

Lithium intoxication and nephrogenic diabetes insipidus: a case report and review of literature

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Abstract: Lithium is one of the drugs used widely in the treatment of mood disorders. However, it has a very narrow therapeutic index and side effects can be seen in many organ systems, one of which affects the kidneys. We can see varying degrees of renal damage associated with acute or chronic lithium use. Lithium intoxication is diagnosed by a rise in the serum lithium concentration, but it must be remembered that serum levels and clinical findings do not always overlap. Treatment of lithium intoxication varies according to the clinical findings. There are various ways of treating lithium intoxication, but there is no specific antidote. The purpose of treatment is to remove the toxin from the body. Here we report a patient who was treated for lithium intoxication and developed diabetes insipidus during follow-up, and discuss the relevant literature.

Keywords: diabetes insipidus, intoxication, lithium

Introduction

Lithium salts have been used in clinical practice since the 1970s. Widely used in the treatment and prophylaxis of bipolar disorder, lithium has a very narrow therapeutic index and toxicity is common in patients taking this agent. The effects of lithium on the kidney, thyroid, and parathyroid causes changes in body weight and the skin, and causes congenital malformations. Although often used to treat patients with a range of mood disorders, lithium has been associated with several forms of renal injury, the most prevalent of which is impaired urinary concentrating ability, which is estimated to be present in at least 50% of individuals on chronic lithium therapy. Drug-induced diabetes insipidus is almost always of the nephrogenic type. Lithium is the most common drug implicated.¹

Case report

A 70-year-old man was admitted to emergency service with speech difficulty and changes in his state of consciousness. He was found to be unable to walk. His general condition was poor, and he was agitated, confused, disorientated, and uncooperative. According to the family, he had been taking lithium for 9 years for bipolar affective disorder and had taken too much lithium on the previous day. There was no family history of diabetes insipidus, renal disease, or endocrine problems. On physical examination, his blood pressure was 100/60 mmHg, his heart rate was 76 beats per minute, and his temperature was 36.8°C. The only features of note were speech difficulty and muscle weakness.

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While in the emergency department, the patient's condition worsened, his agitation increased, and respiratory distress developed, so he was intubated and mechanical ventilation was performed. His laboratory findings were as follows: glucose 154 mg/dL, blood urea nitrogen 16 mg/dL, creatinine 1.1 mg/dL, sodium 137 mmol/L, potassium 4.3 mmol/L, chloride 112 mmol/L, plasma osmolality 288 mOsm/L, and urine density 1005. His renal function tests, thyroid function tests, and adrenocorticotrophic hormone and cortisol levels were normal. His serum lithium level was 2.7 mmol/L (therapeutic range 0.6–1.2 mmol/L). The patient was admitted to the intensive care unit because of his deteriorating clinical condition, where he received emergency hemodialysis.

The patient's urine output increased with 24 hours of hemodialysis (11,000 mL/24 hours). Laboratory findings at that time were as follows: blood urea nitrogen 14 mg/dL, creatinine 0.9 mg/dL, sodium 159 mmol/L, plasma osmolality 329 mOsm/L, and urine density 1005, so the patient was thought to have developed diabetes insipidus, and desmopressin was started at 6 µg three times daily via subcutaneous injection.

Because of the patient's worsened clinical condition, desmopressin was given immediately because there was not adequate time to perform a water deprivation test or desmopressin stimulation test. On day 2 of follow-up, the patient no longer needed mechanical ventilation and was extubated. On day 4 of treatment with desmopressin, laboratory findings were as follows: sodium 148 mmol/L, plasma osmolality 306 mOsm/L, and urine density 1013. His urine output had returned to normal levels (2,850 mL/24 hours), so desmopressin was stopped. The plasma lithium level after hemodialysis was 0.5 mmol/L.

However, on the following day, his serum sodium was 160 mmol/L, his plasma osmolality was 336 mOsm/L, and his urine output was noted to be 5,000 mL/24 hours, so treatment with desmopressin was restarted. The patient's response

to desmopressin is shown in Table 1. One week later, the patient's urine output and laboratory findings had returned to normal levels (sodium 136 mmol/L, plasma osmolality 287 mOsm/L, urine density 1008), so the desmopressin was stopped. The patient recovered without sequelae and was discharged after a psychiatry consultation.

