American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e929147
DOI: 10.12659/AJCR.929147

Received: 2020.10.12
Accepted: 2020.12.04
Available online: 2021.01.05
Published: 2021.02.16

Successful Treatment of an Acute High-Dose Clozapine Poisoning without Detoxication

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 28-year-old
Final Diagnosis: Clozapine poisoning
Symptoms: Drowsiness • hyperventilation • impaired consciousness • respiratory insufficiency • tachycadia
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine • Psychiatry

Objective: Management of emergency care

Background: Clozapine is a well-proven atypical antipsychotic drug used for therapy of treatment-resistant schizophrenia. Over the last decades only a few cases of clozapine poisoning have been reported. Hence, guidelines for in-hospital management are currently not available.

Most of the reported cases underwent detoxication measures as charcoal therapy and/or gastric lavage. However, there is no evidence for primary detoxication to improve clinical outcome. In contrast, use of therapy with intravenous physostigmine in the case of anticholinergic syndrome is restricted due to concerns about safety and dosing.

We present a case of acute high-dose clozapine poisoning without detoxication and complete recovery supported by physostigmine.

Case Report: We report the case of a 28-year-old man with prior diagnosed schizophrenia who presumably ingested 8 g (regular maximum daily dose 900 mg/d) of clozapine with uncertain intent. Initial computed tomography (CT) showed pulmonary infiltrates and widespread pneumomediastinum and soft-tissue emphysema of unknown genesis.

The patient developed a progressive impairment of vigilance and respiratory insufficiency requiring invasive artificial ventilation for 31 h. Afterwards, an anticholinergic syndrome led again to impaired vigilance, tachycardia, and hyperventilation.

To avoid risks associated with artificial ventilation, we applied physostigmine. Subsequently, the anticholinergic syndrome and the pneumomediastinum completely regressed and no further artificial ventilation was needed.

Conclusions: Based on the presumably ingested dosage, we present the likely highest reported nonfatal overdose of clozapine without detoxication. Additionally, we observed widespread pneumomediastinum as an uncommon complication.

Our approach was to refrain from detoxication to minimize complications and to treat early with physostigmine because of anticholinergic syndrome to minimize its impact and to avoid artificial ventilation due do vigilance impairment.

Keywords: Anticholinergic Syndrome • Clozapine • Physostigmine • Poisoning

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/929147

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Background

Clozapine is an established atypical antipsychotic drug used for treatment of schizophrenia. In contrast to conventional neuroleptics, it rarely provokes extrapyramidal adverse effects. Several poisoning-associated symptoms like impaired vigilance, agitation, tachycardia, renal failure, and pulmonary complications such as aspiration pneumonia have been reported [1-3]. Few (and mostly nonfatal) cases of clozapine poisoning have been reported that included detoxication as a management option [1-6]. As clozapine poisoning is uncommon, guidelines for in-hospital management are not available.

We present an acute clozapine poisoning case, with likely the highest reported dose (presumably 8 g) and survival without detoxication.

Case Report

A 28-year-old man with schizophrenia and suspected high-dose clozapine poisoning was admitted to our Emergency Department. The patient had a legal guardian with whom he usually had daily contact. The guardian alerted the police because he could not reach the patient any more. Before admission, the patient was found in his apartment with impaired vigilance of unknown duration without evidence of physical trauma. The emergency medical service found 8 depleted blisters of clozapine (10 tablets per blister, 100 mg/tablet, total 8 g) next to him, presumably ingested, with unclear intent. There were no signs of preceding emesis.

At initial clinical examination, the patient was somnolent with reduced Glasgow coma scale of 11 points, sinus tachycardia (130/min), and hypertension (157/93 mmHg). After consultation with the central emergency poisoning center, a watch and wait strategy including symptomatic therapy was recommended. Cranial computed tomography (CT) was performed without detection of cerebral pathologies. Thoracic CT showed pulmonary infiltrates and atelectasis on both sides. As an incidental finding, a widespread pneumomediastinum and soft-tissue emphysema of unknown genesis was diagnosed (**Figure 1**).

Laboratory findings revealed rhabdomyolysis and a crush syndrome with acute renal failure AKIN II (creatinine=188 µmol/l, myoglobin=6231 µg/l, creatine kinase=367 µkat/l), possibly triggered by the clozapine poisoning. Urine investigations showed no evidence of other drugs.

During the initial hours in the Emergency Department, the patient developed a progressive impairment of vigilance and respiratory insufficiency (GCS=7, peripheral oxygen saturation via pulse oximeter < 90% despite oxygen insufflation via nasal cannula and respiratory rate of 26 per minute) requiring invasive ventilation. The patient initially had no fever. Bronchoscopy and esophagogastroduodenoscopy remained without evidence of an anatomical air leakage.

