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LETTER TO THE EDITORS

Acute rhabdomyolysis during treatment with amisulpride and metformin

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Background

Rhabdomyolysis with increased serum creatine kinase (CK) is a potential side effect associated with the use of some medications, including statins and antipsychotics. Several cases of increased serum CK during or after treatment with atypical antipsychotics such as quetiapine, clozapine, or olanzapine have been reported [1-4]. Conversely, to our knowledge, no cases of rhabdomyolysis during metformin treatment are described in the literature. In this article we report a case of rhabdomyolysis during combined therapy with amisulpride and metformin, but not with either of these drugs alone.

Case report

Our patient is a 25-year-old obese (BMI = 32.2 kg/m^2) male with hyperinsulinemia and a 4-year history of generalized anxiety disorder and dysthymia. He has been treated with benzodiazepines, SSRI, and tricyclic antidepressants without substantial improvement in psychiatric symptoms. For obesity he was previously treated with diet therapy achieving only a small reduction in body weight and in fasting insulin levels.

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In May 2008, before starting any treatment, laboratory tests were performed. CK was normal (110 IU/L) and no other relevant alterations were found. In June 2008 metformin (500 mg three times a day) was started to control hyperinsulinemia and, together with a low-calorie diet, to achieve a greater reduction in body weight. After 2 weeks of therapy, routine laboratory tests were performed. CK remained in the normal range (126 IU/L) during the treatment with metformin.

After 3 weeks, on the advice of the psychiatrist, we decided to start amisulpride (200 mg daily) for psychiatric complaints. After 2 weeks of therapy, biochemical analyses were performed for assessment of safety. All parameters were within normal range, except an elevated CK value of 1,962 IU/L. No other abnormalities were evident and no symptoms and signs were present, so we decided to adopt a "watch and wait" strategy.

A few days later the patient started to complain of generalized muscular weakness, so routine blood tests were repeated. The screening showed a marked CK increase (7,241 IU/L, CK-MB isoenzyme < 1%) with a concomitant increase in AST (95 IU/L), ALT (74 IU/L), aldolase (33 IU/L), and myoglobin (139.3 ng/mL). The patient did not report a history of intramuscular injections or trauma and performed no excessive physical activity in the week before admission.

Electromyography was performed with no evidence of pathologic findings. Muscular biopsy was performed, and there were no signs of muscular disease or enzymatic deficiency. Both drugs were suspended and another determination of serum CK was done. CK started to decline and returned back to normal after 3 weeks (105 IU/L). We decided to reintroduce amisulpride alone, the most likely drug to have caused CK elevation. After 1 week, 2 weeks,

and 1 month of therapy, routine laboratory tests showed that the CK value remained within the normal range.

Discussion

Amisulpride, a substituted benzamide derivative, is an atypical antipsychotic used in the treatment of psychoses and, at lower doses (50–200 mg/daily), of dysthymia. It's a selective dopamine antagonist, with high affinity for D2 and D3 dopaminergic receptors. Like several medications of the same class, amisulpride can cause muscle toxicity in the form of neuroleptic malignant syndrome (NMS), by means of at least two different mechanisms. The first mechanism is the dopaminergic receptor antagonism in the hypothalamus, which could interfere with dopamine's normal role in central thermoregulation, leading to heat production and hyperthermia. The second mechanism is a direct toxicity on muscle cell membranes and an increased calcium release from the sarcoplasmic reticulum. In addition to NMS, isolated CK elevation without signs and symptoms of NMS has been also reported during treatment with atypical antipsychotics, such as quetiapine, clozapine, and olanzapine [3, 5-7]. We failed to find any report of isolated CK elevation with amisulpride, but several cases of NMS after or during treatment with this medication are described in the literature [8, 9].

Metformin is a biguanide oral hypoglycemic agent used to treat type 2 diabetes mellitus and hyperinsulinemia. It is the only biguanide available in Italy because phenformin, another biguanide, was withdrawn due to the high risk of lactic acidosis. Metformin can also cause lactic acidosis, even in patients taking therapeutic doses [10], via a mechanism not fully understood. It accumulates in the intestine, leading to an increased production of lactate, which lowers the pH within the liver and decreases lactate metabolism by suppressing pyruvate carboxylase. It also decreases glucose utilization and increases lactate production by the hepatocytes [11]. We did not find any reports of a direct link between metformin administration and rhabdomyolysis, but such a link has previously been reported with phenformin [12].

The close connection to the administration of both drugs together and the absence of other causes of rhabdomyolysis suggest that the elevated CK levels in this case resulted from the association of both drugs, and this explanation is supported by the fact that theoretically both drugs have the potential to cause muscle toxicity, especially in susceptible patients. While the exact mechanism of the CK elevation is unclear, it's possible that concomitant treatment with amisulpride and metformin caused damage to muscle membranes and a kind of muscle vulnerability to low-grade injury, such as ordinary activity or mild exercise.

Conclusions

Our case report suggests that clinicians should be aware of this interaction and consider measuring CK, particularly if any muscle-related symptoms appears.

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