Discussion

Lithium is recommended as first-line therapy in the guidelines for treatment of bipolar disorder. For more than 50 years, lithium salts have been used in the prophylaxis and treatment of depression and bipolar disorder. Together with other well characterized adverse effects, use of lithium has been limited by its narrow therapeutic index. Patients receiving lithium for bipolar disorder may experience acute or chronic toxicity during treatment. The recommended therapeutic concentration for lithium is 0.8–1.2 mEq/L (0.8–1.2 mmol/L). Although serum lithium concentrations are high in acute lithium intoxication, the target tissues are protected to some degree. Serum lithium concentrations do not reflect tissue levels and the correlation between lithium levels and toxicity is poor, so few symptoms may be seen. In the treatment of acute lithium intoxication, symptoms must be considered rather than serum lithium levels.²

Acute toxicity commonly presents as neurotoxicity, nephrogenic diabetic insipidus, or thyroid dysfunction. In patients taking long-term lithium therapy, concentrations in the therapeutic range are associated with poor memory, fatigue, loss of concentration, and a fine tremor. Lithium has a narrow therapeutic index, so a large proportion of patients on chronic lithium therapy experience at least one episode of toxicity during treatment. The highest intracellular lithium levels are found in the brain and the kidneys. Nephrogenic diabetes insipidus is the most common renal side effect of lithium.² Although nephrogenic diabetes insipidus may persist, acute renal toxicity is temporary. However, patients with severe lithium intoxication have shown persistent

Table 1 Response to desmopressin in a patient with lithium-induced nephrogenic diabetes insipidus

	Glucose (mg/dL)	Blood urea nitrogen (mg/dL)	Sodium (mmol/L)	Plasma osmolality (mOsm/L)	Urine density	Urine volume (mL/24 hours)	Desmopressin dose frequency (6 µg)
Admission	154	16	137	288	1005	–	–
Day 1	104	14	159	329	1005	11000	Three times daily
Day 2	133	13	158	328	1006	6800	Three times daily
Day 3	125	22	158	332	1006	4300	Three times daily
Day 4	89	15	148	306	1013	2850	Stopped
Day 5	165	20	160	336	1005	5000	Three times daily
Day 12	113	25	136	287	1008	2800	Stopped

cerebellar damage with, for example, tremor, ataxia, and dysarthria, and persisting basal ganglia problems have also been described. The clinician should determine the severity of the intoxication from the history and serial lithium levels. In chronic use, nephrogenic diabetes insipidus often becomes irreversible. In one study, patients who had been on lithium for more than 18 years invariably had an irreversible defect.³

Antidiuretic hormone (arginine vasopressin) is secreted by the hypothalamus, and stored and released by the posterior pituitary. This hormone has a key role in the control of body fluids. Its signaling mechanism is mediated by G protein-coupled receptors and is directly related to increased intracellular cyclic adenosine monophosphate. Normally, water permeability of principal cells in the collecting tubule is regulated by antidiuretic hormone. Under the influence of antidiuretic hormone, aquaporin-2 water channels, which normally reside in the endosomes of principal cells, and move to and fuse with the luminal membrane, allow water to be reabsorbed down a favorable concentration gradient.

The ability of the kidneys to retain water and concentrate urine is regulated by antidiuretic hormone, the osmolality of the renal medulla, appropriate sodium transport, and the function of aquaporins.⁴ Aquaporins are water channels inside proteins expressed in the renal tubules and collecting ducts. The greater the activation of aquaporins, the greater the water resorption in the renal collecting ducts, thereby reducing the volume of urine. When expression of aquaporins is inhibited, polyuria ensues. Nephrogenic diabetes insipidus is characterized by an inability of the kidney to concentrate urine, even in the presence of normal concentrations of antidiuretic hormone, causing a clinical polyuric syndrome.

Binding of antidiuretic hormone to the vasopressin receptor V2 receptor stimulates expression of aquaporins in the kidney. Lithium inhibits expression of these aquaporins in the renal collecting duct, mainly aquaporin-2, by mechanisms that are still not fully understood. Most studies show inhibition of adenylate cyclase activity.⁵

At concentrations greater than 1.5 mmol/L, patients become ataxic, hypertonic, hyperreflexic, dysarthric, and confused. A coarse tremor and muscle fasciculation are common. At lithium concentrations greater than 3 mmol/L, patients may progress to seizures, coma, and irreversible brain damage. Diabetes insipidus is a condition marked by polyuria caused by an inability of the kidneys to resorb free water. There are various causes of diabetes insipidus, which can be further classified into central and nephrogenic subgroups.

Central diabetes insipidus is characterized by injury to the neurohypophysial system and is often the result of hypoxic encephalopathy, iatrogenic injury to the pituitary gland during surgical procedures, and autoimmune attack on vasopressin-producing cells in the hypothalamus. Nephrogenic diabetes insipidus is also characterized by an inability of the kidneys to respond to adequate levels of vasopressin, often the result of chronic lithium use, which injures the collecting ducts of the kidneys.⁶ It is also characterized by polydipsia, polyuria, and an inability to concentrate urine, and results from unresponsiveness of the kidneys to the effects of antidiuretic hormone. Polyuria, polydipsia, and nephrogenic diabetes insipidus are frequent complications of treatment with lithium, and may be present shortly after starting treatment.

