CASE REPORT

Successful Management of Acute Antipsychotic Poisoning Induced Multi-Organs Toxicities: A Case Report and Review of Literature

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Abstract

Atypical antipsychotics were usually used in management of many psychiatric disorders. Moreover, suicidal attempts by antipsychotic agents are not rare in clinical practice. Therefore toxicologists should be aware of the early detection and management of those patients. Clozapine is one of the most commonly used antipsychotic drugs due to its well-known efficacy.

Case Presentation: This is a case report of a young previously healthy male patient, who committed suicide by the ingestion of 1000 mg of the atypical antipsychotic drug clozapine. The case highlights the development of severe disturbed level of consciousness, extrapyramidal adverse effects, prolonged QTc with positive troponin, hypokalemia, hyperglycemia, transient hypertension, and elevated liver transaminases.

Discussion: The proper treatment initiation of acute antipsychotic poisoning should be based on the patient's clinical assessment. Early central nervous system and cardiovascular support are the core treatment element. However, the case reported uncommon electrolyte and hepatic disturbances which require early detection and monitoring.

Conclusion: Atypical antipsychotics are not usually a safe treatment option for psychiatric diseases. Acute clozapine poisoning is a serious condition in which early resuscitation is essential for good prognosis. Serious cardiac and metabolic adverse effects should be considered, early investigated and properly monitored. Serum drug level might not be helpful prognostic indicator for acute antipsychotic poisoning.

Keywords: Atypical Antipsychotics, Clozapine, Clozapine Level, Successful Management.

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INTRODUCTION

Second generation or atypical antipsychotics (SGAs) are preferred to be used in the management of many psychiatric disorders due to their high efficacy [1]. Atypical agents have wide receptor occupancy compared to typical agents; therefore, they are claimed to have many adverse effects. In addition to neurological and cardiovascular disturbances, metabolic effects were reported particularly hyperglycemia, dyslipidemia, diabetes mellitus, and blood pressure changes [2]. Moreover, acute poisoning of SGAs due to underlying suicidal tendencies is not rare [3]. In acute poisoning, early detection and management of the variable unexpected side effects is a challenge. The current case report is an interesting example of multiple adverse effects associated with acute clozapine poisoning. The case highlights infrequent metabolic and hepatic disturbances with special concern for their proper management.

CASE PRESENTATION

A 24-year-old single male patient was found unconscious in his room with two empty strips of the antipsychotic medication; he was brought by his family to the Poison Control Center of Alexandria Main University Hospital, Egypt. The family alleged suicidal attempt by around 10 to 15 tablets of clozapine (100mg), which the patient recently brought to help him in his sleeping troubles. By taking history from the family; the patient was

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previously healthy till a month ago, when he started to develop anxiety disorder and a friend advised him that clozapine would be helpful to control his insomnia. There was no other relevant medical or surgical history.

Upon arrival at the emergency room, 2 hours after the alleged drug ingestion, the patient was unconscious. The Glasgow coma scale was 7; Eye opening to pain (2), Flexion response to pain (3), sounds (2). Sialorrhea was obvious. The pupils were constricted and sluggish reactive to light bilaterally.

Vital signs were assessed, where blood pressure was 150/80 mmHg, heart rate was 150 beats per minute, respiratory rate was 30 breaths/min and temperature was 37.5. The chest examination showed diminished air entry bilaterally with transmitted nasal sound. An arterial blood gases (ABG) analysis showed that; pH=7.45, PCO2= 33.8mmHg, PaO2= 95.8mmHg, HCO3 23.3mEq/l and O2 saturation 95%. Abdominal and extremities examinations were unremarkable.

A cardiac examination was done; 12 leads electrocardiogram revealed sinus tachycardia with a rate of 150 beats/ min, PR interval=0.16, QRS duration=0.08, QT segment duration was 0.36 and corrected QT was calculated using Bazzet formula (QTC = QT / √ RR) where QTc was markedly prolonged and equaled 0.5, ST segment= 0.28 and T wave was normal.

In the resuscitation room, the patient was intubated, a nasogastric tube was inserted; gastric lavage was performed, and activated charcoal (50 grams) was given. Continuous cardiac monitoring was started for fear of fatal arrhythmia. The patient was given 500cc of crystalloid hydration then was shifted to the ICU on a mechanical ventilator.

At ICU, the pulse rate was 145 beats per minute and blood pressure was 140/80 mmHg. Follow-up ABG was done; pH: 7.48, paO2: 126, pCO2: 30, HCO3: 21and O2 saturation 99.7%. The blood workup was done as shown in the table (1). Hyperglycemia, hypokalemia, positive cardiac troponin (HScTnI), and elevated aspartate and alanine serum transferases (AST and ALT) were found. A blood sample was taken after 3 hours of the alleged drug intake and it was sent for toxicological analysis by Gas chromatography - flame ionization detector (GC-FID), the diagnosis was confirmed as positive clozapine but unexpectedly the serum concentration of clozapine was 175.6 ng/ml.

