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False lithium toxicity secondary to lithium heparin test tube: A case report and review

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Abstract

This case demonstrates a false elevation of serum lithium concentrations that can occur when blood samples are collected using lithium heparin (green-top) tubes. The patient was a 58-year-old female on chronic lithium therapy for bipolar disorder who presented to the emergency department following an overdose of 5 unidentified medications. The patient was overly sedated and exhibited paradoxical laughter, slurred speech, and mild abdominal pain. The recommended maintenance lithium concentration is 0.6 to 1.0 mmol/L, and she had previously been stable within this therapeutic range. The initial lithium concentration drawn upon admission was 2.05 mmol/L. No intervening treatment was made with the exception of intravenous fluids due to a lack of correlation between clinical presentation and the lithium concentration. Six hours later, a repeat lithium concentration of <0.10 mmol/L was obtained. Upon investigation, it was discovered that the initial blood sample was obtained in a lithium heparin green-top tube instead of the recommended plastic tubes with either sodium heparin or dipotassium ethylenediamine tetraacetic acid as the anticoagulant. As this case demonstrates, lithium heparin tubes have the potential to cause falsely elevated lithium concentrations. It is important for health care professionals to be aware of the false elevations that can occur when blood samples are taken in this type of tube.

Keywords: lithium toxicity, factitious toxicity, lithium heparin test tube, green-top tube, lithium heparin tubes, toxic lithium concentrations

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Background

Lithium is a mood-stabilizing medication indicated for acute mania and bipolar disorder maintenance treatment.[1] The National Institute for Health and Care Excellence and British Association for Psychopharmacology guidelines recommend it as a first-line treatment for bipolar disorder maintenance.[2,3] Recognized off-label uses include treatment of depression and cluster headaches.[1] Various lithium carbonate preparations are available, including a solution, controlled-release tablets, and immediate-release tablets and capsules.[1] There is also a different lithium salt, lithium orotate, that is available over the counter.

Serum lithium concentration monitoring is recommended during initiation and maintenance treatment due to its narrow therapeutic range (traditionally 0.6 to 1.2 mmol/L) and the multitude of factors that can affect serum concentrations (Table 1).[3,4]

Symptoms of acute lithium toxicity are presented in Table 2.[5,6] Clinical presentation can be variable. Intermittent

TABLE 1: Factors affecting lithium concentrations[4]

Increases Lithium Levels	Decreases Lithium Levels
Nonsteroidal anti-inflammatory drugs[a]	Theophylline
Diuretics	Caffeine
Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers	Acetazolamide
Low sodium intake	Mannitol
Dehydration	Sodium bicarbonate

[a]With the exception of sulindac.

hemodialysis is considered the most effective treatment modality for lithium poisoning.[6] A 2015 systematic review[6] recommended extracorporeal treatment (intermittent hemodialysis preferred followed by continuous renal replacement therapy) in patients with lithium poisoning who have impaired kidney function and a lithium concentration of >4 mEq/L or in patients with decreased consciousness, seizures, or significant dysrhythmias. Extracorporeal treatment is also reasonable for patients with a lithium concentration of >5 mEq/L and confusion.[6] Gastric lavage or whole bowel irrigation could be considered if necessary.[6,7]

The lithium assay utilized to obtain lithium concentrations uses a substituted porphyrin compound that results in a change of absorbance of the lithium sample; this absorbance is directly proportional to the concentration of lithium within the sample.[8] It is recommended to use plastic tubes with either sodium heparin or dipotassium ethylenediamine tetraacetic acid as the anticoagulant.[8] When a lithium heparin green-top test tube is used for sample collection, the lithium heparin in the tube reacts with the substituted porphyrin compound; this causes a false elevation of the lithium concentration. We describe the case of a patient with bipolar disorder and no significant clinical signs of lithium toxicity whose serum lithium concentration was critically high.

Case Report

A 58-year-old female presented to the emergency department following an intentional overdose of 5 unidentified medications per her husband's report. Upon presentation, the patient was oversedated and exhibited paradoxical laughter, slurred speech, and mild abdominal pain. The patient was alert and oriented only to self. In the emergency department, the patient's vitals were blood pressure 117/57 mm Hg, pulse 45 beats/min, temperature 36.5°C, respiratory rate 12 breaths/min, and oxygen saturation 95%. A cardiac exam was remarkable for an S2 systolic murmur and bradycardia. Cardiology determined electrocardiogram intervals to be normal. The patient's lungs were clear bilaterally, and the neurologic exam was unremarkable. A urine drug screen was notable only for benzodiazepines. Lab results were also unremarkable with the exception of a lithium concentration of 2.05 mmol/L.

