

Case Report

Lithium Toxicity: The Illusion of PTSD

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Abstract

This case reviews a patient with posttraumatic stress disorder, bipolar disorder and hypertension who experienced an acute decompensation in his mental health status while enrolled in our Veterans Treatment Court. The symptoms were attributed to his posttraumatic stress disorder diagnosis however he was also receiving lithium to address his co-morbid bipolar disorder diagnosis. This case emphasizes the potential danger of misdiagnosing signs and symptoms of chronic lithium toxicity when treating patients with a concurrent psychiatric diagnosis such as posttraumatic stress disorder.

Keywords

- Lithium, Toxicity
- PTSD
- ACE inhibitor
- ARBs
- Renal failure
- Bipolar disorder
- Veterans treatment court

ABBREVIATIONS

PTSD: Posttraumatic Stress Disorder, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, BPD: Bipolar Disorder, VA: Veterans Administration, ED: Emergency Department, ECG: Electrocardiogram, GI: Gastrointestinal, MICU: Medical Intensive Care Unit

INTRODUCTION

Posttraumatic stress disorder (PTSD) is common among Veterans and associated with a number of debilitating symptoms such as nightmares, social isolation, flashbacks, intrusive thoughts, and significant difficulty managing anger [1]. Iraq and Afghanistan combat veterans, specifically those who suffer from PTSD, frequently report difficulty with community reintegration that can involve problems with social functioning, productivity, and self-care, including problems with increased substance use, dangerous driving and increased anger control problems that may ultimately lead to legal involvement [2]. Recent case studies and clinical trials have shown that lithium, considered for many years as the “drug of choice” for managing patients with bipolar disorders (BPDs), [3] may also be beneficial in reducing symptomatology associated with PTSD [4,5]. However, the benefits of lithium are leveraged by the need for vigilant monitoring practices in order to avoid toxic sequelae [6]. In 2014, the American Association of Poison Control Centers reported 6,850 lithium toxicity mentions of which 160 were considered as having “major medical” outcomes (either life-threatening or manifesting residual disability) while 7 resulted in fatalities [7]. For patients on long-term lithium therapy, 75% to 90% will experience a toxic event at some point during their treatment [8].

The narrow therapeutic range of lithium (0.6-1.2 mEq/L) [9] must be underscored and serum levels obtained on a regular basis as a preventative for toxicity. Other laboratory findings

which might be related to toxicity include, but are not limited to, glomerular filtration rate, white blood cells, creatinine, blood urea nitrogen, sodium, platelets, glucose and thyroid stimulating hormone. Special attention should also be given to renal function and factors which may affect elimination [10]. Patients should be monitored for conditions such as gastrointestinal (GI) syndromes, nephrogenic diabetes insipidus and prolonged exposure in warm environments all of which could lead to dehydration and potential hyponatremia [11]. Additionally, certain pharmacologic agents may enhance proximal renal tubular reabsorption of lithium leading to elevated drug levels [12,13]. These drugs, which are commonly prescribed, include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazide diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) [14].

Lithium toxicity is manifested in three patterns: acute toxicity as seen in patients not prescribed lithium but exposed through accidental or intentional exposure; acute-on-chronic positioning resulting from acute ingestion during ongoing lithium treatment; and chronic poisoning which may be related to inadequate medical monitoring, medical illness or introduction of medications that can alter lithium levels in previously stable patients [15-17].

Patients with acute lithium toxicity frequently manifest mild symptoms despite potentially lethal lithium levels [18]. Signs and symptoms of acute toxicity include GI disturbances such as nausea, vomiting, diarrhea with concurrent polydipsia, polyuria, fever, hyponatremia and dehydration. Cardiac changes, as observed on electrocardiography (ECG) tracings, may include sinoatrial node dysfunction, nonspecific T-wave flattening and prolongation of the QT interval. These changes suggest the potential for life threatening arrhythmias such as bradycardia, ventricular tachycardia and ventricular fibrillation [19,20].

In contrast to patients with acute findings, those with chronic toxicity are more likely to have increased severity of symptoms despite non-toxic drug levels [21]. Neurological manifestations are more common with this type of toxicity and may include increasing confusion, ataxia, agitation and tremors. Serious neurological sequelae, which in some cases may become permanent, include delirium, serotonin syndrome and neuroleptic malignant syndrome [22].

