

Management of Lithium Intoxication

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Lithium toxicity is usually insidious in onset and presents with a wide spectrum of clinical symptoms. Symptoms vary from mild lethargy to seizures and coma. Although mild to moderate intoxication can be managed with intravenous saline, cases not responding or severe cases should be treated by hemodialysis. Iatrogenic fluid and electrolyte disorders often complicate therapy.

Although lithium is widely acknowledged to be an effective and specific therapy for bipolar affective disorder (manic-depressive illness), its therapeutic index is notoriously low. The onset of lithium toxicity is often insidious, and mild clinical symptoms can belie potentially lethal serum lithium levels. The following case report describes a typical episode of lithium intoxication and demonstrates several pitfalls that may be encountered in the management of lithium poisoning.

Case Report

A 33-year-old woman with the diagnoses of manic-depressive illness and borderline personality disorder presented to the Family Medical Center (FMC) complaining of intermittent nausea, vomiting, and fatigue of approximately two weeks' duration, with increasing vomiting and weakness the previous two days. She had been on lithium carbonate (LiCO_3) for two years; the dose was increased from 600 mg twice a day to 600 mg three times a day by the consulting psychiatrist four months previously. She had been seen in the FMC twice during the preceding two weeks, at which times her symptoms of increasing depression and lassitude were attributed to recent stressful events in her life. She denied intentional overdose, and a pill count was consistent with medication intake as instructed. Medical history was remarkable for recent musculoskeletal pain treated with zomepirac.

During the physical examination she was in-

attentive and uncooperative, but arousable. Weight was 160 pounds (down 8.5 pounds from 3¹/₂ weeks previously). Vital signs were normal, without orthostatic pulse rise or hypotension. Pertinent findings on physical examination were restricted to the neurological system. Neurological examination revealed appropriate orientation, poor short-term recall, and inconsistent responses to spoken instructions. Bilateral dysmetria was present on the finger to nose test; gait was broad based and ataxic. The deep tendon reflexes were 4+ with ankle clonus. A mild resting tremor was present.

Initial laboratory examination revealed a serum lithium level of 4.02 mEq/L (therapeutic range 0.7 to 1.2 mEq/L) sodium 137 mEq/L, potassium 4.2 mEq/L, chloride 104 mEq/L, CO_2 27 mEq/L, blood urea nitrogen (BUN) 25 mg/dL, and creatinine 1.5 mg/dL. Urinalysis showed moderate ketones, 2+ protein, and a specific gravity of 1.009. The electrocardiogram (ECG) revealed normal sinus rhythm at a rate of 65 beats/min, with PR = 0.20, QRS = 0.06, and QT = 0.4. U waves were present.

The patient was admitted to the hospital with continuous cardiac monitoring and treated initially with intravenous normal saline, 1 L at 200 mL/h followed by normal saline at 150 mL/h. Serum lithium nine hours after admission was 3.16 mEq/L. On the second hospital day, serum sodium was 155 mEq/L, thought to be related to inappropriate fluid restriction and high urine output (6,950 mL in and 7,650 mL out in the first 24 hours). Electrolytes and creatinine improved in response to infusion of free water. Serum lithium was 1.9 mEq/L 24 hours after admission.

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Thirty hours after admission the patient suffered a generalized tonic-clonic seizure lasting five minutes. Serum chemistries obtained shortly after the seizure revealed a sodium of 147 mEq/L, potassium of 3.1 mEq/L, BUN of 3 mg/dL, and creatinine of 0.5 mg/dL. Urine output was 10 L in the preceding 24 hours. An electroencephalogram revealed a markedly abnormal pattern with generalized spikes and waves in a multifocal distribution, consistent with metabolic encephalopathy. The patient was treated with phenytoin.

The diagnosis of nephrogenic diabetes insipidus was made on the basis of inappropriately low urine osmolality with respect to serum osmolality in the setting of lithium intoxication. Urine output decreased appropriately with conservative management. On the 15th hospital day the patient was discharged on phenytoin with improving polyuria, normal electrolytes, and return to her baseline psychological and neurological status.

Clinical Setting of Lithium Intoxication

The symptoms of lithium intoxication are diverse and range from mild nausea and lassitude to convulsions and coma.¹ Even authors who have attempted to correlate specific levels of serum lithium with an orderly progression of symptoms from mild to severe acknowledge that serum lithium may not be an accurate predictor of clinical symptoms.² Most workers agree that early lithium intoxication is almost uniformly accompanied by nonspecific neurological and psychological symptoms such as weakness, tremor, restlessness, apathy, and muscular rigidity.³ Thus the attribution of even subtle changes in mental status and central nervous system function to adverse psychosocial events should be made only with great caution in patients on lithium therapy.

Hansen and Amdisen,³ in their superb literature review and report of 23 cases of lithium intoxication, commented on the usual evolution of lithium poisoning. Twenty-one of their 23 patients were on a stable lithium maintenance dose for months to years; only one ingested an intentional overdose. Conditions affecting fluid and electrolyte balance, such as gastroenteritis, diuretic treatment, vomiting from any cause, dietary intake low in sodium, and decreased fluid intake, commonly precede intoxication. Other recent reviews^{1,3,4} provide more detailed explication of the clinical presentation of lithium intoxication.

