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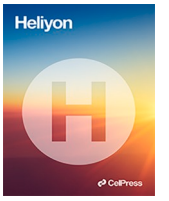

Case report

Successful Treatment of a Patient with brain tissue edema associated with Olanzapine overdose

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A B S T R A C T

Olanzapine is one of the atypical antipsychotic agents which is being increasingly used, and it is synthetic derivative of thienobenzodiazepine with antipsychotic, and antinausea, and antiemetic activities. Olanzapine overdose is mainly associated with the development of anticholinergic toxicity and is characterized by central nervous system (CNS) suppression, tachycardia, and delirium. As little is yet known about the effects of this agent in toxic doses, it is important to report the features of overdose. Herein, we reported a 28-year-old male with a history of mental illness and substance abuse, who was admitted in a comatose state with generalized tonic-clonic seizures. Head computed tomography (CT) and cerebrospinal fluid (CSF) analysis revealed significant cerebral edema and raised intracranial pressure, indicative of olanzapine-induced neurotoxicity. Management involved immediate cessation of olanzapine, administration of intravenous mannitol for cerebral edema, and supportive care. The patient's condition gradually improved with these interventions. Elevated olanzapine plasma concentration confirmed the diagnosis of overdose. Cranial pressure-lowering treatment has a certain effect on improving the condition of patients.

1. Background

Olanzapine, a new antipsychotic drug, is synthetic derivative of thienobenzodiazepine with antipsychotic, antinausea, and antiemetic activities and widely used to treat patients with schizophrenia and manic episodes [1]. Current reports indicate that olanzapine can cause acute peripheral edema in patients, affecting areas such as the foot, ankle, calf [2], eyelids [3] and face [4]. In some cases, it may even lead to generalized edema and pericardial effusion [5,6]. While the occurrence of olanzapine-induced cerebral edema is rare, it can result in symptoms like headache, nausea, vomiting, impaired consciousness, and in severe cases life-threatening symptoms [7].

This current study describes a 28-year-old male patient diagnosed with brain tissue edema associated with olanzapine overdose. Diagnosis of cerebral tissue edema and increased intracranial pressure was confirmed by cranial CT and cerebrospinal fluid (CSF) pressure measurement.

2. Case report

A 28-year-old male patient was discovered in a semi-conscious state at a train station on April 14, 2022, at 20:30. He was unresponsive to calls and manifested generalized tonic-clonic seizures. Additionally, he experienced profuse sweating, urinary

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incontinence, nausea and vomiting of coffee-colored liquid. Each attack of limb convulsion lasted approximately 4–5 minutes with intervals of around 2 minutes. The patient was promptly transported to the emergency department of Zhejiang Provincial People's Hospital by ambulance. Upon admission, his vital signs were recorded: temperature of 37.6 °C, respiration rate of 17 breaths per minute, pulse of 119 beats per minute, and blood pressure of 128/73 mmHg. Neurological examination revealed a coma with some response to painful stimuli, a Glasgow Coma Scale score of 5. The bilateral pupils were equal in size and round with sluggish direct and indirect light reflexes, neck stiffness, positive Kernig's sign, positive bilateral Babinski reflex, and uncooperativeness with the rest of the neurological examination. The patient was unaccompanied and unable to provide a detailed medical history. Drugs intoxication and neuroleptic malignant syndrome (NMS) were diagnosis first, since a bottle of lithium carbonate and an unidentified syringe were found near him. After stabilizing the patient's vital signs, various tests were conducted, including routine blood tests, lithium ion serum concentration measurement, head computed tomography (CT) scan, electroencephalo-graph (EEG). After contraindications were ruled out, a lumbar puncture was conducted on the patient, and a CSF pressure measurement catheter was utilized. A direct CSF pressure reading of 280 mmH_2O (normal range of 80–180 mmH_2O) was obtained and no evidence of intracranial infection were found through CSF test. The head CT scan revealed brain tissue edema (as shown in Fig. 1), and the EEG indicated diffuse slow background activity (as shown in Fig. 2). The patient underwent additional routine tests including biochemical, bacterial, blood routine, renal function, and thyroid function tests, but no significant abnormalities were found.

With the assistance of the police, we contacted the patient's family and discovered that the patient had a history of mental disorder and was taking 10mg of olanzapine daily exceeding six months. Additionally, the patient had a history of multiple drug abuse and had received treatment at drug rehabilitation centers in the past. For a long time, the patient had been taking 300mg of lithium carbonate three times a day. There was no record of head trauma or epilepsy in the patient's medical history. We conducted urine tests for methamphetamine, ecstasy, morphine, ketamine, and cannabis, all of which came back with negative results. We also measured the blood concentration of olanzapine.

