

Lithium and venlafaxine poisoning – a case report

Case report

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Abstract: In treatment of manic-depressive conditions long-term lithium therapy may be combined with an effective and relatively safe antidepressant venlafaxine. Combined overdose may increase the risk of early toxicity of both drugs and of delayed lithium intoxication, responding to symptomatic and renal replacement therapy. We present a patient with combined lithium and venlafaxine self-poisoning with nothing but delayed signs of lithium intoxication with the emphasis on early and late treatment. 41-year old woman attempted suicide by large amount of lithium and venlafaxine. On admission she was asymptomatic, but with increased serum lithium over 5mmol/L. After gastric lavage, active charcoal and laxative administration she was receiving IV fluids. After a delay of 63 hours she deteriorated acutely by disorientation, confusion, fasciculation and tremor and was readmitted to Intensive care unit. In spite serum lithium decreased to 2mmol/L clinical signs were attributed to delayed lithium intoxication. After symptomatic and renal replacement therapy the patient's condition improved after few days. We conclude that decontamination procedures are effective in particular for venlafaxine poisoning. If increased serum lithium levels are noted renal replacement therapy may be started even in asymptomatic patients as delayed lithium intoxication is most likely after few days.

Keywords: *Lithium • Poisoning • Venlafaxine • Renal replacement therapy*

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1. Introduction

Lithium has been used for treatment of bipolar disorders for more than 150 years. In modern psychiatry it is an important pharmacological substance for treatment and prophylaxis of acute manic and/or depressive conditions, as well as for treatment of schizoaffective disorders as it decreases emotional instability [1-4].

The mechanism of lithium efficacy depends on multiple lithium intracellular effects, including neurotransmitter system in the brain, neuropeptide systems, signal transduction pathways in the kidney and thyroid, etc. [1,4].

Lithium therapy is started slowly by uptitrating the dose to the usual final oral dose of 900 mg/day (3-times 300mg per day). During treatment it is important to

control plasma lithium concentrations to avoid lithium toxicity due to its narrow therapeutic window, meaning that therapeutic and toxic doses of lithium are close to each other [1,4]. The therapeutic plasma concentration of lithium for maintenance therapy is between 0.5 and 1.0 mmol/L, even up to 1.2 mmol/L [1,2,5]. For treatment of acute manic episodes, the recommended lithium doses are between 1.0 and 1.2mmol/L, or even up to 1.5mmol/L [1].

In spite of its efficacy side effects of lithium treatment are possible such as polyuria, polydipsia, weight gain, memory disturbances, confusion, hair loss, acne, benign leukocytosis and edema, benign changes in the electrocardiogram, and decreased renal concentrating capacity [2].

Up to 90% of patients on lithium therapy have at least minor symptoms and signs of lithium toxicity at some

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time during therapy, which are possible if serum lithium concentration exceeds 1.5 mmol/L, but in particular with lithium concentrations over 2.0 mmol/L [1,3,4,6].

If serum lithium levels are increased over 1.5 mmol/L, complaints such as tremor, nausea, diarrhea, blurred vision, vertigo, confusion, instability, slurred speech, irregular heart beat and increased deep tendon reflexes occur [3,4].

If serum lithium levels exceed 2.5 mmol/L severe signs of lithium toxicity may occur such as confusion, tremor, coma, seizures, arrhythmias [1-4].

Acute lithium intoxication is most often observed after intentional or accidental ingestion of a large quantity of lithium [3,6,7]. However, the signs of lithium poisoning are expressed with a delay of several hours [1,6,7].

In current therapeutic practice, including psychiatry combined treatment is often observed. Long-term lithium therapy is often combined with other drugs for better control of symptoms and signs of the basic psychiatric disorder, but may be potentially harmful, exposing patients to more toxic side-effects of drugs [8,9].

