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Olanzapine-Induced Neuroleptic Malignant Syndrome with Hypernatremia

Recep Tutuncu[1], Huseyin Gunay[1], Hakan Balibey[1]

ÖZET:

Olanzapine bağlı hipernatremi ile giden malign nöroleptik sendrom

Malign Nöroleptik Sendrom (MNS) antipsikotiklerin nadir görülen fakat ölümcül olabilen bir yan etkisidir. MNS'nin ortaya çıkışında hipernatreminin önemli rolü olabilir ya da akut böbrek yetmezliğine ikincil olarak gelişebilir. Bu yazıda, olanzapin ile tedavi sonrası MNS, hipernatremi ve akut böbrek yetmezliği gelişen 27 yaşında bir erkek hasta bildirilmektedir.

Anahtar sözcükler: Olanzapin, malign nöroleptik sendrom, hipernatremi

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ABSTRACT:

Olanzapine-induced neuroleptic malignant syndrome with hypernatremia

Neuroleptic Malignant syndrome (NMS) is a rare but potentially fatal adverse effect of antipsychotics. In addition, hypernatremia may play a significant role before occurrence of NMS or it may develop secondary to acute renal failure. Herein we report the case of a 27 year old male patient who developed NMS with hypernatremia and acute renal failure following treatment with olanzapine.

Key words: Olanzapine, neuroleptic malignant syndrome, hypernatremia

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[1]M.D., Etimesgut Military Hospital, Ankara - Turkey

Yazışma Adresi / Address reprint requests to: Huseyin Gunay, Etimesgut Military Hospital, Ankara - Turkey

Elektronik posta adresi / E-mail address: huseyingunaydr@yahoo.com

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Olanzapine is supposed to be less frequently associated with the occurrence of neuroleptic malignant syndrome (NMS), which is a rare but potentially fatal adverse event of antipsychotics (1). Johnson and Bruxner published the first case of NMS associated with olanzapine use in 1998. Since then many series of NMS cases have been reported and many reviews have been published. It is more frequent with typical antipsychotics and rarely seen during treatment with atypicals.

NMS is characterized by fever, muscle rigidity, autonomic dysfunction, and altered mental status. In addition to the commonly observed symptoms, several abnormalities in laboratory indices such as increase in serum sodium due to water depletion, leukocytosis, and increases in serum creatinine kinase and other muscle enzymes are also detected (2). Acute renal failure (ARF) is considered as the most serious complication of NMS and as it confers a worse prognosis for NMS, its early identification is prudent (3).

We report a case of a 27-year old male who developed NMS with hypernatremia and ARF following treatment with olanzapine. Informed consent for publication was obtained from the patient. This case raises important questions about hypernatremia with antipsychotics, the possible association between hypernatremia and the other adverse effects, and the direction of causality. According to our knowledge, there is only one case report suggesting an association between olanzapine monotherapy and the occurrence of hypernatremia.

CASE REPORT

A 27 year-old male patient who has been diagnosed with schizophrenia for 6 years was admitted to the psychiatric clinic due to a relapse of psychotic symptoms in the form of social withdrawal, restricted affect and obsessive thought content. He had been on olanzapine monotherapy for 6 years. The dosage was 10 mg/day before the admission. He was a non- smoker. Hypodipsia was observed and recorded by the nursing staff in the clinical follow up. He was hospitalized and put on olanzapine therapy with a dosage of 20 mg/day due to his negative symptoms. At the end of 2 weeks, he was

confused. His blood pressure and heart rate were in the normal ranges. On physical examination initial vital signs were a temperature of 37.2ºC, blood pressure of 130/60 mm Hg, and a pulse of 80 beats/min. Neurological examination revealed minimal rigidity of extremities with no focal neurological deficits otherwise.