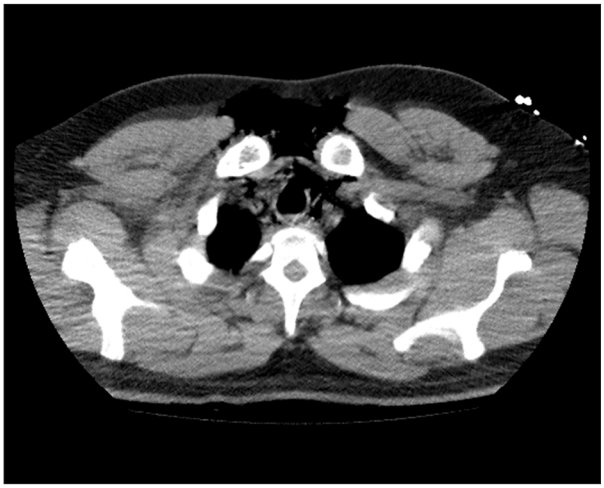

Figure 1. Thoracic CT at day 1: Pneumomediastinum and soft-tissue emphysema.

Based on the initial SOFA score of 15 points, sepsis caused by a community-acquired bilateral pneumonia was diagnosed and treated with Piperacillin/Tazobactam according to the guidelines for management of sepsis.

Approximately 10 h after hospital admission, the patient was admitted to our Intensive Care Unit (ICU). Upon arrival at the ICU, the patient was found to be in septic shock, requiring vasopressors. However, vasopressors could be tapered after sufficient fluid supplementation. Subsequently, the patient became hypertensive and developed moderate tachycardia. Therefore, sodium nitroprusside was required.

After successful respiratory, weaning the patient was extubated after 31 h of invasive ventilation and respiration remained stayed thereafter. The subsequent period of drowsiness (Richmond Agitation-Sedation Scale-2), tachycardia, hypertension, inadequate communication, and hyposalivation was interpreted as an anticholinergic syndrome and treated by intravenous physostigmine. Afterwards, the patient became more awake (Richmond Agitation-Sedation Scale 0), and his tachycardia and hypertension resolved.

The therapy with physostigmine was guided by vital signs and clinical symptoms (drowsiness, salivation, and sweating) and was stopped after a cumulative administration of 21 mg and 2 days of treatment.

At day 6 of hospitalization, a follow-up CT was performed. The pneumomediastinum and soft-tissue emphysema were

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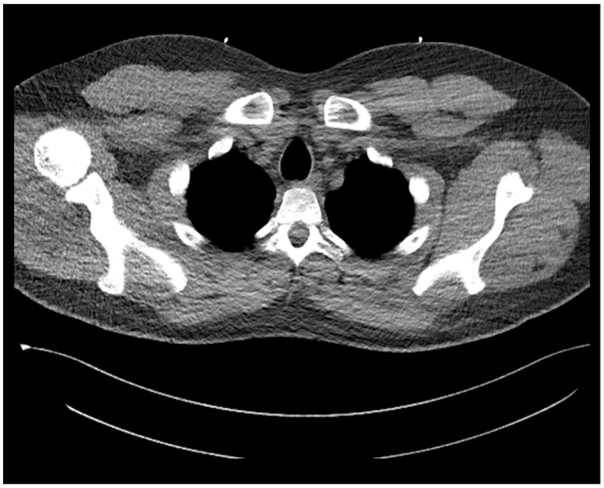

Figure 2. Thoracic CT at day 6: Pneumomediastinum and soft-tissue emphysema completely regressed.

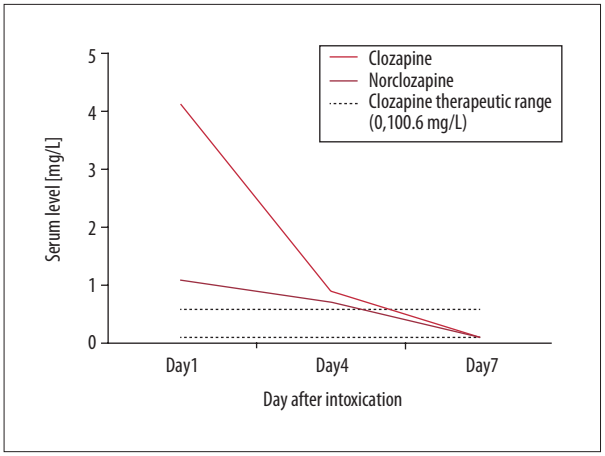

Figure 3. Serum levels of clozapine and major metabolite norclozapine at days 1, 4, and 7 after poisoning.

completely regressed. The pneumonia was clinical and paraclinical in healing process (**Figure 2**).

Retrospective serum clozapine analysis revealed the clozapine level had decreased from toxic to therapeutic at day 4 (**Figure 3**).

After consultation with our psychiatrists on day 6 after poisoning, the patient was directly transferred to the Psychiatry Department. The patient confirmed the clozapine intake without a clear statement concerning the doses, but he denied a suicidal intention.

At the day of transfer, the patient was completely awake (Richmond Agitation-Sedation Scale 0) and oriented, in good general and respiratory condition, without need for oxygen supply. Laboratory findings showed a regression of renal failure, rhabdomyolysis and inflammation (creatinine=78 µmol/l, myoglobin=145 µg/l, white blood count=10.5 GPt/l).

