

QUETIAPINE POISONING ASSOCIATED WITH NEUROLEPTIC MALIGNANT SYNDROME, RHABDOMYOLYSIS AND RENAL FAILURE: A CASE REPORT

Željko Ninčević¹, Davor Lasić², Trpimir Glavina², Marijana Mikačić³,
Mladen Carev¹ & Kristian Podrug³

¹Department of Anaesthesiology and Intensive Care Medicine, University Hospital Centre Split, Split, Croatia

²Department of Psychiatry, University Hospital Centre Split, Split, Croatia

³Department of Internal Intensive Care Medicine, University Hospital Centre Split, Split, Croatia

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INTRODUCTION

Quetiapine extended release (XR) has been used to treat various psychiatric disorders, including psychotic disorders, acute mania and depressive episodes associated with bipolar I and II disorders. Quetiapine XR is generally safe and well tolerated. There are few reports of deaths or significant permanent morbidity associated with quetiapine overdose.

We present a case of I.E.K., a 32-year-old male patient, who was admitted to Intensive care unit University Hospital Centre in Split, Croatia, for intoxication with an extreme overdose of quetiapine (24 g), ingested to attempt suicide. The emergency medical service found the patient comatose with response only to deep painful stimuli and Glasgow Coma Score (GCS) of a 6. He was discovered 15 hours after ingestion of 24 g quetiapine (60 tablets of 400 mg XR) and 5 mg of alprazolam (10 tablets of 0.5 mg) after consuming alcohol through the night. He developed neuroleptic malignant syndrome with rhabdomyolysis and renal failure. After appropriate treatment the patient recovered completely.

CASE REPORT

A 32-year-old male had experienced the first episode of depressed mood in borderline personality disorder eight months before and the episode we report was his second exacerbation. Because of the marital problems, after consuming alcohol he ingested 24 g of quetiapine (60 tablets of 400 mg XR) and 5 mg of alprazolam (10 tablets of 0.5 mg) to attempt suicide. The emergency medical service found the patient 15 hours after ingestion comatose with response only to deep painful stimuli and GCS of a 6. During the transport to the hospital 40 mg of furosemide and 1000 mL saline were administered for detoxification and prophylaxis of hypotension. He had no history of severe somatic disorder, he was non-smoker and he consumed alcohol occasionally. There was no evidence of trauma or infection.

The skin was warm and moist. The pupils were 3 mm, equal, and minimally reactive to light. The abdomen was soft and not distended.

On admission to the Intensive care unit he was hypotensive (96/47 mmHg), with sinus tachycardia of 133 beats per minute and respiratory rate of 25/min. Arterial blood oxygen saturation was 75%. Initial ECG showed slight prolongation of the QRS complex (110 miliseconds). On a chest X-ray inhomogeneous shading of lung parenchyma on both sides was visible.

Immediately upon admittance orotracheal intubation and mechanical ventilation started. Gastric lavage was performed through a nasogastric tube and no pill fragments of ingested tablets were found. He received 60 mg of activated charcoal. Two vials of flumazenil (0.2 mg each) were administered intravenously but the level of consciousness did not improve. The patient became febrile, his axillary temperature measured up to 38.7°C, with profuse sweating. The patient was diagnosed with neuroleptic malignant syndrome based on his clinical presentation and laboratory values. Rhabdomyolysis developed with very high values of creatinephosphokinase (120 000 U/L on the 2nd day), creatinine (518 µmol/L on the 2nd day) and C-reactive protein (318.8 mg/L on the 2nd day), and he became anuric. Both arms and both legs were of high muscle tone and he had a muscular jerks of the whole body. Ultrasound examination of the skeletal muscle of the lower limb showed diffuse edema especially of the lower leg. The muscles of the lower leg were of deteriorated ultrasound structure in terms of rhabdomyolysis (Figure 1).

Central venous catheter and arterial line were inserted for invasive hemodynamic monitoring. Dantrolene 2.5 mg/kg i.v. was administered. Normal saline, fresh frozen plasma, antibiotics (ceftriaxone, moxifloxacin), gastric protection (pantoprazole) and continuous infusion of morphine and midazolam were administered as well as intravenous infusion of norepinephrine. During the same day continuous veno-venous hemodiafiltration (CVVHDF) started. He was on a ventilator six days. When control chest X-rays showed regression of the infiltration of the lung parenchyma continuous sedation

was stopped and he was successfully weaned from the ventilator and extubated. On the day of extubation the contact with the patient has been established, he followed orders, become oriented and aware what he has done. CVVHDF was performed eight days and intermittent hemodialysis was carried out for the next nine days, two hours each day. Gradually there was a regression of elevated laboratory results (Table 1). After weaning from the ventilator right-sided paresis of peroneal nerve that required treatment of physiatrist was observed. Symptoms of neuroleptic malignant syndrome resolved in a week.

After somatic recovery he was transferred to our acute psychiatric ward. Reintroducing antipsychotic treatment has been in line with the treatment algorithm for a major depressive disorder and borderline personality disorder, including clinical presentation by illness stage or severity. We started quetiapine from relatively low doses (25 mg/day) with slow titration up to 400 mg/day over 10 days. The patient remained in the hospital for a 29 days after intoxication with extreme oral overdose of quetiapine to attempt suicide and was discharged without sequelae.



