Lithium-induced hypercalcemia with normal parathyroid hormone: A case report

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Abstract
Long-term use of lithium is a known risk factor for hypercalcemia often due to involvement of the parathyroid gland. Because of this, lithium-induced hypercalcemia typically occurs simultaneously with abnormal parathyroid hormone concentrations. This case report describes a 54-year-old white male who has received lithium therapy intermittently for more than 10 years. During admission to an acute inpatient psychiatric unit, the patient experienced hypercalcemia with normal parathyroid hormone concentrations and no other discernible cause. Based on the Naranjo algorithm, lithium was determined to be the probable cause of hypercalcemia. Current literature suggests that lithium-induced hypercalcemia occurs secondary to hyperparathyroidism; however, this case may provide evidence of another, unidentified cause.

Keywords: lithium, lithium toxicity, hypercalcemia, parathyroid hormone, PTH

Background
Lithium is a medication commonly used to treat bipolar disorder and major depressive disorder. Additionally, it is 1 of only 2 agents that has shown to decrease suicidality. Although lithium treatment has proven effective, it is also associated with a variety of possible adverse effects including renal insufficiency, thyroid and parathyroid gland dysfunction, and hypercalcemia. Hypercalcemia is estimated to occur in more than 20% of patients treated with lithium. In a majority of cases, patients are asymptomatic, and hypercalcemia is found incidentally. Patients typically begin to exhibit symptoms of hypercalcemia when concentrations exceed 12 mg/dL (reference range 8.5-10.1 mg/dL), most commonly myalgia, nausea, vomiting, irritability, and confusion. Additionally, arrhythmias, such as prolonged PR interval, short QT interval, and widened QRS complex can occur. Severely elevated calcium (>14 mg/dL) can cause encephalopathy, pancreatitis, and osseous changes. In cases of chronic hypercalcemia, nephrolithiasis and nephrocalcinosis can occur.

The exact mechanism by which lithium may induce hypercalcemia is not well understood; however, evidence suggests that it may be caused by an exacerbation of underlying hyperparathyroidism or damage to at least one parathyroid gland. The parathyroid gland is a four-lobed gland located posterior to the thyroid that secretes parathyroid hormone (PTH). Calcium and phosphate concentrations are both, in part, regulated by PTH secretion, which, in turn, is regulated by vitamin D. A decrease in serum calcium leads to secretion of PTH. Serum calcium then acts as a negative-feedback loop, signaling the cessation of PTH as serum calcium increases. The half-life of PTH is less than 10 minutes, and its effects are rapidly attenuated after PTH is no longer being secreted. Patients with hyperparathyroidism experience dysregulation of this system, leading to


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elevated PTH in the presence of hypercalcemia. Lithium may contribute to this by causing damage to the parathyroid glands. A second proposed mechanism of lithium-induced hypercalcemia involves calcium sensing receptors (CSRs) present on parathyroid glands. Lithium may act as a competitive antagonist at CSRs, which causes an increase in the serum calcium needed to inhibit PTH. This may damage the parathyroid gland and increase serum calcium. Onset of lithium-induced hyperparathyroidism with manifestations of hypercalcemia and increased PTH is typically seen at least 2 years after initiation of treatment. Diagnosis cannot be made on clinical observation alone as many of the symptoms of hyperparathyroidism and hypercalcemia are similar to those of mental illnesses. Therefore, an increase in PTH (reference range 15-72 pg/mL) and calcium is needed to make a diagnosis.

Treatment of hypercalcemia should be initiated in patients experiencing symptoms and those with a serum calcium greater than 15 mg/dL regardless of physical presentation. The cornerstone of acute hypercalcemia treatment is aggressive fluid resuscitation using intravenous 0.9% sodium chloride with a target urine output of at least 200 mL/h. Low-dose loop diuretics can be considered but used with caution due to the possibility of paradoxical hypercalcemia from bone resorption. Patients resistant to fluid resuscitation can be given calcitonin 4 units/kg every 12 hours intramuscularly or subcutaneously with doubling of the dose if an inadequate response is achieved after 24 hours. In patients with life-threatening symptoms, resistant hypercalcemia, or renal insufficiency, the treatment of choice is initiation of hemodialysis and consultation with an endocrine specialist.

Strategies for long-term management of hypercalcemia include surgical resection of the parathyroid, long-term calcimimetic therapy, and close monitoring without immediate intervention. These treatments are not well studied and no approach has proven more efficacious. Postintervention monitoring is not well defined regardless of the treatment modalities selected. It is reasonable, however, to monitor serum calcium and PTH 2-6 weeks after treatment, at 6 months, and annually thereafter or as clinically indicated.

