

Lithium intoxication in the pre-hospital care with stroke symptoms

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Abstract

Lithium is widely used in psychiatry to treat bipolar affective disorders since 1970 but little is known about the incidence, clinical course and associated factors of acute lithium intoxication. Moderate and severe cases of lithium intoxication are rare.

This case reports a patient with acute lithium intoxication (serum level of 3.7 mmol/L) with neurological symptoms imitating stroke, which affects the differential diagnosis in the pre-hospital and hospital care. Patient was treated with forced diuresis and dismissed 21 days after admission.

Abbreviations:

| | |
|--------|---------------------------------------|
| cAMP | - Cyclic Adenosine Monophosphate |
| CRT | - Capillary Refill Time |
| CT | - Computer Tomography |
| GCS | - Glasgow Coma Scale |
| IV | - intra venous |
| EMS | - Emergency Medical Services |
| ECG | - Electrocardiogram |
| mmol/L | - milimol per litre |
| mmHg | - millimetres of Mercury |
| mEq/L | - milliequivalent per litre (=mmol/L) |

INTRODUCTION

Lithium is widely used in psychiatry to treat bipolar affective disorders since 1970 (Hausmann *et al.* 2015a) but little is known about the incidence, clinical course and associated factors of lithium

intoxication (Ott *et al.*, 2016). Moderate and severe cases of lithium intoxication are rare (Ott *et al.*, 2016) despite the fact that lithium is endorsed as the first-line treatment of bipolar affective disorder. The frequency of moderate to severe lithium intoxication (serum levels of > 1.5 mmol/L) was described (Ott *et al.* (2016)) as 1/100 patient a year (population-based retrospective cohort study on 1101 patients between 1997 and 2013). The risk of intoxication was suggested as high by Oruch *et al.* because "it is used by individuals at high risk of taking an overdose" (Oruch *et al.* 2014, Ott *et al.* 2016). Burguera *et al.* (2017) described that prevalence of acute lithium poisoning is 1% by females with chronical medication of lithium and with age over 60.

Indications for lithium treatment are bipolar affective disorders, primarily for the treatment of acute manic phases of affective or schizoaffective disorders and for the prophylaxis of pathological mood swings. It also enhances the effect of antidepressants in the treatment of depressive episodes, reinforces abstinence in alcoholism and non-alcoholic drug addiction, mitigates some forms of sexual deviations, and suppresses pathological aggression in patients with organic psychiatric disorders. When used in the right doses, lithium is referred to as the most effective thymoprophylactic agent to prevent different phases of bipolar affective disorder (Dreher, 2017; Stetkarova, 2017). Lithium has also been used for hypnic headache as suggested by Dolezil *et al.* (2012).

Lithium ions naturally occur in the body, just like the other alkali metal ions (sodium, potassium, magnesium, calcium). However, the lithium ion concentration is 250 times lower than that of the lithium treated individual. This element affects membrane transport, synthesis and metabolism of neurohormones and neurotransmitters. Lithium interferes with enzyme metabolism – it inhibits adenylate cyclase enzymes, which is responsible for synthesis of "second messenger" cAMP (Schou, 2009).

The pharmacokinetics of lithium is influenced by a number of clinical factors. These include patient age, current lithium plasmatic concentrations, dehydration, concurrent infection, nephrotic syndrome etc. Maximum absorption of the lithium from the gastrointestinal tract occurs after 2–4 hours from the ingestion. Initially, the ions get into the intercellular fluid and then are deposited in the tissues. However, lithium ions enter very slowly into the brain. Within several days of use, intracellular concentrations in the central nervous system and thyroid gland stabilize. 95% of lithium is eliminated from the body by kidneys. Reabsorption is provided by the proximal tubular system along with the reabsorption of sodium. Lithium excretion slows down in the absence of sodium ions, suggesting that diuretic therapy and hyponatremia presents a higher risk of lithium intoxication (Latalova 2010; Dilmen *et al.* 2016).

Despite the indisputable significance of the therapeutic effect of lithium, there are a number of risks associated with lithium toxicity that correlates with serum lithium levels. A blood lithium concentration of 0.8–1.2 mmol/L is considered safe during the acute-phase of treatment, and a concentration of 0.4–0.8 mmol/L is appropriate during the maintenance phase of treatment. Side effects at levels lower than 1.5 mmol/L are manifested primarily at the gastrointestinal tract by nausea, vomiting, diarrhoea and weight gain. Other side effects at these levels include polyuria, polydipsia, tremor, leukocytosis and thrombocytosis. Neurotoxic effects (drowsiness, tremor, speech disorder) and more severe gastrointestinal complaints are also added at levels 1.5–2 mmol/L. In the case of higher levels than 2 mmol/L, there is cardiovascular toxicity, convulsions, coma and even death (Augustin 2005; Ott *et al.* 2016).

