Olanzapine-associated Neuroleptic Malignant Syndrome: A Case Report

Olanzapine Bağlı Nöroleptik Malign Sendrom: Olgu sunumu

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Introduction:
Neuroleptic malignant syndrome (NMS) is an uncommon but potentially lethal drug reaction, most often seen as a complication of antipsychotic treatment. The most common clinical findings in NMS are; hyperthermia, extrapyramidal symptoms, high creatinine kinase (CK) levels, altered mental state and leukocytosis.

Case Report:
A 15-year-old male patient with the diagnosis of mucopolysaccharidosis type 3C and autism spectrum disorder from another center had been prescribed olanzapine 5 mg orally twice daily for psychotic disorder by a child psychiatrist ten days ago. On the seventh day, the mother stopped the drug completely because the patient had an inappetence, agitation, swallowing problem and developed severe muscle rigidity in the prostration position. On the tenth day, the patient was brought to our pediatric emergency department in the prostration position suffering from muscle rigidity in the whole body and was unable to move (Figure 1A). He was firstly administered biperiden as considering extrapyramidal side effect of olanzepine and than diagnosed with NMS after noticing fever. Subsequently dantrolene was administered intravenously at a dose of 2.5mg/kg in addition to the low-dose midazolam infusion. The patient could only received three doses of dantrolene due to lack of availability. On the second day, the treatment was continued with midazolam infusion and bromocriptine administered orally twice a day. He gradually improved over one week, and bromocriptine was tapered gradually but thereafter he developed ventilator-associated pneumonia and discharged in stable condition on day 30 (Figure 1B).

Conclusion:
Early diagnosis of NMS and cessation of the drug, prompt medical intervention are life saving. It is therefore essential for all physicians to become familiar with the diagnosis and treatment of this serious and treatable drug reaction. Our aim is to increase the awareness, and recognition of NMS for reducing its incidence and mortality.

Keywords: *Neuroleptic malignant syndrome, olanzapine, bromocriptine*

Introduction

Neuroleptic malignant syndrome (NMS) is a life-threating neurological disorder, most often caused by an adverse reaction to neuroleptic or antipsychotic drugs. NMS typically consists of muscle rigidity, fever, autonomic instability, and cognitive changes such as delirium, and is associated with elevated plasma creatine phosphokinase (CPK) (1). We present a case in the prostration position with olanzapine related NMS, administered biperiden firstly as considering extrapyramidal side effect of olanzepine and than diagnosed with NMS by noticing fever.

