Massive Creatine Kinase and Hepatic Enzyme Elevation Due to Quetiapine and Valproic Acid Treatment: A Case Report

Ketiapin ve Valproik Asit Tedavisi Bağlı olarak Gelişen Masif Kreatin Kinaz ve Karaciğer Enzim Yüksekliği: Bir Olgu Sunumu

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ABSTRACT
In literature, creatine kinase (CK) elevations related to treatment with atypical antipsychotics have been reported in several case studies. In this paper, we present a case of a patient, whose previous and present medical histories showed a massive increase in serum CK and CK myoglobin-band (CK-MB) during quetiapine treatment and in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) levels during valproic acid treatment. The possible mechanisms underlying the CK elevation related with quetiapine and the symptoms that the clinicians should be careful about will be discussed. (Archives of Neuropsychiatry 2012; 49: 238-240)

Key words: Quetiapine, valproic acid, creatine kinase, hepatic enzymes

Case

A 26-year-old Caucasian man was diagnosed as bipolar disorder four years ago. In his first manic episode, he was treated with lithium, and in the following episodes, with the combination of three drugs: VA, olanzapine and risperidone. Because of the elevations in hepatic enzymes, firstly antipsychotic drugs were stopped. Since the increase in enzyme levels continued, then VA was ceased as well, and hepatic enzyme levels decreased back to normal. He had three manic episodes within the last four years (in 2006, 2008 and 2009), and was not on any medication for the last six months. His first manic episode lasted for three months and the next two episodes recovered within a month each. Several weeks ago,
upon his symptoms of decreased sleep, flight of ideas and distractibility, he again initiated some of his previous drugs, such as VA, lithium and quetiapine.

On admission, he had been using 1500 mg/day lithium, 500 mg/day VA and 200 mg/day quetiapine for the last four days. Serum lithium level was found as 0.47 mEq/L and VA level as 50 mg/L. Laboratory test results were as follows: AST - 1058 U/L (normal ranges for males: 10-40 U/L), ALT - 472 U/L (7-35 U/L) and LDH - 1146 U/L (135-225 U/L). GGT and all routine laboratory tests were within normal ranges. Thyroid functions were normal. The patient was referred to Internal Medicine Department and since abdominal ultrasonography showed no pathology, it was suggested to discontinue the drugs and monitor the enzymes. Since his previous medical history clearly showed that he had hepatic enzyme elevations due to VA treatment, VA was stopped and the quetiapine dose was increased to 400 mg/day. After seven days, hepatic enzymes decreased and the values were: AST - 497 U/L, ALT - 346 U/L and LDH - 686 U/L. The levels of hepatic enzymes during treatment period are shown in Table 1. In that visit, the patient complained of myalgia and the levels were: 11713 U/L for CK (55-170 U/L) and 169.5 U/L for CK-MB (CK-MB <5 ng/ml). The most common causes of CK elevation were excluded; there were no history of trauma, recent surgery, hypothyroidism, recent falls or bruises, physical limitations, excessive physical activity or intramuscular injections. Another possible cause of CK elevation, which is neuroleptic malignant syndrome (NMS), was eliminated since the patient had no other symptoms such as fever or leukocytosis. Besides, he was well oriented and his mental status was normal. A detailed medical history showed that he had increases in CK (approximately 10000 U/L) and CK-MB levels during quetiapine treatment one year ago. This massive elevation in CK levels was then considered to be associated with quetiapine, which was promptly discontinued. Olanzapine 20 mg/day was initiated for the treatment of manic symptoms. The levels of CK and CK-MB during treatment period are shown in Table 2. One month later, he was euthymic, his liver functions were normal and the CK level was in normal range. He is still under treatment with lithium (1500 mg/day) and olanzapine (20 mg/day) and hepatic enzymes and CK, CK-MB levels are in normal ranges.

Discussion

The major pathways of VA biotransformation include b-oxidation and conjugation with glucuronic acid, and only a smaller part of the metabolism occurs via CYP2D6 isoenzyme-dependent oxidation and desaturation reactions (4). Benign elevation in hepatic transaminase levels is one of the common side effects of VA and hepatic failure is thought to be a rare idiosyncratic adverse effect (4). His previous history of elevation in hepatic enzymes suggested a sensitivity to this agent.

