

CLINICAL VIGNETTE

A Case of Lithium Toxicity

Neil Patel, M.D and Carol Lee, M.D.

Case Presentation

A 67-year-old male with a history of bipolar disorder, PTSD, substance-induced psychotic disorder, hypertension and osteoarthritis was brought into the Emergency Department by emergency medical services (EMS) from his board and care facility. Per EMS report, the facility claimed over the past week the patient was acting more tired and confused than usual and had experienced several episodes of enuresis.

Upon initial interview, the patient was somnolent yet easily arousable. He had slow speech and frequently lost track of his thoughts, but answered simple questions. He claimed to be unaware of the reason for his ED visit and only complained of feeling tired and unsteady on his feet.

On exam, the patient had a temperature of 97.2°F via tympanic thermometry, a pulse of 58, blood pressure of 132/78, respiratory rate of 16 and a pulse oximetry reading of 98%. He had dry oral mucous membranes, regular bradycardia and a largely non-focal neurological exam. However, he exhibited a pronounced intention tremor and marked truncal ataxia. Therefore, a presumptive diagnosis of lithium toxicity was entertained, though a posterior fossa cerebrovascular event, Wernicke syndrome and sepsis were still in the differential.

A review of the patient's EMR revealed that he was on lithium carbonate 300mg three times a day for bipolar disorder, aripiprazole for psychosis and amlodipine for hypertension. Besides admitted cocaine use 10 years prior, recent toxicology screens had all been negative.

A rapid bedside glucose was 134 mg/dL and a 12-lead ECG revealed sinus bradycardia, precordial ST depressions, T wave inversions and a slightly prolonged QT_c interval of 460ms (Fig. 1). Serum analysis was significant for a sodium of 149 mEq/L, potassium of 3.5 mEq/L,

BUN of 54 mg/dL, creatinine of 2.6 mg/dL and a lithium level of 3.2 mEq/dL (normal therapeutic range 0.6-1.2 mEq/dL). The patient denied recent changes to his lithium dosage though at this point he did volunteer that he had started taking 600 mg of ibuprofen three times a day for his osteoarthritis. Therefore, a diagnosis of acute-on-chronic versus chronic lithium toxicity was made.

The patient was treated with aggressive normal saline fluid rehydration and oral sodium polystyrene sulfonate was administered. Nephrology was consulted and the patient underwent several rounds of hemodialysis. The patient was admitted to the ICU and after a four day hospital course, he recovered and was discharged on a reduced dose of lithium with instructions not to take any over-the-counter medications or herbal supplements without physician consultation.

Discussion

Lithium has been approved since 1970 by the U.S. Food and Drug Administration for the treatment of bipolar disorder. In addition, it is used off-label to treat a variety of psychiatric and non-psychiatric disorders such as acute mania, PTSD, schizoaffective disorders and neuropathic pain. Though its narrow therapeutic index makes toxic side effects common, lithium still remains one of the most widely used drugs for the treatment of bipolar disorder due to its proven efficacy¹. Indeed, according to the American Association of Poison Control Centers' National Poison Data System 2010 report, there were 6,370 reported cases of lithium toxicity with 133 patients suffering major complications and one patient death².

Lithium is available in either immediate- or sustained-release preparations. Since it is an alkali metal, it is not metabolized and is directly absorbed via the gastrointestinal tract. It does not

bind to serum proteins and thus it is either found free in the extracellular fluid or within cells. This movement from the extracellular to the intracellular compartment takes several hours, making it difficult to predict tissue toxicity on the basis of serum levels alone. It is predominantly renally eliminated and therefore, medications that alter renal function (e.g. ACE inhibitors, NSAIDs, diuretics) can dramatically alter lithium elimination, thereby leading to toxicity. The elimination half-life of lithium ranges from 12-48 hours, with patients on chronic therapy and the elderly having the longest elimination half-lives³.

Though the exact mechanism by which lithium exerts its therapeutic effect is not well understood, it is known that lithium increases the release of serotonin while inhibiting the release of norepinephrine and dopamine. Lithium also antagonizes antidiuretic hormone (ADH), potentially leading to nephrogenic diabetes insipidus (NDI)¹.

