CASE REPORT

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Decrease in Serum Lithium Levels Induced by Ursodeoxycholic Acid: A Case Report

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ABSTRACT

Lithium is a leading therapeutic option for bipolar patients in the treatment of acute and maintenance phases of illness. Lithium levels should be closely monitored due to its narrow therapeutic index. Combination of other treatment regimens with lithium may increase or decrease lithium levels that may cause intoxication symptoms or recurrence of mood episodes. Therefore, clinicians should be aware of the drugs recommended by other medical specialties that may change lithium plasma levels. Nonsteroidal anti-inflammatory drugs, thiazide diuretics, and angiotensin-converting enzyme inhibitors are the best known potential medicines for drug interactions with lithium. In this article, we aimed to present a case report of a patient who was taking lithium for recurrent depression more than 3 years with stable serum levels, but lithium levels decreased fastly after the prescription of ursodeoxycholic acid. The possible mechanism of interaction between lithium and ursodeoxycholic acid was discussed with the current literature.

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INTRODUCTION

Despite lithium being the cornerstone option for both acute and maintenance phases of bipolar disorders, it is also commonly preferred for augmentation of antidepressant treatment or prevention of depressive episodes in unipolar recurrent depression.[1] The optimal steady-state concentration of lithium is generally considered to be 0.8-1.5 mEq/L for acute episodes of mania and 0.6-1.2 mEq/L for maintenance therapy.[2] The elimination half-life of lithium is about 16-30 h, and it is excreted entirely by the kidneys.[3] Blood lithium concentration may change with medications that are recommended for other medical conditions. Particularly nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, and angiotensin-converting enzyme inhibitors (ACEIs) mostly affect serum lithium levels by causing changes in renal function.[2]

In this case report, we aimed to discuss a possible drug interaction in a patient who regularly received lithium for the diagnosis of recurrent depression, underwent cholecystectomy 2 years ago, and had a fast decrease in blood lithium levels after starting ursodeoxycholic acid (UDCA) due to nausea and abdominal pain.

CASE REPORT

A 46-year-old female, who was a housewife with 2 children and lived with her family, had depressive symptoms for nearly 30 years and did not respond adequately to antidepressants. She was started on lithium treatment 24 years before. She has been followed up since September 2017 with the diagnosis of recurrent major depressive disorder at Mazhar Osman Mood Clinic, Department of Psychiatry, Selcuk University Medical School. Informed consent was obtained from the patient.

Two years ago, the patient was admitted to the gastroenterology outpatient clinic with complaints of abdominal bloating and abdominal pain. She was referred to the endocrinology clinic because her blood calcium level was 13.4 mg/dL. Clinical and laboratory examinations revealed a parathyroid adenoma. Based on the recommendations of the nephrology clinic, lithium was discontinued as it was considered to exacerbate hypercalcemia. The patient then underwent parathyroid surgery. After discontinuing lithium treatment, the patient was started on lamotrigine, quetiapine, and duloxetine treatments. The medications were increased to effective doses at regular intervals. However, these treatments were not effective in treating the patient's depression. Following this, lithium was again added to her treatment and titrated to the recommended therapeutic blood level by monitoring her blood calcium levels at regular intervals. The patient reported a significant decline in her complaints. Her Hamilton Depression Rating Scale (HAMD) score was 6 after 2 weeks.

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The patient underwent cholecystectomy a year ago and was administered 125 µg/day of levothyroxine for hypothyroidism. She did not have a history of smoking, alcohol consumption, and substance use. Routine laboratory examinations revealed that her hemogram; serum electrolyte levels; and thyroid, liver, and kidney functions were normal (Na: 139 mEq/L, K: 4.15 mmol/L, Ca: 10.3 mg/dL, fT3: 2.98 ng/L, TSH: 4.97 mU/L, urea: 22 mg/dL, and creatinine: 0.74 mg/dL).

During a routine outpatient clinic visit, the patient presented with recent complaints of malaise and reluctance. Her HAMD score was 5. Her serum lithium levels varied between 0.65 and 0.84 mmol/L during previous follow-ups, with the level being 0.26 mmol/L during the latest follow-up. It was learned that 250 mg per day of UDCA was added to her treatment a week ago due to nausea and abdominal pain. Considering that the patient regularly received lithium for the past 2 years and had good treatment compliance, the change in serum lithium levels was thought to be caused by a possible drug interaction following the addition of UDCA to the treatment. The patient was then referred to the general surgery clinic in order to change or discontinue UDCA. Based on the recommendations of the general surgery clinic, UDCA was discontinued. The lithium dose remained unchanged. The patient's serum lithium level was found to be 0.80 mmol/L a week later.