Venlafaxine is an effective antidepressant – a selective inhibitor of the re-uptake of serotonin and noradrenalin that is sometimes combined with lithium [9, 10]. It is relatively safe. Lowest effective dose is 75 mg per day, but doses up to 600 mg per day can be tolerated without significant side-effects [11]. It is metabolized primarily through the P450 enzyme cytochrome 2D6, that is genetically determined and leads to high serum levels of venlafaxine in cytochrome 2D6 poor-metabolizer genotype [9,10,12]. Ingestion of > 2g may lead to toxicity, presenting as seizures and serotonin syndrome, minor prolongation of QT interval in standard electrocardiogram [13,14]. Arrhythmias, seizures or even sudden cardiac death are observed with massive ingestion of > 8 g [14].

Combination of lithium and venlafaxine overdose increases the risk of serotonin syndrome, presenting as hyperthermia, myoklonus, altered mental state, tachycardia, hypertension, tremor, etc. at lower doses of venlafaxine [9,10].

Patients after acute lithium and venlafaxine intoxication should be treated by gastric lavage and iv. fluids [2, 13,15]. Charcoal administration effectively decreases absorption of the drugs from the gut and enhances elimination, particularly of venlafaxine [10,13].

In lithium toxicity early renal replacement therapy is recommended if serum lithium exceed 3 mmol/L in addition to neurological signs (coma, convulsions, confusion) of lithium poisoning and with acute respiratory and/or renal failure 8 – 12 hours after admission [2,15,16].

We present a patient, chronically treated by combination of lithium and venlafaxine due to depressive

disorder and psycho-organic syndrome, who attempted suicide by ingestion of additional large amount of lithium and venlafaxine with nothing but delayed signs of lithium intoxication. We emphasize early and late treatment .

2. Case report

41-year old woman, who was treated by lithium and venlafaxine for several months due to depressive disorder and psycho-organic syndrome, intentionally ingested approximately 30 g of lithium tablets and 2100 mg of venlafaxine tablets. Approximately 30 minutes after ingestion of tablets she vomited for several times at home. 4.5 hours after self-poisoning she was brought to Emergency department, where gastric lavage was performed, 85 g of charcoal and salinic laxative was administered.

Five hours after self-poisoning the patient was admitted to medical Intensive care unit.

On admission the patient was oriented (Glasgow Coma Scale 15), eupnoic, without tremor, with blood pressure 128/80mmHg and heart rate 80/minute. Clinically, the lungs were clear, physical examination of the heart was within normal, the abdomen was tender with audible normal bowel sounds. On admission blood samples were drawn for routine laboratory testing (complete blood cell count, C-reactive protein, serum electrolytes, urea, creatinine, lithium levels). Admission and in-hospital laboratory data are displayed in Table 1. Among laboratory data serum creatinine was slightly increased to 117 μmol/L and leucocytes to 16,38.10⁹/l. Serum lithium concentration was over 5mmol/L. In standard electrocardiogram there was sinus rhythm, heart rate 92/minute, QT-interval 384 milliseconds, QTc-interval 475 milliseconds.

On admission peripheral iv. catheter was inserted and the patient was monitored noninvasively (continuous electrocardiogram, pulse oximetry, noninvasive blood pressure measurements hourly). The patient received 4600 ml of crystalloids per day within the first 48 hours.

During 48 hours in medical Intensive care unit the patient's clinical condition was normal. QTc-interval in electrocardiogram became normal. After 48 hours, she was transferred to the Department of Psychiatry. At that time, she was oriented, eupnoic and with normal puls and blood pressure. She remembered the gastric lavage and diarrhea after charcoal administration. There were any signs of serotonin syndrome. Babinski and Romberg signs were negative. Minimal tremor of the extremities was noted. Iv. infusion of fluids was prescribed for the first day (5% glucose 1000 ml and 0.9% NaCl

1000 ml) without any other medication. Oral feeding was still not initiated.

During the next 15 hours, her clinical condition deteriorated. The patient was re-admitted to medical Intensive care unit with confusion, disorientation, muscle fasciculations, restlessness and tremor, tachypnea (25/min). Blood pressure was 160/80mmHg, pulse 95/minute. In standard electrocardiogram there was sinus rhythm and normal QTc.

