Review Article

Pharmacometrics in the Management of Lithium-Induced Nephrogenic Diabetes Insipidus

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ABSTRACT

Lithium is a common mood stabilizer for people with bipolar illness. However, prolonged use of lithium can lead to nephrogenic diabetes insipidus (NDI). In the kidneys, lithium decreases the renal response to arginine vasopressin, leading to a reduction in water reabsorption efficiency. The primary mechanism behind lithium-induced NDI is the downregulation and dysfunction of aquaporin-2 water channels in the collecting ducts. Pharmacometrics is the study of using mathematics and statistics to create models that help us understand and predict how a medicine works in the body. Many studies use population pharmacokinetic (popPK) models along with therapeutic drug monitoring (TDM) to find the therapeutic lithium dose. The Bayesian method helps to predict the changes in blood lithium levels and change the dose for successful treatment. Amiloride, thiazides and NSAIDs are current drugs used for lithium-induced nephrogenic diabetes insipidus, but they can reduce the urine output by 40% only. Regular monitoring and using pharmacokinetic models can make lithium treatment safer and more effective.

Keywords: Lithium-induced nephrogenic diabetes insipidus; Pharmacometrics; population pharmacokinetics; Bayesian dose adjustment; Aquaporin-2.

INTRODUCTION

Lithium is a common mood stabilizer for people with bipolar illness[1,2]. It is also given to those who are at risk of having manic or depressive episodes[2] and in some cases of depression that doesn't respond to other treatments. Long-term lithium medication has been shown to greatly decrease suicidal thoughts and mortality in individuals with bipolar illness[2]. However, prolonged use of lithium can lead to several types of ailments with the renal system, thyroid, and parathyroid, including nephrogenic diabetes insipidus (NDI), chronic tubulointerstitial nephropathy, and acute kidney injury (AKI)[3]. Even though lithium leads to NDI, it continues to be utilized. Epidemiological studies indicate that around 20 to 40% of individuals using lithium experience nephrogenic diabetes insipidus[4].Lithium stays to be a crucial and potent drug in psychiatry; yet, its negative impacts on renal, neurological, and endocrine systems provide major health problems[5].In the kidneys, lithium decreases the renal response to arginine vasopressin, leading to a reduction in water reabsorption efficiency. This causes polyuria, natriuresis, and kaliuresis, which are hallmarks of lithium-induced NDI[6]. The majority of research indicates that the primary mechanism behind lithium-induced NDI is the downregulation and dysfunction of aquaporin-2 water channels in the collecting ducts[7]. Polyuria and polydipsia occur when the kidneys fail to respond effectively to vasopressin. Hence, patients receiving lithium therapy must be routinely monitored through haematology, liver function tests (LFT), kidney function tests (KFT), urine analysis, and serum electrolytes[8].Pharmacometrics is the study of using mathematics and statistics to create models that help us understand, describe, and predict how a medicine works in the body, its effects on the body, and how a condition progresses[9].Pharmacometrics integrates knowledge of pharmacology, physiology, and disease with quantitative methods to inform drug development and regulatory decisions[9].The main aim of this study is to explore how pharmacometrics and mathematical methods can be used in the prevention and management of lithium-induced nephrogenic diabetes insipidus. It mainly focuses on how lithium acts in the body, current treatments for NDI, and how modelling tools help make therapy safer and more effective.

PATHOPHYSIOLOGY OF LITHIUM-INDUCED NDI

Over 80% of filtered lithium from the glomeruli is reabsorbed into the bloodstream from the proximal tubules, but it affects kidney function by causing adverse effects primarily in the distal tubules and collecting ducts[10]. The pathophysiological process of lithium-induced nephrogenic diabetes insipidus is shown in Figure 1.

Lithium enters kidney cells mainly through the epithelial sodium channel (ENaC) located on the apical membrane of cortical collecting tubule cells. Normally, the vital function of ENaC is to transport sodium ions from the tubule into the kidney cells. But lithium can effectively replace sodium ions and be transported across the epithelial membrane due to its similarity in size and other properties to sodium[11]. Once lithium enters the principal cells of the kidney through ENaC, it is not efficiently removed from the cells like sodium. This occurs because the Na^+/K^+-ATPase pump located on the basolateral membrane has a lower affinity for lithium than for sodium[10].AQP2 is a water channel protein. Its main function is to reabsorb water from urine into the kidney cells to prevent dehydration. Vasopressin

(an antidiuretic hormone) binds to V2 receptors, activating the adenylyl cyclase–cAMP pathway, which activates protein kinase A (PKA). PKA phosphorylates AQP2, helps to reabsorb water and prevents excessive water loss. Prolonged lithium treatment inhibits this pathway, reducing AQP2 phosphorylation and resulting in polyuria[11].

