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Undetectable serum lithium concentrations after coadministration of liquid lithium citrate and apple juice: A case report

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Abstract

Lithium is a mood-stabilizing medication approved by the FDA for the treatment of acute manic or mixed episodes of bipolar disorder as well as maintenance treatment. Lithium citrate is an oral solution, and the carbonate salt is available as oral capsules or extended-release tablets. A patient with a psychiatric history of PTSD and schizoaffective disorder–bipolar type, maintained on lithium and olanzapine prior to admission, was admitted to an inpatient psychiatric unit due to destabilization, paranoia, and mania. He was started on lithium citrate, administered with apple juice, while admitted due to nonadherence. An initial serum lithium concentration was found to be undetectable. Lithium was then administered with an alternative non–apple juice liquid, at which point serum lithium concentration became detectable and patient clinically improved. Lithium concentrations may be impacted by a number of causes, such as underlying medical conditions, drug interactions, and diet. As the majority of these factors remained stable during the patient's admission and the serum lithium concentration became detectable after switching from apple juice to an alternative non–apple juice liquid, it led to the identification of a possible incompatibility.

Keywords: lithium, lithium citrate, apple juice, serum lithium concentration

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Background

Lithium is a mood-stabilizing medication approved by the FDA for the treatment of acute manic or mixed episodes of bipolar disorder as well as maintenance treatment.[1] The exact mechanism of lithium's antimanic activity is unknown; however, modulation of serotonin, norepinephrine, sodium channel, and glutamate activity may be involved.[2-4] Lithium ion is available in multiple forms, differentiated by the salt moiety. Lithium citrate is an oral solution, and the carbonate salt is available as oral capsules or extended-release (ER) tablets. Eight milliequivalents of lithium citrate is equivalent to 300 mg of lithium carbonate.[1]

Lithium has a narrow therapeutic index with toxicities possible at serum concentrations near the therapeutic range.[5] When treating acute mania or mixed episodes, the goal lithium concentration is 0.8 to 1.2 mEq/L.[1,3] Regular monitoring of lithium concentrations is recommended every 3 to 6 months or sooner during the acute phase of treatment or following a dose adjustment.[1,3,5] The timing of sample collection should be immediately prior to the next dose although this may not always be feasible.[1,3] There are many external factors that may affect serum lithium concentrations (Table 1). This case outlines an incident in which lithium concentrations may have been affected by administration with apple juice.

TABLE 1: Impact on lithium serum concentrations by various causes[3,6]

Interaction	Impact on Lithium Level
Impaired renal function	↑
Drug interactions:	
NSAIDs	↑
ACEIs/ARBs	↑
Thiazide and loop diuretics	↑
Osmotic diuretics/caffeine	↓
Decreased sodium intake	↑
Increased hydration	↓

Case Report

A 47-year-old male veteran with a history of PTSD, schizoaffective disorder–bipolar type, multiple suicide attempts, hypothyroidism, hyperlipidemia, and irritable bowel syndrome was admitted to the inpatient psychiatric unit exhibiting symptoms of mania, paranoia, and delusions. His case was complicated by a history of medication nonadherence resulting in multiple psychiatric admissions. Prior to this admission, he was seen in the mental health clinic where he was noted to be stable on lithium ER tablets 1800 mg daily aside from a hand tremor. A lithium concentration was obtained after this visit and resulted at 2.3 mEq/L; the basic metabolic panel was within normal limits with estimated glomerular filtration rate of 90.2 mL/min stable from baseline. The lithium dose was reduced to 1500 mg daily, and the patient was instructed to hold lithium for 3 days until returning to the clinic. At follow-up, the lithium concentration was 0.35 mEq/L, and he self-reported improvement in mood since holding lithium, leading to subsequent discontinuation of lithium treatment. One month later, he was admitted due to destabilization. The pertinent admission labs were within normal limits. A full timeline of events is outlined in Table 2.

Upon admission, lithium carbonate tablets were ordered, 300 mg in the morning and 600 mg in the evening, which he initially refused. Lithium was switched to lithium citrate 8 mEq (300 mg) in the morning and 16 mEq (600 mg) in the evening to improve adherence. Adherence did improve, but he was unwilling to allow laboratory assessment. He was assessed for side effects to lithium and had none. He then began to take lithium consistently with minimal improvement for 9 days, at which point he was agreeable to having a lithium concentration drawn. An initial serum lithium concentration was found to be undetectable at less than 0.2 mEq/L; renal function remained stable with an estimated glomerular filtration rate of 114 mL/min. Because he responded well to lithium in the past, his lack of response warranted further exploration. It was then noted that he was taking lithium

TABLE 2: Timeline of events; lithium citrate solution 8 mEq is equivalent to lithium carbonate 300 mg tablets

Day	Events
1	Patient admitted to psychiatric unit Restarted lithium ER tabs 300 mg QAM and 600 mg QPM
6	Lithium changed to lithium citrate liquid 8 mEq QAM and 16 mEq QPM as patient refuses tabs
13-18	Patient agrees to take lithium in apple juice on day 13 Dose increased to 16 mEq BID on day 14 Refuses 1 dose of lithium on both day 15 and day 16
19	Patient agrees to have labs drawn for lithium level Results as undetectable
20-31	Lithium changed to ER tabs 1200 mg daily Refuses lithium Changed back to liquid on day 24 Continues to refuse lithium until day 31
26	Juice changed to 2% milk, grape juice, or strawberry kiwi Crystal Light
48	Lithium dose increased to 16 mEq QAM and 24 mEq QPM
69	Patient agrees to have labs drawn for lithium level Results at 0.7 mEq/L
Discharge	Total admission duration was 5 mo Remained adherent to lithium regimen, with discharge level of 0.9 mEq/L