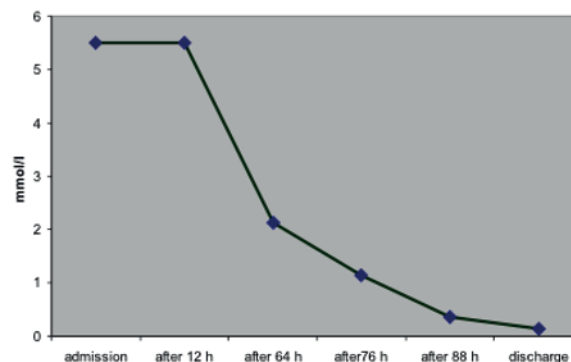
Noninvasive monitoring was restarted. Central venous, arterial and urinary catheters were inserted to measure central venous pressure 4-6-times per day, arterial blood pressure continuously and urine output hourly. Blood samples were drawn to estimate laboratory data (Table 1). Serum lithium was 2.13 mmol/L. Blood gas analysis of arterial blood was normal, while the patient was receiving 2L of oxygen by nasal cannula. Except for slightly increased serum myoglobin to 361µg/L (normal levels 160µg/L) laboratory tests were within normal. Treatment consisted of iv. fluids (5000 ml of crystalloids daily), midazolam 2 to 4 mg/h (total dose up to 90 mg daily in the first 48 hours) and iv. propofol up to 1200 mg in the first 24 hours to reduce severe restlessness, disorientation and confusion of the patient. Pronounced neurological signs were decisive to start renal replacement therapy – continuous veno-venous hemofiltration (CVVH) with ultrafiltration of 50 ml/hour during the next 10 hours as the condition was diagnosed as delayed lithium intoxication. After few hours of renal replacement therapy the patient's condition improved;

Table 1. Laboratory data

Laboratory data (normal levels)	Admission	After 12 hours	After 18 hours	Readmission	Discharge
Erythrocytes (4.2 to 6.3.10 ¹² /L)	4.96	4.60	4.26	4.23	4.02
Leucocytes (4.0 to 10.10 ⁹ /L)	18.59	20.23	17.69	16.38	13.08
Platelets (140 to 340.10 ⁹ /L)	486	355	297	197	164
Serum creatinine (44 to 97 µmol/L)	114	181	117	98	68
Sodium (135 to 145 mmol/L)	132	133	132	140	136
Potassium (3.8 to 5.5 mmol/L)	4.39	5.08	3.44	3.40	3.61
Chloride (97 to 110 mmol/L)	98	101	103	109	101
Arterial pH (7.36 to 7.42)	/	/	/	7.365	7.433
PaO ₂ (10.6 to 13.3 kPa)	/	/	/	13.80	10.20
PaCO ₂ (4.9 to 5.9 kPa)	/	/	/	4.55	5.05
HCO ₃ ⁻ (22 to 26 mmol/L)	/	/	/	19.0	24.9
BE (-2.3 to +2,3 mmol/L)	/	/	/	-5.1	1.2
HbO ₂ (96 to 100%)	92	97	97	97	98
CRP (0 to 5 mg/L)	<3	32	33	52	42
AST(up to 0,58 ukat/L)	0.22	0.29	/	1.14	1.10
ALT (up to 0,74 ukat/L)	0.36	0.33	/	1.16	0.97

Readmission: 64 hours after initial admission; BE, base excess; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase, HCO₃⁻, bicarb; HbO₂, oxygen saturation of hemoglobin;

Figure 1. Lithium levels (mmol/l)



restlessness and confusion disappeared. Lithium levels decreased further and are displayed in Figure 1.

The patient became oriented. However, tremor and slurred speech were still present for the next three days and the patient was still unable to swallow. Nasogastric tube was inserted to feed the patient properly. Clinical signs of lithium poisoning resolved completely after the next few days. Preexisting arterial hypertension was treated by carvedilol, newly diagnosed hypothyrosis by levothyroxine and depression by lorazepam. After a total of 5 days in medical Intensive care unit the patient was transferred to the ordinary ward. On discharge from medical Intensive care unit she was fully oriented with pulse 95/minute, blood pressure 155/90 mm Hg and normal laboratory data (Table 1) and serum lithium of 0,15 mmol/l (Figure 1). During the 5-day stay at the

ordinary ward the patient recovered physically completely. She was oriented with normal blood pressure, pulse and normal reflex of swallowing. Nasogastric tube could be removed and the patient was fed orally.