When evaluating elevated serum calcium in patients prescribed lithium, other causes of hypercalcemia and hyperparathyroidism should be considered. Increased PTH can be caused by parathyroid malignancy, familial abnormalities, or medications, such as thiazide diuretics. Hypercalcemia in the absence of elevated serum PTH may be due to malignancies not involving the parathyroid glands, thyroid dysfunction, and medications, such as thiazide diuretics and theophylline. A PubMed search revealed no published case reports of lithium-induced hypercalcemia with normal PTH. Search terms included lithium, or lithobid, and hypercalcemia, or high calcium, or tsh, or normal TSH, or normal thyroid.

**Case Report**

The patient is a 54-year-old white male with a past medical history significant for bipolar I disorder with psychotic features and posttraumatic stress disorder admitted from the emergency department to the acute psychiatric floor with symptoms of mania and psychosis. Prior to admission, the patient had been taking variable doses of lithium for more than 10 years with poor adherence noted by the patient and prescription fill history. Per hospital records, the maximum daily dose of lithium the patient received was 900 mg. However, during this period, the patient received care at hospitals outside of the health care system, so it is unknown if the dose was adjusted.

In the emergency department, hospital day (HD) 1, serum lithium concentration was negligible at <0.2 mEq/L (reference range 0.6-1.2 mEq/L). Due to past therapeutic success, lithium was reinitiated with 450 mg lithium carbonate sustained action in the emergency department. Once admitted, an additional 900 mg of lithium carbonate sustained action was administered on HD 1 for a total dose of 1350 mg with plans to reinitiate a maintenance dose of 900 mg daily. Labs were not drawn until approximately 12 hours after receiving the 900-mg dose of lithium, so a baseline serum calcium was not available. Also on this day, the patient was continued on his home regimen of quetiapine 300 mg at bedtime. Serum calcium was measured to be at least 11 mg/dL through HD 4. On HD 5, serum lithium was therapeutic at 0.9 mEq/L with an elevated serum calcium of 11.1 mg/dL and normal PTH of 62 pg/mL. On HD 6 the patient remained asymptomatic of hypercalcemia but requested a different medication be started due to fear of thyroid complications he read about in an informational handout. Lithium was discontinued, valproic acid 750 mg twice daily was initiated, and quetiapine was increased to a total daily dose of 400 mg due to continued psychotic symptoms. Serum calcium taken on HD 10 and HD 13 were within normal limits at 10.1 mg/dL (Table). The psychiatric symptoms began to subside, and he was discharged on HD 15 on valproic acid 750 mg twice daily and quetiapine 400 mg daily. No other medications were administered during admission other than haloperidol intramuscularly for agitation on HD 2.

Other potential causes of hypercalcemia were assessed. The patient did not exhibit any other signs of malignancy and had a thyroid-stimulating hormone that was within normal limits at 1.02 μU/mL (reference range 0.36-4.50 μU/mL). Additionally, the patient did not report taking...
any medications, vitamins, or supplements prior to admission, nor was he taking any medications inpatient that were suspected to increase serum calcium. During past trials of lithium therapy, including a time frame of 3 to 6 months prior to admission, the patient experienced a similar rise in serum calcium with a normal PTH (Table). The serum calcium collected in the absence of lithium treatment nearest this admission was 6 months prior. This value (10.1 mg/dL) appears to be the patient’s baseline serum calcium in the absence of lithium, chronically near the upper limit of normal but 10.2 mg/dL. In all cases, serum albumin was within normal limits (3.4-5.5 g/dL), suggesting that serum calcium values were accurate. Using this information, lithium was considered the probable cause of hypercalcemia based on the Naranjo Algorithm Adverse Drug Reaction Probability Scale.18

**Discussion**

This case suggests that lithium-induced hypercalcemia in the absence of elevated PTH may possibly be caused by another, unidentified mechanism. Although a small portion of patients with primary hyperparathyroidism may not experience elevated PTH, cases such as this attributed to lithium-induced hyperparathyroidism have not been reported. Additionally, in this patient, the rapid onset and offset of hypercalcemia does not meet the typical symptomology of patients experiencing lithium-induced hyperparathyroidism.

When treating a patient with hypercalcemia, especially those receiving lithium, it is crucial to treat the underlying cause of the abnormality. Evidence suggests that discontinuing lithium treatment does not restore normal parathyroid function. Furthermore, it is unclear if discontinuing lithium treatment after acute and chronic management of hyperparathyroidism and hypercalcemia increases the likelihood of long-term remission of these abnormalities. The rate of relapse of manic symptoms after stopping lithium therapy is drastically increased, especially within the first 3 months; therefore, the risks and benefits of discontinuing lithium therapy must be carefully considered.20

In this case report, a temporal relationship was observed between the initiation of lithium and the rapid development of hypercalcemia with normal PTH. Based on the events of this case report, it is possible that an unidentified mechanism may contribute to lithium-induced hypercalcemia. Clinicians should be cognizant of the possibility that the use of lithium may result in hypercalcemia even in the presence of normal PTH.

**References**

