A Tale of 2 Lithium Toxicities

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Lithium is one of the oldest treatments in psychiatry and is the mainstay of treatment in bipolar disorder. The exact mechanism of lithium has yet to be elucidated, but it is well understood that lithium has a narrow therapeutic index and is highly associated with overdose and toxicities.[1] The therapeutic range for lithium is generally considered to be 0.5–1.2 mmol/L. Common symptoms of lithium toxicity include gastrointestinal upset, arrhythmias, respiratory distress, confusion, cerebellar dysfunction, and polyneuropathy.[2] Due to the pharmacokinetic properties of lithium, it has been demonstrated that these toxic effects tend to be more common and severe in patients that are chronically treated with lithium.[3] Here, we report the cases of 2 patients, both with lithium toxicity; however, the clinical manifestations were paradoxical.

Case Report

Two women aged 69 and 40 years, respectively, with a past medical history of schizoaffective disorder and home medication of lithium 300 mg twice/d presented to the emergency department. Patient 1 complained of progressively worsening lower extremity weakness and mental status changes. Patient 2 complained of a 1-week history of watery bowel movements and nausea/vomiting. Patient 1 had a lithium level of 2.1 mEq/L and a QTc >485 mS. Patient 2 had a lithium level of 5.7 mEq/L, a QTc of 525 mS, and positive *Clostridium difficile* stool toxin assay. As per the recommendation of the nephrology department, both patients were managed with cessation of lithium and intravenous normal saline. Both patients responded well to this treatment and demonstrated improvement of symptoms.

Discussion

Lithium toxicity is divided into 3 distinct categories: acute, acute on chronic, and chronic. Acute toxicity occurs in patients that do not regularly take lithium and typically presents with gastrointestinal upset, confusion, and slurred speech.[4] Acute on chronic toxicity is an acute overdose in patients that currently take lithium therapy, while chronic toxicity refers to the gradual accumulation of lithium levels in patients currently on lithium therapy.[5] Neurotoxicity more commonly presents in acute on chronic or chronic cases due to lithium's slow distribution into the central nervous system,[4] and it has been shown that the duration of exposure to elevated lithium levels correlates with the severity of neurotoxicity.[3]

Moreover, the absolute serum level of lithium does not correlate with the severity of toxicity, indicating that a gradual increase in lithium levels may present more severely than an acute overdose event.[6] The transport of lithium across cell membranes is conducted via active transport, and cellular uptake has been demonstrated to be higher when serum potassium and calcium levels are low, which may explain why there is a higher incidence of lithium toxicity in dehydrated patients.[7] Additionally, lithium variably enters different tissues, entering the kidneys most rapidly (minutes) and the brain most slowly (hours), which further demonstrates why chronic lithium intake is more likely to result in neurotoxic effects.[8] In the same vein, acute intoxication symptoms tend to resolve faster than chronic intoxications due to the higher amounts of lithium within the intracellular compartment and within the cerebrospinal fluid.[8]

Many clinicians reference the Extracorporeal Treatments in Poisoning Workgroup Criteria to determine when hemodialysis is necessary in lithium toxicity.[9] However, in a 2020 retrospective study, it was demonstrated that these criteria are too broad, and the chronicity of lithium toxicity and kidney function should be considered before initiating hemodialysis.[9] Furthermore, the researchers found that in the case of acute on chronic toxicity, the risks of hemodialysis may outweigh the benefits, as there was no statistically significant difference in clinical outcomes, and these patients were generally at lower risk of mortality due to lithium toxicity.[9] Moreover, they noted that the utilization of hemodialysis does not necessarily enhance brain clearance of lithium and thus does not result in faster improvement of neurological symptoms.[9] However, hemodialysis in the elderly, patients with significantly decreased renal function, or those experiencing purely chronic toxicity may benefit from hemodialysis, and a patient-centered decision should be made in collaboration with nephrology.[9–14]

These cases demonstrate the varying manifestations of lithium toxicity. Patient 2 had severely high levels of lithium (5.7) yet demonstrated much milder symptoms than patient 1. This is likely an artifact of this being a case of acute on chronic toxicity in which this patient had been chronically treated with lithium but acutely had a *Clostridium difficile* infection. However, in patient 1, this was likely chronic lithium toxicity, in which the patient had been treated with lithium over a long period of time but did not have

an acute event that precipitated symptoms. Instead, over the course of time, the patient experienced worsening lower extremity weakness, altered mental status, and diarrhea that could not be explained by an acute infection.

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