Severe Acidosis Followed by Withdrawal Delirium and Dystonia-like Movement after Clozapine Overdose

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**Background:** Due to receptor-binding complexity of clozapine, the symptoms of its overdose and withdrawal are complicated and vary greatly in different patients. **Case Report:** The case report describes a schizophrenic patient who took 5,000 mg clozapine in a suicidal attempt. He suffered from metabolic acidosis, generalized tonic and clonic seizures with respiratory failure. The patient regained clear consciousness after clozapine was withheld. Delirium, dystonia-like movement and rebound psychosis emerged on the 4th day. Clozapine withdrawal was the most likely the cause, and above-symptoms were improved gradually after clozapine was reloaded. **Conclusion:** We suggest that clozapine overdose may lead to lactic acidosis even without the complications of hypotension and respiratory failure. Several mechanisms are attributed to the various presentations of clozapine withdrawal. The manifestations in our patient underscored the risk of severe acidosis after clozapine overdose and the importance of prevention of clozapine withdrawal.

**Keywords:** clozapine, lactic acidosis, intoxication, withdrawal


**Introduction**

Clozapine is effective in treating patients with treatment-resistant schizophrenia. Due to clozapine's receptor-binding complexity, the symptoms of its overdose and withdrawal vary greatly in patients. The overdose of clozapine is also more life-threatening than that of other antipsychotic drugs [1, 2], and is an emergency condition.

We present a case of a young male schizophrenic patient who took 5,000 mg clozapine in a suicidal attempt. He subsequently suffered from a life-threatening condition and developed delirium, dystonia-like movement and rebound psychosis after medication cessation.
Case Report

This 33-year-old male patient was diagnosed with schizophrenia at the age of 22 years, with the initial presentation of auditory hallucinations, persecutory delusion, and depressed mood. He was frequently hospitalized due to suicidal attempts but had poor response to several antipsychotic drugs and electroconvulsive therapy. He began taking clozapine at age of 29 years, but psychotic symptoms were still waxed and waned even with his good drug adherence. Before the overdose, his treatment regimen consisted of daily clozapine 500 mg and haloperidol 5 mg.

At the age of 33 years, the patient was estimated to take more than 5,000 mg clozapine only in this suicidal attempt according to the remaining amount of his medication and the family's report. He was immediately sent to emergency department, where he was found to be fully conscious with stable vital signs. But he lost consciousness after having three episodes of generalized tonic and clonic seizures which occurred about at around 45 to 70 minutes after his taking clozapine. He received gastric lavage and supportive treatment immediately, and regular dosage of clozapine was withheld. Blood samples obtained before the onset of generalized tonic and clonic seizures, showed severe high anion gap metabolic acidosis with respiratory acidosis (pH: 6.881, PCO2: 78.6 mmHg, PO2: 72 mmHg, BEecf: -18 mmol/L, HCO3: 14.7 mmol/L, anion gap: 26.1). Brain CT revealed negative findings. Due to shock and respiratory failure, the patient was intubated and a physical examination was done to rule out possible etiologies of high anion metabolic acidosis including hyperglycemia (blood sugar: 170 mg/dL). The impression was lactic acidosis (lactate: 4.2 mmol/L). Extubation was performed on the second day of hospitalization when he was clear in consciousness without obvious psychotic symptoms.

On the 4th day, the patient developed delirium, dystonia-like movement and severe sweating. Because of more expressed fragmented paranoid ideation in this period, the exacerbated psychotic symptoms were also speculated. The symptoms of delirium and dystonia-like movement were improved gradually after reloading of clozapine, the course of delirium had lasted for five days. Suspected causes of his delirium include the sequel of the metabolic acidosis or seizure attack, but he did not show any specific findings in the results of blood cell count, basic chemical tests and electroencephalography. Most likely, delirium was a clozapine withdrawal syndrome under the consideration of the complicated symptoms of dystonia, severe sweating after an abrupt clozapine withholding.

Due to persistent psychosis, the patient's treatment regimens were adjusted to clozapine 400 mg/day and sulpiride 400 mg/day after discharge. The psychotic symptoms were improved mildly under the regimen.

Discussion

The presentation of clozapine overdose in this patient consisted of generalized tonic and clonic seizures, respiratory suppression, coma and severe metabolic acidosis. The common clinical manifestation includes cardiovascular (tachycardia and hypotension, rarely dysrhythmia), neurological (drowsiness, lethargy, confusion, disorientation, delirium, coma, seizure, and areflexia), and autonomic (hypersalivation, mydriasis, blurred vision, respiratory depression, and hypothermia) signs and symptoms (www.thomsonhc.com/micromed) [2]. The overall mortality was about 12%. 
No specific antidote exists for clozapine overdose, and supportive treatment is needed [1]. Based on the findings of the limited data and reports of metabolic acidosis following clozapine overdose, we suggest that the cause of which is mainly by due to lactic acidosis secondary to the event of hypotension, hypoxia or hyperglycemia [3]. But in our patient, the initial blood sample was collected before the seizures and hypotension occurred, raising the question whether the clozapine overdose itself led to lactic acidosis through an unknown mechanism.

In our patient, the presentation of clozapine withdrawal included delirium, dystonic-like movement, sweating and rebound psychosis. The multi-receptor profile of clozapine appears to be responsible for the withdrawal symptoms, suggesting specific mechanisms, include cholinergic rebound, dopaminergic supersensitivity (a special role of D$_4$ receptors) and the possibility of serotonergic, noradrenergic and GABA-ergic involvements [1, 4].

The presentation of cholinergic rebound may be mild, with the symptoms or signs such as nausea, vomiting, diaphoresis, restlessness, insomnia, or flu-like symptoms [5]. But it can also be severe enough to affect the central nervous system, presenting as consciousness change or delirium [5]. But the evidence also existed to show that agitation, diaphoresis, fever, mental status change and shivering, may also be attributed to serotonin rebound due to the 5-HT$_{2A}$ antagonistic property of clozapine [6].

Our patient had also dystonic-like movement after abrupt clozapine withdrawal. In the literature, only one case series report describes clozapine withdrawal-emergent dystonia and dyskinesia [7], in which the subjects were reported to have exhibited severe dystonia after clozapine withdrawal that lasted for 5-14 days and improved after reloading of clozapine.

The risk of rapid exacerbation of psychosis after withdrawal of clozapine appears greater than after withdrawal of classical antipsychotic agents. Some withdrawal psychosis has been reported in people without a psychiatric history [8], and it appears that psychosis may be a feature of drug withdrawal rather than the re-emergence of an underlying illness. Mechanisms of rebound psychosis may be related to adaptation of the brain to long-term drug use, but exploratory studies are scarce [9]. The rebound psychosis in our patient could be attributed to multiple etiologies including unremitting delirium due to cholinergic rebound, the refractory status of schizophrenia itself, and dopamine supersensitivity [8, 9].

Besides, the combined use of clozapine and sulpiride use is based on the evidence of previous placebo control trial [10]. The better treatment response of this combined use can be explained by the selective enhancement of D$_3$ blockage by sulpiride [11, 12].

The clinical manifestations in this patient underscored the risk of severe acidosis after clozapine overdose even without hyperglycemia and the importance of prevention of withdrawal when clozapine use is stopped abruptly.

References

Clozapine Intoxication and Withdrawal