Discussion

In recent decades only a few and mostly nonfatal cases of clozapine poisoning have been reported, all including detoxification measures [1-6]. Different factors may be responsible for this low incidence. A leading cause may be the restricted and supervised use of the drug [4]. Clozapine is not a first-line therapy, but is reserved for treatment-resistant schizophrenia. Furthermore, weekly laboratory examinations are recommended, especially at the beginning of therapy, to exclude agranulocytosis [7]. This supervision helps maintain patient medication compliance, particularly in case of adverse effects. Most adverse effects disappear during the initial 4-6 weeks of treatment due to the development of tolerance [8,9]. Based on this clinical experience, some authors postulate greater toxicity in patients with acute clozapine poisoning who have not been exposed to it previously [4,10]. The evidence and pathophysiology of this hypothesis remain uncertain.

As clozapine poisoning is uncommon, guidelines for in-hospital management are not available. Therefore, our therapy was based on an evidence-based consensus guideline for out-of-hospital management as well as several position papers published by the European Association of Poison Centers and Clinical Toxicologists and the American Academy of Clinical Toxicology [11-14].

Specific antidotes for clozapine are not available. In general, treatment measures are mostly limited to symptomatic therapy such as monitoring, airway management, and intravenous fluids in case of hypotension [14]. In previous case reports, detoxication with activated charcoal therapy and gastric lavage were performed and recommended [1,3,4,15]. These treatment measures need to be discussed critically. Firstly, there is no evidence that primary detoxication by charcoal therapy and gastric lavage improves clinical outcome [11,12,14]. Secondly, especially in clozapine poisoning, depressed levels of consciousness are common, so charcoal therapy and gastric lavage are contraindicated in case of unprotected airways [11,12]. Thirdly, secondary detoxication measures such as forced diuresis and renal replacement therapy are ineffective because of the mostly hepatic metabolism of clozapine [15].

Based on this knowledge, we decided against performing established primary and secondary detoxication. In addition, unlike previously reported complications, our patient suffered a widespread pneumomediastinum of unknown genesis. Retrospectively, it was most likely caused by emesis. This circumstance supports our restrictive management regarding detoxication.

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To date, the highest reported oral intake of clozapine was 16 g [4] and the highest reported serum peak level was 9100 ng/ml [3]. Both cases were nonfatal and treated with activated charcoal therapy and/or gastric lavage. Based on the presumably ingested dosage (8 g), our case is the likely highest reported nonfatal overdose of clozapine without applying detoxication measures but with complete recovery of the poisoning-associated effects of pneumonia, rhabdomyolysis, and anticholinergic syndrome.

Rhabdomyolysis is known to be caused by different drug intoxications and has been also reported in clozapine overdose, as indicated by elevated creatinine kinase levels [16]. Usually, causal associations between drugs and adverse events are based on clinical judgement [17]. To enable a more objective assessment of adverse drug reactions, Naranjo et al designed a probability scale [17]. According to this, rhabdomyolysis in our patient was possibly (4 points) related to clozapine [17]. However, in our case, immobilization and infection may also be contributing factors for the development of rhabdomyolysis. Considering these causes, our treatment focused on discontinuation of clozapine and administration of anti-infective therapy supported by fluid supplementation.

Another serious complication following clozapine poisoning is anticholinergic syndrome. The pharmacological property of clozapine provides antipsychotic effects mainly by inhibition of dopamine D4-receptors [18]. In contrast, lower affinity to D2 and other dopamine receptors minimizes the incidence of extrapyramidal adverse effects [18]. However, due to inhibition of muscarinic receptor M1, clozapine may induce anticholinergic adverse effects which may aggravate to an anticholinergic syndrome [18,19]. Several studies supported cholinesterase inhibitors for treatment of anticholinergic syndrome [19-22]. However, only physostigmine can cross the blood-brain barrier and thereby antagonize central as well as peripheral anticholinergic effects [23]. Nevertheless, its use is limited due to concerns about safety and dosing, although most adverse effects are avoidable by conservative dosing strategies [19].

In our patient, we detected peripheral and central nervous system symptoms like mydriasis, tachycardia, and delirium. As the non-pharmacological delirium therapy remained ineffective, we decided to apply physostigmine for diagnostic as well as therapeutic reasons. Within several minutes, the patient showed improved vigilance and thereby confirmed our diagnosis of an anticholinergic delirium. However, physostigmine has a rapid plasma elimination, which resulted in recurrence of depressed consciousness. To avoid the need for invasive airway management, we continued the therapy with physostigmine, leading to complete physical recovery without adverse effects.

Conclusions

The present case suggests that relying on a symptomatic therapy without detoxication, even in cases of an acute high-dosage clozapine poisoning, can be sufficient.

In patients with refractory delirium and peripheral anticholinergic signs (eg, mydriasis, hyposalivation, dry skin) with suspected anticholinergic syndrome, we tend to recommend early treatment with physostigmine as a diagnostic and therapeutic approach. Physostigmine may shorten the time to recovery and lower the incidence of complications compared to invasive airway management. Drug administration should be monitored by ECG and antagonized by atropine in case of adverse effects (eg, bradycardiac arrhythmias).

Physicians should also be vigilant for uncommon complications such as a pneumomediastinum that might be caused by unprovoked emesis.

Conflict of Interest

None

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