Management

When confronted with a patient in whom lithium poisoning is suspected, the usual clinical strategy in toxicology applies—curtail intake of the offending agent, and encourage elimination of the poison through the most expedient means available.

After a complete history and physical examination, the initial laboratory examination should include a serum lithium level, serum electrolytes, BUN, creatinine, complete blood count, and urinalysis. In many situations, serum and urine toxicologic screenings will be appropriate. Although there is no specific electrolyte abnormality associated with lithium intoxication, Hansen and Amdisen³ identified either hypernatremia or hyponatremia in approximately one half of their patients, and one fourth were hypokalemic. The value of the serum lithium is obvious, although it must be emphasized that levels within the normal range may be associated with clinical toxicity, especially in the acute overdose.⁵ In addition, response of serum lithium to initial therapy is a crucial guide to appropriate management (see below). The urinalysis should include evaluation of osmolality, as it provides a clue to the presence of significant nephrogenic diabetes insipidus if inappropriately low compared with serum osmolality.

Although cardiac morbidity is seldom clinically significant, most patients demonstrate abnormal electrocardiograms, primarily manifested by ST depression and inverted T waves. Nevertheless, occasional case reports describe atrioventricular block, ventricular and supraventricular arrhythmias, and, rarely, myocardial infarction, albeit usually in patients with concurrent medical illness.⁶ Continuous cardiac monitoring is therefore advisable.

Special attention should be directed toward discontinuation of chronic medications that decrease lithium excretion. Hydrochlorothiazide decreases lithium clearance and is contraindicated in poisoning. Similarly, prostaglandin inhibitors such as indomethacin and other nonsteroidal anti-inflammatory drugs may also inhibit maximal renal clearance of lithium.⁷ The temptation to place hypertensive patients on a low-sodium diet should be resisted, as it is well known that such diets impair the excretion of lithium.⁸

The clinician must be prepared to accept some empiricism in the management of lithium toxicity

because no randomized controlled prospective studies to determine optimal therapy have been performed. Therefore, what follows is a distillation of recommendations from current workers in the field.

Over 98 percent of ingested lithium is excreted in the urine,⁹ and after emptying the stomach of unabsorbed tablets, increasing the elimination of lithium through the urine is the first step in therapy. Unfortunately, no one method consistently increases urinary excretion of lithium.

Most authors make a distinction between the treatment of patients with mild to moderate symptoms and the treatment of those with either severe symptoms or lithium levels greater than 3 to 4 mEq/L.^{2,4,10} Patients with serum lithium levels less than 2.5 mEq/L who are not stuporous and have relatively well maintained neurological functioning can be initially treated with rapid intravenous infusion of normal saline (with 1 to 2 L over 6 hours). If the serum lithium decreases by 20 percent or more and the clinical condition is stable, normal saline infusion may be continued. However, because of the relatively high frequency of hypernatremia induced by large sodium loads, serum sodium must be carefully and frequently monitored. Forced diuresis with furosemide appears not to be more efficacious than saline alone.³ Furthermore, although some sources suggest aminophylline as an effective agent in increasing lithium excretion, Thomsen and Schou¹⁰ withdrew their proposal for such treatment (originally forwarded on theoretical grounds) after clinical trials showed minimal salutary effect. Some authors advocate forced alkaline diuresis.^{2,5}

There is little controversy regarding the treatment of patients with severe clinical symptoms or serum lithium levels greater than 4 mEq/L. The standard of care for these patients is hemodialysis, which should be carried out for long periods (8 to 12 hours) because of the large tissue storage pool of lithium. Peritoneal dialysis is less optimal, as the dialysis clearance of lithium is approximately one third of the 50 mL/min that can be achieved by hemodialysis.¹⁰

Hansen and Amdisen³ would reserve saline infusion only for those patients with serum lithium less than 2.5 mEq/L, normal renal function, and a short period (several days) of presumed intoxication. Other workers place the cutoff point at 3 mEq/L.⁴ These investigators agree, however, that a serum lithium of 1.0 mEq/L must be achieved

after 30 hours of treatment if dialysis is to be avoided. Regardless of which mode of therapy is chosen, scrupulous attention must be directed toward preventing iatrogenic fluid and electrolyte imbalance.

The case presented above might have been managed differently. The prescription of zomepirac for mild musculoskeletal pain may have contributed to an elevation of the serum lithium level. It is likely that the psychological symptoms present several weeks prior to admission were manifestations of toxicity in spite of a recent increase in stressful life events. By most criteria, dialysis at a level of 4 mEq/L would have been preferable to saline infusion, even though the patient's serum lithium did decrease appropriately. Further, iatrogenic hypernatremia supervened during treatment, although its relationship to the seizure is unclear. Fortunately the patient regained her previous level of function as her complications were vigorously and appropriately treated.

Summary

Lithium toxicity is usually insidious in onset, and initial symptoms can be subtle. Appropriate therapy includes cessation of lithium intake, and intravenous infusion of normal saline in patients with mild to moderate clinical symptoms and only slightly elevated serum lithium levels. Hemodialysis is the treatment of choice in severe intoxication. Care must be taken to avoid iatrogenic fluid and electrolyte disorders.

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