Original article DOI: 10.2478/aiht-2022-73-3635

Olanzapine poisoning in patients treated at the National Poison Control Centre in Belgrade, Serbia in 2017 and 2018: a brief review of serum concentrations and clinical symptoms

Snežana Đorđević, Nataša Perković Vukčević, Marko Antunović, Vesna Kilibarda, Gordana Vuković Ercegović, Jasmina Jović Stošić, and Slavica Vučinić

University of Defence, Military Medical Academy Medical Faculty, National Poison Control Centre, Belgrade, Serbia

[Received in February 2022; Similarity Check in February 2022; Accepted in May 2022]

Olanzapine is a thienobenzodiazepine class antipsychotic that strongly antagonises the 5-HT2A serotonin receptor, but acute poisonings are reported rarely. Symptoms of an overdose include disorder of consciousness, hypersalivation, myosis, and coma. Serum concentration higher than 0.1 mg/L is toxic, while concentration above 1 mg/L can be fatal. Here we report key data about 61 patients admitted to the National Poison Control Centre in Belgrade, Serbia over olanzapine poisoning in 2017 and 2018. The ingested doses ranged from 35 to 1680 mg, and time from ingestion to determination from two to 24 hours. In 34 patients olanzapine serum concentrations were in the therapeutic range and in 27 in the toxic range. In five patients they were higher than fatal, but only one patient died. The most common symptoms of poisoning were depressed consciousness (fluctuating from somnolence to coma), tachycardia, hypersalivation, hypotension, myosis, and high creatine kinase. All patients but one recovered fully after nonspecific detoxification and symptomatic and supportive therapy.

KEY WORDS: liquid chromatography mass spectrometry; overdose; serum concentration; therapy; thienobenzodiazepines

Olanzapine belongs to a new generation of thienobenzodiazepine class antipsychotics that antagonise serotonin (5-HT2A), dopamine (D1, D2, D3, D4), histamine (H1), and muscarinic receptors to treat schizophrenia and bipolar disorder (1–2). Therapeutic serum concentrations range between 0.01 and 0.05 mg/L, while the toxic threshold is 0.1 mg/L. Fatalities generally occur at serum concentrations above 1 mg/L (3, 4). As it has an extensive first-pass metabolism that varies largely between individuals, olanzapine is increasingly used in intentional overdoses, and overdosing, intentional or not, can result in nonlinear pharmacokinetics and high blood concentrations. Data about olanzapine overdosing and severity of poisoning are limited. The main symptoms include central nervous depression, myosis, tachycardia, hypotension, generalised myoclonus, hyperpyrexia, muscular rigidity, leucocytosis, elevated creatine phosphokinase (CK) levels, and unpredictable fluctuations between somnolence and coma or between agitation or aggression. This is the reason why olanzapine overdosing requires careful clinical monitoring, but rarely specific therapeutic intervention (5). However, no relationship between overdose and effects or length of hospitalisation has been established this far (6–10). We only know that ingestion of massive doses of olanzapine can lead to respiratory depression, coma, and rarely death (11). In these cases, mechanical ventilation is required for up to several days (12–14). Fortunately, acute olanzapine poisonings are still relatively rare and mostly with mild consequences.

The aim of our study was to analyse olanzapine poisonings recorded and treated at the Serbian National Poison Control Centre (NPCC) in 2017–2018, and try to see if there was a pattern or relationship between concentrations established in patient serum and symptoms or outcome.

PATIENTS AND METHODS

The study included 61 incidents of olanzapine poisoning in 60 patients admitted to the emergency room of the NPCC in 2017 to 2018 (one patient was admitted on two occasions). Their blood was taken as part of standard diagnostic procedure and medical treatment in accordance with the Declaration of Helsinki and the procedure approved by the Ethics Committee of the Military Medical Academy.