Lithium is always dosed according to the plasma concentration in the blood (ideally between 0.6–1.0 mmol/L) and the target concentration levels vary depending on the diagnosis (Hausmann *et al.* 2015a). In an acute manic phase manifested by significant manic behaviour, such as low sleep, tachypsychism, disinhibited behaviour, etc., the plasma concentration of lithium should be even between 1 and 1.2 mmol/L. Since it is a very high concentration, it is necessary to determine blood levels every 2–5 days (Dreher 2017). If the patient is in a hypomanic episode and therefore has less intense symptoms such as agitation, loss of criticality, expansive behaviour, etc., but is oriented, the target plasma concentration should be approximately 0.8 mmol/L (Dreher, 2017). There are also rare non-fatal cases with the lithium serum levels concentration of 5.5 mmol/L (Hausmann *et al.* 2015b).

Lithium intoxication is one of the most serious complications of lithium therapy due to the low range of levels that lead to the therapeutic effect and levels that are already causing side effects (Dreher 2017). It is important to think about the possibility of intoxication in pre-hospital emergency care based on a patient medical history and clinical course. The basic symptoms might be easily misinterpreted. Acute intoxication usually occurs after ingestion of a high dose of lithium by mistake or deliberately. This type of intoxication is predominantly manifested at the level of the gastrointestinal tract, but may progress to neuromuscular symptoms as also the chronic intoxication manifests by the neurological symptoms (Hausmann *et al.* 2015a; Hirt & Vorel 2016).

CASE REPORT

The Medical Dispatch Centre sent an ambulance with paramedic to a call of 66 years old lady with deterioration of medical conditions. The crew found the patient in the bed, conscious but confused. The Emergency Medical Services (EMS) was called by her husband who provided basic situation information: she is unable to walk for 3 days because of weakness, she did not want to eat and drink because of vomiting, and she had diarrhoea and tremor for 3 days. The husband was able to provide patient history – hypertension, depressions and bipolar affective disease. She has a chronic medication – ramipril, amlodipine, mirtazapine, acetylsalicylate acid and lithium carbonate with no allergies in patient history. She was in stroke pension and lived in a house with husband.

Findings of the patient assessment are shown in Table 1.

In the pre-hospital setting the crew secured the IV line with normal saline and transport the patient to the nearest hospital with neurology department, because of missed therapeutic window for the acute stroke. The differential diagnosis was stroke.

Tab. 1. Patient assessment findings (Ref.: authors)

| Assessment | Findings | |
|------------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A | Airway | Patent airway. |
| B | Breathing | Eupnoeic, respiratory rate 12 / min, oxygen saturation of 95% without supplementary oxygen, clear breathing sounds without pathologic findings. No dyspnoea. |
| C | Circulation | Heart rate of 81 / min, regular sinus rhythm without pathological findings, capillary refill time less than 2 s, blood pressure 180/80 mmHg. |
| D | Disability | Conscious, GCS 4-3-5 (12), pupils equal and reactive to light, bulbs in middle position, sensation on all limbs undisturbed, lateralisation cannot be investigated because of the reduced muscle strength on both sides. The tongue crawls in the centre. Meningeal symptoms have been ruled out. Dysarthria. Tremor and involuntary movements were present. There is an obvious short-term memory disorder, the patient responds only to short questions. The measured blood glucose level was 8.1 mmol /L. |
| E | Exposure | Apparent reduced turgor of the skin, swelling absent, no trauma. Body temperature 37.1 °C. |

After the handover, the neurological examination indicated acute CT scan also with differential diagnosis of stroke. Clonazepam was administered because of tremor. Patient condition worsened rapidly after the CT scan. She became unconscious with saturation of 84% and hypotension (80/50 mmHg). After the administration of supplemental oxygen (8 l/min) the saturation has risen up to 97%. Resuscitation team was called.

After the intubation (with midazolam and sufentanil) patient became bradycardic with no pulse. Advanced Life Support was started and after 8 minutes of CPR with 2 mg of epinephrine the ROSC was achieved. Patient remained unstable with support of norepinephrine (blood pressure 108/50 mmHg, pulse 83/min, prolonged CRT) and transferred to the intensive care unit.