We administered mannitol 125ml intravenously every 8 hours to reduce intracranial pressure according to the increased intracranial pressure and the signs of head CT. After one day of treatment, the patient's consciousness improved to a drowsy state, but he still manifested manic and partial seizure-like episodes (Video). By the second day, his consciousness had returned to normal, and the patient insisted on being discharged. On the third day, we received the results of the blood drug concentration test of lithium carbonate and olanzapine. Utilizing inductively coupled plasma mass spectrometry (ICP-MS), the serum lithium ion concentration was determined to be 0.17 μg/ml (within the range of 4.00–8.00 μg/ml). In parallel, liquid chromatography-tandem mass spectrometry (LC-MS/MS) revealed the serum olanzapine level to be 168.0 ng/ml (higher than the normal range of 20.0–80.0 ng/ml), indicating olanzapine intoxication. Communicate with the patient over the phone, we advised him to discontinue the use of olanzapine and stop taking the culprit drug.

3. Discussion

This article focuses on a patient who has been taking antipsychotic drugs for a long time and experiencing symptoms such as coma, generalized tonic-clonic seizures, fever, and tachycardia. Various tests were conducted to assess the patient's blood routine, white blood cells, C-reactive protein (CRP), procalcitonin, arterial blood gas, thyroid function, electrolytes, liver and kidney function, and protein content in CSF. All the results were within the normal range, and the head CT scan showed no abnormal occupying lesions, ruling out severe electrolyte imbalances, hepatic encephalopathy, renal encephalopathy, thyroid toxicosis, as well as conditions such as head trauma, intracranial tumors, hemorrhagic or ischemic strokes, bacterial or viral encephalitis/meningitis, and hypoxic brain injury. Moreover, the absence of specific laboratory markers, including elevated leukocyte counts and serum creatinine phosphokinase levels, does not substantiate a diagnosis of NMS [8]. Combining the patient's head CT, EEG, and other examinations, and the significant improvement in consciousness within one day after discontinuing olanzapine and receiving intracranial pressure reduction treatment, supported the diagnosis of cerebral edema. Considering the patient's history of taking 10mg of olanzapine daily and 300mg

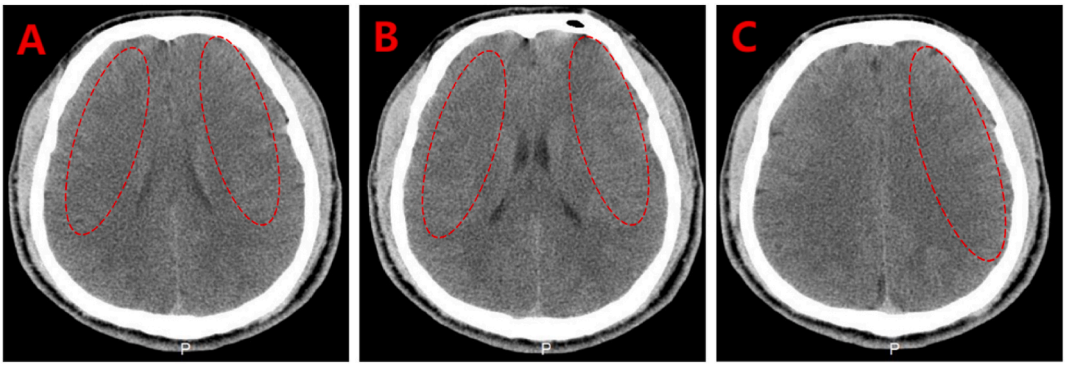

Fig. 1. The cranial CT of the patient.
The findings from figure A, B and C indicate a slightly hypodense brain parenchyma with poorly delineated gray and white matter, suggesting the presence of possible cerebral edema.

