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# A rare case of fatal poisoning during long-term therapy with lithium carbonate – suicide, chronic poisoning or psychiatric malpractice?

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**Summary**

The study aims to present a case of atypical poisoning with lithium carbonate in a 57-yearold woman treated for bipolar affective disorder with lithium carbonate for about 30 years. The patient was admitted to the hospital with significant agitation. An important finding obtained from the family interview was the patient's significant weight loss over the past year. In the hospital, the patient received haloperidol and clonazepam. Laboratory tests showed a very high blood lithium concentration of 3.79 mmol/l (N: 0.6–1.2 mmol/l) and elevated serum concentrations of creatinine (3.6 mg/dl) and urea (110 mg/dl). The patient was transferred to the toxicology department, where hemodialysis was performed and intensive treatment initiated. Despite the rapid decrease in lithium levels, her condition gradually deteriorated. The patient died on the fifth day of hospitalization. The autopsy revealed polycystic kidney disease (PKD). During the preparation of the medico-legal report on the correctness of the medical treatment, it was assumed that the cause of death was lithium carbonate poisoning in the course of advanced chronic kidney disease due to PKD, probably a consequence of long-term lithium therapy. The analysis of medical records revealed that despite her psychiatrist's recommendation, the patient had been refusing the monitoring of lithium levels for the past 18 years. This case demonstrates that both psychiatrists and toxicologists should be aware of possible lithium poisoning upon

the deterioration of renal function. Therefore, assessment of renal function should be an integral part of lithium therapy monitoring.

**Key words**: lithium toxicity, renal failure, polycystic kidney disease

## Introduction

Lithium carbonate is a first-generation mood stabilizer commonly used to treat the bipolar affective disorder (BPAD) [1, 2]. It was first used in the treatment of mania in 1949. The therapeutic efficacy of the drug is similar to that of valproates and carbamazepine. It is used primarily in the management of moderate mania and the prevention of BPAD [3].

Monotherapy with lithium salts results in complete resolution of signs and symptoms in one-third of patients (the group of so-called excellent lithium responders) who have a typical disease with moderate episode frequency and asymptomatic periods of remission between episodes. Long-term lithium administration also results in a fivefold reduction in the risk of suicidal behavior.

Severe lithium poisoning is rare, and it is typically characterized by confusion, seizures and memory impairment, and may lead to coma [4, 5]. It may also disrupt the cardiac conduction system, causing bradycardia and cardiac arrhythmias. Poisonings are most often accidental, but suicidal attempts using this drug have also been reported [6]. Kidney adverse drug reactions (ADRs) related to lithium salt intake include nephrogenic diabetes insipidus, chronic tubulointerstitial nephropathy, acute kidney injury, and nephrotic syndrome [7].

This study aims to present a case of atypical poisoning with lithium carbonate from the consultative practice of the Department of Forensic Medicine and Forensic Toxicology of the Medical University of Silesia in Katowice.

## Case study

A 57-year-old female patient treated for BPAD with lithium carbonate for about 30 years, mainly outpatient, was admitted to hospital without her consent on 13 July 2015 under Article 23 of the Mental Health Protection Act. The patient was brought by an ambulance, probably called by the neighbors. In the patient care report, the paramedic wrote: “the patient was running around the flat and up and down the staircase naked, she demolished the flat, is coherent; apparently she is undergoing psychiatric treatment.” Also, the emergency room doctor noted the following: “The patient is agitated, she shouts out single clear sentences but becomes unintelligible with longer utterances. General condition: extreme emaciation, inadequate hygiene. Mental condition: the patient is conscious, not fully coherent, agitated, anxious, exclaims single sentences. Preliminary diagnosis: Psychosis NOS. F29.” In the justification for involuntary admission, the doctor wrote: “the patient trashed her flat and tried to hit a nurse in the A&E room.” As revealed by her brother, the patient had been treated at a mental health clinic for many years, taking lithium salts (0.25 g – recently four tablets per day) and clomipramine (SR 75 mg – 1 tablet per day). Moreover, she had lost about

25 kg in weight over the past year and was diagnosed for this reason – the ultrasound only revealed a solitary lesion in her right kidney. Two days before admission to the hospital, the patient was consulted in the emergency room, but she did not consent to hospitalization.

In the hospital, treatment was started with haloperidol 2.5 mg twice a day and clonazepam 1 mg twice a day, and the patient was also given intravenous hydration. On the day of admission, basic laboratory tests were ordered, including lithium levels. At night the patient was agitated and incoherent; she was immobilized; she struggled and repeatedly shouted. On the second day of hospitalization, the patient developed a fever of 38.8°C. Laboratory tests showed, among others, a very high blood lithium concentration of 3.79 mmol/l (N: 0.6–1.2 mmol/l] (Table 1) and elevated serum concentrations of sodium (153 mmol/l), creatinine (3.6 mg/dl) and urea (110 mg/dl). Following a telephone consultation, the patient was referred to the clinical toxicology department for further treatment.

