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Lithium induce nephropathy; an updated review

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Abstract

Lithium is an effective and useful treatment for bipolar disorder and some central nervous system diseases. It has a narrow therapeutic index which results to acute and/or chronic intoxication. Lithium toxicity is as a result of prescribing error, reduced kidney elimination, drug-drug interactions or intentional overdose. Nephrotoxicity is one of clinical findings of chronic, acute and acute-on-chronic toxicity. Lithium was associated with increased risk of nephrogenic diabetes insipidus, kidney microcysts, tubulointerstitial disease for example tubular atrophy and chronic focal interstitial fibrosis and end-stage renal disease (ESRD). Several mechanisms such as blocks of sodium transportation through the amiloride-sensitive epithelial sodium channel and hyperparathyroidism were descriptive for the lithium nephropathy. Physicians should consider balance of risks before lithium therapy and monitor patients initial and during treatment according to clinical practice guidelines. Supportive care, withdrawal of lithium, gastrointestinal decontamination, increases renal perfusion, glomerular filtration rate, extracorporeal might be considered to lithium treatments.

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Introduction

Lithium is one of the old and efficient antipsychotic drugs, which it still remains the most common therapy for bipolar disorder (1). Additionally, lithium has beneficial properties in multiple other central nervous system diseases containing multiple sclerosis, neurotoxicity associated to human immunodeficiency virus, stroke, and Huntington disease (2-4). Likewise, it had the capability to protect against mania, depression and diminishing the short-term mortality and risk of suicide (2).

Core tip

Lithium is an effective and useful treatment for bipolar disorder and some central nervous system diseases. It has a narrow therapeutic index which results to acute and/or chronic intoxication. Nephrotoxicity is one of clinical findings of chronic, acute and acute-on-chronic toxicity.

Pharmacokinetics of lithium

Pharmacokinetics of lithium is subject to considerable inter-individual differences which, haven a narrow therapeutic window, mention close monitoring of its serum value. In fact, a narrow therapeutic index leads to a necessity for routine monitoring of various organs including endocrine and renal function (5). Recently much attention has been directed toward the effects of lithium on kidney function and the risk of teratogenicity (6). Three features of lithium toxicity are defined: acute, acute-on-chronic, and finally chronic. Acute toxicity has clinical findings with predominant gastrointestinal symptoms including nausea, vomiting, and diarrhea. Additionally, neurologic symptoms has late presentation, while the lithium redistributes slowly into the central nervous system (7). Lithium chronic toxicity can cause kidney and neurological disorders. In addition, acute lithium toxicity can cause nephrogenic diabetes insipidus. Its chronic toxicity includes renal insufficiency due to segmental glomerulosclerosis and interstitial fibrosis, especially in elderly individuals and long-term users (8).

Materials and Methods

This literature was prepared through searching PubMed/Medline, Scopus, TOXNET, Google Scholar, EMBASE, EBSCO and directory of open access journals (DOAJ) up to January 1, 2016. The search was conducted,

using combination of the following key words and/or their equivalents; lithium, intoxication, poisoning, diabetes insipidus, kidney microcysts, nephropathy, nephrogenic diabetes insipidus, hyperparathyroidism and hemodialysis. Titles and abstracts of surveys were investigated of clinical trials, cohort studies, review article, case-control studies, and case reports that relevance to the intended topic.

Lithium induced nephrogenic diabetes insipidus

Sometimes, clinicians avoid the lithium therapy. Perhaps, they perceive that lithium is an unsafe drug and they should monitor the renal function, endocrine function and serum lithium level closely in patients who receiving it for long term. However, the patients who had administered lithium had a numerically but not statistically increased risk of renal failure.

Long term treatment patients with lithium salts can cause nephrogenic diabetes insipidus that present with polyuria and polydipsia as a result of a urinary concentrating defect and volume depletion (9). As reviewed by McKnight et al, the glomerular filtration rate (GFR) in chronic lithium users was diminished gradually and progressive reduction of GFR can lead to end-stage kidney insufficiency even though when the absolute risk is low. Likewise, urinary concentrating ability due to diminishing tubular renal function was reduced by about 15% of normal maximum (8). Usually, this nephropathy is asymptomatic. Urinary sediment and blood pressure is near normal, and proteinuria is absent or minimal (10). Finally, it might manifest itself as end-stage kidney insufficiency, which may lead to dialysis or kidney transplantation (11).

