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Lithium-induced Nephrogenic Diabetes Insipidus–A Case Report and Discussion on the Pathophysiological Mechanism

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Abstract

Lithium is a useful treatment for bipolar disorder; it attenuates the recurrence of affective episodes and reduces the risk of suicide among bipolar patients. Nevertheless, lithium has a plethora of side effects some of which are serious and may be irreversible. Among the most troubling side effects of lithium is its nephrotoxicity. Herein we report a case of a bipolar patient who developed signs of lithium-induced nephrotoxicity including overt polyuria after 18 years of lithium treatment. Due to concerns that his renal function will continue to deteriorate, two trials to switch him to other psychotropic drugs were done following which he committed two aggressive suicidal attempts. As a result, a joint decision was reached between the patient, his family, psychiatrist and nephrologist that lithium is a "life-saving" treatment for him and lithium was never stopped again. To date, at 68 years old and after nearly 40 years of lithium treatment the patient is mentally stable and reasonably functional. His kidney function continued to deteriorate slowly through the years and he is now a candidate for hemodialysis. This case report emphasizes the need to balance between concerns regarding the damage to the kidney which is a result of long-term lithium treatment to the significant therapeutic benefit of lithium as a mood stabilizer and anti-suicidal drug.

Keywords: Bipolar disorder; Creatinine; Lithium; Polyuria; Suicide

Introduction

Lithium is the gold standard treatment for bipolar disorder [1,2]. It attenuates the recurrence of affective episodes [1,2] and reduces suicidal attempts and suicidal death among bipolar patients [3,4]. However, despite its established therapeutic efficacy, long-term lithium treatment is complicated by two limitations: (*i*) lithium has a narrow therapeutic index and increased risk of intoxication, and, (*ii*) lithium has several side effects, some of which are severe and occasionally irreversible [5-7].

Lithium is a simple chemical that does not undergo hepatic metabolism. Nevertheless, addressing its therapeutic and toxicological profiles necessitates acknowledgement of the variability among patients in their response to the drug. The therapeutic response and the toxicological profile of lithium may greatly differ among patients even at similar plasma levels, due to inter-individual variations in sensitivity to the drug and differences in renal excretion [2,5,6,8]. Patients can differ in their response to lithium due to different age, gender, ethnic background, comorbidities, interaction with other medications and genetic variations [2,5,6,8]. Plasma levels do not always predict the severity of lithium intoxication despite being a principal factor that guides the clinical assessment of patients. Some patients develop signs of lithium toxicity while having plasma concentrations that are within the recommended therapeutic range [9]. Thus, assessment of a patient's situation must mainly rely on the clinical presentation and severity of symptoms [10]. Several factors may affect plasma lithium levels and the risk for toxicity. Impaired renal function is one of the major factors that may lead to lithium intoxication due to decreased elimination and accumulation of the drug [10-12]. Many drugs may influence lithium clearance by altering renal blood flow, glomerular filtration rate (GFR) and sodium balance. For example, Non-steroidal Anti-inflammatory Drugs (NSAIDs) are known to reduce lithium clearance, resulting in elevated plasma concentrations of the drug [10-12]. These drugs inhibit the Enzyme Cyclooxygenase (COX) and thereby diminish prostaglandins (PGs) production. Inhibition of PGs synthesis reduces renal blood flow and GFR, the result of which is enhancement of lithium reabsorption [10-12]. The interaction between lithium and NSAIDs occurs with classical NSAIDs as well as selective COX-2 inhibitors. However, this interaction seems to be less frequent with aspirin than other NSAIDs [11,12]. Angiotensin Converting Enzyme (ACE) inhibitors may increase the risk for toxicity because they reduce glomerular perfusion pressure (due to dilatation of efferent arterioles) and decrease lithium glomerular filtration [10-12]. Furthermore, medical conditions that are associated with volume depletion and diminished renal blood flow such as diarrhea and sepsis may reduce GFR and increase the risk of lithium toxicity.