Table 1. **Serum lithium concentrations measured during the patient's hospitalization**

| Date and time of measurement | First day, 15:48 | Third day, 00:22 | Third day, 07:41 | Third day, 17:32 |
|---|---|---|---|---|
| Serum lithium concentration [mmol/l] | 3.79 | 0.85 | 0.93 | 1.12 |

On admission to the toxicology department, the patient was in a serious state, conscious but incoherent, physically agitated, in a stable respiratory and circulatory condition, normotensive (115/55 mm Hg), and with normal heart activity on the ECG monitor. Significant laboratory findings included increased renal parameters and hypernatremia. Due to psychomotor agitation, direct immobilization and a continuous infusion of sedative drugs were applied. After insertion of a dialysis catheter through the right internal jugular vein, one-hour hemodialysis (HD) procedure was performed, achieving a reduction in lithium concentration to therapeutic values. During HD, bradycardia of up to 44 beats per minute was observed, which resolved after administration of atropine. Due to hypotension reaching 75/40 mmHg, norepinephrine infusion was administered, followed by dopamine. Three hours after the end of HD, due to increasing respiratory failure, the patient was intubated and put on a ventilator. Control blood lithium concentrations were below toxic values (Table 1). On the second day of hospitalization, there were four episodes of sudden cardiac arrest: one with asystole and three with ventricular fibrillation. Due to recurrent, complex ventricular arrhythmias in the form of sustained and non-sustained ventricular tachycardia and numerous additional contractions (bigeminy, pairs), the amiodarone infusion was ordered, and an endocavitary electrode was placed to stimulate the heart. In addition, empirical antibiotic therapy with amoxicillin and clavulanic acid was introduced due to developing pneumonia with fever and increased laboratory inflammatory markers (with numerous risk factors for infection: respiratory therapy, central line, dialysis catheter). Antipyretic drugs were also administered. Despite intensive treatment, the patient's condition deteriorated, and she died after five days of treatment. The clinical diagnosis was as follows: "Accidental lithium overdose in a patient on chronic lithium

treatment complicated by multiple organ failure –acute cardiorespiratory failure, renal failure and complex ventricular arrhythmias. Acute liver injury and its failure. Pneumonia. Electrolyte disturbances."

A university department of forensic medicine carried out a medico-legal autopsy and additional histopathological and neuropathological examinations. No post-mortem determinations of lithium concentrations in internal organs were performed. The autopsy revealed, among others, polycystic kidney disease (PKD) with cysts size ranging from 0.1 to 2.0 cm. During the preparation of the medico-legal report on the correctness of the medical treatment of the patient, it was assumed that the underlying cause of death was lithium poisoning in the course of chronic kidney disease due to PKD. The analysis of the case revealed that the patient constantly refused the monitoring of blood lithium levels for the past 18 years, despite the recommendations of her attending psychiatrist, which was confirmed by multiple medical entries in the outpatient documentation.

The recommendations for monitoring blood lithium levels are not considered a medical standard. According to Polish guidelines (*Pharmacological treatment standards for chosen mental disorders*), the blood lithium concentration should be monitored during therapy [2]. It is recommended that in the initial period of lithium treatment, its blood levels are to be determined every 1–2 weeks, whereas, during the prevention of relapse of affective disorders, determinations are required only every 2–3 months. Periodic control is also particularly recommended (justified) in patients with renal impairment, thyroid insufficiency, pregnancy, dehydration cases. It is also recommended for monitoring therapeutic adherence (patient's compliance with medical recommendations). Follow-up tests are also warranted when the dosage of lithium carbonate is modified. The blood should be drawn before taking the morning dose, approximately 12 hours after the evening one (the so-called 12-hour level) [8]. For the prevention of relapse of affective disorders, the concentration should be maintained in the range of 0.5–0.8 mmol/l, and for the treatment of manic episodes, it should be between 0.8–1.0 mmol/l. The concentration should not exceed 1.2 mmol/l.

According to toxicological literature, serum lithium concentration does not directly correlate with the concentration of lithium in the brain (central nervous system) – the target organ for this drug. There have been reported cases of neurotoxic effects at therapeutic serum lithium levels, although such cases are rare [9]. In chronic poisoning with lithium compounds, as opposed to acute poisoning, there is usually a correlation between lithium concentration in the blood and the severity of toxic signs and symptoms. Suppose toxic levels of lithium persist in the blood for a long time. In that case, these ions gradually distribute to the central nervous system, which leads to the appearance of toxic concentrations of lithium in the cerebrospinal fluid and the occurrence of neurological signs and symptoms of poisoning.