Figure 1. Disturbed ultrasound structure of popliteal muscles affected by rhabdomyolysis

Table 1. Laboratory findings before CVVHDF (1st day) and after CVVHDF has started (2nd day)

Day	1	2	3	4	5	9	10
Pletelets (x10 ⁹ /L)	216	191	125	117	127	135	170
Urea (mmol/L)	9	14.9	17.9	16.7	17.9	21.3	22.2
Creatinine (μmol/L)	191	518	471	433	415	386	400
Creatinine phosphokinase (U/L)	92 000	120 846	58 622	33 913	17 829	2 470	2 353
Myoglobin (μg/L)			41 142			9 829	
Potassium (mmol/L)	4.3	5.5	3.9	4.6	3.7	4.4	3.2
Total bilirubin (μmol/L)	12	10.2	8.8	8.2	7.8	9.6	7.6
AST (U/L)	36	2 222	886	720	538	200	152
ALT (U/L)	22	598	366	340	325	245	228
GGT (U/L)	44	34	23	76	80	191	192
CRP (mg/L)		318.8	306		205.3		

DISCUSSION

Quetiapine is an atypical antipsychotic that has been used to treat various psychiatric disorders in adults, including psychotic disorders, acute mania and depressive episodes associated with bipolar I and II disorders (DeVane & Nemeroff 2001). Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain (serotonin 5-HT_{1A} and 5-HT₂, dopamine D₁ and D₂, histamine H₁, and adrenergic alpha₁ and alpha₂ receptors). In comparison to other antipsychotic agents, quetiapine has less antimuscarinic and alpha₁ antagonist receptor activity. The antipsychotic effect is explained by the antagonistic effect on D₂ receptors and 5-HT_{2A} receptors (Dev 2000). Adverse effects like sedation and somnolence are explained by antagonism of histamin H₁ receptors. Ortostatic dysregulation, hypotension, and tachycardia are associated

with an antagonistic effect on alpha₁-adrenergic receptors. Quetiapine has also been reported to have an antagonistic effect on M₁-muscarinic receptors resulting in anticholinergic mediated tachycardia (DeVane & Nemeroff 2001). Several reports have revealed the relative safety of quetiapine in overdose up to 20 000 mg. The first such case report was an intoxication with an extreme dose of quetiapine (36 000 mg), ingested by 32-year-old female (62 kg bodyweight) to attempt suicide. Symptoms associated with intoxication were coma without arterial hypotension, persistent tachycardia, hyperglycaemia and transient hypothyroidism. QTc-interval was moderately extended. Management consisted of intubation for airway protection, gastric lavage, the use of activated charcoal, i.v. saline and observation. The patient recovered completely without residual symptoms (Muller et al. 2009).

The first fatal case has been published by Fernandes & Marcil (2002), factors possibly contributing to the death of the 52-year-old patient were a history of cardiac dysrhythmia and hypertensive heart disease. Ngo et al. (2008) in a 5-year retrospective case series found 945 cases of acute quetiapine overdose in adults, among them 3 deaths, all of whom had coma, tachycardia, and respiratory depression requiring ventilatory support.

Consequences of acute quetiapine overdose included coma, respiratory depression, and hypotension, but in our case the patient experienced neuroleptic malignant syndrome, rhabdomyolysis and acute renal failure (Smith et al. 2004).

Neuroleptic malignant syndrome is a rare, but life-threatening, idiosyncratic reaction characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction. The syndrome was first described by Delay and colleagues in 1960, in patients treated with high-potency antipsychotics. The mortality rate rises to about 50% if neuroleptic malignant syndrome is complicated by renal failure. Once the syndrome starts, it usually evolves over 24-72 hours (Chiou et al 2015). Treated with dantrolen, while taking care of comorbid symptoms in Intensive care unit, in our case as in literature, symptoms of neuroleptic malignant syndrome resolved within a week.

Each psychopharmac, regardless of its administration safety and the positive clinical experiences, can pose a potential risk of side effects. The treatment of overdose with quetiapine is mainly supportive, as there is no specific antidote to quetiapine. According to Burns (2001) risk of death after poisoning with quetiapine is low, but large overdose may cause serious clinical features such as loss of consciousness, respiratory depression, hypotension, tachycardia, arrhythmia, seizures, neuroleptic malignant syndrome, rhabdomyolysis and acute renal failure. Despite quetiapine's safety record in overdose, medical comorbidity in extreme overdoses may contribute to a fatal outcome. All patients with acute quetiapine overdose who require hospitalization should be monitored in an intensive care unit setting.

CONCLUSION

We described a case with complicated clinical presentation, but recovered without any consequences. Unique characteristics in this case included symptoms of developed Neuroleptic malignant syndrome with rhabdomyolysis and acute renal failure as a consequences of intoxication after extreme overdose of quetiapine to attempt suicide. Still, quetiapine extended release (XR) is a safe atypical antipsychotic. Our patient recovered

completely without residual symptoms, but we must always keep in mind that overdose with quetiapine may be associated with coma, respiratory depression, hypotension, QT prolongation, neuroleptic malignant syndrome, extreme rhabdomyolysis and acute renal failure. Major overdoses of quetiapine warrant close observation in an intensive care setting.

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Contribution of individual authors:

Željko Ninčević was involved with the patient's care, data collection and manuscript preparation.

Davor Lasić was involved with conception and design, manuscript preparation and writing the paper.

Trpimir Glavina was involved with writing the paper.

Mladen Carev was involved in manuscript preparation, reviewed draft manuscript.

Marijana Mikačić was involved with the patient's care and manuscript preparation.

Kristian Podrug was involved with the patient's care and data collection.

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Correspondence:

Željko Ninčević MD, PhD

Department of Anaesthesiology and Intensive Care Medicine, University Hospital Centre Split

Spinčićeva 1, 21000 Split, Croatia

E-mail: zeljko.nincevic@gmail.com