One of the most worrisome side effects of lithium is impairment of kidney function. Potential deleterious effects of lithium on renal function include a decrease in urinary concentrating capacity and a reduction in glomerular filtration rate, among other complications [5-7,13-20]. The most common renal side effect of lithium is Nephrogenic Diabetes Insipidus (NDI) [5,7]. Important factors that contribute to the development of lithium-induced NDI are: increased blood lithium levels, long duration of treatment and high incidence of lithium intoxication episodes [5-7,13-20]. Importantly, NDI may appear even after lithium cessation [21] and withdrawal of lithium does not necessarily reverse the impairment in urinary concentrating ability [7,16,17,22]. This article presents a case of a patient who suffered several episodes of lithium-induced NDI and gradually developed a chronic kidney disease. Thereafter, it discusses the

pathophysiological mechanism(s) underlying lithium-induced NDI.

Case Report

A male patient started to receive lithium at the age of 28 years after being diagnosed as having bipolar disorder. Lithium treatment was continued for nearly 18 years during which plasma lithium concentrations where within the therapeutic range (0.6-1.2 mEq/L) and no documentation of lithium intoxication episodes. At age 46 years the patient was referred to a nephrologist (A.S.) due to complaints on dry mouth, polydipsia, polyuria and deterioration in renal function. His clinical assessment at the nephrology clinic revealed the following findings: blood pressure was normal; plasma creatinine =1.4 mg/dl, urea =34 mg/dl, sodium =139 mEq/L; eGFR =57 ml/min; urine output =8 L/day, without proteinuria, glucosuria, red blood cells or casts; kidney ultrasound was normal. After an initial examination, a water deprivation test was performed revealing the following results: before the test – plasma osmolality =283 mOsm/kg, urine osmolality =164 mOsm/kg; 6 hours after water deprivation – plasma osmolality =298 mOsm/kg, urine osmolality =165 mOsm/kg; after administration of vasopressin – urine osmolality =174 mOsm/kg. After the test, a diagnosis of lithium-induced NDI was made and lithium was stopped and the patient was switched to other psychotropic drugs (such as valproate, carbamazepine, antipsychotics). The cessation of lithium did *not* alleviate the symptoms of NDI and after 2 months the patient attempted suicide and was hospitalized for several weeks. During hospitalization lithium was reinstated and the patient became affectively stable (euthymic) and resumed his job. After 5 years (age~51 years), lithium was stopped due to further deterioration in kidney function (plasma creatinine =1.7 mg/dl, eGFR =47 ml/min). The patient was treated with other mood stabilizers for few months after which he committed a suicide attempt once again and was hospitalized. A joint meeting was conducted between the treating psychiatrist, nephrologist, patient and his family – and it was decided to reinstate lithium despite the possibility of further deterioration in NDI and renal function. It was also agreed upon that lithium is a "life-saving" treatment for the patient and that it will not be stopped again even if it will lead to renal replacement therapy. Today, after nearly 40 years of treatment with lithium (excluding two pauses of few months) and 21 years of a nephrologist follow-up, the patient is mentally stable and reasonably functional. The dose of lithium is adjusted according to its plasma concentration. His renal data is as follows: plasma creatinine =4.1 mg/dl, eGFR =16 ml/min; urine output =6-7 L/day, proteinuria =800 mg/day; renal ultrasound – echogenic kidney with decreased corticomedullar differentiation and cortical cysts; the patient is on the waiting list for hemodialysis.

Mechanism of Lithium-induced NDI

The pathophysiological mechanisms underlying lithium-induced NDI are not clearly understood. Understanding the physiological processes involving renal sodium and water homeostasis is a key point. In the kidney, on the apical membrane of proximal tubules and principal cells of the collecting duct the major proteins that transport lithium into cells are the sodium-hydrogen exchanger (NHE) and the epithelial sodium channel (ENaC), respectively (Figure 1) [10,23-25]. It is established that lithium can substitute for sodium and enter cells through sodium-transporting systems [10,23-25] particularly during states of dehydration and volume depletion. There are other transporting systems that may transfer lithium into tubular cells such as the sodium-phosphate cotransporter (Figure 1) [10,23-25], however, their relevance to the entry of lithium into kidney cells is still unknown. On the basolateral side of proximal and distal tubules, the most likely possibility for lithium to be extruded out of cells (to the blood) is through the sodium-sodium exchanger (Figure 1) [10,23-25].