The signs and symptoms of the patient had progressed over the preceding 12 hours. Severe rigidity and tremor developed, with a temperature of 39 °C. His blood pressure was 110/80mmHg. He appeared lethargic and unresponsive. Laboratory findings showed severe hypernatremia with signs of rhabdomyolysis and normal CBC results. His blood investigations were as follows: blood glucose level of 138 mg/dl (normal range:70.00–110.00 mg/dl); urea 41 mg/dl (normal range: 7.00-25.00 mg/dl) ; creatinine 2.0 mg/dl (normal range:0.6–1.5 mg/dl); sodium 189 mmol/L (normal range:136–148 mmol/L); potassium 2.7 mmol/L (normal range:3.5–5.2 mmol/L); white cell count 7200 mm^3; hemoglobin 15.2 g/dL; platelet count $161\times10^3/mm^3$. His creatinine kinase (CK) levels were as follows: 1970 IU/L (day 1 in Psychiatry Ward), 3780 IU/L (day 2 in Intensive Care Unit). The results of cranial computed tomography were also normal, particularly with regard to brain tumor or other space-occupying lesions.

He was transferred to the intensive care unit. Olanzapine was promptly discontinued, and he was diagnosed with NMS and ARF. Two weeks later, the patient was physiologically stable and was transferred back to inpatient psychiatric ward. He was successfully recovered from ARF by hemodialysis.

DISCUSSION

The patient in the index case met the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV) criteria for NMS as he had two major features (muscle rigidity,elevated temperature) and four minor features (elevated creatinine phosphokinase, altered mentation, mutism, and tremor) (4). In addition, the patient was diagnosed with ARF. The latter was considered secondary to rhabdomyolysis and hypernatremia (3).

It is not clear, but the occurrence of hypodipsic hypernatremia which is related to the patients' negative symptoms, may be the key factor in this case (5). Dehydration also impairs dissipation of heat by causing vasomotor constriction and predisposes to NMS (6).

The exact mechanism of hypernatremia-induced NMS is not clear. From the available evidence, severe hypernatremia appears sufficient to induce muscle injury by interfering with dopaminergic pathways in the central nervous system (7,8). Permanent muscle rigidity causes damage to the muscle cells which results in myoglobinemia, myoglobinuria, and elevations in muscle related creatinine phosphokinase. These symptoms eventually lead to ARF (9).

ARF is the most serious complication of neuroleptic malignant syndrome. It occurs in about 16% of all NMS cases and increases the mortality rate to nearly 50%. In the present case, ARF is the result of dehydration and muscle damage which lead to renal vasoconstriction, intratubular myoglobin deposition, and nephrotoxicity (3). Hypernatremia might be due to renal failure, or hypernatremia might cause ARF,. but there is no laboratory finding for confirmation.

The classical hypothesis that NMS is primarily caused by dopamine (D2) blockage is not supported by the results of this study. Olanzapine, with a low affinity to D2 receptors, causes few extrapyramidal symptoms. Yet, it can cause NMS. Recently, several authors have proposed that alternative mechanisms may be responsible for the development of NMS. In addition to dopamine, other neurotransmitters, such as serotonin, norepinephrine, gamma-aminobutyric acid, acetylcholine, and the imbalance between them may also be involved in the pathogenesis of NMS (1).

Furthermore, this case highlights that monotherapy with an atypical antipsychotic may lead to NMS despite a patient being maintained on the same drug for several years, a rare but documented adverse effect (3). Herein, NMS occurred within 14 days of increasing the dosage. In the literature, it is stated that 90% of NMS cases occur within 30 days of initiating or increasing the dosage of the offending agent (10).

In conclusion, olanzapine should be used judiciously and dose escalation should be gradual, as it is done with typical antipsychotics due to the possibility of development of potentially lethal NMS. In particular, we would like to emphasize the need to identify possible precipitating factors and early recognition of the symptoms such as dehydration and hypernatremia. Although the solution for hypodipsia is simple through voluntary oral water intake, if not diagnosed, serious consequences can occur such as repeated hypernatremic episodes, intense rhabdomyolysis, ARF, and NMS with elevated morbidity.

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