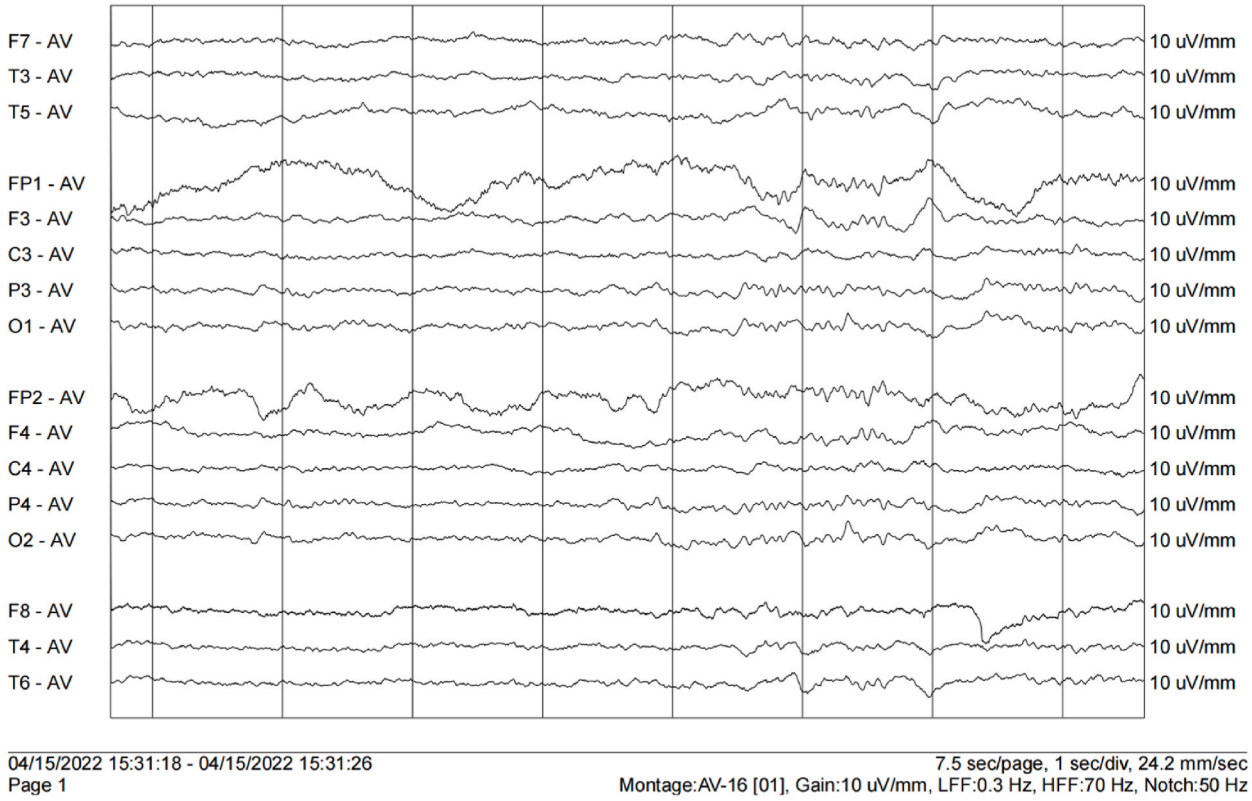

Fig. 2. The EEG of the patient.
Background activity: no typical alpha rhythm was seen in the occipital region bilaterally when the eyes were quietly closed, and each lead was dominated by a mixture of multiple 4–7 Hz, 40–60 μV theta waves and a small number of 2–3 Hz, 60–80 μV delta waves. The left and right sides are basically symmetrical. **Fast wave:** each conductor emits a small amount of 15–20 Hz low amplitude β waves. Wave **amplitude characteristics:** low-moderate wave amplitude. **Hyperventilation:** HV cannot cooperate. **Abnormal waves:** no typical epileptiform discharges such as sharp waves and spikes are seen. Seizure **phase: no** seizures. **Somatosensory:** stimulation of both upper limbs separately, EEG visible reactivity.

of lithium carbonate three times a day exceeding six months, we suspected intoxication from these drugs. The blood drug concentration results confirmed our suspicion, as the blood concentration of olanzapine was more than twice the upper limit of the normal maintenance concentration, indicating olanzapine intoxication. Surprisingly, low concentration of lithium ion was detected. The final clinical diagnosis was isolated brain edema induced by an overdose of olanzapine.

Olanzapine-induced peripheral edema has been documented in multiple cases [9]. The mechanism behind olanzapine-induced edema may involve increased blood viscosity, resulting in thrombosis and obstruction of blood circulation in the affected area, commonly observed in the lower extremities. The elevation of cyclic-phosphate adenosine (CAMP) and the blockade of the 5-HT2 receptor through increased CAMP can also lead to vasodilation and edema [10], which might explain the brain tissue edema.

4. Conclusion

High concentrations of olanzapine may result in brain tissue edema. Early recognition and treatment of drug-induced cerebral edema are paramount to preventing long-term neurological sequelae and improving patient outcomes. Future research should aim to elucidate the underlying mechanisms of olanzapine-induced edema and explore effective therapeutic strategies to mitigate its adverse effects.

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Ethics approval and consent to participate

The of the research ethics and informed consent to our manuscript.

CRediT authorship contribution statement

Houwen Zhang: Writing – original draft. **Fangzheng Cao:** Investigation. **Sheng Zhang:** Resources. **Zhongxiu Wang:** Methodology. **Chunrong Li:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Chunrong Li reports financial support was provided by Zhejiang Provincial People's Hospital. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30201.

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