Known past medical history included bipolar disorder type I, anxiety, depression, arthritis, and irritable bowel syndrome. Patient's home medications included lithium carbonate (prescribed as 300 mg twice daily and 450 mg at bedtime), ropinirole, over-the-counter naproxen, lamotrigine, eszopiclone, carvedilol, and alprazolam. The patient reported currently using tobacco and alcohol; however, the patient did not state frequency.

Management consisted of 0.9% normal saline with 20 mEq of potassium. Carvedilol was held on admission due to bradycardia along with alprazolam and eszopiclone due to oversedation. Lithium was not restarted. The patient did not receive dialysis to treat the lithium concentration; this was due to the patient's case not being severe enough and the lack of correlation between clinical presentation and lithium concentration. A repeat lithium concentration of <0.10 mmol/L was drawn approximately 6 hours later. An investigation into the differing laboratory values was initiated. The laboratory reported that the initial blood sample obtained was in a green-top tube that contained lithium heparin, resulting in a falsely elevated lithium result.

TABLE 2: Symptoms of lithium toxicity[5,6]

Serum Concentration, mEq/L	Signs and Symptoms
~1.5 to 2.5	Nausea, vomiting, fine tremor, drowsiness, ataxia
~2.5 to 3.5	Muscle weakness, coordination difficulties, confusion, electrocardiogram changes
>3.5	Coma, seizures, cardiopulmonary collapse

Discussion

A literature search was performed utilizing the following terms: *lithium toxicity*, *factitious toxicity*, *lithium heparin test tube*, *green-top tube*, *lithium heparin tubes*, and *toxic lithium levels*. Searches were conducted on CINAHL, Ovid, PubMed, Embase, and Google Scholar; literature from August 12, 2019, and prior was evaluated. Only articles discussing falsely elevated lithium concentrations due to processing in lithium heparin tubes were utilized in this review as this was deemed to be the most likely cause of the elevated lithium concentration in the patient case. Eight articles met our criteria: 8 case reports, including a case report with a study. In the first study[9] below, incomplete volume blood draws were also noted to impact the fictitious increase in lithium concentrations along with utilizing lithium heparin tubes. No other potential causes for false lithium concentrations were discussed in the following publications.

Wills et al[9] conducted a study that demonstrated the effect lithium heparin test tubes have on lithium concentrations after experiencing a false elevation in a 12-year-old patient with suspected lithium intoxication. Although the patient lacked clinical signs and symptoms of lithium toxicity, the patient's lithium concentration was 9.2 mmol/L. After evaluation, it was found that utilization of a lithium heparin test tube was the likely cause of the false elevation. The authors then undertook a study collecting blood samples from five volunteers not on lithium therapy. Mean serum lithium concentration (mmol/L) for the control was 0.16; mean concentrations from lithium heparin test tubes (light green top) with 57 USP units of lithium at full draw, 2 cc, and 1 cc were 1.05, 1.99, and 3.31, respectively. Concentrations from lithium heparin test tubes (dark green top) with 72 USP units of lithium at full draw, 2 cc, and 1 cc were 1.07, 2.35, and 4.04, respectively. This study[9] showed that a clinically significant change in lithium concentration occurs with the use of lithium heparin test tubes and the change can be further exacerbated when the sample volume is incomplete.

Chung et al[10] reported a case study in which a patient on lithium presented with headache, nausea, vomiting, and altered mental status. A lithium concentration was checked with a result of >3.0 mEq/L; a repeat concentration after hemodialysis was <0.20 mEq/L. The original sample was found to have been collected in a lithium heparin test tube. The authors[10] concluded the patient underwent unnecessary hemodialysis due to the false elevation of the serum lithium concentration.

Quattrocchi et al[11] published a case study describing a patient on lithium who had blood samples collected in both a sodium heparin tube and lithium heparin tube by accident. The lithium concentration from the lithium heparin tube was 1.79 mEq/L; the concentration from the sodium heparin tube was 0.41 mEq/L. A repeat concentration from the original lithium heparin tube was 1.8 mEq/L. The patient displayed no signs of lithium toxicity and outcomes were not reported.[11]

A newborn, whose mother was on lithium, was found to be lethargic at birth with respiratory distress and reduced muscle tone.[12] A lithium concentration was checked shortly after and was 3.58 mmol/L. The infant was given intravenous fluids, and the lithium concentration decreased over the following few days. On the sixth day of life, the lithium concentration was routinely checked and was found to be elevated at 2.6 mmol/L. A repeat sample was intentionally distributed into lithium heparin tubes; results ranged from 1.6 to 2.8 mmol/L. A repeat concentration in a sodium heparin tube returned at 0.06 mmol/L. The authors[12] concluded that utilizing lithium-coated test tubes for processing of lithium serum concentrations may be occurring more often than suspected due to lack of anticoagulant identification on some test tubes.

