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

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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 elevated 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 X Terra C18 column (3.5 μm, 4.6×150 mm)
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).

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. He was in a coma, his level of consciousness fluctuated, and had tachycardia and hypotension, followed by complications of severe leucopenia/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.

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**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   |
| 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
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
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.

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Teška trovanja olanzapinom – analitički podatci Nacionalnog 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 hipsalivacijom 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 tekućinske 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 i potpornog liječenja svi pacijenti osim jednog su se potpuno oporavili.

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