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What affects chronic lithium poisoning in psychiatric patients?- a case report

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ABSTRACT

INTRODUCTION: Despite medical developments, drug poisoning still occurs. Lithium is a drug that has been used for more than 60 years as a mood stabilizer in the treatment and prevention of bipolar disorder, mania and recurrent depression. Lithium is the most commonly prescribed mood stabilizer. It has a narrow therapeutic index. Its target concentration in acute mania should be 0.6-1.5 mEq/L and 0.6-0.8 mEq/L for maintenance therapy. Because of this, there is a risk of lithium intoxication. We would like to present to you the case of a patient with chronic lithium poisoning.

MATERIALS AND METHOD: Patient information was collected from hospital records available in the clinical toxicology department. In addition, we conducted a literature review on lithium treatment, its toxicity, side effects and pharmacokinetics using PubMed.

CASE REPORT: The patient, 58, was referred for lithium poisoning and admitted to the Clinical Toxicology and Cardiology Department in Lublin for treatment. The patient had a previous diagnosis of bipolar affective disorder, hypertension and obesity. According to the history, the patient was admitted to the psychiatric ward due to deterioration of her mental state for a month. She was found to have a high lithium level -2.98 mmol/L and elevated renal function parameters-creatinine 2.13 mg/dl. During treatment with hemodialysis, these parameters returned to normal.

CONCLUSION: It is important to remember that lithium has a narrow therapeutic range. Attention should be paid during lithium treatment to situations that increase the risk of adverse effects and the development of toxicity, and serum lithium concentrations should be monitored during treatment.

KEYWORDS: drug overdose; lithium; lithium overdose

INTRODUCTION

Despite medical developments, drug poisoning still occurs. Lithium is a drug that has been used for more than 60 years as a mood stabilizer in the treatment and prophylaxis of bipolar disorder, mania and recurrent depression. [1, 2] It reduces the risk of suicide, short-term mortality and violent behavior. [3, 4] Higher concentrations of lithium in tap water have been shown to be associated with less rape, homicide and suicidal behavior in the community. [1]

Lithium is the most commonly prescribed and least expensive mood stabilizer for the above-mentioned indications [4, 5], and of its salts, lithium carbonate is the most commonly used.[6] Despite this drug's long history of use, its mechanism of action is not fully understood. [7] It acts on glycogen synthase kinase-3 β (GSK3 β), serine/retreonin protein kinase, exhibits anti-inflammatory abilities (attenuation of neuroinflammation), and transiently increases serotonin release by decreasing norepinephrine and dopamine release from nerve endings which contributes to its properties. [6, 8, 9] Renal function, thyroid function, calcium, body weight should be checked, and electrocardiography may be performed before starting treatment with this product. These tests should be repeated every 6 weeks, 3 months, every 6 months, then annually, depending on the source. [3, 4, 10]

Lithium has a narrow therapeutic index. [11] Its target concentration in acute mania should be 0.6-1.5 mEq/L and 0.6-0.8 mEq/L for maintenance therapy. [5] European guidelines (from the National Institute for Health and Clinical Excellence [NICE]) recommend a much narrower plasma concentration of 0.6-0.8 mEq/L, while guidelines in the US recommend concentrations of 0.5-1.2 mEq/L . [1] It has been shown that increased excitability of human neurons and increased network activity can be caused by therapeutic concentrations of lithium. [12] On the other hand, during concentrations near the upper limit of the reference range of therapeutic concentrations, toxicity features may develop. [11] Lithium levels above 2 mEq/L are a life-threatening condition. [5]

Lithium carbonate is absorbed almost completely from the gastrointestinal tract. [7] Administration of lithium after a meal may delay its absorption, which may result in a decrease in its side effects, but should not affect the extent of its absorption. [5] Approximately 1-2 h after administration, there are maximum concentrations of immediate-release formulations, and 5-6 h after extended-release formulations. Peak concentrations in the brain are delayed and occur after about 24 h due to the fact that lithium must cross the blood-brain barrier. [1] The half-life is about 19h, although there are individual differences in this regard. [7] Lithium is eliminated by the kidneys and its clearance ranges from 0.6 to 2.4 L/h depending on individual variability. [5] The daily dose is usually 0.5 to 1.25 g of lithium carbonate. [7] It is recommended to take it in divided doses. [10] The dose should be increased gradually, and the therapeutic effect occurs after 1-3 weeks of treatment. [7]