DISCUSSION

Lithium is mainly eliminated via glomerular filtration. In total, 80% of the filtered lithium is reabsorbed in the proximal tubule.[4] Conditions that can disrupt fluid and electrolyte balance (such as sodium and potassium imbalance) may alter the lithium level in the blood.[2] Sodium competitively inhibits lithium reabsorption.[4] In the present case, considering that there was no change in the fluid intake, hypothyroidism was controlled and the patient returned to the euthyroid state with treatment, and serum electrolyte levels were within the normal range, the decrease in serum lithium levels was thought to be due to the use of UDCA.

Ursodeoxycholic acid is a secondary bile acid that reduces intestinal cholesterol absorption and biliary cholesterol secretion.[5] We think it is crucial to consider that lithium levels are changed by UDCA, which is commonly used for treating diseases, such as cholelithiasis, primary sclerosing cholangitis, and alkaline reflux gastritis.[6] Conversely, it should be considered that pharmaceutical auxiliary substances (not UDCA) can change serum lithium levels. In this respect, sodium lauryl sulfate and magnesium stearate draw attention. Sodium is also a monovalent cation and is largely reabsorbed in the proximal tubule of the kidney. In the proximal tubule, lithium is handled similar to sodium. The sodium–hydrogen pump is mainly responsible for sodium reabsorption in the proximal tubule. Moreover, this pump is the main transport pathway that pumps lithium inside the cell, and the maximal transport rate of lithium is twofold slower than that of sodium.[2] Lithium is a monovalent cation that can compete with sodium in the proximal tubule. Thus, sodium can be reabsorbed to a greater extent than lithium and may increase the excretion of lithium. The $Na/K/2Cl^-$ co-transporter in the thick ascending limb of Henle's loop is another mode of lithium reabsorption. Lithium can replace sodium in this transport phase.[7] In this study, 3-10% of filtered lithium is reabsorbed from Henle distal tubule. This transportation was mediated by the paracellular pathway and maintained by the transepithelial voltage difference created by potassium efflux by the renal outer medullary K^+(ROMK2) and $Na/K/2Cl^-$ co-transporter activity.[8]

Magnesium stearate is another auxiliary substance; magnesium is a divalent cation that is reabsorbed mostly in the thick ascending limb of Henle's loop.[9] Calcium and magnesium ions undergo competitive inhibition in the thick ascending limb of Henle's loop. In other words, magnesium excretion increases in the case of hypercalcemia, while calcium excretion increases in the case of hypermagnesemia.[10] A similar situation exists between lithium and magnesium ions. Lithium and magnesium ions have similar physiochemical features that may lead to competitive binding to the cellular surfaces.[11] Lithium inhibits the glycogen synthase kinase 3 (GSK-3) enzyme in the kidney via direct competition for a magnesium-binding site on GSK-3β. Mg concentration determines the power of lithium's inhibition. Thus, higher magnesium concentrations can reduce the impact of lithium.[12,13] Many psychotropic drugs cause GSK-3β inhibition through increased phosphorylation. GSK-3β is inactive when it is phosphorylated. Lithium is one of the strongest inhibitors of this enzyme. AKT/β-arrestin (1 or 2)/PP2A protein complex plays an important role in blocking AKT. AKT is a kinase that phosphorylates GSK-3β. When lithium is available, AKT/β-arrestin (1 veya 2)/PP2A complex becomes unstable due to competition that prevents the Mg^{+2} ion from fixing on the β-arrestin.[13] Based on this information, we think that sodium or magnesium additives can increase lithium excretion by reducing lithium reabsorption and thereby decrease serum lithium levels in the present case.

CONCLUSION

There were no case reports in the literature regarding the interaction between lithium and UDCA. The fact that UDCA, which is widely used for gastrointestinal complaints, reduces lithium levels may lead to new episodes of depression. In this regard, when UDCA is added to the treatment of patients taking lithium, clinicians should be aware of pharmaceutical auxiliary substances, closely monitor lithium blood concentration, and cooperate with other physicians during the treatment.

Informed Consent: Written informed consent was obtained from the participant who participated in this case.

Conflict of Interest: The authors have no conflicts of interest to declare.

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