At the ICU, 3 ampoules of potassium chloride were given to correct hypokalemia after that, follow-up ECG showed improvement of sinus tachycardia and QTc=0.46. The consciousness level started to improve with fluid therapy and multiple-dose activated charcoal. The patient was weaned from the ventilator after 24 hours at that time the GCS was 13; spontaneous eye opening (4), obey commands (6), inappropriate words (3). Dysarthria, hallucinations and agitation were evident. After exclusion of Neuroleptic malignant syndrome by clinical and laboratory investigations; the patient was indicated for benzatropine administration. Cogentin 2mg was added by a dose of one

Table 1. The laboratory investigations of the patient along the three days of the hospital stay.

Laboratory investigation	First day	Second day	Third day	Reference range
Hemoglobin	12.9 g/dl (normal)	-	-	11–14 g/dl
Total leukocyte count	16,000/dl (elevated)	-	-	5,000–15,500/dl
Platelet count	299,000/dl (normal)	-	-	150,000–450,000/dl
Arterial blood gases (ABG)	pH=7.45, PCO2=33.8, PaO2=95.8, HCO3=23.3, O2 sat.= 97%.	pH=7.48, PCO2=28.2, PaO2=126, HCO3=21, O2sat.=99.7%.	pH= 7.42, PCO2=36.3, PaO2=110.9, HCO3=23.3, O2sat.=98.2%	pH=7.35-7.45 PCO2=35-45 mmHg PaO2=60-100 mmHg HCO3=22-26
Blood urea nitrogen	13 mg/dl (normal)	-	-	7-18 mg/dl
Serum Urea	28 mg/dL (normal)	-	-	19–42 mg/dl
Serum creatinine	1.1 mg/dL (normal)	-	-	0.55–1.1 mg/dl
Serum Sodium	140 mmol/L (normal)	142 mmol/L	140 mmol/L	136–145 mmol/L
Serum Potassium	2.8 mmol/l (low)	3.2mmol/l	3.8mmol/l	3.5-5.1 mmol/l
Random blood sugar	140 mg/dl (elevated)	115mg/dl	105mg/dl	74-106 mg/dl
Alanine transaminase (ALT)	80 U/l (elevated)	72 U/l (elevated)	46 U/L (normal)	10-49 U/L
Aspartate transaminase (AST)	60 U/l (elevated)	52 U/L (elevated)	32 U/L (normal)	15-37 U/L
CK total	68 U/L (normal)	204 U/L (elevated)	59 U/L (normal)	0-195 U/L
CKMB	5ng/ml	3.7 ng/ml	0.00 ng/ml	0-5 ng/ml
HS c troponin	2.5 (positive)	0.0047 ng/ml	0.0015 ng/ml	0-0.047 ng/ml
Serum clozapine level (By GC-FID)	175.6 ng/ml	-	-	350-500ng/ml (therapeutic dose)

GC-FID: Gas chromatography- flame ionization detector

DISCUSSION

on the second day.

Due to the elevated liver enzymes, the consultation with a hepatologist and exclusion of any medical hepatic disease was done, drug-induced liver insult was diagnosed; follow-up on liver enzymes was done on the next day and the levels were declining. After four days of hospital admission, the patient was discharged after complete recovery.

The article presents an interesting case of acute clozapine poisoning. Clozapine is an atypical antipsychotic drug; the mechanism of action of this drug is mainly by blockage of dopamine (D2) receptors. However, atypical agents have additional effects on serotonin, alpha-1 adrenergic, muscarinic, and histamine receptors [4]. Therefore, recent research studies accuse those drugs of having several metabolic, cardiac, and other long-term effects, especially in chronic use [5].

From the toxicological clinical point of view, acute poisoning is an emergency in which the most important step is early and effective management. The central nervous system is the most significant concern in the poisoning of those drugs; therefore early assessment of the Glasgow Coma Scale (GCS) is essential [6]. In the present case, the patient GCS was a severe (score points 7) in addition to the massive sialorrhea, which is a risk for aspiration pneumonia so the patient was indicated for endotracheal intubation [7].

Although clozapine is not frequently associated with extrapyramidal side effects like the typical agents do [8] , the present case developed dysarthria and restlessness, which are considered parts of the movement disorders of extrapyramidal syndrome, the symptoms were improved by the addition of benztropine that coincide with Pringsheim et al 2011[9].

Cardiovascular (CV) toxicity and sudden cardiac arrest have been increased among psychiatric patients and sometimes it is linked to antipsychotic medications [10]. Therefore, a cardiac examination should be a core element in the examination of those patients. In the present case, the patient developed evident cardiotoxicity, where hypertension, sinus tachycardia, prolonged QTc, and positive cardiac troponin were present.

Clozapine is known to be associated with orthostatic hypotension. However, transient hypertension with acute clozapine poisoning was described in the literature. (11) The mechanism proposed for that is its strong alpha-adrenergic blockade property, increased catecholamine and myocarditis [11]. Rapid drug elimination was helpful in the correction of hypertension as noticed in the present case [12].

