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RESEARCH ARTICLE

LITHIUM TOXICITY ARRIVES DUE TO A POSSIBLE DRUG-DRUG INTERACTION: A CASE REPORT

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Abbreviations:

BPD: Bipolar Disorder
ADR: Adverse Drug Reaction
ACEI: Angiotensin-Converting Enzyme Inhibitors
ARB: Angiotensin Receptor Blocker
NSAID: Nonsteroidal Anti-Inflammatory Drugs

ABSTRACT

Bipolar disorder (BPD) is a serious mental disorder characterized by episodes of depression, hypomania/mania and mixed episodes, with inter episodic recovery. For over 60 years, lithium carbonate has been used as first-line therapy for the treatment of bipolar disorder as mood-stabilizing drugs. Lithium is probably more effective in preventing mania than depression, and reduces the risk of suicide in people with BPD. Neurological disturbances caused by lithium range from simple side effects to acute neurotoxicity. Here we have reported case report of A 57-year-old Hypertensive female presented to the emergency department with lithium toxicity. This adverse drug reaction (ADR) after excluding other causative factors was categorized under " Probable" category and reported via vigiflow. All the medications were stopped immediately and she was then subjected to two sessions of hemodialysis. She was also given IV fluid hydration with normal saline. On discharge she was conscious and psychologically stable. Being vigilant for the early signs and symptoms of lithium toxicity can help in early diagnosis and prompt treatment. Narrow therapeutic index remains a major limitation of lithium treatment as it requires close monitoring and identification of neurologic adverse events.In clinical practice it has been observed that valproate is replacing lithium for elderly patients with bipolar disorder because valproic acid offers comparable efficacy, and the advantage of greater safety.

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INTRODUCTION

Bipolar disorder (BPD) is a serious mental disorder characterized by episodes of depression, hypomania/mania and mixed episodes, with inter episodic recovery. The illness usually starts in adolescence or early adulthood and has significant negative impact on life. For over 60 years, lithium carbonate has been used as first-line therapy for the treatment of bipolar disorder as mood-stabilizing drug. Lithium is probably more effective in preventing mania than depression, and reduces the risk of suicide in people with BPD (Kessing, 2014; Baldessarini *et al*., 2006). The therapeutic range of lithium is 0.6 to 1.2 mEq/L. Lithium toxicity usually occurs at serum levels >1.5mEq/Land also occur within therapeutic plasma concentrations in patients taking lithium chronically.

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The most common side effect of Lithium in the therapeutic dose range is fine postural hand tremor, indistinguishable from essential tremor. Severity and risk for tremor are dose dependent. At peak serum levels of Lithium, patients may complain of incoordination, ataxia, or slurred speech. Patients may also complain of mental fatigue, seizures, encephalopathy and coma at higher serum Lithium levels. This is reversible with drug discontinuation or dose reduction. Rarely, lithium is reported to cause irreversible, permanent neurological sequelae such as cerebellar impairment, dementia, parkinsonian syndromes, choreoathetosis, brain stem syndromes, and peripheral neuropathies (Schneider, 1994). This Case Report examines the clinical presentation of adverse events, predominantly neurological, associated with lithium intoxication in a hypertensive patient on maintenance therapy with a lithium carbonate.

Table 1. Grading wise treatment of Lithium toxicity

Grade	S. lithium mEq/L	Clinical Features	Treatment
1	1.5 – 2.5	Nausea, Vomiting, Tremor, Hyperreflexia, Ataxia, Agitation, Muscular Weakness	Hydration Kayexalate (Sodium Polystyrene)
2	2.5 – 3.5	Hypotension, Stupor Rigidity, Hypertonia	As above +/- dialysis
3	>3.5	Coma, Seizures, Myoclonus, Collapse	Hemodialysis

Case History: A 57-year-old female presented to the emergency department with c/o giddiness followed by altered sensorium. It was associated with salivation, uncontrollable micturition (history of voiding in clothes), inability to walk and speak since 7days. Before 7days she was relatively asymptomatic. Then she developed above symptoms which worsened gradually so was brought to our hospital. Two hours after her admission her relatives informed that she had ingested 2 extra tablets of lithium for two consecutive days before her symptoms started (total 1600mg/day for 2 days). She was a known case of Bipolar disorder and Hypertension since 20years.She was on treatment of Lithium carbonate (400mg) one tablet twice daily and Telmisartan +Hydrochlorothiazide (40+12.5mg) once daily. She had a history of two episodes of mania in the past. After lithium was started she achieved remission within 5- 6 months. She has been on treatment with lithium carbonate 800 mg/day for the last 20 years. On examination she was semi-conscious, disoriented, had hand tremors, ataxic gait and was not responding to verbal commands. On admission her vitals and random blood sugar were normal. Her CT brain was normal. On routine investigation her blood urea level was 66mg/dl (Normal level: 7to 20mg/dl) and creatinine level was 1.77 mg/dl (Normal level: 0.6 to 1.2 mg/dl). Considering this higher value nephrology reference was done. Primary impression of? Lithium toxicity /impending Acute Renal Failure was made. Serum lithium level monitoring was advised. Hydration of patient with normal saline 150ml/hr daily was also advised.

