CASE REPORT

DOI: 10.5336/caserep.2021-83290

Neurotoxicity and Renal Impairment in a Patient with Acute Poisoning with Antipsychotic Drugs-Literature Review

Natasha SIMONOVSKA[a], Aleksandra BABULOVSKA[a], Zanina PEREVSKA[a], Kristin KOSTADINOVSKI[a]

[a]University Clinic of Toxicology, Clinical Centre, "Mother Teresa", Medical Faculty, Sts Cyril and Methodius University in Skopje, Skopje, REPUBLIC OF NORTH MACEDONIA

ABSTRACT Neuroleptic malignant syndrome is a rare, severe and potentially fatal condition characterized by hyperthermia, muscle rigidity, changes in mental status (delirium, altered consciousness). There are many risk factors responsible for development of this syndrome such as the use of high-dose, high-potency and long-acting antipsychotic drugs, rapid increase in the dosage, using multiple antipsychotic drugs or other medications like antidepressants and mood stabilizers, especially lithium. A correlation between chronic kidney diesease and sudden lithium intoxication has been postulated, but the relationship between both remains unclear. We present here a case with neurotoxicity, rhabdomyolysis, renal impairment and hyperparathyroidism caused by acute poisoning with lithium, haloperidol, diazepam. The purpose of this case report is to increase awareness and vigilance of the fact that concurrent use of multiple antipsychotic and other drugs may cause multiple organ failures.

Keywords: Antipsychotic agents; lithium; neuroleptic malignant syndrome; renal insufficiency

Using multiple antipsychotic drugs (APDs) or other medications like antidepressants and mood stabilizers, especially lithium could be associated with neuroleptic malignant syndrome (NMS).[1] Prolonged administration of lithium may be toxic at 1.2 mmol/l or greater.[2,3] Sudden lithium intoxication may result in chronic kidney disease.[4] There are lack of results about the incidence, clinical course and other associated factors of acute lithium toxicity. Oruch in his study suggests that lithium poisoning occurs frequently, since it is used by individuals at high risk of taking an overdose.[5]

We present here a case with neurotoxicity, rhabdomyolysis, renal impairment and hyperparathyroidism caused by acute poisoning with lithium, haloperidol, diazepam.

CASE REPORT

A 50-year-old male (weight: 72 kg, height: 173 cm), with a history of bipolar disorder was admitted in January 2021 due to suicidal attempt with unknown amounts of lithium carbonas tablets of 300 mg, 7 tablets of haloperidol of 10 mg and 10 tablets diazepam of 5 mg. The drugs had been taken 45 minutes before the patient was brought to the emergency room. His medical history showed that he was treated for bipolar disorder in a period longer than ten years with several hospitalizations in psychiatric clinics. From the medical record of the national electronic system "My term" the patient in the last three years had 6 hospitalizations in psychiatric clinics. The last one was in December 2019. The treatment of the patient was modified due to fluctuations in his mental state.

Correspondence: Natasha SIMONOVSKA
University Clinic of Toxicology, Clinical Centre, "Mother Teresa", Medical Faculty,
Sts Cyril and Methodius University in Skopje, REPUBLIC OF NORTH MACEDONIA
E-mail: N.Simonovska@yahoo.com

Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 23 Mar 2021 ***Received in revised form:*** 27 Apr 2021 ***Accepted:*** 29 Apr 2021 ***Available online:*** 06 May 2021

He was treated with lithium, haloperidol, biperiden, diazepam and lamotrigine.

The patient was admitted to the emergency department with impaired consciousness, with 79% oxygen saturation, blood pressure 90/60 mmHg, respiratory rate 28/min, afebrile, pupillary miosis with third grade of poison severity score. Laboratory results showed an increased level of myoglobin, lithium, urea and creatinine. Electrocardiogram was with heart rate of 90/min, without other significant changes. Coronavirus disease-2019 test was negative. Arterial blood gas analyses showed acidosis pH: 7.32, arterial oxygen partial pressure (PaO_2): 5.65, base excess: (BE) -6.30, bicarbonate (HCO_3^-): 18.8, oxyhemoglobin (O_2Hb): 77.5%. The other parameters were in normal range. On admission, the patient underwent gastric lavage, whole bowel irrigation, nasogastric tube, and a single dose of medical charcoal 1 g/kg, intravenous fluids, flumazenil antidote 1 mg/10 mL were applied. He was on continuous oxygen support and the saturation was 95-97%. The first hemodialysis (HD) was done the same day and after that the acidosis was corrected. The second day of admission, he was still with impaired consciousness, disoriented and experienced cramps and tremors in his limb muscles, and an increased muscle tone. He had fever (38.5-39.6 °C) in the next eight days, tremor and diaphoresis. Within the next days, myoglobin, urea, creatinine, chlorides, C-reactive protein, sodium, calcium in serum and D-dimer levels started to increase (Table 1).