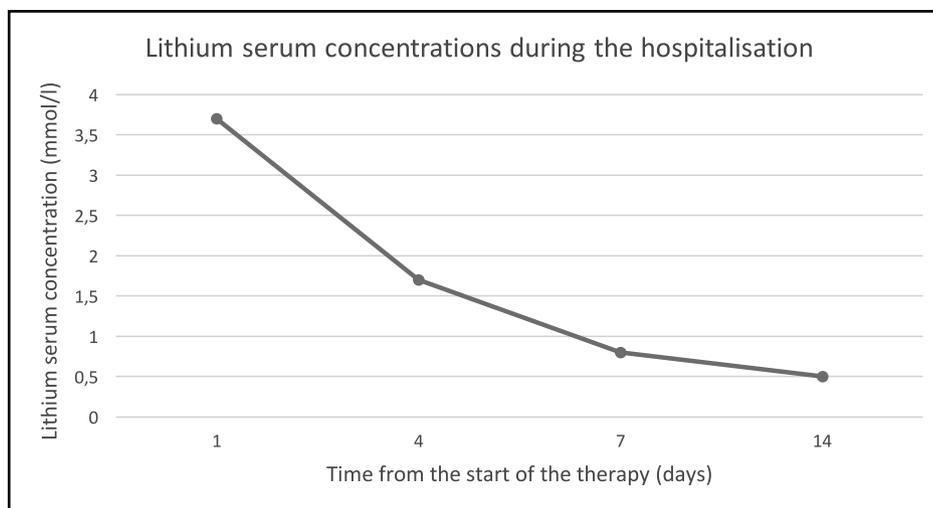
The possibility of lithium intoxication came up due to the patient's history and blood samples were sent immediately for confirmation. Lithium serum level was 3.7 mmol/L. Renal function was not affected and forced diuresis on high furosemide support was indicated. Serum lithium levels decreased to the therapeutic levels on fifth day after admission as shown in the Figure 1.

Patient was able to continue treatment with lithium carbonate on the seventh day of hospitalisation.

The hospitalisation was complicated by catheter and urinary infections, which prolonged hospital stay. 21 days after admission patient was dismissed to psychiatric care for further treatment. Patient was conscious, oriented, without movement disorders and tremor. Vital signs – respiratory rate 13/min, oxygen saturation 95% without supplementary oxygen, blood pressure 120/40 mmHg, pulse 78 /min.

DISCUSSION

Common clinical symptoms of acute and acute-on-chronic lithium intoxication listed by Hausmann *et al.* (2015a) are gastrointestinal symptoms (nausea, vomiting, and diarrhoea), cardiac symptoms (ECG changes, arrhythmias, prolonged QTc intervals, and bradycardia) and neurological symptoms (late-developing: SILET – syndrome of irreversible lithium effectuated neurotoxicity). The chronic intoxication differs in the neurological symptoms, which are developing gradually – sluggishness, ataxia, confusion, agitation and tremor

**Fig. 1.** Lithium serum concentration during the hospitalisation (Ref.: authors)

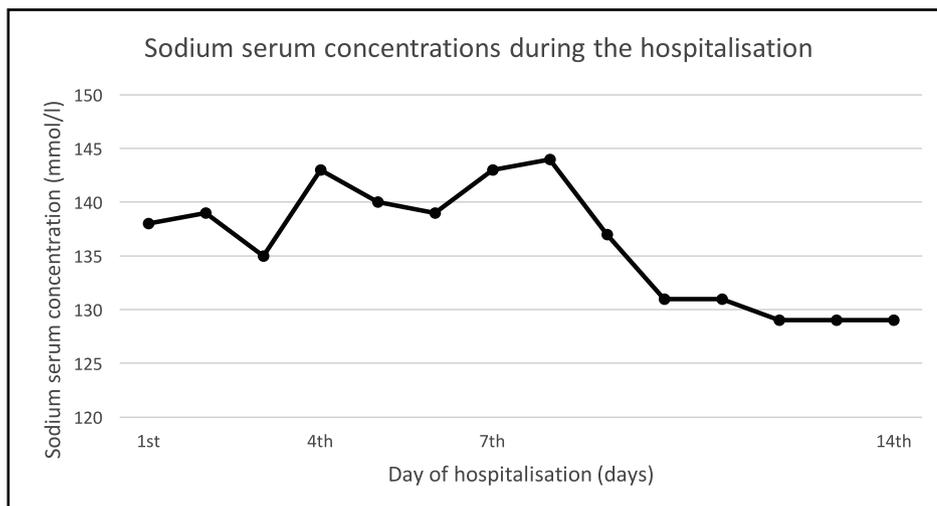


Fig. 2. Sodium serum concentrations during the hospitalisation (Ref.: authors)

(Hausmann 2015a). This case represents patient with acute-on-chronic and probably also chronic severe lithium intoxication with the neurological and gastrointestinal symptoms as listed above.