Side effects of lithium therapy include tremor, diarrhea, thirst, polyuria, weight gain, nausea, acne, hyperparathyroidism, hypothyroidism, renal impairment, cognitive impairment, decreased emotional and/or perceptual intensity, cardiac arrhythmias, psoriasis. [4] Lithium can induce nephrogenic diabetes insipidus and increases the risk of congenital malformations (Ebstein's anomaly). [3] It should be noted that chronic lithium therapy increases the risk of acquired hypothyroidism, which in turn increases the risk of developing neurotoxicity in patients with chronic poisoning. [11] It is interesting to note that a low, short-term dose of lithium can be beneficial, having renal-protective effects, alleviating kidney and podocyte damage, while long-term exposure to high doses of lithium is nephrotoxic. [8] The literature describes cases of acquired lithium nonresponse in patients who had previously responded adequately to therapeutic concentrations. [10]

MATERIALS AND METHOD

Patient information was collected from hospital records available in the clinical toxicology department. In addition, we conducted a literature review on lithium treatment, its toxicity, side effects and pharmacokinetics using PubMed.

CASE REPORT

The patient, 58, was referred for lithium intoxication from the Center for Mental Health from Radzyń Podlaski, then admitted to the Clinical Toxicology and Cardiology Department in Lublin for treatment. The patient had a previous diagnosis of bipolar affective disorder, hypertension and obesity. The history showed that the patient had been admitted to the psychiatric ward due to deterioration of her mental state for a month.

The patient remained in a state of depressed mood, was psychomotorically slowed down and uttered delusional content; for several days the patient had not taken food or drink, had not taken prescribed medications, and there was muscle tremor. The patient was continuously treated with lithium (750 mg/d) and lamotrigine. In the psychiatric ward- she was found to have a high lithium level -2.98 mmol/l and elevated renal function parameters-creatinine 2.13 mg/dl. Due to concomitant diseases, the patient was receiving bisoprolol, lamotrigine, indapamide + perindopril, lercanidipine on a regular basis. At the time of admission, the patient was in a moderate-to-severe general condition, she was conscious, in a significantly impaired state, responded to simple questions, auscultation over the lung fields, alveolar murmur weakened, heart rate measured 80/min, tones quiet, BP 165/85 mmHg, saturation 94% On the first day of hospitalization, a dialysis puncture was inserted into the right internal jugular vein and a 4-hour hemodialysis procedure was performed. After dialysis, the lithium concentration was 1.1 mmol/L. After the treatment, there was a partial improvement in the general condition and normalization of renal parameters creatinine 1.05- at the end of treatment. During the stay, the patient was reluctant to make verbal contact and periodically refused to take meals and oral medications. After arranging the place, the patient was discharged and transported by medical transport to the psychiatric ward at SP ZOZ in Radzyń Podlaski.

DISCUSSION

Lithium has a narrow therapeutic window. [5] Toxic concentrations are close to therapeutic concentrations. [7] Levels above 2 mEq/L are a life-threatening condition. [5] Lithium poisoning is usually unintentional. According to the National Poison Data System, only 18% of poisonings across the United States in 2013 were the result of an intentional overdose. [11]

Table number 1 (Tab. 1.) lists symptoms according to the degree of poisoning (a classification developed by Hansen and Amdisen). [4, 9, 11]

Tab. 1. Classification of lithium poisoning developed by Hansen and Amdisen.

	DEGREE OF POISONING		
	Mild poisoning (Grade 1):	Moderate poisoning (Grade 2):	Severe poisoning (Grade 3):
LITHIUM CONCENTRATION	1,5-2,5 mEq/L	2,5-3,5 mEq/L	>3,5 mEq/L
SYMPTOMS	cognitive impairment, drowsiness, dysarthria, vomiting, tremor, hyperreflexia, agitation, ataxia, muscle weakness	confusion, disturbed gait, muscle twitching, vomiting, stupor, rigidity, hypertonia, hypotension	delirium, convulsions, ataxia, renal dysfunction, coma, convulsions, myoclonia, collapse

Lithium poisoning can be acute, acute to chronic or chronic.[9] Acute toxicity is usually caused by overdose, while chronic toxicity develops over several days or weeks as lithium accumulates in peripheral compartments. [1] Acute to chronic lithium toxicity occurs in patients who have an existing body burden of lithium from maintenance therapy and are acutely exposed to a high lithium burden. [9]

Table number 2 (Tab. 2.) lists symptoms by system. [10]

Table number 2 (Tab. 2.) Symptoms of lithium toxicity by system.