She was transferred again to the Department of psychiatry for further treatment of depressive disorder. She was initially treated by lorazepam and discharged later with bupropion and antidepressant quetiapine fumarate.

After discharge the patient was scheduled for psychiatric control every 3 months. Unfortunately, she was readmitted to the Department of psychiatry only a week after discharge due to aggravation of depressive disorder in spite of double antidepressant therapy. After two months of in-hospital treatment she was discharged with neurontin, rivotril, reseroquel SR, flurazepam and levothyroxine.

Within the next nine months she was treated at outpatient clinic at several occasions. Finally, her depression satisfactorily improved by duloxetine, quetiapine, gabapentin, clonazepam, flurazepam, topiramate and levothyroxine.

3. Discussion

We treated a patient after a suicidal attempt with lithium and venlafaxine, who developed clinical signs of nothing but lithium poisoning with a substantial delay.

Our patient was asymptomatic on admission and for more than 48 hours. The only pathological finding was increased serum lithium level. The delay in symptom onset of such duration after lithium self-poisoning was not observed before to our knowledge [1,3,6]. Neither was such prolonged delay observed after venlafaxine self-poisoning [12,14,17].

Regarding venlafaxine self-poisoning only slightly prolonged QTc interval in standard electrocardiogram was observed on first admission to Intensive care unit, but not later on. The possible causes could be elimination of the drug by extensive vomiting before admission, gastric lavage with charcoal administration and diarrhea due to saline laxative, administered in Emergency department [13,14]. In addition, there are data that QTc may be erroneously high in patients with tachycardia in venlafaxine overdose [14].

Combined effect of overdose of both drugs was observed in case reports, demonstrating signs of serotonin syndrome due to enhanced serotonin concentration in the central nervous system [9,10]. However, the occurrence of serotonin syndrome may be decreased by intensive elimination of the drugs by gastric lavage, charcoal administration and forced diarrhoea [13,14]. In addition, venlafaxine may be eliminated also by active

metabolism through cytochrome 2D6, being genetically determined [10,12]. In our patient early vomiting, early gastric lavage, active charcoal administration and laxatives were administered to eliminate the drugs from the bowel.

We ascribed the symptoms and signs at the second admission to Intensive care unit to lithium poisoning and not to venlafaxine due to absence of seizures, hyperthermia, respiratory failure and muscular rigidity [2,9,13,14].

The side effects of lithium treatment in case of manic-depressive disorder are well known, but often difficult to distinguish not only from acute lithium poisoning but also from manic-depressive disorder itself. In spite of prior combined treatment of venlafaxine and lithium in our patient, depression was uncontrolled and the patient attempted suicide. However, the switch to other antidepressants later on was at first ineffective as well. Depression resumed only a week after discharge from the hospital, necessitating even a long hospitalization. Depression could be managed not earlier than nine months later by combination of novel antidepressants.

In acute lithium self-poisoning, either intentional or accidental, signs are expressed with a delay of several hours [2,3]. In acute lithium poisoning plasma concentrations of lithium increase most often in 0.5 to 2 hours, but also later on, depending on intestinal resorption [2]. After reaching plasma, lithium is distributed in the brain within the next 24 hours and this delay in distribution of lithium in central nervous system is responsible for the delay in symptom onset if resorption of lithium from the bowel is normal [1,2].

When lithium therapy is combined with other pharmacological agents such as sedatives, antipsychotics, diuretics, etc., increase in serum lithium can result from decreased renal lithium clearance [1,2,8]. However, late increase of serum lithium may also be the consequence of residual and delayed lithium absorption from the bowel, especially in chronic psychiatric patients who take lithium regularly and in whom peristalsis is impaired [1,2,7]. This could also be the case in our patient, who took lithium on regular basis.

Patients with acute-on-chronic lithium overdose, also more likely developed clinical toxicity, as their brain concentration of lithium has already reached equilibrium with their plasma concentration [2]. In such cases, even moderately high serum concentration may be associated with severe symptoms [2]. In our patient acute self poisoning was after chronic treatment.