The following case reveals some potential pitfalls in the diagnosis of lithium toxicity for patients who are treated for other major mental illnesses and conditions. It is well published in the literature that patients who suffer from mental illness may have difficulty communicating their medical needs and their symptomatology may mimic those of physical medical conditions. This can occasionally lead to a missed, delayed or inaccurate diagnosis as described in the following case presentation [23].

CASE PRESENTATION

The patient is a 57 year old male who presented to the Veterans Administration (VA) Medical Center Emergency Department (ED) with a chief complaint of nausea, vomiting and diarrhea during the previous 14 hours. The patient was awake, fully alert, and denied chest pain or any respiratory difficulty. He stated that he was experiencing polyuria but denied polydipsia, dysuria, hematuria or weight changes. He related mood instability and a worsening of mental health symptoms in the week leading up to the ED admission. His ECG revealed a normal QTcB with no ST segment changes. The patient has a significant medical history including PTSD, BPD, hypertension, hyperlipidemia, and chronic pain from a lumbar injury. He is on full military disability due to PTSD and retired from military service one year prior to this ED evaluation. His active medications included lithium carbonate, lurasidone, amlodipine/valsartan, lisinopril, atorvastatin, clopidogrel and various vitamin supplements.

A review of the medical records revealed that approximately one month prior to the ED admission, the patient had been ordered by the Veterans Treatment Court to undergo a mental health evaluation. The patient was under court supervision due to PTSD and a traffic arrest stemming from hydrocodone abuse. The evaluation was requested after the patient's family and court members noted a significant decline in the patient's mental status and increased PTSD related symptoms such as anxiety, agitation, difficulty concentrating and hand tremors. During the requested psychiatric and neuropsychological evaluations, the patient reported that he had increased his lithium dosage citing that he received a greater benefit by doing so. The patient was noted by evaluators to have anxiety, memory and concentration difficulties which were attributed to existing diagnosis of PTSD. The patient self-reported sleep, concentration and memory difficulties along with occasional nightmares and flashbacks. Though "diarrhea due to the drug" was noted in past medical notes, the patient at that time denied nausea, diarrhea, tremors and excessive exposure to elevated outdoor temperatures during this visit. The lithium level during this evaluation had risen from the previous month's level of 0.49 mEq/L to 0.85 mEq/L. Lithium carbonate, amlodipine/valsartan and lisinopril were listed among the patient's medications and informed consent had been obtained during each visit including the potential for drug interactions.

In the 2 weeks prior to presenting to the ED, the patient's PTSD symptoms continued to escalate, including nightmares and flashbacks, which led the family to contemplate a law enforcement intervention to enact an involuntary psychiatric assessment and admission as appropriate. The acute onset of nausea, vomiting and diarrhea led to the ED evaluation at which time the lithium level had risen from the prior month's level of 0.85 mEq/L to 2.08 mEq/L (Table 1).

Treatment – The patient received intravenous (IV) fluids, anti-emetics, ECG monitoring and initially empirical antibiotics pending the outcome of the blood cultures. Lithium and lurasidone were both held due to the toxicity and ECG monitoring was continued. Blood cultures yielded no growth and therefore antibiotics were discontinued. Dialysis was not recommended after consultation with nephrology. The patient was transferred to the MICU and showed significant improvement with IV fluids. Over the course of the patient's 5-day hospitalization, the laboratory levels returned to baseline as indicated below (Table 2).

As part of the patient's management plan, the lithium and lurasidone were discontinued and replaced with paliperidone. Lisinopril was discontinued and replaced with nifedipine.

The patient was discharged with full resolution of GI symptoms and a significant improvement in cognitive function and mood stability.

An interview was conducted with the patient approximately 1 month subsequent to discharge. The patient's affect and concentration were much improved. Tremors had abated and the patient exhibited enthusiasm as to his ability to now re-engage with group therapy. The patient stated that his ability to

Table 1: Laboratory Findings – Upon arrival in the ED, the patient's laboratory findings revealed lithium toxicity, renal failure and significant leukocytosis. Significant lab values were as follows:

Laboratory Test	Result
Lithium	2.08 mEq/L
Creatinine	4.2 mg/dL
Blood urea nitrogen	35 mg/dL
Sodium	135 mEq/L
WBC	43.59 x 10 ⁹ /L
Platelets	438.0 x 10 ⁹ /L
Glucose	118 mg/dL

Table 2: Course of the patient's 5-day hospitalization.