Lithium accumulates in the distal tubular cells of the kidneys at concentrations 10–20 times higher than in serum, and at toxic serum concentrations is associated with degenerative changes and necrosis of the tubular cells. Chronic treatment with lithium commonly produces a defect in the concentrating ability of the kidney due to inhibition of generation of cyclic adenosine monophosphate by antidiuretic hormone at the distal tubule, with lithium probably acting via adenylate cyclase and possibly also at a point distal to the generation of cyclic adenosine monophosphate. About 30%–90% of patients show lowered maximum urine osmolality.⁷

Lithium is filtered completely at the glomerulus and absorbed in the proximal tubule, so the clearance of lithium is approximately 30% of creatinine clearance. Its predominant toxicity is at the distal tubule and is related partially to effects on inhibition of adenylate cyclase and generation of cyclic adenosine monophosphate. This inhibition promotes accumulation of glycogen, so glycogen can be seen clearly in the distal tubules on renal biopsy. Deposition of glycogen causes tubular dysfunction, and later, tubule loss and scarring can be seen. At doses in the toxic range, the proximal tubules may also be affected. Therefore, low-dose (and usually chronic) toxicity is associated with distal tubular abnormalities, and high-dose toxicity characteristically manifests as proximal tubular damage, when a prerenal effect is often also seen.

The exact mechanism of action of lithium is not clearly understood. It affects two intracellular signaling pathways, ie, inositol monophosphate and glycogen synthase kinase-3.⁸ Lithium decreases intracellular inositol, which may be the mechanism for mood stabilization, and also inhibits glycogen synthase kinase-3, a component of diverse signaling pathways involved in energy metabolism, neuroprotection, and neuroplasticity.

Lithium enters the collecting tubule cells via highly selective sodium and lithium channels located in the apical membrane, causing increased sodium excretion and decreased renal tubule responsiveness to aldosterone and antidiuretic hormone. These channels are stimulated by aldosterone and inhibited by amiloride.⁹

Lithium is a small molecule (74 Da) with no protein or tissue binding, so is amenable to hemodialysis. Lithium is freely distributed throughout total body water, with a volume of distribution of 0.6–0.9 L/kg, although the volume may be smaller in the elderly, who have less lean body mass and less total body water. At the usual oral dose of 1200–1800 mg/day, steady-state serum levels are typically reached within 5 days. The half-life for lithium is approximately 18 hours in adults and 36 hours in the elderly. Hemodialysis is now accepted as the treatment of choice for serum lithium concentrations in excess of 3.5 mmol/L or in a clinically unstable patient. Lithium is easily removed by dialysis, but its intracellular concentration falls slowly because of slow movement between compartments, and serum concentrations may rise after hemodialysis as further lithium moves out of the intracellular compartment, as seen in our patient. Current recommendations state that hemodialysis should be continued until lithium concentrations are consistently below 1 mmol/L after equilibrium has been established. The issue to address in the treatment of lithium toxicity is maintaining the perfect salt-water balance.¹⁰ The goal of treatment is to obtain the support therapy which can remove the toxin from the body. Hemodialysis is one of the methods which can be used in the treatment of lithium intoxication, and is used especially for patients in whom the lithium concentration is over 3.5 mEq/L or those with concomitant renal failure, heart failure, and pulmonary edema. In our patient, although the lithium level was 2.7 mEq/L, his clinical condition was poor (he was disorientated and uncooperative), so he received emergency hemodialysis.

Thiazide diuretics are a therapeutic option in nephrogenic diabetes insipidus, but hydrochlorothiazide should be used with caution in these cases because of the potential to increase lithium toxicity. Amiloride would be a better option because, in addition to its natriuretic action (causing contraction of extracellular volume, consequent decrease in glomerular filtration, and ultimately leading to decreased urine volume), it also reduces entry of lithium into the distal tubule cells.⁴

Another treatment option is a nonsteroidal anti-inflammatory drug such as indomethacin, but this should not be given on a long-term basis because of its side effects.¹¹ Some patients with congenital nephrogenic diabetes insipidus

respond to large doses of desmopressin.¹² Large doses of desmopressin can reverse lithium-induced vasopressin-resistant polyuria in the rat.¹³ One report demonstrated that some patients with lithium-induced nephrogenic diabetes insipidus can have a partial response to large doses of desmopressin, and the authors suggested that high-dose desmopressin therapy should be considered as a means of treating patients with nephrogenic diabetes insipidus during lithium therapy.¹⁴ Diabetes insipidus developed in our patient during follow-up, so large doses of desmopressin were administered, after which urine volume and plasma osmolality decreased. The rises in urine volume and plasma osmolality after cessation of desmopressin indicated a response to treatment with this agent. After hemodialysis, the lithium levels decreased and the patient did not need further treatment with desmopressin.

Therefore, in the follow-up of a patient with lithium intoxication, the clinician must be careful about nephrogenic diabetes insipidus and take the decision to start hemodialysis quickly. The clinician is also reminded that nephrogenic diabetes insipidus due to lithium intoxication may respond to treatment with desmopressin as well as thiazides, amiloride, and nonsteroidal anti-inflammatory drugs. More studies are needed about the use of desmopressin in the treatment of nephrogenic diabetes insipidus due to lithium intoxication.

Disclosure

The authors report no conflicts of interest in this work.

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