To determine olanzapine concentrations in the serum, we developed and validated an in-house liquid chromatography with electrospray ionisation mass spectrometry (ESI-LC/MS) method using a Micromass ZQ2000 ESI-LC/MS System (Waters Corporation, Milford, MA, USA). Olanzapine was separated from matrix compounds on the XTerra C_{18} column (3.5 μm, 4.6×150 mm)

Corresponding author: Snežana Đorđević, University of Defence, Military Medical Academy Medical Faculty, Crnotravska 17, 11040 Belgrade, Serbia, E-mail: *ivezicnela@gmail.com*

with mobile phase at 30 °C, which was a mixture of 5 mmol/L ammonium formiate (pH 3.5) and acetonitrile mixed in gradient mode. The analytical conditions for the mass spectrometric detector were: capillary voltage 3 kV, ion source temperature 125 °C, desolvation temperature 430 °C, desolvation nitrogen flow 400 L/h, and nitrogen flow on the cone 50 L/h. Olanzapine was determined at m/z 313.

RESULTS AND DISCUSSION

In 2017, 15 patients (10 women and 5 men) had olanzapine concentrations in therapeutic range, and 16 in toxic and even lethal range (15 women and 1 man). In 2018, 19 patients (17 women and 2 men) had therapeutic and 11 (7 women and 4 men) toxic olanzapine serum concentrations. The average ingested dose was 280 mg (35–1680 mg) and average time from ingestion to olanzapine determination was 10 h (2–24 h). Most patients had no or mild clinical symptoms of tachycardia and hypotension.

Twenty-eight patients were hospitalised for acute poisoning, while others were discharged after ambulatory treatment. One patient required mechanical ventilation and one was intubated. On admission, 16 patients were in a coma, and 12 presented with mild disturbances of consciousness (7 with sopor and 5 with somnolence). Thirteen had complications like bronchopneumonia and rhabdomyolysis, one developed acute renal failure, and one leucopoenia. According to the Poisoning Severity Score (PSS) proposed by Persson et al. (15), five of the 28 hospitalised patients had mild poisoning (PSS 1), eight pronounced or prolonged poisoning signs or symptoms (PSS 2), 14 severe signs or symptoms (PSS 3), and one patient died (PSS 4). Mean hospitalisation lasted 6.9±6.4 days (2–28 days).

Thirty-four patients (15 in 2017 and 19 in 2018) had serum olanzapine concentration in the therapeutic range, and 27 above the 0.1 mg/L threshold (16 in 2017 and 11 in 2018) (Figure 1). Table 1 lists patients with serum olanzapine concentrations above the lethal threshold of 1 mg/L. Three recovered after therapy, and one died. Patient 2 was admitted to the Emergency Department for overdose twice in three months, first time, allegedly, with 1680 mg. After the second poisoning (ingested dose unknown), olanzapine was determined once a day over the four days of hospitalisation (Figure 2).

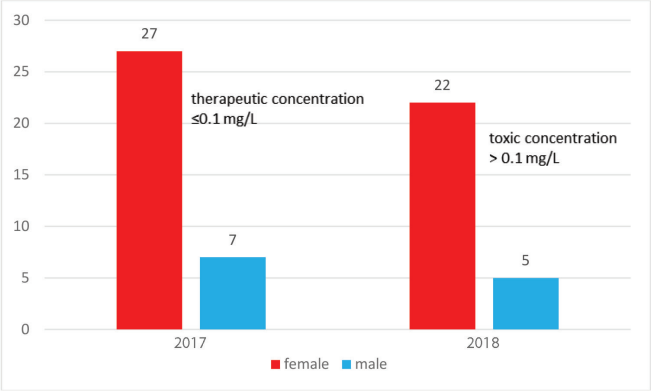


Figure 1 Total number of patients admitted to NPCC in 2017/18

Patient 3, a 59-year-old woman who ingested a much lower olanzapine dose (560 mg) and had much lower serum concentration on admission, which peaked on day 5 in the hospital (Figure 3), had severe hypotension and did not respond to supportive and inotropic therapy (dopamine). Intravenous lipid emulsion had transitory positive effects on consciousness and hypotension, but complications with bronchopneumonia and acute renal failure eventually resulted in death 18 days after admission. She combined olanzapine with other drugs prescribed for her standard psychiatric therapy, including clozapine (1000 mg), zolpidem (300 mg), lamotrigine (unknown dose), and midazolam (990 mg). Table 2 shows her serum concentrations of these drugs throughout hospitalisation.

