Case Report

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A Rare Cause of Serotonin Syndrome: Chronic Olanzapine Use

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Abstract

Serotonin syndrome is a life-threatening, undesirable drug reaction. It is a combination of symptoms caused by over activation at central and peripheral serotonin receptors secondary to high serotonin levels. Olanzapine, a second generation antipsychotic agent, is an antagonist of serotonin receptor. Despite the effect of serotonin antagonism, it is reported that olanzapine may paradoxically trigger serotonin syndrome. In this case report, we present a patient with SS due to chronic olanzapine use accompanied by bullous drug reaction.

Key words: serotonin syndrome, olanzapine, atypical antipsychotic

Özet

Serotonin sendromu hayatı tehdit eden, istenmeyen bir ilaç reaksiyonudur. Yüksek serotonin düzeylerine ikincil olarak merkezi ve periferik serotonin reseptörlerinde aşırı aktivasyonun neden olduğu semptomların bir birleşimidir. İkinci kuşak bir antipsikotik ajan olan Olanzapin, serotonin reseptörünün bir antagonistidir. Serotonin antagonizmasının etkisine rağmen, olanzapinin serotonin sendromunu paradoksal olarak tetikleyebileceği bildirilmiştir. Bu olgu sunumunda, büllöz ilaç reaksiyonunun eşlik ettiği kronik olanzapin kullanımı nedeniyle oluşan serotonin sendromlu bir hastayı sunuyoruz.

Anahtar kelimeler: serotonin sendromu, olanzapin, atipik antipsikotik

Introduction

Serotonin syndrome (SS) is a life-threatening, undesirable drug reaction caused by the increase in serotonergic activity in the central and peripheral nervous system. The syndrome which is considered as one of the entities under the heading 'toxic syndromes' or 'toxidromes', is actually an idiosyncratic reaction. The use of serotonin-inducing agents, including selective serotonin reuptake inhibitors (SSRI) and monoamine-oxidase inhibitors (MAOI) are accepted to have the potential for development of SS[1].

Olanzapine is a second generation antipsychotic agent which is an antagonist of serotonin and dopamine receptor (5HT-2A, D2). Despite serotonin antagonism, it has been rarely reported to cause SS in the literature[2].

In this case report, we present a patient with SS due to chronic olanzapine use accompanied by bullous drug reaction.

Case Report

A 27-year-old male presented to the emergency department (ED) with altered mental status. It was learned from his family that previous day, the patient had come home in a dazed state and gone to sleep directly, but he could not be awakened on the day the he was brought to the ED by ambulance. The patient who had been using valproic acid and olanzapine for five years due to bipolar disorder, was also hospitalized for drug abuse a year ago. The vital signs were blood pressure:100/60 mm/hg, pulse:111/min, fever:38.2°C, saturation:92%. The physical examination revealed that the general status was moderate, he was confused, the pupillary myotic, bilateral light reflex was positive and had had no lateralizing deficit. There were also multiple sterile bullous lesions due to drug reaction in lower extremities of the patient (Figure-1). The other system examinations were normal. The laboratory results were glucose:113 mg/dl, urea:51 mg/dl, creatinine:1.74 mg/dl, alanine amino transferase (ALT):958 U/L, aspartate amino transferase (AST):696 U/L, amylase: 449 U/L, lipase: 82 U/L, troponin:8216 pg/ml, creatine kinase-MB (CK-MB):45.5 ng/ml and blood paracetamol level:<4.89 µg/ml. Blood gas parameters were within normal limits. Cocaine, opiate and paracetamol were found positive in urine drug test. Electrocardiography (ECG) and echocardiography were normal except for sinus tachycardia. The patient was monitored and 0.4 mg of naloxane was given intravenously (IV). Appropriate fluid, electrolyte and anti-

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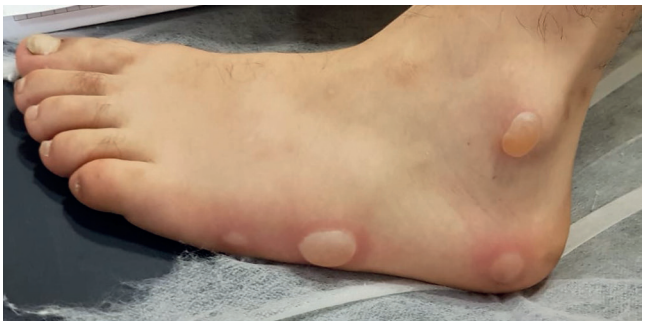