	SYMPTOMS
NERVOUS SYSTEM	disorientation state, cerebellar symptoms such as tremor, dysarthria, ataxia and nystagmus, extrapyramidal and neuromuscular symptoms, fasciculations, fibrillations and myoclonus, polyneuropathy
DIGESTIVE SYSTEM	nausea, vomiting ,diarrhea
KIDNEYS	polyuria, polydipsia, nephrogenic diabetes insipidus

CARDIOVASCULAR SYSTEM	arrhythmia, low blood pressure, rarely shock
IN ADDITION, THERE MAY BE	adult respiratory distress syndrome, thermoregulatory disorders

In acute overdose, abnormal patterns of neuronal network activity appear in human iPSC neuronal circuits resembling chemically induced epileptic activity. [12]

The only symptoms to distinguish acute from chronic poisoning are those of the gastrointestinal tract, and they occur frequently in acute poisoning and hardly at all in chronic poisoning. [9]

Chronic poisoning is the most common type of lithium poisoning and usually results from ingestion of lithium in amounts greater than its elimination. It is most often caused by impaired renal function. [11] Chronic lithium toxicity has a worse prognosis than acute lithium toxicity. [1] Its worst complication is neurotoxicity. [13] The risk of neurotoxicity is lowest in acute poisoning and highest in chronic poisoning. [11] The syndrome of irreversible lithium-induced neurotoxicity (SILENT) has been described, in which patients have chronic cerebellar sequelae (tremor, extrapyramidal symptoms, difficulty walking, nystagmus, dysarthria and cognitive deficits) even after withdrawal and normalization of lithium levels. [9] The severity of this neurotoxicity correlates poorly with lithium concentrations, which return to normal fairly quickly. Most of this type of poisoning occurs in elderly patients with acute kidney damage. Often these conditions are compounded by drug interactions and dehydration. [13]

Situations that can exacerbate the onset of lithium poisoning are: prescription/dispensing errors, impaired renal elimination of lithium (kidney disease, old age), dehydration, increased water and/or salt loss (e.g., gastrointestinal infection, increased sweating), decreased water and/or salt intake (e.g., various medical conditions) diabetes, drug interactions, hypothyroidism, surgery, diarrhea, vomiting, heart failure, renal failure. [3, 4, 11]

Several classes of drugs are involved in the development of lithium toxicity. [1] Table number 3 (Tab. 3.) includes drugs that react with lithium. Particularly noteworthy are drugs that increase the concentration of lithium at steady state, which can cause symptoms of toxicity. [1, 4, 5, 7, 11, 14]

Table number 3 (Tab. 3.) Drugs that react with lithium.

<p>SUBSTANCES THAT INCREASE SERUM LITHIUM LEVELS</p>	<p>Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers β-blockers Cisplatin Cyclooxygenase-2 inhibitors Cyclosporine A Methyldopa Metronidazole Nonsteroidal anti-inflammatory drugs (indomethacin, ketoprofen) Phenytoin Tetracycline Thiazide diuretics Verapamil</p>
<p>SUBSTANCES THAT LOWER SERUM LITHIUM LEVELS</p>	<p>Acetazolamide Aminophylline Theophylline Topiramate Caffeine Nifedipine Osmotic diuretics Sodium bicarbonate Bulk-forming laxatives</p>
<p>DRUGS THAT MAY WORSEN NEUROTOXICITY</p>	<p>Antidepressants Antipsychotics Carbamazepine Diltiazem Verapamil Serotonin receptor agonists Piroxicam Phenytoin</p>
<p>SUBSTANCES POSSIBLE TO AGGRAVATE THYROID CHANGES</p>	<p>Iodide salts or iodine Phenytoin Carbamazepine</p>

SUBSTANCES THAT CAN INCREASE POLYURIA	Antidepressants Phenytoin
MAY CONTRIBUTE TO SINUS NODE DYSFUNCTION	Carbamazepine

The patient admitted to the Clinical Department of Toxicology and Cardiology in Lublin presented features of lithium poisoning and renal failure. According to the history, before admission to Radzyn Podlaski, the patient's condition had been deteriorating for a month and the symptoms indicated chronic lithium poisoning (depressed mood, psychomotor retardation, delusional utterances, muscle tremor). The most common cause of chronic lithium poisoning is due to impaired renal function as a result of lithium use. It is worth noting that the patient had not taken food or drink for several days, which exacerbated the onset of renal failure. It is also important to note the medications the patient was taking. The patient was taking a drug with the trade name: Noliprel Bi-forte, it is a combination of indapamide and perindopril. This drug is not recommended during treatment with lithium, it can increase its concentration and exacerbate its toxic effects. The manufacturer notes that if treatment with this drug and lithium is required, blood lithium levels should be monitored frequently. [15]

In our patient, the renal failure that resulted in the development of chronic lithium poisoning was most likely compounded by several factors-an inadequate dose of lithium that exceeded the ability of the kidneys to eliminate it, the use of medications that increase serum lithium concentrations, and dehydration.