ER = extended release; QAM = every morning; QPM = every evening.

citrate with apple juice, which was identified as a potential incompatibility based on a 2007 liquid compatibility chart created by the Center for Behavioral Medicine in Kansas City, Missouri. In light of the possible incompatibility, he was subsequently administered lithium with 2% milk, grape juice, or strawberry-kiwi juice. After this change, he refused his medications for several days but then resumed taking lithium. Despite being adherent to medications, he continued to refuse labs. Toward the end of the month, the lithium dose was increased to 16 mEq (600 mg) in the morning and 24 mEq (900 mg) in the evening. For nearly the next month, he continued to be adherent with medications but consistently refused lab draws. When he was agreeable to laboratory assessment, the lithium concentration was detectable at 0.7 mEq/L.

During this time period, olanzapine was switched to paliperidone tablets and then the long-acting monthly injectable. Benztropine was also added due to mild parkinsonian tremor. The total inpatient hospitalization duration was 5 months. Lithium concentration on discharge was 0.9 mEq/L. Upon discharge, his overall behavior improved significantly, and he was no longer

exhibiting symptoms of paranoia, mania, or delusional behavior.

Discussion

Lithium concentrations may be impacted by a number of causes, including underlying medical conditions, drug interactions, and diet (Table 1). Enteral absorption of lithium is rapid with oral lithium citrate solution absorbed within 1 hour.[3,5] Lithium carbonate regular-release and ER formulations are absorbed more slowly (1 to 3 hours and 3 to 6 hours, respectively).[5] Similarly, bioavailability varies between lithium formulations. Lithium solution and regular-release products have nearly complete bioavailability, and the ER preparations may have a bioavailability as low as 60%.[5] The plasma protein binding of lithium is negligible with a volume of distribution equaling that of total body water.[1,3,5] Lithium does not undergo metabolism, and is excreted via the kidneys.[1,5] Individuals who are elderly or renally impaired may have decreased clearance and higher lithium concentrations.[3] In this case, the patient was young, healthy, and had adequate renal function. Renal function was stable throughout admission. Given he was previously able to achieve therapeutic, and supratherapeutic, lithium concentrations prior to admission, it is unlikely renal function played a role in the undetectable lithium concentration.

In young, healthy individuals, the serum half-life of lithium is about 24 hours, and steady state concentrations are achieved within 3 to 4 days; thus, lithium concentrations should be measured 3 to 4 days after dose adjustments with concentrations drawn immediately prior to the next dose to accurately represent trough concentrations.[3] In this case, the patient had received an adequate number of doses, and lithium concentrations were timed appropriately relative to dose adjustments and administration despite occasional refusal of assessments.

Lithium concentrations may be impacted by concomitant medications. As lithium is eliminated renally, concentrations are most impacted by medications that alter renal function. Thiazide and loop diuretics, ACEIs, ARBs, and NSAIDs can increase the serum concentration of lithium. Osmotic diuretics and caffeine can decrease serum concentration.[3] The patient was not taking the aforementioned medications, nor was he drinking excessive amounts of caffeine, making it unlikely that the negligible lithium concentration was due to a drug interaction.

Diet and hydration status may also contribute to fluctuating lithium concentrations. When an individual is dehydrated, the lithium concentration may increase due to a decreased volume of distribution and decreased renal function.[6] Conversely, excessive fluid intake may potentially decrease lithium concentrations. Salt intake can impact the lithium concentration; if salt intake is markedly reduced, it can lead to compensatory sodium (and, thus, lithium) conservation in the kidneys, which may then cause lithium concentrations to rise.[6] In turn, a high-sodium diet could cause lithium concentrations to decrease. In this case, hydration status and salt intake did not fluctuate from baseline during the admission, thus indicating these factors likely did not impact the low lithium concentration.

Juices may impact the absorption of medications.[7] In reviewing this case, the patient was given lithium citrate with apple juice exclusively prior to the negligible lithium concentration measurement. When this juice was switched, the lithium concentration became detectable, and the patient clinically improved. There is limited evidence available regarding compatibility of lithium and juices. One study found that apple juice can irreversibly block the OATP2B1 transporter, thus decreasing the serum concentration of medications that use this transporter for absorption although lithium does not utilize this transporter.[7] Other hypothetical causes included the impact of sodium content and pH on lithium absorption; however, these were ruled out as apple juice's chemical properties do not differ significantly from other fruit juices. Although the liquid compatibility chart from the Center for Behavioral Medicine, a well-established psychiatric pharmacy residency program, indicated that apple juice and lithium are incompatible, this chart was not supported by references and has since been updated to remove the incompatibility. Two review articles on compatibilities of liquid psychotropic medications list that lithium citrate is compatible with apple juice although the methods and data used to determine this compatibility are neither described nor referenced.[8,9]

In considering and ruling out potential causes of the undetectable lithium level, a Naranjo assessment was conducted to assess the causality of the coadministration of lithium citrate and apple juice. A calculated score of 6 indicated a probable causality.

Conclusion

In this case report, a patient was found to have undetectable serum lithium concentrations after coadministering lithium citrate with apple juice. After switching to an alternative beverage, the levels became detectable, and he improved clinically. With a Naranjo assessment indicating probable causality, the underlying mechanism as to why administration with apple juice resulted in a negligible concentration is unclear as the limited literature states lithium citrate is compatible with

apple juice. Coadministration of liquid medications and beverages should be done carefully, assessing for food-drug interactions to ensure that patients are receiving therapeutic pharmacotherapy.

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