RENAL TOXICITY OF LITHIUM

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SUMMARY – Lithium is a therapeutic agent currently in widespread use for the treatment of bipolar disorder. Chronic lithium ingestion in patients with bipolar (manic-depressive) illness has been associated with several different forms of renal injury. Nephrogenic diabetes insipidus is most common, but renal tubular acidosis, nephrotic syndrome, and chronic interstitial nephritis have also been described. Therapy for lithium poisoining depends on the adequacy of renal function and the degree of intoxication.

Key words: *Lithium, poisoning; Poisoning, therapy; Lithium, pharmacokinetics; Biological transport; Lithium therapeutic use*

Introduction

Normally, lithium is not present in significant amounts in body fluids (less than 0.2 mmol/L). Lithium salts have been used therapeutically for almost 150 years, beginning with their use in the treatment of gout (or uric acid diathesis) in the 1850s[1]. The widespread use of lithium became problematic and it was abandoned because of serious toxicity.

The modern era of lithium usage as a pharmacologic agent began with its 'rediscovery' in 1950 by Cade and clinical studies by Schou in the 1950s that established lithium as an efficacious treatment of manic-depressive illness[1]. Lithium is now the drug of choice for treating bipolar affective disorders. It is successful in improving both the manic and depressive symptoms in 70% to 80% of patients[2]. Lithium may also be used to treat alcoholism, schizoaffective disorders, and cluster headaches[3]. Thus, lithium is an indispensable pharmaceutical component of modern psychiatric therapy.

Unfortunately, lithium has a narrow therapeutic index, with therapeutic levels between 0.6 and 1.5 mmol/L[2-4]. The optimal steady-state concentration of lithium for maintenance treatment of bipolar disorders is generally considered to be 0.6 to 1.2 mmol/L, with slightly elevated steady-state concentrations (0.8 to 1.5 mmol/L) indicated for the acute management of manic episodes[5]. Because toxicity can occur at levels higher than 1.5 mmol/L, lithium levels must be carefully monitored and lithium dosage adjusted as necessary. This is especially true following changes in other medications that alter renal function, such as angiotensin-converting enzyme inhibitors (ACEi) or nonsteroidal anti-inflammatory drugs (NSAIDs).

Lithium Pharmacology

Lithium is a univalent cation that must be administered with an anion. Lithium is generally administered orally, either as a liquid (lithium citrate) or a capsule (lithium carbonate). A 300-mg lithium carbonate tablet contains 8.12 mmol of lithium ion[2]. Lithium is completely absorbed from the upper gastrointestinal (GI) tract in about 8 h, with peak serum levels occurring 1 to 2 h after oral administration[2,5]. Lithium is also available in sustained-release preparations; serum levels generally peak 4 to 5 h after ingestion but can continue to rise for 3 to 4 days in patients poisoned with these long-acting preparations[3,5]. In addition, some patients take lithium as a single dose at bedtime rather than as a split dose twice a day, and may have morning lithium levels that are higher than with twice-a-day dosing[5]. Thus, one must interpret serum lith-

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ium levels after a potentially toxic ingestion relative to the time that the ingestion occurred.

Lithium is distributed in total body water and does not bind to serum proteins[2]. It has a volume of distribution of 0.7 to 0.9 L/kg[2]. Tissue distribution after ingestion is a complex phenomenon, with preferential uptake in certain compartments (*e.g.*, kidney, thyroid, bone) over others (*e.g.*, liver, muscle) [5]. Significant delays in reaching steady state exist for some tissues, *e.g.*, the distribution in the brain is delayed by approximately 24 h compared with plasma[5]. The concentration of lithium within the cerebrospinal fluid is only 40% of serum levels due to its transport out of the cerebrospinal fluid by brain capillary endothelium and/or arachnoid membranes[2].

Lithium has a variable half-life within plasma. Factors altering its half-life include patient age, duration of lithium therapy, and level of renal function[2]. Lithium has an elimination half-life of 12 to 27 h after a single dose, but its elimination half-life can increase to as long as 58 h in elderly individuals or patients taking lithium chronically[2]. Thus, one must measure lithium levels several times after a toxic ingestion, because its rate of elimination is variable and cannot be predicted in any given patient. The pharmacokinetic disposition of lithium is generally described as an open, two-compartment model, and clinical comparisons by convention are made using serum samples acquired during the terminal phase (*i.e.*, at least 10 h after an oral dose) [5].