Nowadays, sudden cardiac arrest among patients using antipsychotics is frequently reported [13]. In the present case, QTc was markedly prolonged (0.5); QTc prolongation is associated with an increased risk of torsade de pointes and fatal ventricular arrhythmias which require close cardiac monitoring [14]. Due to the effect of SGA on potassium channels of the heart, the role of electrolyte disturbance should not be neglected during the management of cardiac toxicity [10].

Hypokalemia was detected and the correction of potassium level helped in the improvement of sinus tachycardia and hypertension [15]. Although, many scholars argue that the mechanism of hypokalemia is still unclear. In acute poisoning, it could be explained by the catecholaminergic surge and the increase of insulin level mediated by alpha 2 adrenergic receptors with subsequent potassium shift from the outside to the inside of cells [15].

Cardiac troponins are widely used for the detection of drug-induced cardiac insult [16]. Myocarditis is reported to be a rare complication which occurs with clozapine use [17]. Despite being rare, myocarditis should not be excluded in the present case especially in the presence of positive cardiac troponin. Furthermore, echocardiography, if available, might be helpful to confirm myocarditis by revealing regional wall-motion abnormalities. However, echocardiography might be unhelpful in the presence of less extensive disease [18].

Metabolic syndrome is recently claimed to be linked to the chronic use of the new antipsychotics [19]. In addition, acute poisoning of clozapine can result in impaired glycemic control, which coincides with the finding of the current case [20]. Several factors are postulated to contribute to hyperglycemia in chronic use, such as increased appetite, and insulin resistance [5]. However, clozapine-induced acute-onset hyperglycemia is relatively difficult to be explained by this theory [20]. In acute settings, the anticholinergic effect of clozapine in addition to the oxidative stress process and mitochondrial damage of pancreatic insulin-secreting cells could be a possible explanation for hyperglycemia [20].

The exact onset of clozapine-induced hepatic impairment is unknown, but evidence of its hepatotoxicity is supported by other case reports [21, 22]. The mechanism could be explained by clozapine-induced disturbance of cytochrome p450 IA2 enzyme activity. In the presented case, the patient developed asymptomatic elevation of serum liver transaminases [21]. Therefore, close monitoring, follow-up, and supportive measures to rapidly eliminate the drug were required to manage the patient's condition.

Regarding the diagnosis and prognosis of the case; the peak plasma concentration of clozapine occurs within 1.5-2.5 hours after a single dose [23]. The serum level of clozapine could be a helpful diagnostic tool in acute poisoning and a possible predictive tool especially for coma [24]. However, different factors can influence the absorption rate such as sex, age, administered dose, disease of the liver, and drug-drug interaction. In the presented case, the level was measured after three hours of alleged drug intake, and despite the severity of the patient clinical condition, it was not strongly elevated. Moreover, recent guidelines recommend clinical assessment as a critical tool in the management of acute poisoning, which supports the researchers' recommendations [25].

Table (2) summarizes most of the reviewed articles and case reports, which were recently published on antipsychotic medications specifically clozapine and the unusual findings reported by the authors.

Table 2. A number of review articles and case reports on antipsychotic drugs and the reported adverse effects with their use

The study	Type of the study	Reported findings
Coulter D, Director I. 2003 [11]	Review article	Hypertension
Alves BB, et al. 2019 [12]	Case report and review	Hypertension
Li XQ, etal.2021 [10]	Systematic review	Cardiotoxicity
Hoorn EJ, van der Poel MF. 2014 [15]	Case report	Hypokalemic Hypertension
Kumar P, et al. 2019 [20]	Case report	Hyperglycemia
Wu chou et al. 2014 [21]	Case report and literature review	Hepatotoxicity
Lopes L, etal.2023 [22]	Case report	Asymptomatic hepatitis
Hirsch L, et al. 2017 [5]	Systematic review	Metabolic side effects
Yuen, etal.2021 [19]	Review article	Metabolic side effects
Gupta S, etal.2019 [7]	Review article	Sialorrhea
Current case report	Case report and literature review	Sialorrhea, Hyperglycemia, hypertension, Hypokalemia, QTc prolongation, elevated hepatic transaminases

CONCLUSION

- Atypical antipsychotics should not be thought to be a safe option in the management of psychiatric disorders. Moreover, additional cardiac and metabolic risks should be considered.
- The successful management of patients depends on early resuscitation and supportive measures, such as gastric lavage, activated charcoal, intravenous fluids, and correction of electrolyte disturbances together with continuous monitoring of any uncommon findings.
- The serum level of clozapine was a weak predictor of severity and could not be relayed upon.

Contributions

All authors contributed equally in the writing and revision of the manuscript.

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Human Ethics: Informed consent was taken from the patient for the publication of his clinical data. Confidentiality of all data was considered and preserved. Ethical approval for this study procedure was obtained from the ethical committee of Alexandria University (IRB number: 00012098, Protocol serial number: 0201595).

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