At the time of admission, the patient was in moderate-to-severe general condition, was conscious, in much impaired communication, and answered simple questions. During her stay, the patient was reluctant to make verbal contact and periodically refused to take meals and oral medications. We have no information on the development of neurotoxicity and SILENT syndrome.

Elderly and pediatric patients are most at risk for unintentional lithium toxicity, as they are often unable to tolerate plasma concentrations near the upper end of the recommended therapeutic range, experiencing side effects at concentrations that are generally well tolerated in adults. [1, 14]

There is no known specific antidote for lithium poisoning. [7] Treatment of the poisoned patient includes assessment and stabilization of airway, breathing and circulation in an appropriately monitored environment, and discontinuation of lithium as soon as possible after the onset of adverse effects. [7, 11] Volume resuscitation with intravenous isotonic saline should be sought. In cases of acute overdose, intestinal irrigation is recommended rather than activated charcoal. [9] Because lithium is small (6.94 Da), does not bind to plasma proteins and has a relatively small volume of distribution (0.8-1.2 L/kg) and relatively slow endogenous clearance (15-20 mL/min), it is an easily dialyzable substance. [11]

Intermittent hemodialysis (HD) is described as the most effective intervention to remove lithium from the body. [9] It should be used in patients with neurological symptoms, severe toxicity, and subsequent monitoring of lithium levels in the body. [7] Rapid reduction of plasma lithium by dialysis can prevent accumulation in the brain (toxic compartment) and/or create a favorable concentration gradient to facilitate diffusion of lithium back into the plasma (nontoxic compartment). [11] The recommendations of the Extracorporeal Treatments in Poisoning (EXTRIP) Working Group for lithium poisoning are included in table number 4 (Tab. 4.) . [7, 9]

Table number 4 (Tab. 4.) Recommendations of the Extracorporeal Treatments in Poisoning (EXTRIP) Working Group for lithium poisoning .

CLINICAL SITUATION	PROCEDURE	CONTINUATION OF TREATMENT
severe lithium poisoning	Extracorporeal treatment recommended	Extracorporeal treatment should be continued until clinical improvement is evident or [Li+] is <1.0 mEq/L. Extracorporeal treatment should be continued for at least 6 hours if [Li+] is not readily measurable. Hemodialysis is the preferred method of extracorporeal treatment, but continuous RRT is an acceptable alternative.
renal function is impaired and [Li+] is >4.0 mEq/L, or in the presence of decreased level of consciousness, seizures, or life-threatening cardiac arrhythmias regardless of [Li+]	Extracorporeal treatment recommended	
if [Li+] is >5.0 mEq/L, there is significant disorientation, or the expected time to reduce [Li+] to <1.0 mEq/L is >36 hours	Extracorporeal treatment suggested	
mild cases of poisoning	Discontinue the drug for 1 - 2 days and possibly increase the supply of NaCl and water (resumption of treatment should be started with lower doses, serum lithium concentrations should be monitored.	

The patient at the Radzyń Podlaski Ward was found to have a high lithium level -2.98 mmol/l and elevated renal function parameters-creatinine 2.13 mg/dl. Due to the fact that at the time of admission the patient was in a moderate-to-severe general condition, she was conscious, but significantly impaired in communication, responding to simple questions, auscultation over the lung fields, alveolar murmur weakened, heart rate steady 80/min, tones quiet, BP 165/85 mmHg, saturation 94%, it was decided to insert a dialysis line on the first day of hospitalization. This was followed by a 4-hour hemodialysis procedure. After dialysis, the lithium concentration was 1.1 mmol/L. After the treatment, a partial improvement of the general condition and normalization of renal parameters creatinine 1.05- at the end of treatment were achieved.

After an overdose, it is recommended that re-treatment with lithium should be implemented slowly after clinical improvement, therapeutic plasma concentrations are achieved, and the individual patient's lithium re-poisoning is considered. [11]

CONCLUSION

During lithium therapy, it is important to remember that lithium has a narrow therapeutic range. The risk of developing side effects, and the potential development of toxicity, increases with age, drug interactions, dehydration, and sodium deficiency. Pay attention to the medications the patient is taking, and monitor serum lithium levels as treatment progresses.

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