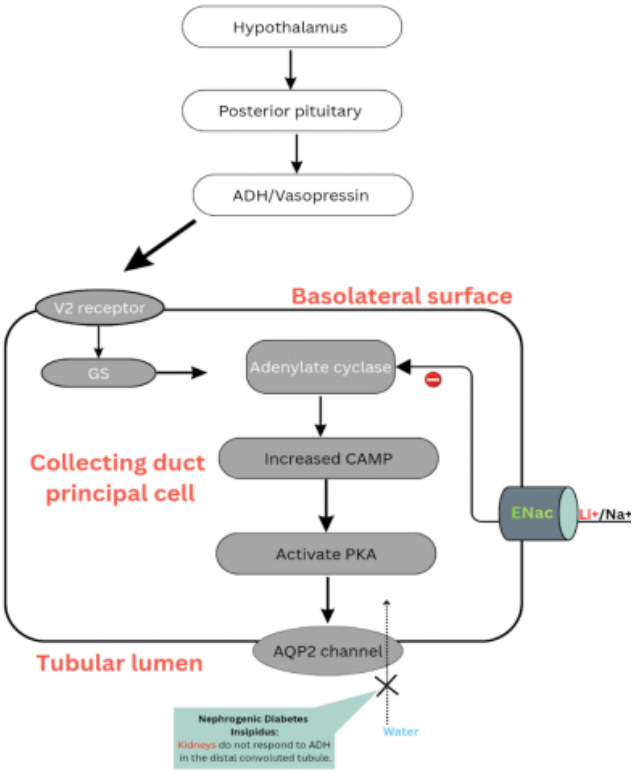

Figure 1: Pathophysiology of lithium-induced nephrogenic diabetes insipidus. Lithium enters principal cells via ENaC and inhibits the vasopressin–cAMP–AQP2 signalling pathway, resulting in decreased water reabsorption and polyuria. Adapted and modified from Mutter C.M. et al., "Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management." Cureus 2021; 13(2): e13523. Licensed under CC BY 4.0.

When lithium causes nephrogenic diabetes insipidus, it increases the activity of COX-2 and leads to an increased PGE2 production. Normally, PGE2 binds to EP3 receptors and lowers the cAMP level inside the cells. As a result, less cAMP leads to the breakdown of AQP2 and affects the effect of the antidiuretic hormone[10]. There are two important pathways (the inositol pathway and the protein kinase C pathway) that help to regulate the cAMP production. When lithium levels increase in the body, it lowers the cAMP production and inactivates protein kinase A (PKA). Because of this, AQP2 is less phosphorylated and cannot reach the apical membrane of the collecting duct. As a result, it reduces the reabsorption of water and produces more dilute urine[10]. GSK3-beta is a protein that helps to maintain the fluid balance through its control of AQP2. It is also responsible for cell division and regulation of the cell cycle[11]. When GSK-3 is inhibited by lithium, it lowers AQP2 and increases beta-catenin[12].

PHARMACOMETRICS AND LITHIUM PHARMACOKINETICS/ PHARMACODYNAMICS

Lithium pk principles

Like other drugs, lithium doesn't get broken down. Instead, it just passes through the kidney, and about 80% is absorbed again in the proximal tubule[13].Lithium leaves the body more slowly than creatinine. So, the dose should be reduced for kidney patients to prevent toxicity[14].The normal effective dose of lithium is 0.4–0.8 mEq/L, but in acute mania the dose gets increased up to 1.2 mEq/L[13].In patients with normal kidney function, the lithium leaves at a rate of 0.6–2.4 L/hour, and its half-life is 16–30 hours. But, in case of toxicity, haemodialysis can be used to eliminate the lithium from the blood[15].Taking lithium with drugs such as diuretics or ACE inhibitors makes the body remove lithium more slowly and can lead to toxicity[14].

Population pk models and bayesian dose adjustment

Nowadays, many studies use population pharmacokinetic (popPK) models along with therapeutic drug monitoring (TDM) to find the therapeutic lithium dose. Other psychiatric drugs also need careful dosing for safe and effective treatment[13].With advancements in pharmacokinetics and computer modelling, population pharmacokinetics (popPK) is widely used in medical practice to find out the effects of drugs and the best dose for patient safety. Researchers perform population pharmacokinetic (PPK) tests in lithium studies to see how body weight and age affect lithium clearance[16]. Using Bayesian measurements along with these PK models helps doctors decide the best dosage plan[15].

pk-pd relationship to urine concentration ability

Taking lithium for a long period can cause frequent urination. This happens when the kidneys stop responding properly to vasopressin and make fewer AQP2 channels that control body fluids[14]. Kidney function and creatinine clearance are responsible for the excretion of lithium from the body. Because of this, lithium levels can vary from one person to another. Continuous lithium use makes the kidneys unable to concentrate on urine properly. PK–PD studies also show how kidney removal of lithium influences how the drug works in the body[15].