Due to these multitudinous interactions, complex two-compartment pharmacokinetics and prolonged elimination-half life, lithium toxicity tends to manifest with a varied array of clinical signs and symptoms. For ease of consideration, lithium toxicity can be divided into acute, acute-on-chronic and chronic intoxications.

Patients with an acute lithium intoxication will usually be lithium-naïve with a single, isolated episode of a large ingestion of either immediate or sustained-release preparations of lithium. Since lithium is absorbed directly via the GI tract without a significant first-pass hepatic effect, the cardinal symptoms of an acute intoxication will be predominantly GI symptoms (nausea, vomiting and diarrhea). Serum levels of lithium in the acute setting may correlate better with clinical symptoms than in patients with chronic intoxication, but caution must still be applied since sustained-release preparations can take up to 12 hours before peak serum concentrations are seen⁴.

Chronic lithium intoxication is more common than acute ingestions, usually resulting from an inadvertent decrease in renal elimination of lithium either via dehydration, hyponatremia or drug-drug interactions. Patients with chronic intoxication tend to present with symptoms and signs of neuro- and nephro-toxicity rather than

GI effects. Indeed, tremor tends to be one of the earliest findings of lithium intoxication and providers should be vigilant to examine all patients on lithium for this potentially ominous sign. As neurotoxicity progresses, patients may manifest truncal ataxia, cerebellar dysfunction, memory loss, psychomotor retardation, lethargy and finally coma⁵. There are case reports indicating that some of these neurotoxic side effects may be irreversible. Most patients on chronic lithium therapy will develop some degree of polyuria (due to the antagonistic effect of lithium with respect to ADH), though an unfortunate few will develop a true nephrogenic diabetes insipidus (NDI). These latter patients will experience severe polyuria, dehydration, hypernatremia and inappropriately dilute urine. As these patients lose fluid, the renal proximal convoluted tubule will enhance the reabsorption of lithium, furthering its toxicity⁶.

Patients with an acute-on-chronic ingestion will typically manifest signs and symptoms somewhere along the spectrum between an acute and a chronic overdose. ECG changes can be noted in either state and may demonstrate sinus bradycardia, ST depressions, T wave inversions and prolonged QRS and QT_c intervals, as was noted in our patient⁷.

The diagnosis of lithium toxicity is usually made by measuring a serum lithium level. However, owing to the two-compartment distribution pharmacokinetics of lithium, a serum level is not always predictive of clinical severity since end-organ levels of lithium may be vastly different than the serum value⁴. This is especially true in cases of chronic toxicity. Therefore, one must primarily rely on the history and physical exam to presumptively make this diagnosis. In cases of suspected acute overdose, especially of sustained-release preparations, one must measure serial lithium levels as delayed absorption can lead to falsely low levels if measured early after an ingestion.

Likewise, treatment decisions are best based upon the patient's clinical state rather than upon an isolated serum level. The first priority is the acute stabilization of the patient, including assuring airway protection. The treatment paradigm then revolves around four principal therapies: decontamination, hydration, sodium polystyrene sulfonate and hemodialysis, based

upon the type of intoxication (acute versus chronic) and the patient's clinical state³⁻⁵.

Decontamination is best employed if there is an acute overdose of a sustained-release preparation of lithium. The modality of choice is whole bowel irrigation with polyethylene glycol to evacuate the GI tract of any unabsorbed lithium. Charcoal unfortunately does not adsorb lithium and therefore is of no benefit³⁻⁵.

Dehydration and hyponatremia are responsible for many cases of chronic lithium toxicity. Dehydration not only decreases the amount of lithium filtered by the kidney due to vasoconstriction of the afferent arteriole, but also causes the proximal convoluted tubule to reabsorb the little lithium that is filtered. Hyponatremia also decreases lithium clearance, mostly via this latter mechanism. Therefore, first line treatment involves aggressive fluid resuscitation with normal saline. Use of diuretics is *not* recommended as these agents can lead to dehydration and hyponatremia, worsening lithium toxicity³⁻⁵.

