induced rhabdomyolysis.<sup>1</sup>

Antipsychotic agents are among the drugs that cause rhabdomyolysis infrequently, this being a rare and little documented adverse effect. Rhabdomyolysis induced by antipsychotics is usually associated with neuroleptic malignant syndrome (NMS), although it may occur alone. Elevation of CPK occurs in both cases, but NMS also courses with hyperthermia, autonomic instability, and cognitive impairment.<sup>1,2</sup>

The mechanisms by which antipsychotics produce rhabdomyolysis are unknown, although hypotheses have been proposed.<sup>1,2,5</sup> Antipsychotics may intermittently increase the permeability of the myocyte cell membrane in vulnerable patients by antagonizing serotonin 5-HT<sub>2A</sub>, compromising muscular glucose uptake, causing changes in the sarcolemma, and increasing permeability to CPK. This mechanism has not been demonstrated,<sup>1,6,7</sup> but it is postulated that antipsychotics with more affinity for these receptors, including paliperidone, are associated with a higher incidence of rhabdomyolysis. An alternative mechanism is the blockade of dopamine D<sub>2</sub> receptors at the level of the nigrostriatal tract, resulting in rigidity, parkinsonism, and akathisia.<sup>1</sup>

We report the case of a patient who developed rhabdomyolysis after starting treatment with oral paliperidone.

#### Case description

The patient was a 47-year-old single woman who lived alone after moving from another city due to a family conflict. Her father had recently died. She was on sick leave for tarsal osteoarthritis, but had no noteworthy medical history other than hypercholesterolemia (without statin treatment) and appendectomy. She denies any toxin use. She was diagnosed 15 years earlier with brief reactive psychosis and cluster A personality disorder, but was not monitored or treated by a psychiatrist because she did not pursue it. She had two admissions to the psychiatric short hospitalization unit, 9 years and 15 years earlier, in both cases for exacerbation of psychosis.

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Her family history includes a brother with a diagnosis of schizophrenia and a mother and two brothers with unspecified mental illness.

During our emergency room assessment, the patient presented affective clinical manifestations of diminished emotional tone with psychotic suspicions and paranoid delusions, which had a significant behavioral impact and resulted in a tendency to social isolation and disturbances in sleep and appetite.

After ruling out drug use (including heroin, cocaine, and others) by laboratory tests, she was admitted to the hospital with a diagnosis of psychotic disorder not otherwise specified, where oral paliperidone (6 mg/day) and diazepam (10 mg/day) were prescribed. An interconsultation with internal medicine was requested during admission due to the occurrence of myalgia. Subsequently, on day 9 of admission a CPK value of 1324 IU/L was obtained. In the same laboratory test, a natremia value within normal range (139 mmol/L) was obtained. After ruling out other possible causes of CPK elevation and observing complete resolution of symptoms after discontinuing oral paliperidone, we diagnosed rhabdomyolysis secondary to oral paliperidone. Hydration measures were started to avoid potential complications.

The changes in CPK value in relation to antipsychotic treatment during admission are shown in Table 1.

At discharge, the diagnosis was paranoid reaction in a patient with personality disorder; the treatment prescribed was quetiapine 100 mg/day, diazepam 10 mg/day, and abundant fluid intake.

### Discussion

Even though antipsychotic agents rarely cause rhabdomyolysis, several published studies suggest an association between antipsychotics and rhabdomyolysis. Rhabdomyolysis usually occurs as a side effect of antipsychotics in association with NMS, and, more rarely, serotonin syndrome. Some authors defend the existence of atypical or incomplete NMS, a less serious or incomplete form that has been associated with atypical antipsychotics.<sup>8</sup> However, cases of isolated rhabdomyolysis associated with antipsychotics have been reported.<sup>1,2</sup>

In our review, we found several studies that describe cases of rhabdomyolysis induced by antipsychotics, specifically aripiprazole,<sup>1,6,7</sup> oral and intramuscular olanzapine at both normal doses and overdoses,<sup>1,9</sup> and quetiapine at both normal doses and overdoses.<sup>1,4,10-12</sup> There have been reports of rhabdomyolysis induced by other antipsychotics, but other risk factors for rhabdomyolysis were present and the direct causal relation between them is not as clear. Rhabdomyolysis induced by clozapine in the presence of lithium, TEC, or psychogenic polydipsia has been reported, as well as

Tabla 1 Variations in CPK Values in Relation to Antipsychotic Type and Dose Administered During Admission		
Day of Admission	CPK (IU/L)	Antipsychotic Treatment
1	¿?	Oral paliperidone (6 mg/day)
9	1324	Oral paliperidone (9 mg/day)
10	1524	
14	1153	Oral paliperidone (6 mg/day)
15	750	Quetiapine (100 mg/day)
43	59	

rhabdomyolysis induced by ziprasidone in conjunction with other potential rhabdomyolysis-inducing drugs, such as statins and mirtazapine.<sup>1</sup> Risperidone-induced cases of rhabdomyolysis have been reported in both the absence and presence of other risk factors for rhabdomyolysis.<sup>1,5</sup> We found only two studies that mentioned oral paliperidone in relation to the induction of rhabdomyolysis.<sup>1,2</sup> In these two studies, 5 and 1 cases were reported, respectively, the first study with a dose of 6 mg/day (compared to 9 mg/day in the case reported here), and the second study with an unspecified dose. In another study, myalgia was reported as a side effect of parenteral paliperidone in 1% of patients studied versus placebo, although it was not determined whether the symptom occurred within the context of an episode of rhabdomyolysis or as an isolated symptom.<sup>13</sup> Packard et al. were considered the first authors to demonstrate the association between paliperidone and rhabdomyolysis in a recent excellent review that analyzed a total of 673 cases of patients with rhabdomyolysis from several studies, collected between January 2009 and October 2011; 10.5% of these cases were caused by antipsychotic agents.<sup>1</sup>