Lithium Renal Handling

Lithium is excreted almost entirely by the kidneys[2]. Lithium is freely filtered by the glomerulus since it is not bound to serum proteins[2]. In the proximal tubule, lithium is handled similarly to sodium[2]. Thus, factors that decrease glomerular filtration rate (GFR) or increase proximal tubule reabsorption, such as volume depletion, will increase serum lithium levels. Conversely, factors that decrease proximal tubule sodium reabsorption, such as carbonic anhydrase inhibitors, aminophylline, or osmotic diuretics, will increase lithium excretion and decrease serum lithium levels.

Approximately 80% of the lithium that is filtered by the glomerulus is reabsorbed and the remainder is excreted in the urine[2]. Of the filtered lithium, 60% is reabsorbed in the proximal tubule and 20% between the loop of Henle and the collecting duct[2]. Lithium reabsorption can be decreased by loop diuretics and by amiloride, indicating that some lithium reabsorption occurs in both the thick ascending limb of the loop of Henle and in the cortical collecting duct[2].

Clinical Presentation of Lithium Intoxication

There are three types of lithium poisoning: acute, acute on chronic, and chronic[3]. Acute poisoning occurs in individuals who are not being treated with lithium. Typically, acute poisoning occurs in someone who lives in a household with a patient being treated with lithium and ingests it accidentally, such as a child. Acute poisoning can also occur voluntarily, typically as a suicide attempt. Acute poisoning generally carries less risk, and patients have milder symptoms than observed in other forms of lithium poisoning[5], since the elimination half-life is shorter in lithium-naive individuals. Lithium levels need to be followed serially and hemodialysis may be indicated, especially if renal function is compromised.

Acute on chronic poisoning occurs in patients being treated with lithium who take an overdose[5]. This ingestion may be accidental or intentional, especially in patients with bipolar disorders who are manifesting depression. This form of poisoning is generally more severe than acute poisoning due to the prolongation of the lithium elimination half-life[5]. Serum concentrations above 3 to 4 mmol/L are often associated with severe symptoms[5] and generally require hemodialysis.

Chronic toxicity occurs in patients receiving chronic lithium therapy[5]. Chronic poisoning can occur in patients whose lithium dosage has been increased or in individuals whose renal function has decreased, resulting in an increase in serum lithium levels[5]. The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorized as mild (1.5 to 2.0 mmol/L), moderate (2.0 to 2.5 mmol/L), or severe (more than 2.5 mmol/L)[5]. Toxic symptoms may be present even when concentrations are well within the recommended therapeutic range[3,5]. Symptoms associated with mild poisoning include lethargy, drowsiness, coarse hand tremor, muscle weakness, nausea, vomiting, and diarrhea[2,5]. Moderate toxicity is associated with confusion, dysarthria, nystagmus, ataxia, myoclonic twitches, and ECG changes (flat or inverted T waves)[2,5]. Severe toxicity, which can be life-threatening, is associated with grossly impaired consciousness, increased deep tendon reflexes, seizures, syncope, renal insufficiency, coma, and death[2,5] (Table 1). However, the clinical presentation of lithium toxicity is only loosely correlated with serum drug concentrations, and there is great variability in severity associated with the given con-

Table 1. Clinical symptoms associated with lithium poisoining

Organ system	Acute poisoining	Chronic poisoining
Endocrine	None	Hypothyroidism
Gastrointestinal	Nausea, vomiting	Minimal
Heart	Prolonged QT interval, ST and T wave changes	Myocarditis
Hematologic	Leukocytosis	Aplastic anemia
Neurologic	Tremor, weakness, apathy, hyperreflexia, myopathy, peripheral neuropathy, confusion, coma	Same
Renal	Urine concentrating defect	Chronic interstitial nephritis, nephrogenic diabetes insipidus, renal failure
Skin	None	Dermatitis, ulcers

centration. Thus, management of toxicity should be dictated primarily by patient presentation and not serum concentrations.