Procalcitonin level was slightly elevated (0.821). Toxicological test for benzodiazepines was positive. Other biochemical analyses and hormone levels of thyroid stimulating hormone, fT4,angiotensin-converting enzyme in serum, immunoglobulins were in normal range. Paraprotein in serum and Bence Jones proteins in urine were negative. The determined electrolytes in urine were with decreased values [potassium: 9.74(U), calcium: 0.36(U), sodium: 42.2(U), chloride:3 9.42(U), phosphates: 2.57(U)]. Increased parathormone values in serum were determined: 311.1…269 pg/mL, osteocalcin: 40.67 ng/mL, β-cross L: 1.67 ng/mL, kappa chains: 88.9 mg/l, lambda chains: 108.0 mg/l. Blood cultures were sterile. The CT scans of the lungs and brain were with normal finding. Dilated-pupil fundus examination was within normal limits. A lumbar puncture was performed and the result of the cerebrospinal fluid was sterile. Specialists in infectious diseases, nephrology, neurology and psychiatry were also consulted. The second day, was done another HD. Antibiotic drug ceftriaxone of 2 gr was initiated the second day along with low molecular weight heparin-nadroparin calcium subcutaneous 0.6 mL (5700 IU). On the eleventh day of hospitalization, the patient was conscious and contactable. On the twelfth day of hospitalization, he was afebrile. He was discharged with therapy prescribed by a psychiatrist: diazepam 3x5 mg, lamotrigine 25+25+50 mg, biperiden 2 mg 2x1, haloperidol 10 mg 2x1/2.

TABLE 1: Altered biochemical parameters in the patient with acute poisoning with lithium.

	15.01	16.01	17.01	18.01	19.01	20.01	21.01	22.01	25.01
Myoglobin (s) (<75.0 ng/mL)	**79**	**215**	**561**	**357**	**420**	**444**	**621**	**362**	**89**
CK (s) (24-173 U/l)	32	64	**876**	**592**	**396**	**267**	**354**	**241**	**193**
Na (s) (137-145 mmol/l)	137	141	139	143	**151**	**156**	**159**	**157**	**143**
Ca (s) (2.1-2.6 mmol/l)	2.6	2.5	2.5	**2.7**	**2.8**	**2.7**	**2.9**	**2.8**	**2.9**
Lithium (s) (0.5-1.5 mmol/l)	**3.93**	**>4.0**	**1.9**	**1.6**	/	1.2	/	/	/
Urea (s) (2.7-7.8 mmol/l)	**11.8**	**5.3**	**10.0**	**15.6**	**19.7**	**20**	**25**	**25**	**15.6**
Creatinine (s) (45-109 umol/l)	**213**	**160**	**228**	**273**	**337**	**320**	**351**	**333**	**182**
CRP (s) (<6 mg/l)	0.4	/	/	**130**	**96**	**57**	**26.10**	**15**	**12**
Cl (s) (101-109 mmol/l)	106	/	/	**121**	/	**125**	**129**	**128**	**116**
D dimer (<500 ng/mL)	/	/	/	**2320**	/	/	**5944**	/	**1931**
CrCl (mL/min)	37	50	35	**29**	**24**	**25**	**23**	**24**	**44**

(s)-(serum); ng/Ml: Nanograms per milliliter; CK: Creatine kinase; U/l: Units per liter; mmol/l: Millimoles per liter; Na: Sodium; Ca: Calcium; umol/l: Micromoles per liter; mg/l: Milligrams per liter; CRP: C-reactive protein; Cl: Chloride; CrCl: Calculated creatinine clearance (cockcroft-gault equation); mL/min: Milliliter/minute.

When he was discharged, the electrolytes and diuresis were normalized. The patient was advised further examinations and follow-up by a nephrologist, endocrinologist and a hematologist. This case is presented with previous patient consent receipt information.

DISCUSSION

NMS is associated with severe muscle rigidity and has at least two of the following associated symptoms: diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, or laboratory evidence of elevated creatine kinase (CK).[6] Taking lithium and neuroleptic medications are at greater risk of developing NMS than those taking antipsychotic medications without lithium.[7] In our case, the patient who took lithium and haloperidol in high doses developed NMS with muscle rigidity, fever, tremor, sweating, altered consciousness, laboratory evidence of rhabdomyolysis (elevated levels of myoglobin, CK).