As discussed by Nielsen et al, this disorder may be associated with a loss of alpha epithelial sodium channel subunit that regulation by aldosterone (12). Epithelial sodium channel include, three homologous subunits (α, β, and γ) and it is the important site of sodium transport across the apical plasma membrane in the connecting tubule and cortical collecting duct (13,14). Kortenoeven et al, found that lithium blocks of sodium transportation through the amiloride-sensitive epithelial sodium channel, which is associated with renal sodium wasting due to risen urinary sodium excretion and reduced responsiveness to aldosterone and vasopressin. Blocking of epithelial sodium channel prevents lithium-induced glycogen synthase kinase3 (GSK-3β) inactivation and water channel aquaporin-2 (AQP_2) down regulation in vitro. As well amiloride therapy could attenuate lithium diabetes insipidus (13).

A recent experimental animal study were detected that lithium can inhibit magnesium-dependent guanine nucleotide-binding (G) proteins, vasopressin-sensitive adenylate cyclase, and reduced cyclic adenosine monophosphate in the cell membranes of distal tubular kidney cells. Thus, the vasopressin-regulated AQP_2 is reduced translocation, and the distal tubules make resistant to the action of vasopressin. Therefore urine cannot concentrate (12). A more recent experimental study showed that decreased ability to concentrate urine was due to lithium acutely disrupting the cyclic adenosine monophosphate-dependent pathway, chronically falling urea transporters and AQP_2 expression in the inner medulla while return to normal levels after ceasing lithium using, whereas AQP_2 levels failed to recover to normal levels (15).

Additionally, it was found that, lithium interacts with GSK-3β which increases cyclooxygenase-2 ($COX\text{-}_2$). $COX\text{-}_2$ activity increases the extraction of prostaglandin in the renal (13).

Several investigation, revealed that, prolonged lithium use might result hyperchloremic metabolic acidosis due to by reduced net proton secretion in the collecting duct and/or rise return diffusion of acid equivalents.

Tubulointerstitial disease induced by lithium

Chronic tubulointerstitial nephropathy was defined in long time lithium therapy especially in patients who suffered of end-stage renal failure (8), however this morphologic lesion is not specific for lithium therapy. The incidence of chronic kidney disease (CKD) and end-stage renal failure are more prevalent in old populations particularly with the presence of hypertension and diabetes (16,17).

In an experimental study by Aziz, the tubulointerstitial disease related to lithium was the result of degeneration and necrosis in the renal glomeruli and tubules, tubular atrophy, chronic focal interstitial fibrosis particularly on the cortical region of the kidney in chronic lithium therapy which develops to permanent renal impairment (18). Moreover, the reduction of creatinine clearance and the intensity of interstitial fibrosis might be related to the duration of lithium therapy and its cumulative dose (8). Focal segmental glomerulosclerosis as well as multiple microcysts were reported by magnetic resonance imaging (19). However, the exact amount of dose and duration of lithium therapy in the clinical setting is not clear yet. Walker et al reported that a therapeutic dose of lithium over 6 months in rats could progress the renal fibrosis and tubular atrophy in the absence of any critical degree of inflammation. In addition, increasing the proportion of macrophages, interstitial fibrosis, and tubular atrophy were presented in the renal tissue biopsies (20).

Hyperchloremic metabolic acidosis is caused by chronic lithium intoxication. It can increase renal ammonia excretion and impair urinary acidification in the collecting ducts and distal nephrons leading to reducing the GFR (21). The effect of lithium on acquaporin-2 leads to the disturbances of collecting tubules, and consequently interstitial fibrosis and impair renal function. As a parallel mechanism, mast cells may be a factor in lithium induced nephropathy too (22). While, GSK-3β stimulates apoptosis and inhibits cell proliferation (6), lithium inhibits GSK-3β, thus it can induce formation of micro-cysts in the proximal and distal of nephrons. Importantly, the micro-cysts may contain papillary projections which may go toward a malignant stage (23).