The transport of water into renal tubular cells is mediated through the water channel protein aquaporin (AQP) (Figure 1) [26]. AQP1 is abundantly expressed in the proximal tubule and descending loop of Henle where it is localized to the apical and basolateral membranes [26]. In the collecting duct, the transport of water into principal cells is mediated mainly by AQP2 (Figure 1) [27]. The exit of water occurs through AQP3 and AQP4. Normally, water permeability of principal cells is regulated by vasopressin. Vasopressin activates V2 receptors and increases intracellular cyclic adenosine monophosphate (cAMP), leading to translocation of AQP2 from intracellular vesicles to the apical membrane [27,28]. Prostaglandins also play a role in the regulation of sodium and water

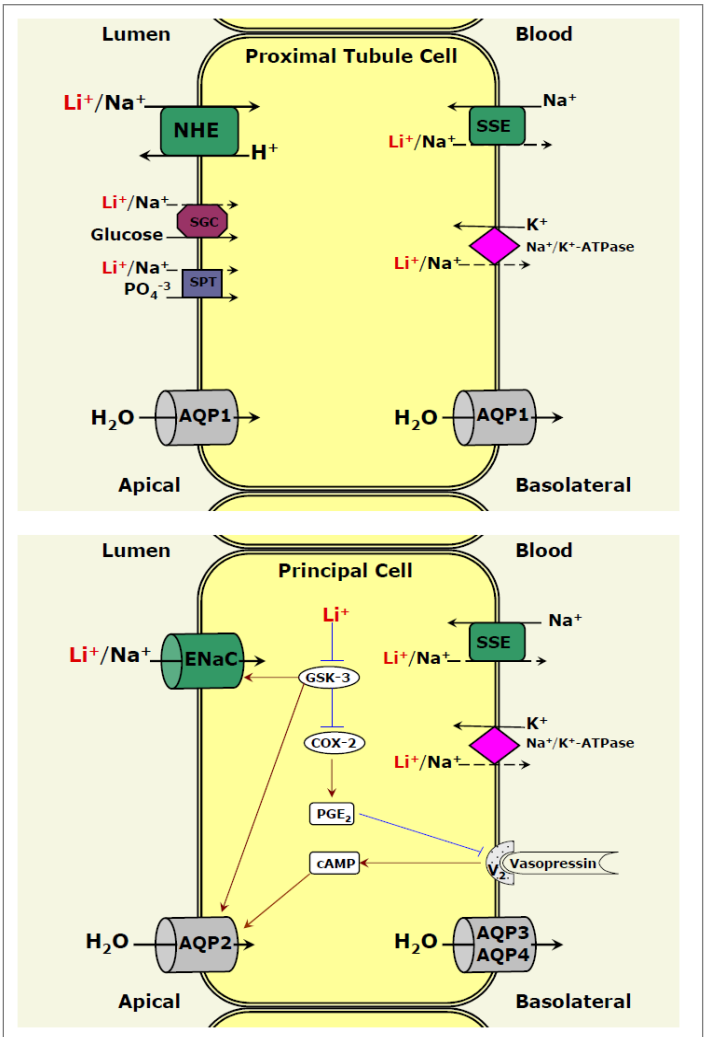

Figure 1: Lithium transport in kidney cells. In proximal tubule cells (top panel) and principal cells of the collecting duct (lower panel) lithium may substitute for sodium and be transported *via* sodium-transporting systems. Lithium is transported into proximal tubule cells and principal cells through NHE and ENaC, respectively. Other pathways for entry of lithium are less likely and may include: the sodium-glucose cotransporter, the sodium-phosphate transporter and the sodium-amino acids cotransporter. These pathways may be particularly active during states of dehydration and volume depletion. Extrusion of lithium to the blood may occur through SSE or Na^+/K^+-ATPase. Lithium inhibits GSK-3 leading to increased COX-2 expression and PGE_2 synthesis. This results in diminished vasopressin activity and decreased AQP2 levels on apical membrane of principal cells, which leads to increased urination. Abbreviations: AQP, aquaporin; COX-2, cyclooxygenase 2; ENaC, epithelial sodium channel; GSK-3, glycogen synthase kinase 3; NHE, sodium-hydrogen exchanger; SSE, sodium-sodium exchanger; PGE_2, Prostaglandin E_2; SGC, sodium-glucose cotransporter; SPT, sodium-phosphate transporter.

reabsorption [29]. PGE_2 is the main prostaglandin synthesized in the kidney [29] and its effect on renal function seems to be site-specific [29-31]. For example, in the collecting duct, PGE_2 attenuates the antidiuretic effect of vasopressin [31].