Lithium intoxication occurs most often in the long-term use of the drug, for example due to impaired renal function or hypovolemia. Another factor increasing the toxicity is sodium deficiency (Dilmen *et al.* 2016). This patient did not have hyponatremia as associated factor – the serum level of sodium was 138 mmol/L on the admission and stayed normal for whole hospitalisation (levels of sodium during hospitalisation are shown on the Figure 2). Another common cause of lithium intoxication is dehydration (Hausmann *et al.* 2015a) and this patient vomited, had reduced turgor of the skin and also diarrhoea.

There was a misinterpretation of the symptoms in the pre-hospital care. Neurological symptoms as dysarthria, vertigo, sluggishness and weakness, malfunction of short-term memory imitated the stroke symptoms. Lateralisation as one of the basic stroke symptoms couldn't be evaluated due to the limitation of the patient's mobility. These symptoms firstly occurred several days before the EMS was called. Due to the situation and symptoms, EMS crew decided to transfer the patient to nearest neurology. Even the first neurological examination was closed with probability of a stroke. Main symptoms for stroke in the Czech Republic according to the FACE acronym are: lateralisation of one arm or monoparesis/hemiparesis, dysarthria, paresis of cephalic nerves (Sedova *et al.* 2017). Only after deterioration of patient's status and due to no ischemia signs on CT scan results, another differential diagnosis was made and the blood samples were sent for the serum concentration of lithium.

There is variability of recommendations described for the approach to lithium intoxication. Despite that Hausmann *et al.* (2015a) published a review article with recommendation that the general approach is

similar to other poisoning – airway management if the patient mental status is altered and gastric lavage shortly after the intoxication. Oral activated charcoal had no effect. Intravenous hydration provided with isotonic saline is recommended as treatment. Sodium levels might be closely monitored to prevent hypernatremia. *Despite convention, forced diuresis is not able to enhance lithium excretion and is not recommended except for truly volume-depleted patients* (Hausmann *et al.* 2015a). This patient was dehydrated and after the deterioration needed support of catecholamines thus fulfilled the criteria for forced diuresis. This was done by furosemide and the renal and cardiac function was closely monitored. Based on the risk of hypernatremia, there is a variant that respects the current recommendation for infusion procedures in the Czech Republic – a crystalline solution with a reduced salt content is suitable for fluid resuscitation (Pekara *et al.*, 2017).

Hausmann *et al.* (2015a) mentioned that if the renal or cardiac function does not allow the forced diuresis or the patient did not fulfil the criteria haemodialysis is indicated and is more effective than other methods of lithium elimination. Another recommendation was published by Decker *et al.* (2015) who provided the levels of serum lithium concentration where the extracorporeal methods are recommended. *Extracorporeal treatment is recommended if kidney function is impaired and the [Li+] is >4.0 mEq/L, or in the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of the [Li+] (1D). Extracorporeal treatment is suggested if the [Li+] is >5.0 mEq/L, significant confusion is present, or the expected time to reduce the [Li+] to <1.0 mEq/L is >36 hours (2D).* This case represents a patient where the extracorporeal methods could be indicated, as serum lithium levels were borderline and the neurological examination showed decreased level of consciousness and tremor. Despite of that, forced diuresis worked well.

Another case report was published by Stetkarova *et al.* (2017) with the initial lithium serum levels of 2.7 mmol/L, which might be interpreted as moderate intoxication, presented with weakness of limbs, myoclonus, speech impairment and memory disturbances. Part of these symptoms seems to be similar to our case. Even in this case report, first differential diagnose was autoimmune encephalitis. Another interesting case was reported from China, where patient have had plasmatic concentrations around 0.6 mmol/L, but despite of that, had symptoms of Lithium intoxication. This suggests, that patient's sensitivity to lithium may differ. Also, this patient was treated by infusion of Mannitol, mainly due to the loss of consciousness (Peng 2014).

CONCLUSION

We presented a case of acute-on-chronic or more chronic lithium intoxication of elderly patient with bipolar affective disease and depressions who developed gastrointestinal and neurological symptoms of lithium intoxication, which was in the pre-hospital care and also during the first neurological examination in the hospital misinterpreted as stroke symptoms. This case was resolved on intensive care unit by forced diuresis, close monitoring of renal and cardiac functions and levels of serum sodium. The patient was dismissed 21 days after the admission with good neurological outcome.

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AUTHORS CONTRIBUTION

All of the authors made important intellectual contributions to the manuscript and all authors approved the final version before submission.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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