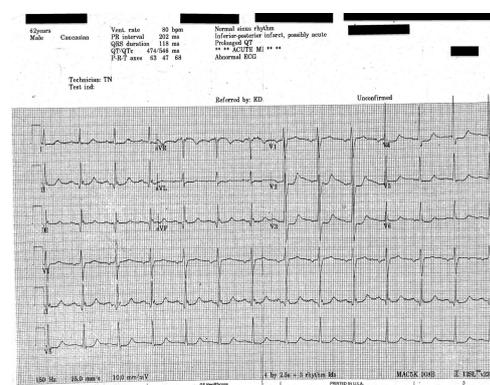
Sodium polystyrene sulfonate is an orally or rectally administered cation-exchange resin that is commonly used for the treatment of hyperkalemia, but will also exchange lithium for sodium. There is very little evidence supporting its use in lithium intoxication though it has been shown to decrease serum levels of lithium⁸.

In patients that cannot tolerate aggressive fluid hydration or those with severe toxicity, hemodialysis remains the best option for eliminating lithium. Unfortunately, there are no evidence-based guidelines for the initiation of dialysis in lithium toxicity. Nevertheless, expert consensus guidelines recommend initiating dialysis in patients with a lithium level >4 mEq/L in acute toxicity (>2.5 mEq/L in chronic toxicity), severe neurotoxicity, renal impairment, inability to tolerate aggressive fluid hydration and in those patients with no change or increasing serum levels of lithium despite aggressive non-invasive therapy^{4,9}.

As is evident, owing to its diverse effects, lithium toxicity can easily be missed if a proper history and exam are not conducted. One must also be wary of chronic toxicity, which can develop insidiously due to a decrease in renal clearance. Diagnosis is also complicated by the

fact that serum levels correlate poorly with the severity of clinical toxicity. Furthermore, once a diagnosis is established, one is then confronted with a lack of evidence with respect to the best of course of treatment. Nonetheless, by focusing on the patient's clinical state and understanding the pharmacokinetics and biologic effects of lithium, one may safely deliver the lithium-intoxicated patient from harm's way.

Figure 1. ECG demonstrating the electrocardiographic effects of lithium toxicity including ST depressions and prolonged QT_c interval.



REFERENCES

1. **Schou M.** Forty years of lithium treatment. *Arch Gen Psychiatry.* 1997 Jan;54(1):9-13; discussion 14-5. Review. PubMed PMID: 9006394.
2. **Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Dart RC.** 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. *Clin Toxicol (Phila).* 2011 Dec;49(10):910-41. doi: 10.3109/15563650.2011.635149. PubMed PMID: 22165864.
3. **Hung O.** Lithium. In: Marx JA, Hockberger RS, Walls RM, editors. *Rosen's emergency medicine: concepts and clinical practice*, 7th ed. Philadelphia: Mosby; 2010.
4. **Thundiyil JG, Olson KR.** In: Shannon MW, Borron SW, Burns MJ, editors. *Haddad and Winchester's clinical management of poisoning and drug overdose*, 4th ed. Philadelphia: Saunders Elsevier; 2007.
5. **Schneider SM, Coughbah DJ.** Lithium. In: Tintinalli JE, Kelen GD, Stapczynski JS, editors. *Emergency medicine: a comprehensive study guide*, 7th ed. New York: McGraw-Hill; 2011.
6. **Bendz H, Aurell M.** Drug-induced diabetes insipidus: incidence, prevention and management. *Drug Saf.* 1999 Dec;21(6):449-56. Review. PubMed PMID: 10612269.
7. **Hsu CH, Liu PY, Chen JH, Yeh TL, Tsai HY, Lin LJ.** Electrocardiographic abnormalities as predictors

- for over-range lithium levels. *Cardiology*. 2005;103(2):101-6. Epub 2004 Nov 30. PubMed PMID: 15591709.
8. **Ghannoum M, Lavergne V, Yue CS, Ayoub P, Perreault MM, Roy L.** Successful treatment of lithium toxicity with sodium polystyrene sulfonate: a retrospective cohort study. *Clin Toxicol (Phila)*. 2010 Jan;48(1):34-41. doi:10.3109/15563650903344785. PubMed PMID: 19842945.
 9. **Bailey B, McGuigan M.** Comparison of patients hemodialyzed for lithium poisoning and those for whom dialysis was recommended by PCC but not done: what lesson can we learn? *Clin Nephrol*. 2000 Nov;54(5):388-92. PubMed PMID: 11105800.

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