Lithium decreases the antidiuretic effect of vasopressin after short as well as long-term treatment duration [32,33]. The mechanisms by which chronic lithium therapy may reduce the antidiuretic effect of vasopressin are: First, lithium enhances PGE_2 production, which decreases vasopressin-induced cAMP synthesis [33]. Induction of COX-2 is a crucial mechanism by which medullary interstitial cells adapt successfully to the rapid shifts in ambient tonicity normally occurring in renal medulla [34]. These adaptive mechanisms are partially regulated by the enzyme glycogen synthase kinase 3β (GSK-3β), which is regarded as an up-stream modulator of COX-2 expression [34]. Lithium inhibits GSK-3β [35,36], which results in increased expression of COX-2 (*i.e.*, GSK-3β negatively regulates COX-2 expression) [34]. Thus, the regulation of renal sodium and water homeostasis by the GSK-3β-COX-2 pathway may be summarized as follows: (*i*) PGE_2 increases urination by attenuating the antidiuretic action of vasopressin; (*ii*) GSK-3β enhances the antidiuretic action of vasopressin by decreasing COX-2 expression and reducing PGE_2 synthesis; (*iii*) lithium inhibits GSK-3β leading to increased COX-2 expression and PGE_2 synthesis the result of which is diminished vasopressin activity and increased urination (Figure 1). These understandings were probably the basis for using NSAIDs and COX-2 inhibitors as a treatment against lithium-induced NDI [27,37,38]. Second, lithium reduces AQP2 gene transcription through a PG-independent mechanism, leading to further decrease in urinary concentrating ability [39]. Third, lithium induces remodeling of collecting duct which characterized by a decrease in the number of principal cells and an increase in the number of intercalated cells [40]. Fourth, lithium was found to decrease the ratio between principal and intercalated cells in mice collecting duct due to G2 (cell cycle) arrest in principal cells [41]. The decrease in principal/intercalated cell ratio was accompanied with features of NDI.

The management and treatment of a patient with lithium-induced NDI should take into account several important factors including: severity of NDI, risk of affective deterioration if lithium is stopped, stage of tubulointerstitial damage (if the damage is irreversible the patient will not necessarily benefit from the cessation of lithium), and, availability and feasibility of treatment options (for example, if a severe NDI develops due to acute lithium intoxication, hemodialysis should be immediately considered to minimize the damage to the kidney). Several pharmacological interventions have been suggested as a treatment for lithium-induced NDI. The potassium-sparing diuretic amiloride is one of the established options [15,42,43]. Other options are thiazide diuretics and vasopressin; however, their efficacy and safety remain to be ascertained. Classical NSAIDs and selective COX-2 inhibitors have also been tried [33,37,38] but these drugs increase the risk of lithium toxicity and may not be the best choice for additive therapy.

Concluding Remarks

This case report emphasizes the need to balance between concerns regarding the damage to the kidney which is a result of long-term lithium treatment to the significant therapeutic benefit of lithium as a mood stabilizer and anti-suicidal drug. Our patient committed suicide attempts at two occasions after lithium cessation due to concerns regarding deterioration in renal function and aggravation of NDI. One of those suicidal attempts (or others that lithium probably prevented) could "bear fruit" and kill the patient at an early age. Therefore, treating psychiatrists and nephrologists must perform a risk-benefit calculation before deciding to stop lithium in bipolar patients, particularly when the cessation of lithium is not expected to lead to improvement in kidney function. On the other hand, it is essential that clinicians pursue *preventive* strategies to minimize the risk of developing impairments in kidney function in lithium-treated patients. This may include: prescribing the *lowest effective* dose of lithium; rigorous monitoring of plasma lithium levels in order to avoid episodes of intoxication and acute nephrotoxicity; annual examination of creatinine clearance (GFR); avoid co-administration of other drugs that may increase plasma lithium levels such as NSAIDs, ACE inhibitors and diuretic drugs; and, assessment of other determinants of renal function, such as plasma calcium, proteinuria and peripheral edema.

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