Laboratory Test	Result
Lithium	0.36 mEq/L
Creatinine	0.9 mg/dL
Blood urea nitrogen	10 mg/dL
Sodium	138 mEq/L
WBC	13.32 x 10 ⁹ /L
Platelets	383.0 x 10 ⁹ /L
Glucose	113 mg/dL

“think clearly” now permitted him to act on directions provided by his medical and mental health practitioners.

DISCUSSION

This case reveals some potential pitfalls in the diagnosis of lithium toxicity for patients who are treated for other major mental illnesses and conditions. It is well published in the literature that patients who suffer from mental illness may have difficulty communicating their medical needs and this can occasionally lead to a missed or delayed diagnosis [24]. With this taken into consideration, this clinical case review leads down a path that is most consistent with acute-on-chronic lithium toxicity. The chief complaint, upon presentation to the ED, was a GI disturbance specifically nausea, vomiting and diarrhea. Laboratory findings confirmed a significant elevation of lithium, creatinine and white blood cell levels making the diagnosis of acute lithium toxicity relatively straightforward. What is not as evident is the etiology of acute toxicity in this particular case. The patient's GI disturbance could have induced a dehydration state which potentially led to renal failure and acute lithium toxicity. However, the same GI symptoms could have occurred, not as a precursor, but as a result of acute lithium toxicity. In a recent evaluation, the patient self-reported increasing his lithium dosage to abate symptoms. As per the patient's history in the ED, his symptomatology had worsened in the week prior to admission so the question arises as to whether the patient had again increased his lithium dosage. Any responses would have been questionable given the patient's state of confusion and poor memory. This case again typifies the challenges faced by practitioners when treating patients with lithium who concurrently are being managed for psychiatric illnesses such as PTSD.

A number of factors created the “perfect storm” for potential misdiagnosis of chronic lithium toxicity.

- Symptomatology, clinical presentation and history should be the primary factors for determining chronic toxicity however, in this case, the symptoms were essentially identical to those associated with the patient's PTSD (e.g. confusion, sleep difficulty, agitation, anger and irritability). Inadvertently, the patient also may have contributed to a potentially missed diagnosis as he deemed his symptoms to be that of PTSD. Without a history of toxicity, he was naïve as to the associated symptoms. Risk factors that should have warranted suspicion included the escalation of symptoms as noted by family and court officials, and the presence of two prescriptions - an ACE inhibitor and ARB - both of which can precipitate lithium toxicity.
- Serum lithium levels, during the 3 month period prior to the ED visit, were all noted to be below the 1.5 mEq/L toxic cutoff level; however, this type of neurotoxicity is not correlated with serum concentrations and a normal finding does not rule out toxicity. Practitioners should review levels for fluctuation as this may be a potential sign of poor compliance. In the referenced case, the levels were 1.43 mEq/L, 0.49 mEq/L and 0.86 mEq/L (oldest to most recent) with a level of 2.08 mEq/L upon arrival at the ED.

This case highlights the impact of co-morbid medical and

mental health disorders on our population of Veterans who are also diagnosed with PTSD. Misdiagnosing medical conditions which mimic mental health disease, is an ongoing challenge for practitioners. Thyroid dysfunction and hypoglycemia represent clinical scenarios responsible for altered mental status and therefore can be possibly mistaken for mental health related difficulties; however, each of these can easily be confirmed by laboratory findings unlike lithium toxicity. Though potentially beneficial in the treatment of PTSD, the complex surveillance accompanying ongoing lithium therapy must be considered.

As clinicians, we are challenged to look beyond our Veterans' primary mental illness to ensure that we're safely and effectively providing the best quality of care. To serve our Nation's Veterans, we must do this as a team, from the community Veteran Treatment Courts to the Department of Veterans Affairs, with attention to both mental health and medical care needs.

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