Accordingly, it was found that lithium could change histopathological capillaries and induced nephropathy in rats. They also found, a thiazide diuretic and an angiotensin converting enzyme inhibitor could modify the

rise in systolic blood pressure related to lithium-induced nephropathy. They concluded tubular atrophy might be associated with an interstitial capillaries diminution and with a rise in the tubule-capillary distance (24). Furthermore, a recent research was detected a compensatory hypertrophy of the renal glomeruli as an increase in the number of glomerular capillaries in lithium nephrotoxicity (18). Capillary electrophoresis coupled to a mass spectrometer from a urine-sample might be helpful to identify early lithium-induced renal changes (23).

Lithium associated kidney microcysts

Increasing in the echogenicity of the renal parenchyma, presence of microcysts, and multiple punctate echogenic foci was detected in chronic lithium users (19). Distal tubular dilatation and microcysts in distal and collecting tubules were also reported in chronic lithium therapy by magnetic resonance imaging. The microcysts were found in both cortex and medulla, predominantly in the zones with extensive atrophy and fibrosis. Also, they were multiple and bilateral (25).

It is assumed that, GSK-3β with von Hippel–Lindau tumor protein are the microtubule dynamic regulators that are responsible for maintenance of primary cilia (26). It is assumed that, lithium inhibits GSK-3β, hence primary cilia disturbances could trigger cyst formation (11).

Khan and El-Mallakh proposed the anti-apoptotic effect of lithium as the mechanism of microcyst formation. During the normal renal maintenance process, lithium may induce invaginations and ultimately cysts of the inappropriate growth of the renal tubular epithelial cells due to preventing of apoptosis. These cysts can limit the renal function. Therefore, monitoring of kidneys should be considered using sonography and radiographic imaging (19).

Rookmaaker et al, suggested that long-term lithium therapy, make an increase of collecting duct cell proliferation derived tumors. Thus, lithium predisposes to formation and development of adenomas and carcinomas (27). Furthermore, a retrospective study showed that different subtypes of the renal cancers were higher in lithium-treated patients compared with lithium-free patients with CKD as well as the general population (9). In spite of these findings, a case-control study showed that, stage and subtype of upper urinary tract cancer did not significantly increase in the over 5 years of lithium administration (26).

Nephropathy related to hyperparathyroidism and hypercalcemia

Several surveys described the association of primary hyperparathyroidism with lithium therapy. The incidence of hyperparathyroidism in lithium users was higher than that of general population particularly in women and in individuals over 60 years or more (28,29).

In chronic lithium users, the bone mineral decreased, but the serum levels of immunoreactive parathyroid hormone, calcium and magnesium increased during the treatment with lithium. Previous studies had not define the main etiology of lithium-associated hyperparathyroidism. It is not clear whether lithium by itself initiates these diseases. However an underlying state of hyperparathyroidism may be possible (30). It may be associated with a direct influence of lithium on both the growth of parathyroid tissue and decrease parathyroid cell sensitivity to calcium. However, total calcium and ionized calcium levels may not increase during lithium therapy in all cases (28,30).

Lithium induced hyperparathyroidism is the result of anatomical lesions such as adenomas and multi-glandular hyperplasia. Its mechanism may be through inhibition of the tissue adenyl cyclase (28). In fact, hypercalcemia and hyperparathyroidism have the same etiologically related to nephropathy of lithium therapy (28). A little increased in serum calcium-ion concentrations in concert with plasma volume depletion resulting to diabetes insipidus and/or reduced calciuria. This condition in patients with renal failure may cause nephrolithiasis or nephrocalcinosis too (11).

Risk factors for lithium nephrotoxicity

Although the exact risk factors for serious renal impairment after lithium therapy have been unknown but several investigations were explained in this field.

A retrospective study showed that taking lithium was associated with a decline in renal function (34.4% of patients with a GFR less than 60 ml/min/1.73 m^2, versus 13.1% in controls). Additionally, their GFR was correlated with the proportion of years that patients had taken lithium. In spite of this finding, however, they suggested that end-stage renal disease (ESRD) rarely occurred in patients who have taken lithium for long-term (around 1%) (29).