The most common manifestation of lithium toxicity is altered mental status[2]. Lithium poisoning frequently results in electrocardiogram (ECG) changes including transient ST segment depression and inverted T-waves in the lateral precordial leads[2]. Occasional patients develop sinus node dysfunction and syncope[2]. Lithium toxicity may also cause GI symptoms, including nausea, vomiting, diarrhea, bloating, and epigastric pain[2]. Care must be taken to distinguish GI symptoms from cardiac symptoms, especially in patients who also present with an abnormal ECG. Lithium can occasionally cause peripheral neuropathy or myopathy[2].

Lithium is concentrated within the thyroid and inhibits thyroid synthesis and release[3]. Thus, lithium can cause hypothyroidism and hypothermia[2,3]. However, it can also cause thyrotoxicosis and hyperthermia[2,3]. Lithium may also cause hyperparathyroidism and hypercalcemia[5]. A recent study of hyperthyroidism and long-term lithium therapy followed patients for an average of 19 years and found an increased incidence and prevalence of hyperthyroidism, with a tendency towards promotion of parathyroid hyperplasia and hypercalcemia[6]. This study also found that the hypercalcemia was either irreversible or only very slowly reversible[6], in contrast to earlier case reports of patients treated with lithium for 10 d to 6 years in whom serum calcium levels returned to normal values within 1 to 4 weeks after lithium therapy had been withdrawn. These findings suggest an association between the duration of lithium treatment and the degree of persistence of hypercalcemia. Since hypercalcemia can cause nephrogenic diabetes insipidus, it could exacerbate lithium-induced nephrogenic diabetes insipidus.

Lithium does not always result in hypercalcemia, and some patients maintain normal calcium levels despite elevated serum parathyroid hormone levels. A recent 2-year prospective study followed 53 patients and found that their parathyroid hormone levels increased progressively over the course of the study[7]. However, there was no change in serum calcium or phosphorus, or in the tubular reabsorption of phosphate (relative to GFR) [7]. The fasting and 24-h urinary calcium excretion values were significantly decreased over the 2 years of the study, suggesting that bone resorption was reduced[7].

Chronic lithium ingestion has been associated with several different forms of renal injury. Nephrogenic diabetes insipidus is the most common, but renal tubular acidosis, nephrotic syndrome, and chronic interstitial nephritis have also been described[8].

Nephrogenic diabetes insipidus

Chronic lithium ingestion led to resistance to antidiuretic hormone (ADH), resulting in polyuria and polydipsia in up to 20 percent of patients[1]. Lithium appears to act by accumulating in the collecting tubule cells, after entering these cells through sodium channels in the luminal membrane[2]. It then interferes with the ability of ADH to increase water permeability. How this occurs is incompletely understood, but a number of different mechanisms may be involved[3,5].

The first mechanism is decreased stimulation of adenylate cyclase (mediated in part by enhanced activity of Gi, the inhibitory guanine regulatory protein that reduces

the activity of adenylate cyclase)[3]. The second mechanism is reduced density of ADH receptors[5], and the last one includes a post-cyclic AMP defect which may be mediated by downregulation of aquaporin-2, the collecting tubule water channel[4]. The water channels are normally stored in the cytosol; under the influence of ADH, they move to the fuse with the luminal membrane, thereby allowing water to be reabsorbed down the favorable concentration gradient.

It should not be assumed that polyuria in a patient taking lithium is due to nephrogenic diabetes insipidus. Both central diabetes insipidus (DI) and primary polydipsia have been described in patients treated with lithium; they may be induced by lithium or may reflect the underlying psychiatric disease, particularly the use of psychotropic medications which induce dry mouth, thereby stimulating thirst and producing a picture of primary polydipsia[1,9]. One report, for example, evaluated 142 patients who had been taking lithium for more than 15 years[9]. A concentrating defect was present in 44%, while 12% had overt nephrogenic DI; in comparison, 53% complained of increased thirst, primarily those taking other psychotropic medications.

Thus, a water restriction test should be performed to establish the correct diagnosis, since the treatment of these disorders is different.

Renal tubular acidosis

Tubular defect in the distal nephron can also impair the ability to maximally acidify the urine. This is most often manifested as the incomplete form of type 1 (distal) renal tubular acidosis, in which the urine pH is persistently above 5.3, but the extracellular pH and bicarbonate concentration are within the normal range. A lithium-induced decrease in the activity of the H-ATPase pump in the collecting tubules may be at least in part responsible for the acidification defect, since this pump accounts for most of distal hydrogen secretion.