THERAPEUTIC STRATEGIES FOR LITHIUM-INDUCED NDI

Amiloride

Amiloride is the selected medication and essential treatment preference for lithium use. Because it inhibits the distal nephron epithelial sodium channel (ENAC). They prevent damage from the principal cells and shield the main cells from harm and decrease the polyuria and polydipsia[17].

Thiazide diuretics

Thiazides may also upregulate AQP2 and distal Na^+ transporters (such as ENaC) in response to lithium-induced NDI, enhancing urine concentration and water absorption. Lithium entrance through ENaC channels can be reduced,

whereas the action of thiazides is amplified when combined with amiloride[18,19].

NSAIDS (Indomethacin)

Increases the production of prostaglandin E_2 (PGE_2) through COX-2 activation, which in turn increases AQP2 expression. NSAIDs reduce renal PGE_2 levels by blocking COX-1/COX-2. Lower PGE_2 improves AQP2 expression, increases cAMP activity, and increases urine concentrating ability[18,19].

Desmopressin (DDAVP)

DDAVP, a synthetic ADH analogue, acts on V2 receptors in the collecting ducts to increase AQP2 expression and water reabsorption even when responsiveness is partially preserved. A dosage: oral 60–180 µg/day, suitably titrated. Efficiency: Reported cases show a 20 to 50 percent reduction in urine output and an increase in urine osmolality in patients with residual ADH sensitivity[20,21].

Combination therapies

Thiazide diuretic + Amiloride

Hydrochlorothiazide improves proximal sodium and water reabsorption by mildly depleting urine volume. By blocking the entry of lithium into collecting duct cells through ENaC, amiloride avoids further renal toxicity. reduces polyuria by approximately 40–60%. stops the buildup of lithium in the kidney[22].

Thiazide + NSAID

Indomethacin inhibits renal prostaglandin synthesis, which increases the action of ADH and decreases urine flow. For an additive effect, combine with thiazide[22].

Non-pharmacological approaches (diet, fluid strategies)

Dietary Adjustments: a. Diet Low in Salt Limit sodium consumption to approximately <2 g/day (≈5 g NaCl). Lower plasma osmolality → decreased urine output b. Diet Low in Protein Avoid high-protein diets; limit your daily protein intake to 0.8–1.0 g/kg. reduces osmotic diuresis by reducing urea generation. Avoid alcohol and caffeine. Both can exacerbate dehydration by increasing urine production. Track and Control the Electrolyte-Fluid Equilibrium Frequent observation of serum creatinine, eGFR, and sodium and osmolality levels Lithium levels Renal function: Teach patients how to identify the signs of dehydration, which include thirst, weakness, lightheadedness, and confusion[23].

MODEL-INFORMED CLINICAL PATHWAYS FOR NDI MANAGEMENT

Now, pharmacokinetics and computer modelling have improved a lot. Population pharmacokinetics (PPK) is often used to check drug effects in patients and help adjust doses for personalised treatment[16].

Using NONMEM and Monte Carlo methods, a population pharmacokinetic (PPK) model of lithium carbonate was developed in patients with bipolar disorder to study how different factors affect blood levels and to help guide personalised dosing[16].

A population pharmacokinetic method helps identify how a drug's effects differ depending on a person's age, weight, and kidney function. The Bayesian method also helps design personalised dosing[15].

EMERGING AND EXPERIMENTAL THERAPIES

Amiloride, thiazides and NSAIDs are current drugs used for lithium-induced nephrogenic diabetes insipidus, but they can reduce the urine output by 40% only. They cannot bring back to normal levels[20].

Recent research says that activating the Keap1/Nrf2 signalling pathway may help treat lithium-induced nephrogenic diabetes insipidus[24].

Along with regular monitoring of lithium levels, population pharmacokinetics (popPK) also helps to adjust the dose for each patient. Checking these models with real-life patient data helps make the treatment safer and more effective[13].

RESEARCH GAPS AND FUTURE DIRECTIONS

Even though there have been several developments in lithium-induced nephrogenic diabetes insipidus and pharmacometrics modelling, some things remain unclear. Only a few studies use real patient data with PK-PD models. The continuous effects of lithium on kidney function are also not fully known. Future research should focus on new treatment targets, improving personalised dosing, and testing novel therapies such as Keap1/Nrf2 activators. Filling these gaps can make lithium therapy safer and more effective.

CONCLUSION

Lithium is a commonly used drug for treating bipolar disorder, but it can lead to kidney problems such as NDI. Doctors use tools like PK-PD modelling and the Bayesian method to calculate the right dose for each patient and monitor them regularly. Current treatments are not fully effective, while new approaches may improve outcomes. Regular monitoring and using pharmacokinetic models can make lithium treatment safer and more effective, showing how important personalised care is to manage side effects.

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