Her serum lithium level was found to be 3.51mmol/L (Normal level: 0.6 to 1.2 mEq/L) hence all the medications were stopped immediately and she was then subjected to two sessions of hemodialysis (one dialysis over 8hours on alternate days). She was continued with IV fluid hydration with normal saline 80ml/hr daily. On day 6, her laboratory tests showed serum lithium 1.20mmol/L, creatinine 0.96 mg/dl, blood urea 22 mg/dl. Gradually she improved, and regained consciousness and started following verbal commands. During her management psychiatric reference was advised. She took discharge against medical advice. The causality assessment was done using the Naranjo ADR probability scale. This adverse drug reaction (ADR) after excluding other causative factors categorized under " Probable " category and reported via vigiflowto the National coordinating centrePvPI for ADR monitoring with reference ID: 2018-51438 (Naranjo *et al*., 1981)

DISCUSSION

Lithium carbonate, most commonly used for the treatment of bipolar disorder, is administered orally. It is completely and rapidly absorbed from the gastrointestinal tract and largely dependent on renal function for elimination (Porto *et al*., 2009). As a result of the narrow therapeutic index, lithium levels are routinely monitored. The therapeutic range of lithium is 0.6 to1.2 mEq/L, with toxicity observed at levels of >1.5 mEq/L.

Management of lithium toxicity in our center is done as mentioned in Table 1 (Baird-Gunning *et al*., 2016). Cerebellar symptoms are the most common presentation of lithium toxicity and occur at significantly less serum lithium levels. Cerebellar symptoms at therapeutic serum lithium levels have been also been reported as features of toxicity. Some case reports in older subjects indicate that lithium toxicity can occur at mildly raised blood levels also i.e.(0.5–0.8 mEq/L) (Price, 1994). Lithium overdose was clearly responsible for lithium toxicity in this patient. Long-lasting neurological sequelae preceded acute lithium poisoning. Possible risk factors predisposing to high serum levels include concomitant use of other drugs (e.g., Thiazide diuretics, Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin receptor blocker(ARBs) and nonsteroidal anti-inflammatory drugs (NSAIDs), antipsychotics, tricyclic antidepressants, and anticonvulsants), and coexistent illness, such as hypertension, renal failure, heart failure, acute gastroenteritis, and epilepsy. This patient has been taking both lithium and hydrochlorothiazide for the last 20 years. The drug interaction between hydrochlorothiazide and lithium is well known. Hydrochlorothiazide reduces the clearance of lithium and this may be one of the factors which added to lithium toxicity in this patient. Another drug interaction which is likely in this patient is that between lithium and telmisartan; the mechanism for this drug interaction is not clear but is also related to a reduction of clearance of lithium (Ma, 2012). Elderly patients usually have physical and neurological comorbidities, chronic illnesses, incomplete therapeutic response. They are more sensitive to side effects and toxicity of frequently prescribed psychotropic drugs such as benzodiazepines, antidepressants, antipsychotics and Lithium. These can provoke serious adverse drug reactions (Zarse et al., 2011). Renal function also declines with aging, mainly due to sclerotic changes in the glomeruli. Mood stabilizer treatment is associated with acute neurotoxicity manifested as tremors (e.g. fine tremor to coarse tremor), frequent urination, and thirst, slurred speech, dysarthria, ataxia and in long-term adverse events like seizures, encephalopathy and coma occurs. Narrow therapeutic index remains a major limitation of lithium treatment as it requires close monitoring and identification of neurologic adverse events. In clinical practice it has been observed that valproate is replacing lithium for elderly patients with bipolar disorder because valproic acid offers comparable efficacy, and the advantage of greater safety (Baldessarini *et al*., 1999).

Conclusion

Clinicians need to be aware of the possibility of persistent neurologic sequelae that may follow acute lithium toxicity. Being vigilant for the early signs and symptoms of lithium toxicity can help in early diagnosis and prompt treatment.Patient education about adverse events remains an important issue of lithium treatment, which also improves patient compliance. Selection of newer mood stabilizers should be based both on efficacy and safety according to risk and benefit.

The best way to prevent lithium toxicity is to control the serum concentration regularly by periodic monitoring specifically when there is volume depletion or patient receiving NSAIDS, ACE inhibitors, ARBs, or Diuretics.

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