In contrast, one 50-year-old patient presented with severe poisoning after ingesting "only" 120 mg of olanzapine and with initial serum concentration of 0.4 mg/L (Figure 4). He was in a coma, his level of consciousness fluctuated, and had tachycardia and hypotension, followed by complications of severe leucopoenia/neutropenia, bronchopneumonia (required mechanical ventilation), and rhabdomyolysis (CK 1648 IU/L), whereas renal function remained normal. The patient's condition was critical for two days after admission, and he was treated with granulocyte colony stimulating factor (G-SF) and antibiotics for febrile neutropenia. Eventually, he completely recovered and was discharged on day 12 of hospitalisation.

Table 1 Patients with serum olanzapine concentrations above the lethal threshold of 1 mg/L

Patient	Sex	Age	Ingested dose	Time from ingestion to blood collection	Concentration (mg/L)	PSS
1	male	26	about 150 mg	6 h	3.40	2
2	female	26	1680 mg	5 h	2.44	3
			unknown	>12 h	1.75	3
3	female	59	560 mg	3 h	1.53*	4
4	male	43	unknown	>24 h	1.18	3

* Highest serum concentration measured in this patient. PSS – Poisoning Severity Score

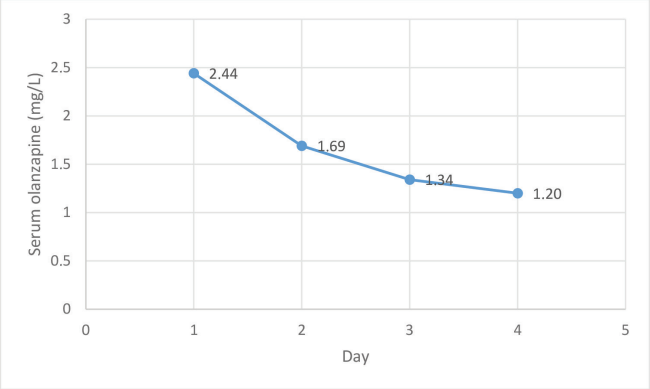


Figure 2 Olanzapine serum concentrations in patient 2 over four days of hospitalisation after the second admission for overdosing three months apart

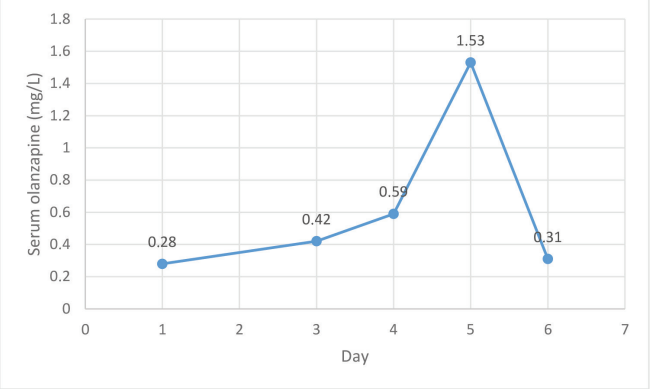


Figure 3 Olanzapine serum concentrations in overdosed patient 4 over six days with fatal outcome

Figure 5 shows creatine phosphokinase (CK) levels measured in hospitalised patients. Thirteen patients had normal CK levels (200 IU/L for women and 300 IU/L for men), and 15 above the normal range, eight of whom higher than 1000 IU/L (the highest was 15920 IU/L). High CK points to rhabdomyolysis caused by olanzapine overdose, probably due to antagonism with serotonin, dopamine, histamine, and α1 adrenergic receptors. Its main complication can be acute renal failure (9). Keyal et al. (10) described a case of olanzapine poisoning after ingestion of 400 mg which resulted in CK level of 5780 IU/L on admission. Most of our patients, however, had normal renal function. Acute renal failure was observed in one patient with severe hypotension and CK of 3250 IU/L.

All hospitalised patients received nonspecific detoxification, symptomatic and supportive treatment, including low molecular heparin. The female patient who was admitted in a coma and had high serum olanzapine concentration (2.44 mg/L, see Table 1) after reportedly ingesting 1680 mg of olanzapine was also intubated and received 20 % lipid emulsion solution for hypotension, which is in line with earlier reports (8, 16, 17). Heart pressure was restored, and serum olanzapine dropped after four days (Figure 2) but remained in the lethal range. Complications that followed her severe poisoning included bilateral pneumonia and rhabdomyolysis, yet she fully recovered and was discharged from the hospital after 20 days.