Nephrotic syndrome

Lithium has infrequently been associated with the nephrotic syndrome. Most cases are due to minimal change disease[10,11], but focal glomerulosclerosis has also been described[12]. The mechanism by which lithium leads to glomerular injury is not understood, but the course is highly suggestive of an etiologic role of lithium. Proteinuria generally begins within 1.5 to 10 months after the onset of therapy and, in minimal change disease, completely or partially resolves in most patients one to four weeks after lithium has been discontinued[10]. In several patients, reinstitution of lithium led to recurrent nephrosis[10,11]. Corticosteroids have occasionally been required to induce remission; it is possible that the minimal change disease in such cases was unrelated to lithium[10].

The relationship to focal glomerulosclerosis is less clear. In three patients, for example, cessation of lithium did not lead to resolution of the disease[12], suggesting either no relation to lithium or possible focal glomerulosclerosis secondary to tubular injury induced by chronic lithium therapy.

Chronic interstitial nephritis

The question of whether chronic lithium therapy causes chronic interstitial nephritis remains controversial[13-16]. In several studies in which renal biopsies were performed in lithium-treated patients, either for polyuria or reduced GFR, abnormal biopsy results were found that were consistent with chronic interstitial nephritis[13]. These biopsy findings included tubular atrophy and dilation, sclerotic glomeruli, cyst formation, and cortical and medullary fibrosis[13]. These patients either had no change, or only a mild decrease, in GFR[13,14]. A cohort of 86 patients without prior renal disease who were treated with lithium for 10 years were followed at Johns Hopkins Hospital in Baltimore. In these patients serum creatinine increased from 1.0 to 1.2 mmol/L[14]. The authors report that there was a significant positive correlation between the duration of lithium therapy and the level of serum creatinine, but the *r* value was only 0.32 and the final average serum creatinine was still within the normal range[14].

These studies[13,14] used healthy subjects as controls. Subsequent investigators studied psychiatric patients as control subjects who were not being treated with lithium and found that histologic lesions on renal biopsy in these patients were similar to those treated with lithium[13]. This finding has raised the question of whether chronic interstitial nephritis results from having a psychiatric disorder rather than from lithium *per se*. Another study found that patients treated with both lithium and neuroleptics had more sclerotic glomeruli and more advanced tubulointerstitial changes on renal biopsy than patients treated solely with lithium[13].

However, these patients also had more advanced psychiatric disorders and had been treated with lithium for longer periods of time[13]. Some Australian studies report on a lesion that occurs in lithium-treated patients but not in psychiatric control subjects: the distal tubules and collect-

ing ducts have cytoplasmic swelling with glycogen accumulation, dilated tubules, and microcyst formation[13].

Thus, the issue of whether lithium poses a serious risk for chronic interstitial nephritis and renal failure is unresolved. Rarely, patients have been reported to develop the nephrotic syndrome from lithium[14]. At present, the most prudent approach is to follow serum creatinine levels closely in lithium-treated patients and to maintain lithium levels as low as possible to decrease the risk of toxicity while controlling the patient's psychiatric symptoms. Renal function must be followed carefully throughout the course of treatment with lithium since the development of diabetes insipidus and chronic interstitial nephritis is often irreversible, even when lithium therapy is discontinued[13]. Thus, it is important to detect decreases in renal function early so that lithium can be stopped, or the dose decreased, before serious loss of renal function occurs.

Risk Factors for Lithium Intoxication

Factors that increase the risk for chronic toxicity in previously stable patients include other medications, illness, and alterations in potassium or sodium levels. Drugs that alter renal function can increase the risk of chronic lithium toxicity[2,17,18]. Among these, ACEi, NSAID, and thiazide diuretics increase the reabsorption of lithium and result in increased serum lithium concentrations.

Thiazide diuretics have a significant potential to increase serum lithium concentrations. These diuretics induce natriuresis that leads to a compensatory increase in the reabsorption of sodium (and lithium) in the proximal tubule[5]. This effect of thiazide diuretics has been suggested in many case reports, describing lithium toxicity subsequent to thiazide initiation, and has also been documented in a handful of small controlled studies[5]. In general, therapeutic doses of thiazide diuretics result in a 25% to 40% decrease in lithium clearance with a concomitant increase in serum lithium levels[5]. The nature of this interaction is quite variable and the most conservative approach is simply to avoid the use of thiazide diuretics if possible.