NMS is a potentially fatal process characterized by hyperthermia, autonomic instability, altered mental status and severe muscular rigidity. Laboratory analysis often reveals leukocytosis, elevated serum CK level and minimal to moderate elevations of LDH, AST and ALT (5). Although the patient’s CK was high, since he had no muscular rigidity or other symptoms, such as fever, leukocytosis and altered mental status, NMS was eliminated.

In recent years, CK elevations related to use of atypical antipsychotics have been reported in several case studies in the absence of neuroleptic malignant syndrome. Two of them were about rhabdomyolysis due to quetiapine overdose (6,7). However, in some of the other cases, quetiapine doses were between 25 and 1200 mg/day (3,8,9); our patient used 400 mg/day. One limitation of this report is that it lacks the baseline CK and CK-MB values. Yet, the decrease in the levels after the discontinuation of quetiapine suggests a casual relation. In addition, in the patient’s medical history, there was a previous increase of CK due to quetiapine use.

Pharmacologically, quetiapine has antagonistic effects on serotonin 5-HT1A, 5-HT2A, dopamine D1, D2, histamine H1, and adrenergic α1, α2 receptors and it is mostly metabolized in the liver via the cytochrome p450 isoenzyme CYP3A4 (10). The pathophysiology of neuroleptic-associated CK elevation is still unclear. Meltzer et al. suggested that the increase in CK activity may reflect the ability of atypical antipsychotic agents to increase the cell membrane permeability intermittently (11). The presence of 5-HT2A receptor in skeletal muscle and the 5HT2A receptor blockade caused by the atypicals could produce this CK elevation through a sarcolemma permeability enhancing effect. Devarajan and Dursun also suggested a dopaminergic nigrostriatal pathway blockade-mediated “central mechanism”, however, our case did not seem to comply with this mechanism, as quetiapine does not appear to block the dopaminergic nigrostriatal pathway (12). Elevations in CK levels associated with atypical antipsychotic use are benign in almost all cases, and risk of related renal damage appears minimal (13). Thus, routine monitoring is not recommended; yet, it is necessary to monitor the enzymes. Since his previous medical history clearly showed that he had hepatic enzyme elevations due to VA treatment, VA was stopped and the quetiapine dose was increased to 400 mg/day. After seven days, hepatic enzymes decreased and the values were: AST - 497 U/L, ALT - 346 U/L and LDH - 686 U/L. The levels of hepatic enzymes during treatment period are shown in Table 1. In that visit, the patient complained of myalgia and the levels were: 11713 U/L for CK (55-170 U/L) and 169.5 U/L for CK-MB (CK-MB <5 ng/ml). The most common causes of CK elevation were excluded; there were no history of trauma, recent surgery, hypothyroidism, recent falls or bruises, physical limitations, excessive physical activity or intramuscular injections. Another possible cause of CK elevation, which is neuroleptic malignant syndrome (NMS), was eliminated since the patient had no other symptoms such as fever or leukocytosis. Besides, he was well oriented and his mental status was normal. A detailed medical history showed that he had increases in CK (approximately 10000 U/L) and CK-MB levels during quetiapine treatment one year ago. This massive elevation in CK levels was then considered to be associated with quetiapine, which was promptly discontinued. Olanzapine 20 mg/day was initiated for the treatment of manic symptoms. The levels of CK and CK-MB during treatment period are shown in Table 2. One month later, he was euthymic, his liver functions were normal and the CK level was in normal range. He is still under treatment with lithium (1500 mg/day) and olanzapine (20 mg/day) and hepatic enzymes and CK, CK-MB levels are in normal ranges.
clinicians should ask their patients about muscle damage-related symptoms such as myalgia, especially those who had experienced these symptoms during previous antipsychotic treatments. Further research would suggest new mechanisms for the CK elevations associated with atypical antipsychotic drugs.

References

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