An additional case study[13] involving a newborn born to a mother on lithium therapy detailed a falsely elevated lithium concentration due to collection of a blood sample in a lithium heparin tube. The mother's serum lithium concentration was 0.4 mmol/L. The infant had a lithium concentration drawn secondary to jitteriness and poor feeding, and it was found to be 4.9 mmol/L 8 hours after birth. The infant was monitored and given intravenous fluids. The possibility of a falsely elevated concentration was considered, and a repeat concentration was 0.4 mmol/L. Symptoms desisted within hours, and the infant was discharged home the following day.[13]

Richman et al[14] wrote a case study involving a patient on lithium and clozapine presenting with altered mental status, bilateral hand tremor, fatigue, vomiting, polyuria, and acute renal failure. A lithium concentration was drawn within 1 hour of presentation, and the result was >4.3 mEq/L. A repeat concentration drawn 2 hours later following no treatment was 1.2 mEq/L; however, the results did not come back until after the patient had received hemodialysis. The original sample was collected in a lithium heparin tube, which had falsely elevated the lithium concentration.[14]

In 1 report,[15] a 33-year-old female presented to an emergency department after ingestion of an unknown amount of multiple medications, including lithium, venlafaxine, valproic acid, and clonazepam. Activated charcoal was administered. The patient was noted to be alert and oriented with an initial lithium concentration of 2.7 mEq/L. A second lithium concentration drawn 2 hours

later had increased to 3.1 mEq/L. The patient was provided supportive care and admitted to an intensive care unit. Two subsequent lithium concentrations were 3.6 mEq/L and 5.6 mEq/L. A laboratory error was suspected given the patient's presentation. The fourth sample (5.6 mEq/L) was found to have been drawn in a green-top test tube. No further treatment was given.[15]

A patient who ingested an unknown amount of nortriptyline and lithium was reported by Lee et al.[16] The lithium concentration at presentation was 1.4 mEq/L; the lithium concentration 13 hours after admission was 3.1 mEq/L followed by 1.6 mEq/L 15 hours after admission. Review of records showed that the second lithium concentration (3.1 mEq/L) was collected in a lithium heparin tube. The authors[16] concluded that analyzing lithium concentrations from samples collected in green-top tubes can falsely elevate the concentration by approximately 1.5 mEq/L.

The literature search supported the assumption that using a green-top tube for lithium monitoring resulted in a falsely elevated lithium concentration of 2.05 mmol/L in our patient case. The patient's presentation was not wholly consistent with lithium toxicity; therefore, no interventions were made. A list of home medications included naproxen although the frequency of use was not determined during admission. Nonsteroidal anti-inflammatory drugs are known to increase lithium concentrations (see Table 1). A repeat lithium concentration was obtained 6 hours later and was undetectable.

The patient was noted to be a poor historian throughout admission and was discharged to inpatient psychiatry due to ongoing depressive symptoms and questionable suicidal intent. By identifying the discrepancy between the lithium concentration and patient presentation, unnecessary treatment for lithium toxicity was avoided.

The prevalence of falsely elevated lithium concentrations due to use of lithium heparin test tubes is unknown as is the number of patients receiving unnecessary medical intervention secondary to this. Quattrocchi et al[11] commented that the patient label often covers up the test tube manufacturer label, which includes the test tube contents. This is particularly problematic when there are multiple green-top test tubes with different heparin compounds, such as sodium heparin, lithium heparin, and ammonium heparin. The need for awareness is of great importance when considering both laboratory interpretation and clinical decision making. It has been estimated that up to 75% of total laboratory errors occur in the preanalytical phase of testing.[17] Given this information, continued education and training of phlebotomy personnel would be a most reasonable target for decreasing overall laboratory errors. However, human error is unavoidable, and safeguards should ideally be in place to address critically elevated concentrations to ensure appropriate treatment.

The occurrence was discussed with the laboratory in question. It was not originally clear that the lithium concentration of 2.05 mmol/L was an incorrect value in the electronic medical record, and this was adjusted with the additional help of the electronic medical record vendor.

Conclusion

Obtaining accurate serum lithium concentrations is important to provide patients with appropriate treatment. To avoid falsely elevated concentrations, blood samples obtained to measure lithium concentrations should be drawn in tubes that do not contain lithium heparin. This will prevent false elevations in serum lithium concentrations and possible subsequent unnecessary medical intervention.

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