Another risk factor is a concurrent illness that results in decreased circulating volume, either true volume depletion or decreased effective circulating volume. A common example is a patient acquiring a viral illness, such as cold, flu, or gastroenteritis, that results in decreased oral intake or increased gastrointestinal losses. The decrease in circulating volume will stimulate proximal tubule sodium reabsorption, similar to the effect of thiazide diuretics, and will also result in an increase in proximal lithium reabsorption and serum lithium levels.

Other risk factors include alterations in serum potassium or sodium concentrations. Sodium restriction enhances the renal tubular reabsorption of lithium[19], thus leading to potentially toxic serum levels of lithium. Serum potassium concentrations can have variable effects on serum lithium levels.

Treatment for Lithium Intoxication

The general approach to any poisoned patient must include the following elements[20] (Table 2):

- Evaluation, including the recognition that poisoning has occurred, identification of the agents involved, assessment of severity, and prediction of toxicity.
- Management, consisting of supportive care, prevention of drug absorption, and when appropriate, the administration of antidotes and enhancement of drug elimination.

Table 2. Treatment for lithium poisoining

Protect oral airway if consciousness is impaired	
Intravenous normal saline if volume depleted	
Whole bowel irrigation with polyethylene glycol	
Sodium polystyrene sulfonate	
Hemodialysis	
Lithium level >6 mmol/L:	any patient
Lithium level >4 mmol/L:	any patient on chronic lithium therapy
Lithium level 2.5 - 4 mmol/L:	any patient with severe neurologic symptoms, renal insufficiency, or hemodynamically or neurologically unstable
Lithium level <2.5 mmol/L:	hemodialysis indicated only for patients with end-stage renal disease or patients whose lithium levels increase upon admission or who fail to reach a lithium level <1 mmol/L in 30 h

Therapy of lithium poisoning depends upon the adequacy of renal function and the degree of intoxication. There are also several general measures that should be followed including cessation of other drugs that may have additive side effects (such as a phenothiazine or haloperidol) and evaluation of thyroid function[21]. Patients with severe intoxication or significant cardiac disease should be monitored in an intensive care unit.

Fluid repletion

Restoration of sodium and water balance in hypovolemic subjects is essential to maximize lithium clearance. It is important to appreciate that the plasma sodium concentration must be monitored in patients who have underlying nephrogenic diabetes insipidus. The combination of isotonic saline to restore euvolemia and hypotonic losses in the urine will predictably lead to hypernatremia, which can exacerbate neurologic symptoms. Thus, a hypotonic solution, such as half-isotonic saline, should be given to these patients.

Contrary to previous recommendations, fluid administration and forced diuresis are of limited efficacy in patients who are normovolemic. The fractional excretion of lithium does not change consistently in this setting[2] and hypernatremia may be induced[1,2].

Decreased intestinal absorption

Oral activated charcoal does not limit the absorption of charged particles such as lithium[11]. Nevertheless, it should be given in acute lithium overdose to adsorb other drugs that may have been ingested.

A preliminary report suggests that whole bowel irrigation with polyethylene glycol solution was effective after the acute ingestion of sustained release lithium[11]. However, the efficacy of this procedure needs to be confirmed before it can be recommended for routine therapy.

Hemodialysis

The primary modality for removing lithium is hemodialysis (HD). Peritoneal dialysis clears only 9 to 15 ml/min of lithium and is not recommended for treating lithium poisoning[2,3]. Conventional HD can reduce plasma lithium by 1 mmol/L *per* 4 h of treatment[3]. High flux should be capable of removing more lithium *per* hour of HD, but published values are not available. The dialysis catheter should be left in place because treatment must often be repeated since HD does not clear intracellular lithium effectively. Thus, serum lithium levels often rebound after HD as the intracellular lithium exits cells and reenters the bloodstream. Lithium levels may also rise in patients who have ingested a sustained-release lithium preparation due to continued lithium absorption from the GI tract. Thus, lithium levels must be checked frequently, even after HD[3].