Case Report

A 15-year-old male patient with the diagnosis of mucopolysaccharidosis type 3C and autism spectrum disorder was prescribed olanzapine 5 mg orally twice daily for psychotic disorder by a child psychiatrist from another health center, ten days ago. On the sixth day, dystonic postural movements developed in the patient's arms and legs and the dose of olanzapine was reduced to 2.5 mg orally twice daily and biperiden 2 mg orally twice daily was added to the treatment. His mother stopped the medication due to worsening of the symptoms on the seventh day. The patient went into altered sensorium, stopped feding and sleeping on the eighth day and was referred to our hospital on the tenth day. On admission, the patient was brought to our pediatric emergency department in the prostration position suffering from muscle rigidity in the whole body and was unable to move (Figure 1A). He was afebrile with the temperature of 36.7°C, pulse rate was 122/min, the blood pressure was 164/79 mmHg, the respiratory frequency was 24 per minute, capillary glycemia was 120 mg/dL, oxygen saturation was 95. On physical examination, he was agitated with a Glasgow Coma Scale of 9/15 (E4M4V1) and had mildly coarse facial features, diaphoresis, generalized rigidity and jaw-closing oromandibular dystonia in the prostration position. We initially considered the diagnostic hypothesis of extrapyramidal syndrome due to the use of antipsychotic. After the intramuscular administration of one dosage of biperiden (5 mg), he was able to move a little and sit but his rigidity, agitation, and other complaints persisted. Within a few hours, he developed a temperature of 37.8°C. Subsequently the family reported that he had rarely fever for several days and used antibiotics and antipyretics for upper respiratory infection. Laboratory examination revealed elevated serum CPK (5580 IU/L), Na (151 mmol/L), blood urea (71 mg/dL) and AST (154 U/L). The other laboratory parameters were normal. At this moment, we considered the hypothesis of NMS as the occurrence of muscle rigidity, hypertension, tachycardia, fever and increased CPK. Brain computed tomography was normal. Since intravenous lorazepam was not present in our pediatric emergency unit, intravenous low-dose midazolam infusion (0.5 mcg/kg/min) was initiated for agitation and generalized dystonia. Then the patient was transferred to our tertiary level pediatric intensive care unit (PICU). Intravenous fluids were used to maintain euvolemic state. His blood pressure, rigidity and agitation decreased after midazolam infusion, subsequently dantrolene was *administered* intravenously at a *dose of* 2.5 mg/kg. After the first dose of dantrolene, his fever, tachypnea and stiffness decreased, her blood pressure remained within normal limits. Within a few hours he developed increased respiratory failure requiring intubation. Although the maintenance dose of dantrolene was planned to be 1 mg four times a day, the patient could only receive three doses of medication due to lack of availability. On the second day of the PICU, the treatment was continued with low-dose midazolam infusion and bromocriptine 2.5 mg administered orally twice daily. In the follow-up, the patient developed ventilator-associated pneumonia. He improved over one week and midazolam used for sedation was ceased at first, then bromocriptine was tapered gradually over three weeks. He was discharged in stable condition with normal laboratory parameters with on day 30
(Figure 1B).

Discussion

NMS is a potential danger to patients, being treated with the medications that interfere with the dopaminergic system. The first symptoms of NMS are usually mental state changes, dysautonomia, muscular rigidity and hyperthermia. The diagnosis can be difficult and mainly based on the clinical findings, supported by laboratory tests and ruling out the other possibilities such as infections, brain lesions, toxic encephalopathy, central anticholinergic syndrome, heat stroke and malignant hyperthermia, serotonin syndrome (selective serotonin reuptake inhibitors toxicity) etc (1, 2).

Serotonin syndrome is the most common diagnosis related to NMS. The milestones that characterize serotonin syndrome are shivering, hyperreflexia, myoclonus, and ataxia. Features which distinguish NMS from serotonin syndrome include bradykinesia, muscle rigidity, elevated white blood cell (WBC) and plasma CPK level (3). A raised WBC count and plasma CPK level will be reported due to increased muscular activity and rhabdomyolysis. The patient with NMS may suffer hypertensive crisis and metabolic acidosis. The fever is believed to be caused by hypothalamic dopamine receptor blockade. The antipsycotic drugs cause an increased calcium release from the sarcoplasmic reticulum of muscle cells which can result in rigidity and cell breakdown (1,2). However, patients with olanzapine-induced NMS usually do not have fever (4).

The treatment generally based on the removal of the offending medication and supportive care in an intensive care unit. Benefits of specific treatments such as dantrolene, electroconvulsive therapy, dopamine agonists such as bromocriptine and amantadine are still debated, but can be considered if there is no clinical improvement (4-6). Anticholinergics may cause symptoms resembling NMS, and may also be associated with the occurrence of delirium (5). Our case was firstly administered biperiden, an anticholinergic drug, considering extrapyramidal side effect of olanzepine and than diagnosed with NMS after noticing fever and elevated serum CPK level and successfully treated with supportive care and bromocriptine after several doses of dantrolene. In conclusion; early diagnosis of NMS, cessation of the drug, and prompt medical intervention are life saving. It is therefore essential for all physicians to become familiar with the diagnosis and treatment of this serious and treatable drug reaction. Our aim is to increase the awareness, and recognition of NMS for reducing its incidence and mortality.

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Figure.1A: The patient in the prostration position on admission, 1B: The patient after the treatment