Our findings seem to confirm literature reports of no correlation between clinical findings and ingested olanzapine doses or serum concentrations. Most of our patients had typical clinical signs and symptoms, which were resolved with supportive therapy even in severe cases in which olanzapine concentrations are potentially lethal (>1 mg/L). The case in point is our patient 2, who overdosed with 1680 mg on first admission, yet her serum concentration was lower than in our male patient (3.40 mg/L), who reportedly ingested over ten times lower dose (150 mg). Similar findings were reported by Arora et al. (7), who presented a case of a patient who ingested 1600 mg and required minimal therapy. There are reports of patients surviving and completely recovering from an overdose with 800 mg of olanzapine and serum concentration of 0.991 mg/L or overdosing with 550 mg and 280 mg which led to serum concentrations of 0.815 mg/L and 0.41 mg/l, respectively (3, 18–20).

The highest serum olanzapine concentration in our study of 3.4 mg/L was found in a 26-year-old male patient, who reportedly ingested about 150 mg and presented deeply somnolent and with tachycardia (130 bpm). Having received non-specific supportive therapy, he totally recovered after only two days. In contrast, our female patient 3, who reportedly took only a third of the dose taken by our patient 2 of 1680 mg, and whose serum concentration was lower than in other two severe cases (1.53 mg/L) died from complications. However, she also took high doses of clozapine, zolpidem, midazolam, and lamotrigine, which probably contributed to prolonged coma, complications, and death. This is in line with

Table 2 Serum concentrations of co-ingested drugs (mg/L) during the hospitalisation

Day	Olanzapine (mg/L)	Clozapine (mg/L)	Norclozapine (mg/L)	Lamotrigine (mg/L)	Midazolam (mg/L)	Zolpidem (mg/L)
1	0.28	0.29	0.02	3.62	0.21	0.83
2	0.42	0.22	0.03	2.19	<LOD	0.19
3	0.59	0.49	<LOD	2.74	<LOD	0.15
4	1.53	0.68	<LOD	3.5	<LOD	0.14
5	0.31	0.7	<LOD	< 1.0	<LOD	0.06

LOD – limit of detection

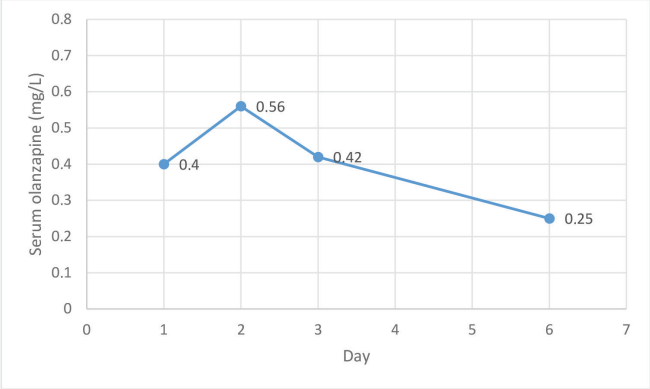
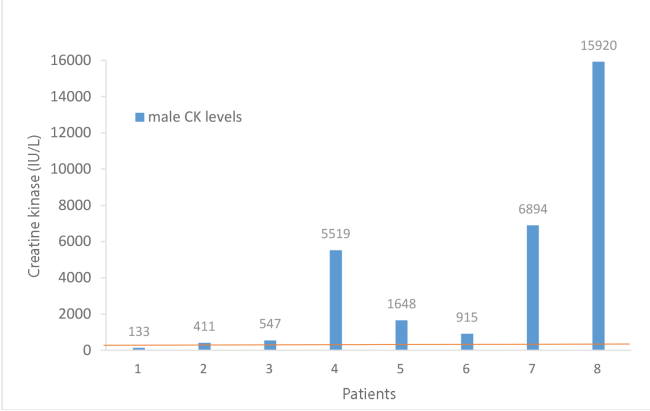
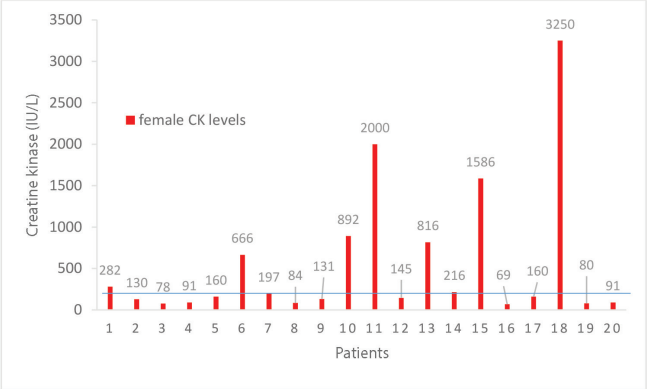