Most symptoms in severe lithium intoxication are related to mental status changes. It has even been suggested that intoxication can occur even despite normal lithium levels.[8] The concentration of lithium in our patient on admission was above 4 mmol/l.

Impaired renal function increases the risk of lithium retention. Acute lithium exposure can lead to overt diabetes insipidus and consequently to dehydration.[9] In our case, the patient had a history of mild increased level of urea (up to 10 mmol/l) and creatinine (up to 190 umol/l) over the past 5 years. In comparison with literature reports regarding the overt diabetes insipidus, our patient developed polyuria during the hospitalization (with diuresis up to 4900 mL per day).

In the examined cohorts and published data, HD treatment was used in 1-11% of cases. It remains unclear which patients to dialyze, and clinical practice remains variable.[10] Recent recommendations indicate a need for HD in patients with a lithium level of >5 mmol/L or a level of 4 mmol/L in the presence of renal impairment as long as life-threatening symptoms are absent.[11] In our case, the first concentrations of lithium were 3.93… above 4.0 mmol/l and two HD sessions were done the first two days.

In conclusion, acute poisoning with APDs is potentially life-threatening. Concurrent use of multiple antipsychotic and other drugs may cause multiple organ failures. Early detection and appropriate treatment when NMS development is suspected may prevent death.

Acknowledgements

The authors are grateful to the University Clinic for Toxicology for facilitating this work and Lenche Danevska for English proofreading of the manuscript.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Simonovska Natasha;* ***Design:*** *Simonovska Natasha;* ***Control/Supervision:*** *Simonovska Natasha, Babulovska Aleksandra;* ***Data Collection and/or Processing:*** *Kostadinovski Kristin;* ***Materials:*** *Kostadinovski Kristin.*

REFERENCES

1. Szota AM, Radajewska I, Grudzka P, Araszkiewicz A. Lamotrigine, quetiapine and aripiprazole-induced neuroleptic malignant syndrome in a patient with renal failure caused by lithium: a case report. BMC Psychiatry. 2020;20(1):179. [Crossref] [PubMed] [PMC]
2. Bschor T. Lithium in the treatment of major depressive disorder. Drugs. 2014;74(8):855-62. [Crossref] [PubMed]
3. Haussmann R, Bauer M, von Bonin S, Grof P, Lewitzka U. Treatment of lithium intoxication: facing the need for evidence. Int J Bipolar Disord. 2015;3(1):23. [Crossref] [PubMed] [PMC]
4. Ott M, Stegmayr B, Salander Renberg E, Werneke U. Lithium intoxication: Incidence, clinical course and renal function - a population-based retrospective cohort study. J Psychopharmacol. 2016;30(10):1008-19. [Crossref] [PubMed] [PMC]
5. Oruch R, Elderbi MA, Khattab HA, Pryme IF, Lund A. Lithium: a review of pharmacology, clinical uses, and toxicity. Eur J Pharmacol. 2014;740:464-73. [Crossref] [PubMed]
6. Yang Y, Guo Y, Zhang A. Neuroleptic malignant syndrome in a patient treated with lithium carbonate and haloperidol. Shanghai Arch Psychiatry. 2014;26(6):368-70. [PubMed] [PMC]
7. Bourgeois JA, Kahn DR. Neuroleptic malignant syndrome following administration of risperidone and lithium. J Clin Psychopharmacol. 2003;23(3):315-7. [Crossref] [PubMed]
8. Peng J. Case report on lithium intoxication with normal lithium levels. Shanghai Arch Psychiatry. 2014;26(2):103-4. [PubMed] [PMC]
9. Erden A, Karagöz H, Başak M, Karahan S, Cetinkaya A, Avci D, et al. Lithium intoxication and nephrogenic diabetes insipidus: a case report and review of literature. Int J Gen Med. 2013;6:535-9. [Crossref] [PubMed] [PMC]
10. Roberts DM, Gosselin S. Variability in the management of lithium poisoning. Semin Dial. 2014;27(4):390-4. [Crossref] [PubMed]
11. Decker BS, Goldfarb DS, Dargan PI, Friesen M, Gosselin S, Hoffman RS, et al; EXTRIP Workgroup. Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol. 2015;10(5):875-87. [Crossref] [PubMed] [PMC]