In our patient we also observed hypothyroidism, which needed treatment by levothyroxine. It is well established that chronic lithium therapy may inhibit thyroid hormone release, resulting in hypothyroidism and even goiter [1,2].

Monitoring of thyroid function is therefore needed, if lithium therapy is given [1,2].

Basic treatment of acute poisoning, either venlafaxine or lithium includes gastrointestinal lavage, administration of charcoal and symptomatic therapy such as administration of iv. fluids to force the diuresis [1,2,13,14]. This was also the basic therapy in our patient at first admission to medical intensive care unit, where asymptomatic period persisted for 48 hours resulting in discharge from Intensive care unit to the Department of psychiatry. Additional 15 hours were necessary for symptoms and signs of lithium poisoning to develop, proving that initial symptomatic therapy was ineffective. Lithium is namely excreted almost entirely through the kidneys whereby almost 80% of lithium filtered in the glomeruli is reabsorbed, resulting in lithium clearance rate of only 9 to 15ml/min [1,2]. When kidneys function normally, lithium clearance rate is 10-40 ml/min; however, by renal replacement therapy such as hemodialysis lithium clearance rate of 70-170 ml/min is reached [1,2]. Conventional hemodialysis reduces plasma lithium by 1 mEq/L in 4 hours of treatment [1]. Obviously, renal replacement therapy is effective in lithium poisoning. It is recommended with serum lithium over 3 to 4 mEq/L in addition to neurological signs (coma, convulsions), acute respiratory and/or renal failure in the first 8 – 12 hours after admission [1].

A possibility in totally asymptomatic patients after moderate lithium overdose is falsely elevated serum lithium if lithium-heparin coated collecting tubes are used as it was described by Nordt SP *et al.* [18]. In our patient blood to estimate serum lithium was collected in a yellow-top tube, containing gel. In addition, our patient was asymptomatic during the first 48 hours after admission, when serum lithium level was increased and became symptomatic approximately 63 hours later, when serum lithium was already decreasing. Similar case reports were observed by others as well, illustrating the unique pharmacokinetic profile of lithium [19].

Renal replacement therapy with the use of bicarbonate is particularly effective in lithium intoxication [2]. Due

to repeated influx of lithium from cells to serum, it is required to control the serum concentrations of lithium and repeat renal replacement therapy [1]. Rebound of lithium toxicity occurs because hemodialysis removes lithium from the extracellular space faster than lithium can move from intracellular space [1-3,16]. After dialysis, lithium diffuses down the dialysis-induced concentration gradient, increasing lithium serum levels [1,2,16,19,20].

Venlafaxine self-poisoning mostly requires monitoring and symptomatic treatment such as iv. infusion of fluids, benzodiazepines to manage agitation and muscle rigidity, in more severe cases even mechanical ventilation, paralysis and active cooling [13,14,17]. Elimination of the drug is extremely important. Gastric lavage and oral activated charcoal is necessary in all patients ingesting more than 1.000 mg of venlafaxine within 2 hours and whole bowel irrigation in patients who have ingested more than 60 mg/kg or 7 grams of the extended release preparation [13,14]. In contrast to lithium there is no evidence of enhanced elimination of venlafaxine with forced diuresis, urinary pH manipulation, haemodialysis or haemoperfusion [13].

In our case we decided to start renal replacement therapy, which was veno-venous hemofiltration, mainly because of clinical signs of lithium poisoning in spite serum lithium concentration was only 2.13 mmol/L. That is in contrast with current recommendations in lithium poisoning, which advise renal replacement therapy if serum lithium is over 3 mmol/L in addition to signs of poisoning at the same time [1-3,18,21].

We conclude that in combined lithium and venlafaxine poisoning decontamination procedures are effective in particular for venlafaxine. If increased serum lithium levels are noted renal replacement therapy may be started even in asymptomatic patients as delayed lithium intoxication is most likely after few days. Our conclusions are also that further research is required, regarding the choice between haemodialysis and continuous veno-venous haemofiltration to establish the potential benefits of assisted elimination on clinical outcome in patient with lithium poisoning.