In the analyzed case, the patient refused to perform the check-ups recommended by the doctor. Of course, such tests cannot be performed without the patient's consent. Therefore, the doctor was faced with the decision of whether to deny the patient the drug that was necessary for effective treatment of bipolar disorder due to a lack of cooperation or to prescribe it despite these difficulties due to her mental health condi-

tion. No standards or guidelines say that the doctor should refuse to prescribe lithium when the patient is uncooperative. In each case, a personalized decision is made at the doctor's discretion. However, the case described here may indicate the need to refuse to prescribe the drug if the patient does not have periodic check-ups. An option to treat with another mood-stabilizing medication that does not require laboratory monitoring could be considered. From an ethical point of view, it is a choice between two courses of action in the patient's interest, of which one ensures treatment maintenance and relapse prevention with proven efficacy, and the other ensures that the patient is not exposed to the risk of overdose (poisoning). Regular testing of lithium levels, serum creatinine and GFR in the discussed patient could have led to the detection of advanced kidney disease and, consequently, a change in the therapeutic management. As stated in the summary of product characteristics, "Due to the increased risk of toxic effects, lithium should not be administered to patients with severe kidney disease."

It cannot be ruled out that the patient took a single high dose of lithium (e.g., for suicidal purposes). However, according to the authors, it is more likely that the reason for the increase in lithium concentration (while maintaining a constant dose) was the deterioration of kidney function – the development of chronic PKD, as indicated by post-mortem findings. A similar case has already been described in the literature [10]. The patient was at the age when renal excretory function typically deteriorates due to autosomal dominant polycystic kidney disease (ADPKD). Determination of the chronic disease stage is impossible as we have no earlier assessments (within a preceding three-month period) of laboratory parameters. Additionally, cachexia of the patient increases the error in the estimation of glomerular filtration rate (GFR) based on Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration equations widely used in daily clinical practice. Lack of appetite and weight loss may be considered as symptoms of an advanced stage of chronic kidney disease. Therefore, it can be presumed that the patient was taking a constant dose of the drug, but the impaired excretion of lithium caused lithium accumulation in the body. However, it cannot be ruled out that small cystic lesions formed in the kidneys were caused by the long-time exposure to lithium, especially since they were not clearly visualized in abdominal ultrasound examination, which would be very likely in the case of ADPKD. Microcysts occurring in the kidneys during lithium treatment are detected by magnetic resonance imaging [11]. They usually appear after about 20 years and are 1 to 3 mm in diameter [12]. In the study of Jończyk-Potoczna et al. [13], it was stated that the changes characteristic for lithium nephropathy, detectable by ultrasound examination, are rare and seen only in patients treated with lithium for 20 years or more, and the presence of macrocysts in the kidneys of lithium-treated bipolar patients is associated with impaired renal function.

The problem of interstitial nephropathy, which occurs most often after 10–20 years of lithium treatment and is manifested by an increase in creatinine concentration and a decrease in GFR, is pointed out by Rybakowski [2] in the latest Polish discussion on the use of lithium in psychiatry. According to the author, in patients with lithium nephropathy, renal function should be frequently monitored, and in the case of progressive changes, the dose of lithium should be reduced. An example of such approach can be

found in the study of Abramowicz et al. [14] which presents the results of observation of patients treated with lithium whose GFR was lower than 50 ml/min/1.73 $m^2$. The patient with GFR 32 ml/min/1.73 $m^2$, after five years, had a 14% decrease in GFR, and a 10% increase in serum creatinine. In him, the dose of lithium was decreased by one-third and he was placed on systematic nephrological observation [14].

Lithium is excreted from the body almost exclusively through the kidneys (95–98%). Hence, the main factor determining lithium elimination is its renal clearance [15]. Approximately 70% of the excreted lithium ions are reabsorbed in the proximal convoluted tubule and about 10–15% in the descending nephron loop. Lithium is excreted in two phases. In acute overdose, about two-thirds is excreted within 6–12 hours, and the remainder is excreted within 10–14 days [16]. It should be emphasized that the primary indication for hospitalization should be the clinical condition of the patient and not the blood lithium concentration alone. Chronic users of lithium salts may tolerate well blood lithium concentrations above therapeutic values [17].

## Conclusions

Both psychiatrists and toxicologists should be aware of possible lithium poisoning due to concomitant kidney disease. Therefore monitoring of renal function should be an integral part of lithium therapy. In the authors' opinion, it is justified to determine serum creatinine concentration at least once a year in patients with average values (similarly to patients with diabetes) to prevent complications illustrated in the presented case. The described case may contribute to the formulation of clear guidelines by the National Consultant in psychiatry on dealing with patients who refuse to perform follow-up examinations recommended to ensure patient safety during treatment.

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