Indications for HD

HD should be performed in any patient with lithium intoxication who presents with coma, convulsions, respiratory failure, deteriorating mental status, or renal failure[3]. HD should also be performed in anyone whose lithium excretion is impaired[3]; this is assessed by measuring serial lithium levels. If the lithium level fails to decrease despite conservative therapy, either due to continued GI absorption or diffusion of lithium from cells, then HD should be performed[3]. Another kinetic criterion for instituting dialysis is if more lithium can be cleared by a single HD treatment than by the kidneys in 24 h[3].

One should also strongly consider hemodialysis for any patient on chronic lithium therapy with serum lithium levels exceeding 4 mmol/L, or for patients with lithium levels between 2.5 and 4 mmol/L who develop serious cardiac or neurologic symptoms[3]. Patients on chronic lithium therapy are at a higher risk of permanent deficits from lithium poisoning than patients with acute poisoning since intracellular lithium levels are thought to be responsible for irreversible toxicity[4]. Thus, acutely poisoned individuals may not need HD until lithium levels reach 6 to 8 mmol/L[3]. Dialysis is rarely indicated in patients with serum lithium levels below 2.5 mmil/L[3]. However, several lithium levels must be measured as the level may rise after admission.

A decision to initiate dialysis should be made approximately 8 to 12 h after admission. This decision should be based on serial lithium levels, level of renal function, and the patient's overall clinical condition. Because HD is very effective in removing lithium from the blood and has minimal side effects, it should be undertaken whenever the nephrologist has any doubts about not performing dialysis. HD should be performed using a bicarbonate bath and not with an acetate bath, as lithium clearance from intracellular stores is reduced when an acetate bath is used[2]. A case report describes the use of a high phosphorus bath to prevent hypophosphatemia after HD for lithium intoxication. Alternatively, serum phosphorus should be checked after HD and hypophosphatemia corrected orally.

After initiating HD, lithium levels must continue to be checked frequently, because they often rebound. Typically, at least two HD treatments are necessary in patients requiring dialysis[2,3]. Serum lithium levels can rise for up to 3 to 4 days after admission[22,23]. In one case report, lithium levels began to increase after the patient had been allowed to resume eating due to absorption of residual lithium from the GI tract[23]. These experiences emphasize the need for prolonged, close monitoring of lithium-poisoned patients, especially those receiving sustained-release lithium preparations[22,23].

Continuous renal replacement therapies have been used on a limited basis for treating lithium poisoning[24]. Continuous arteriovenous hemodialysis (CAVHD) and continuous venovenous hemodialysis (VVHD) can clear 60 to 85 L/day of lithium and their continuous nature decreases concerns about lithium rebound. Continuous therapies do not reduce lithium levels as quickly as HD and are often limited by the need for anticoagulation. They may be particularly useful for patients with chronic poisoning in whom intracellular lithium accumulation poses a substantial risk of permanent sequels[24,25].

Additional extracorporeal modalities

There is only limited experience with extracorporeal modalities other than conventional dialysis in the treatment of severe lithium toxicity. One goal of these modalities is to minimize rebound.

Continuous arteriovenous hemodiafiltration (CAVHDF) is an alternative that can significantly augment lithium removal[21,22]. In one report of four patients treated with this modality, the initial plasma levels of 4.0, 4.6, 4.4 and 3.2 mmol/L decreased to 1.2, 0.8 and 1.1 mmol/L after treatment for 15, 19, 35 and 21 hours, respectively[22]. There was no rebound increase levels 24 to 36 hours of hemodiafiltration discontinuation.

The combination of HD followed by CVVHD was safe and effective in the treatment of two children with lithium intoxication[23]. No rebound in lithium levels was observed in either patient.

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Sažetak

BUBREŽNO OŠTEĆENJE ZBOG TROVANJA LITIJEM

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Litij je tvar koja se rabi u liječenju bipolarnih bolesti. Kronična uporaba litija u bolesnika s bipolarnim (manično-depresivnim) bolestima često je vezana uz različita oštećenja bubrežne funkcije. Najčešće se javlja nefrogeni dijabetes insipidus, ali su u literaturi opisani i slučajevi bubrežne tubularne acidoze, nefrotskog sindroma i kroničnog tubulointersticijskog nefritisa. Liječenje otrovanja litijem ovisi o bubrežnoj funkciji i stupnju otrovanja litijem.

Ključne riječi: *Litij, trovanje; Trovanje, liječenje; Litij, farmakokinetika; Biološki transport; Terapijska primjena litija*