Figure 4 Olanzapine serum concentrations in a 50-year-old patient who ingested 120 mg of olanzapine



a)



b)

Figure 5 Creatinine kinase levels (IU/L) in hospitalised male (a) and female (b) patients with lines representing threshold values (300 IU/L for men and 200 IU/L for women)

case reports of prolonged (cardio)toxicity and seizures, when olanzapine was taken with propranolol and amlodipine (21) or citalopram (22).

CONCLUSION

The main limitation of our study is its retrospective design, which is liable to inaccuracies in documented risk assessment. However, all data were double-checked and estimated independently by two experienced toxicologists. Another potential limitation is that information about ingested doses was mostly given by the patients or persons who accompanied them on admission, but all poisonings were confirmed by serum analysis.

Our findings confirm that there is no clear relationship between ingested olanzapine dose, its serum levels, and severity of symptoms. As there is no specific antidote for olanzapine poisoning, treatment should start with detoxification and continue with supportive therapy until symptoms are resolved.

REFERENCES

1. Ritter J, Flower R, Henderson G, Loke YK, MacEwan D, Rang H. Rang & Dale's Pharmacology. 9th ed. Amsterdam: Elsevier Science; 2019.
2. Fulton B, Goa KL. Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. Drugs 1997;53:281–98. doi: 10.2165/00003495-199753020-00007
3. Moffat AC, Osselton D, Widdop B, Watts J. Clarke's Analysis of Drugs and Poisons. 4th ed. London: Pharmaceutical Press; 2011.
4. Robertson M, McMullin M. Olanzapine concentrations in clinical serum and postmortem blood specimens-when does therapeutic become toxic? J Forensic Sci 2000;45:418–21. doi: 10.1520/JFS14697J
5. Palenzona S, Meier PJ, Kupferschmidt H, Rauber-Luethy C. The clinical picture of olanzapine poisoning with special reference to fluctuating mental status. J Toxicol Clin Toxicol 2004;42:27–32. doi: 10.1081/clt-120028741
6. Singh LK, Praharai SK, Sahu M. Nonfatal suicidal overdose of olanzapine in an adolescent. Curr Drug Saf 2012;7:328–9. doi: 10.2174/157488612804096605
7. Arora M, Praharai SK. Nonfatal suicidal olanzapine overdose: a case report. Clin Neuropharmacol 2006;29:190–1. doi: 10.1097/01.WNF.0000228175.90959.43
8. McAllister RK, Tutt CD, Colvin CS. Lipid 20 % emulsion ameliorates the symptoms of olanzapine toxicity in a 4-year-old. Am J Emerg Med 2012;30(6):1012.e1–2. doi: 10.1016/j.ajem.2011.03.025
9. Boz Z, Hu M, Yu Y, Huang XF. N-acetylcysteine prevents olanzapine-induced oxidative stress in mHypoA-59 hypothalamic neurons. Sci Rep 2020;10:19185. doi: 10.1038/s41598-020-75356-3
10. Keyal N, Shrestha GS, Pradhan S, Maharjan R, Acharya PS, Marhatta MN. Olanzapine overdose presenting with acute muscle toxicity. Int J Crit Illn Ini Sci 2017;7:69–71. doi: 10.4103/2229-5151.201962