References

- [1] Timmer R.T., Sands J.M., Lithium intoxication, *J. Am. Soc. Nephrol.*, 1999, 10, 666-674
- [2] Grandjean E.M., Aubry J.M., Lithium: Update human knowledge using an evidence-based approach, *C.N.S. Drugs*, 2009, 23, 397-418
- [3] Chen K.P., Shen W.W., Lu M.L., Implication of serum concentration monitoring in patients with lithium intoxication, *Psychiatry. Clin. Neurosci.*, 2004, 58, 25-29
- [4] Malhi G.S., Tanious M., Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations, *C.N.S. Drugs*, 2011, 25, 289-298
- [5] Chiu C.C., Shen W.W., Chen K.P., Lu M.L., Application of the Cockcroft-Gault method to estimate lithium dosage requirement, *Psychiatry. Clin. Neurosci.*, 2007, 61, 269-274

- [6] Yoshimura R., Yamada Y., Ueda N., Nakamura J., Changes in plasma monoamine metabolites during acute lithium intoxication, *Hum. Psychopharmacol.*, 2000, 15, 357-360
- [7] Dupuis R.E., Cooper A.A., Rosamond L.J., Campbell-Bright S., Multiple delayed peak lithium concentrations following acute intoxication with an extended-release product, *Ann. Pharmacother.*, 1996, 30, 356-360
- [8] Müller-Oerlinghausen B., Drug interactions with lithium: a guide for clinicians, *C.N.S. Drugs*, 1999, 11, 41-48
- [9] Birmes P., Coppin D., Schmitt L., Lauque D., Serotonin syndrome: a brief review, *C.M.A.J.*, 2003, 168, 1439-1442
- [10] Adan-Manes J., Novalbos J., Lopez-Rodriguez R., Ayuso-Mateos J.L., Abad-Santos F., Lithium and venlafaxine interactions: a case of serotonin syndrome, *J. Clin. Pharm. Therapeutics*, 2006, 31, 397-400
- [11] Harrison C.L., Ferrier N., Young A.H., Tolerability of high-dose venlafaxine in depressed patients, *J. Psychopharmacol.*, 2004, 18, 200-2004
- [12] Fisher M., Unterecker S., Pfuhlmann B., Overdose of venlafaxine with mild outcome, *Neuroscience & Medicine*, 2012, 3, 327-329
- [13] Kumar V.V.P., Isbister G.K., Dufful S., The effect of decontamination procedures on the pharmacodynamics of venlafaxine in overdose, *Br. J. Clin. Pharmacol.*, 2011, 72, 125-132
- [14] Isbister G.K., Electrocardiogram changes and arrhythmias in venlafaxine overdose, *Br. J. Clin. Pharmacol.*, 2009, 67, 5, 572-576
- [15] Okusa M.D., Crystal L.J., Clinical manifestations and management of acute lithium intoxication, *Am. J. Med.*, 1994, 97, 383-389
- [16] Bosinski T., Bailie G.R., Eisele G., Massive and extended rebound of serum lithium concentrations following hemodialysis in two chronic overdose cases, *Am. J. Emerg. Med.*, 1998, 16, 98-100
- [17] Bosse G.M., Spiller M.S., Collins A.M., A fatal case of venlafaxine overdose, *J. Med. Toxicol.*, 2008, 4, 18-20
- [18] Nordt P.S., Cantrell F.L., Elevated lithium level: a case and brief overview of lithium poisoning, *Psychosom. Med.*, 1999, 61, 564-565
- [19] Vermeire S., Vanbrabant P., Van Boxtael P., Sabbe M., Severity (and treatment) of chronic lithium poisoning: clinical signs or lab results as a criterion?, *Acta. Clin. Belg.*, 2010, 65, 127-128
- [20] Pühr J., Hack J., Early J., Price W., Meggs W., Lithium overdose with electrocardiogram changes suggesting ischemia, *J. Med. Toxicol.*, 2008, 4, 170-172
- [21] Goodman J.W., Goldfarb D.S., The role of continuous renal replacement therapy in the treatment of poisoning, *Semin. Dial.*, 2006, 19, 402-407