Figure-1. Multiple sterile bullous lesions due to drug reaction

pyretic treatment was initiated. In the follow-up examinations, he had increased fever (39.1°C) and tremor. Muscular rigidity and hyperreflexia were detected in bilateral lower extremities. Serotonin syndrome was considered because of the patient's history and new onset symptoms. All medications were discontinued. The patient was started on external cooling, supportive therapy and cyproheptadine 2 mg/5 mL syrup. After 12 mg loading, 2 mg cyproheptadinewas given every two hours. The patient was admitted to the intensive care unit. On the second day of the follow-up, the fever of the patient decreased, his mental status became normal, also rigidity and hyperreflexia were resolved. He was discharged without any sequelae on the fifth day of hospitalization.

Discussion

Serotonin syndrome is a combination of symptoms caused by over activation at central and peripheral serotonin receptors secondary to high serotonin levels[1]. It is usually easy to skip the diagnosis because of mild symptoms attributed to the general side effects of drugs. The findings may range from mild constitutional symptoms to a life-threatening complex syndrome. In mild cases, tachycardia, tremor, mydriasis, sweating can be seen and usually no fever is observed. In moderate severity syndrome, hyperthermia (>40°C), hyperactive bowel sounds, horizontal ocular clonus, agitation can be seen. In severe cases, hyperthermia (exceeding 41°C), hemodynamic instability, muscle rigidity and delirium are seen. Hyperreflexia, rigidity and clonus are more prominent in the lower extremities[3].

In the literature, SS is reported as a diagnosis of exclusion. There is no diagnostic test to confirm the presence of the syndrome. The most important diagnostic stage is the clinician's suspicion. In the history, the initiation of a serotonergic drug, the dose change or the addition of other drugs should be questioned. Although many diagnostic criteria are described, Hunter Seratonin Toxicity Criteria (HSTC) has the highest sensitivity and specificity rates. According to the HSTC, in addition to the use of a serotoninergic drug, presence of one of the following criteria is efficient for the diagnosis; spontaneous clonus, inducible clonus plus agitation or diaphoresis, ocular clonus plus agitation or diaphoresis, tremor plus hyperreflexia, hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus[4]. Patients with peripheral hypertonus and trunk rigidity are at great risk for possible respiratory failure. Nonspecific abnormalities may also be observed in the laboratory results[1].

Neuroleptic malignant syndrome (NMS), malign hyperthermia, anticholinergic toxicity, sympathomimetic drug intoxication, encephalitis, heat stroke and central hyperthermia should be considered as the differential diagnosis. SS that is accompanied by hyperreflexia usually develops in 24 hours, however NMS which is accompanied by bradireflexia, has a slower onset that may extend to weeks. Anticholinergic toxicity is associated with hyperthermia, altered mental status and mydriasis, urinary retention and decreased bowel; but increased muscle tone and reflexes are not expected. An increase in end-tidal carbon dioxide level, widespread rigidity and hyporeflexia are observed in malignant hyperthermia, which may develop after exposure to inhalation anesthetics and depolarizing muscle relaxants. In other differential diagnoses, neuromuscular activation findings that was observed in SS are not expected[1, 3].

In a patient who is thought to have SS, all serotonergic agents should be discontinued and supportive treatment should be initiated. In most cases, symptoms are resolved within 24 hours. Affective sedation may be achieved with benzodiazepines if needed. In severe cases, cyproheptadine, which is a 5HT-2A receptor blocker, may be initiated. Although it provides symptomatic relief in mild to moderate cases, it does not shorten the duration of the recovery phase. The recommended starting dose is 12 mg and a 2 mg maintenance dose may be administered every 2 hours as long as the symptoms persist. Antipyretics are not useful because the fever in SS is dependent on increased muscle activity, not central[5].

Antipsychotic drugs, olanzapine and risperidone paradoxically both trigger SS and are reported to be used in the treatment of this syndrome. Since olanzapine is a 5HT-2A receptor antagonist, its use in treatment of SS is reasonable, but it is underlined that it may also cause SS in chronic use. Although the underlying mechanism is not clear in the literature, it has been reported that chronic olanzapine treatment may cause different interactions on the basis of receptors and neurotransmitters in each patient[6, 7].

Conclusion

Because of the widespread use of serotonergic drugs, it is important for clinicians to keep the SS in mind in patients with altered mental status, fever and neuromuscular hyperactivity. However, it should be remembered that early suspicion and early treatment may prevent from mortality and morbidity.

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