11. Nelson L, Howland MA, Lewin N, Smith S, Goldfrank L, Hoffman R. Goldfrank's Toxicologic Emergencies. 11th ed. New York: McGraw Hill Education; 2019.
12. Tse G, Warner M, Waring S. Prolonged toxicity after massive olanzapine overdose: two cases with confirmatory laboratory data. J Toxicol Sci 2008;33:363–5. doi: 10.2131/jts.33.363
13. Morgan M, Hacket LP, Isbisiter GK. Olanzapine overdose: a series of analytically confirmed cases. Int Clin Psychopharmacol 2007;22:183–6. doi: 10.1097/YIC.0b013e32805aedf5
14. Johal BK, Shelly MP. Olanzapine overdose. Anaesthesia 2000;55:929. doi: 10.1046/j.1365-2044.2000.01664-25.x
15. Persson H, Sjöberg G, Haines J, de Garbino J. Poisoning severity score. Grading of acute poisoning. J Clin Toxicol 1998;36:205–13. doi: 10.3109/15563659809028940
16. Yeniocak S, Kalkan A, Metin D, Demirel A, Sut R, Akkoc I. Successful intravenous lipid emulsion therapy: Olanzapine intoxication. Acute Med 2018;17:96–7. PMID: 29882560
17. Yurtlu B, Hanci V, Gür A, Turan I. Intravenous lipid infusion restores consciousness associated with olanzapine overdose. Anesth Analg 2012;114:914–5. doi: 10.1213/ANE.0b013e318213f377
18. Chue P, Singer P. A review of olanzapine-associated toxicity and fatality in overdose. J Psychiatry Neurosci 2003;28:253–61. PMCID: PMC165790
19. Lennestål R, Asplund C, Nilsson M, Lakso HA, Mjörndal T, Hägg S. Serum levels of olanzapine in a non-fatal overdose. J Anal Toxicol 2007;31:119–21. doi: 10.1093/jat/31.2.119
20. Ballestros S, Martínez M, Ballestros M, de la Torre C, Rodríguez-Borregán J. A severe case of olanzapine overdose with analytical data. Clin Toxicol (Phila) 2007;45:412–5. doi: 10.1080/15563650601072183
21. Hopkins L, Sunkersing J, Jaques A. Too many pills to swallow: A case of a mixed overdose. J Intensive Care Soc 2017;18:247–50. doi: 10.1177/1751143717693860
22. Lung D, Wu A, Gerona R. Cardiotoxicity in a citalopram and olanzapine overdose. J Emerg Med 2013;45:554–8. doi: 10.1016/j.jemermed.2013.04.033

Teška trovanja olanzapinom – analitički podatci Nacionalnoga centra za kontrolu trovanja u Beogradu u dvogodišnjem razdoblju

Olanzapin je antipsihotik koji pripada grupi tienobenzodiazepina. Kao i drugi atipični antipsihotici, olanzapin je jak antagonist 5-HT2A serotoninskih receptora. Akutna trovanja olanzapinom su rijetka. Simptomi predoziranja uključuju duboki ili fluktuirajući poremećaj stanja svijesti s hipersalivacijom i miozom, kao i komu i smrt u slučaju ingestije velikih doza. Koncentracije olanzapina u serumu veće od 0,1 mg/L smatraju se toksičnima, a letalnima veće od 1 mg/L. U radu su prikazana akutna trovanja olanzapinom zabilježena u Nacionalnom centru za kontrolu trovanja u Beogradu tijekom dvije godine. Koncentracije olanzapina u serumu pacijenata akutno otrovanih olanzapinom određene su pouzdanom metodom tekuće kromatografije s masenom spektrometrijom. Registriran je 61 pacijent s predoziranjem olanzapinom: u njih 34 koncentracije olanzapina bile su u terapijskom opsegu, a u njih 27 zabilježene su toksične koncentracije. Pet pacijenata imalo je koncentracije veće od letalnih, a zabilježen je i jedan smrtni ishod. Najčešći simptomi trovanja bili su hipotenzija, tahikardija i povećanje aktivnosti enzima kreatin kinaze. Nakon primjene nespecifičnog detoksikacijskog simptomatskog i potpornog liječenja svi pacijenti osim jednog su se potpuno oporavili.

KLJUČNE RIJEČI: predoziranje; serumska koncentracija; tekućinska kromatografija-spektrometrija masa; terapija