Aiff et al suggested that the end-stage renal failure is a markedly elevated risk in older consumers of lithium (nearly 8 times the age adjusted population rate in patients elder than 55 years). Also, they reported a yearly increase in median serum creatinine levels from the first year of lithium treatment. However, evidences of chronic kidney insufficiency was observed in one-third of the patients who had administered lithium for 10–29 years (31).

A Danish investigation addresses direct correlation of serum lithium level and proportion of renal function. Also, age, sex, and diabetes were associated with the development of chronic nephrotoxicity. Females were at greater risk for development of renal damage than men. Additionally, adverse effects happened in early stage of treatment and in relation with higher lithium concentrations (29). It is possible that baseline estimated GFR, co-prescriptions of nephrotoxic drugs, comorbidities and episodes of lithium toxicity be as the significant predictors for diminution of GFR while mean serum lithium level and duration of exposure to lithium were not significant factors (32).

It was also detected that not only gender and age predict the severity of lithium intoxication but also use of certain classes of antihypertensive agents influence the lithium toxicity (24).

Management of lithium nephrotoxicity

Several research have focused on the managing the risk

of lithium-induced nephropathy. They recommend to check laboratory parameters before starting and during of lithium treatment (8,33) These parameters were include GFR, thyroid-stimulating hormone, serum electrolytes, urinalysis and complete 24-hour urine collection to assess urine concentration, creatinine, proportion of proteinuria, serum concentration of parathyroid hormone, serum calcium and vitamin D. In fact GFR below 60 ml/min/1.73 m^2 or creatinine clearances below than 40 ml/min is an indication to refer to a nephrologist to stop lithium therapy.

Managements for severe lithium poisoning (either acute or acute on chronic) include supportive care, withdrawal of lithium, gastric lavage and/or whole bowel irrigation with a polyethylene glycol. In addition, lithium can eliminate by intravenous isotonic saline administration which increases renal perfusion and GFR. Urine output and electrolyte should monitor especially in patients with CKD and congestive heart failure. Amiloride is a potential treatment for diabetes insipidus, but there are limited data for its use in acute care state (33).

Lithium is a low weight molecule with low protein binding and relatively low valium distribution based on pharmacokinetic properties, thus extracorporeal modalities, such as hemodialysis was used in severe lithium toxicity (34).

Although the clinical relationship between serum lithium level and toxicity is complex, previous research suggested to maintain level of serum lithium about 0.6–1.2 mEq/l. Serum lithium level higher than 1.5 mEq/l may have toxic effect especially in chronic users (34). It is recommended to consider extracorporeal modalities in the treatment of lithium poisoning patients with (*a*) serum lithium level higher than 3 mEq/l with clinical features of kidney impairment and (*b*) absolute serum lithium level higher than 6 mEq/l as the acute poisoning state and 30 serum level of higher than 5 mEq/l for chronic intoxications (7).

Finally, for the prophylaxis of recurrence of psychiatric disorders in patients with nephropathy, the decision to substitute lithium with another mood stabilizer should be considered after revealing of impaired renal function in a patient undergoing lithium treatment (11,35).

Conclusion

Lithium is associated with increased risk of nephrogenic diabetes insipidus, kidney microcysts, tubulointerstitial disease such as tubular atrophy and chronic focal interstitial fibrosis, and hyperparathyroidism with several mechanisms that can progress to end stage renal disease.

Serial monitoring of kidney function and serum lithium concentration are keys for early detection of nephrotoxicity. Hence physicians should consider balance of risks before lithium therapy and monitor patients initial and during treatment as to stop lithium taking on risk assessment. A serum calcium and serum concentration of parathyroid hormone should be added to baseline blood tests (glomerular filtration and parathyroid hormone). Also, radiologic imaging and renal sonography may be considered as a part of treatment modalities. Hemodialysis may be necessary in some especial conditions of lithium toxicity.

Authors' contribution

MH prepared the primary draft. SSBM, MRA and MRT searched the data and conducted primary editing. Editing the final manuscript done by MH and MRA. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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