Simultaneous use of several antipsychotics and use of high-dose antipsychotics seem to predispose to rhabdomyolysis.<sup>1,2</sup> One study shows a positive correlation between CPK values and the dose of olanzapine ingested.<sup>14</sup>

The infrequency of antipsychotic-induced rhabdomyolysis, coupled with the low specificity of symptoms, contribute to the difficulty of diagnosing this condition.<sup>2</sup> We think that it is essential to know the possible causes and the signs and symptoms of rhabdomyolysis in order to suspect its development at the onset of laboratory abnormalities, mainly elevated serum CPK and myoglobinuria. Myalgia was the symptom that suggested rhabdomyolysis in our case, which was subsequently confirmed by the laboratory findings. Skeletal muscle biopsy, although uncommon, can be used to confirm the diagnosis in dubious cases.

The period between the initiation of antipsychotic treatment and the onset of rhabdomyolysis may differ con-

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siderably from one case to another, which further hinders the diagnosis. In various studies,<sup>2,9</sup> cases were found in which the interval ranged between 2 to 5 days and one and a half to two years after starting antipsychotic treatment. Generally speaking, a causal relationship between rhabdomyolysis and an antipsychotic is recognized when the temporal sequence after administration is compatible and the condition resolves after the drug is stopped.<sup>10</sup> Discontinuation of the suspected drug and a rapid and aggressive therapeutic intervention help to avoid possible complications.<sup>2</sup> In the case reported here, simply discontinuing the antipsychotic favored resolution of the picture.

The fact that we did not order myoglobinuria measurement to study our patient's possible renal impairment was a limitation to our case, although it must be noted that abnormal myoglobinuria is not required to confirm the diagnosis of rhabdomyolysis.<sup>9</sup>

Further investigations are needed to determine which antipsychotics are associated with a greater risk of inducing rhabdomyolysis and the mechanisms involved.

### CONFLICT OF INTERESTS

The authors state that they have no conflict of interests.

### REFERENCES

1. Packard K, Price P, Hanson A. Antipsychotic Use and Risk of Rhabdomyolysis. *J Pharm Pract.* 2014 Jan 15.
2. Star K, Iessa N, Almandil NB, Wilton L, Curran S, Edwards IR, et al. Rhabdomyolysis reported for children and adolescents treated with antipsychotic medicines: a case series analysis. *J Child Adolesc Psychopharmacol.* 2012;22:440-51.
3. Elsayed EF, Reilly RF. Rhabdomyolysis: A review, with emphasis on the pediatric population. *Pediatr Nephrol.* 2010;25:7-18.
4. Velasco-Montes J, Oriñuela-González I, Sanjuán-López AZ. Rhabdomyolysis secondary to quetiapine. *Actas Esp Psiquiatr.* 2012;40:97-9.
5. Risperidone: rhabdomyolysis. *Prescrire Int.* 2013;22:128.
6. Chang KY, Wu YF. Aripiprazole-associated rhabdomyolysis in a patient with schizophrenia. *J Neuropsychiatry Clin Neurosci.* 2011;23:E51.
7. Marzetti E, Bocchino L, Teramo S, Scudieri G, Aulisa AG. Rhabdomyolysis in a patient on aripiprazole with traumatic hip prosthesis luxation. *J Neuropsychiatry Clin Neurosci.* 2012;24:E40-E41.
8. Espino García A, Madrid Valls M, Mur Garcés R, Nadal Braqué N. Malignant neuroleptic syndrome linked to haloperidol. *Aten Primaria.* 2001 May 31;27(9):677.
9. Karakaya P, Yis U, Kurul SH, Türkmen MA. Rhabdomyolysis associated with olanzapine treatment in a child with Autism. *Pediatr Emerg Care.* 2010;26:41-2.
10. Ceri M, Unverdi S, Altay M, Duranay M. Comment on: low-dose quetiapine-induced severe rhabdomyolysis. *Ren Fail.* 2011;33:463-4.
11. Dickmann JR, Dickmann LM. An uncommonly recognized cause of rhabdomyolysis after quetiapine intoxication. *Am J Emerg Med.* 2010;28:1060.
12. Stephani C, Trenkwalder C. Rhabdomyolysis after low-dose quetiapine in a patient with Parkinson's disease with drug-induced psychosis: a case report. *Mov Disord.* 2010;25:790-1.
13. Pandina GJ, Lindenmayer JP, Lull J, Lim P, Gopal S, Herben V, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of Paliperidone Palmitate in adults with acutely exacerbated Schizophrenia. *J Clin Psychopharmacol.* 2010;30:235-44.
14. Warring WS, Wrate J, Bateman DN. Olanzapine overdose is associated with acute muscle toxicity. *Hum Exp Toxicol.* 2006;25(12):735-40.