



Lithium use in the elderly demands caution and vigilance.

Vivek Suman and Manshi Kashyap

Department of Medicine, Lady Hardinge Medical College, New Delhi, India.

Abstract

Lithium is a popular drug in the field of psychiatry, used widely as a mood stabilizer in bipolar affective disorder. However, it has a narrow therapeutic index, between 0.6 and 1.5 mEq/L. Toxicity can occur at levels >1.5 mEq/L, hence thus monitoring of serum drug level is vital. Furthermore, the range of Lithium's therapeutic index can be further lower in the elderly, especially in the presence of renal disease, as the drug metabolism in this age group has considerable variation from an average adult. Following is a case report to exemplify Lithium Intoxication and of its narrow therapeutic index; and to develop further understanding on and the clinical implications of the age related changes that affect the pharmacokinetics and pharmacodynamics of the drug.

Keywords: Therapeutic Index, elderly, serum level, intoxication.

1. Introduction

Lithium has been widely used as a mood stabilizer for decades. Its therapeutic use had begun in the 1880s when John Aulde and Carl Lange observed that lithium could be used to treat symptoms associated with depression. However its use was aborted due to the serious toxicity associated with the widespread use of lithium in tonics, elixirs, and as a salt substitute. Later, in the 1950s, various clinical studies by Schou established lithium as an effective treatment of manic-depressive illness. In bipolar disorder, Lithium is more effective in preventing mania than depression. It is also used as an adjunct to other antipsychotics and antidepressants.

Lithium has a narrow therapeutic index, between 0.6 and 1.5 mEq/L. Toxicity can occur at levels >1.5 mEq/L, thus requires routine monitoring of serum drug levels. As it is eliminated by the kidneys, risk of toxicity increases in the face of deranged renal function. The half life of lithium is 18-24 hours which increases up to 60 hours in the elderly or with chronic use. Common adverse effects of Lithium include hand tremors, confusion, decreased memory, nephrogenic diabetes

insipidus like state (polyuria, polydipsia), leukocytosis, extapyramidal symptoms and hyperreflexia. Hypothyroidism may occur in 1-4% of people. Various electrocardiographic changes may also occur, including nonspecific T-wave flattening, sinus node dysfunction and prolonged QT interval. But despite all its adverse effects, it continues to be a popular drug in the field of psychiatry because of its efficacy in treating bipolar disorders as well as its use to treat alcoholism, schizoaffective disorders and cluster headaches. It also has neuroprotective effects and anti-suicide properties.

Herein, we describe an elderly male who presented to us in acute confusional state due to lithium intoxication, who later recovered after withdrawal of the drug and supportive therapy.

2. Case report

2.1 History

A 65 years old elderly male presented to the medical emergency with history of tremors and acute confusional state for the past two days. Patient was a known case of Bipolar Affective Disorder and Seizure disorder for which he had been on treatment since 10

years. The medications being administered included Sodium Valproate (1000 mg/day) and Lithium (1200 mg/day). On evaluating the treatment records and probing the attendant further, it was found that the dose of Lithium that was being administered to the patient had been increased two weeks back (from a dose of 900mg/day to 1200mg/day) following a manic episode. However, no serum drug level was available during the course of his treatment. Following the increase in dose, patient developed tremors and gradually became confused, as evidenced by decrease in verbal output, inability to recognize his relatives and disorientation to his surrounding environment. Oral intake had been poor in the past two days. Lithium was stopped at the time of admission and its serum level was sent and report was awaited. His past history was significant for stroke two years back for which he had been on aspirin and atorvastatin. There was no evidence of other chronic disease like hypertension or diabetes mellitus in the patient.

2.2 Examination

On presentation, the patient was stuporous, with a Glasgow Coma Score (GCS) of 9/15. Patient seemed dehydrated. His initial vital signs were normal (BP: 130/80, HR: 68 beats per minute). Bilateral planter response was extensor. Bilateral Knee and ankle reflexes as well as biceps, triceps and supinator reflexes were brisk. Higher mental functions, gait, motor and cranial nerve examination couldn't be elicited at the time of admission. No abnormality was detected on his Respiratory, Cardiovascular and Abdominal examination.

2.3. Investigations

Non Contrast CT Scan (NCCT) Head was performed immediately. It was suggestive of an old infarct of size 10*6mm in the left thalamic region with no perilesional edema. There was no evidence of any acute infarct/hemorrhage or any evidence of midline shift and raised intracranial pressure. No abnormality was detected in the ECG and Chest X ray. The routine investigations revealed leucocytosis with predominant neutrophils and deranged kidney function; Urea: 103 mg/dl and Creatinine: 1.3 mg/dl, suggestive of prerenal azotemia. Hypernatremia was also present. Lumbar puncture was subsequently done; no abnormality was detected in the CSF (TLC < 5/cu-mm; Total Protein: 44.4 mg/dl; Glucose: 62 mg/dl and ADA: 1U/L). However, serum Lithium level was indicative of intoxication – 1.53 meq/L. The reference normal range

reported by the Laboratory is 0.40-1.20 meq/L; warning range of 1.20-1.50 meq/L with risk of intoxication at >1.50 meq/L.

2.4. Treatment

Patient was given supportive treatment with a combination of IV fluids and free water to improve his hydration status, while correcting or preventing hypernatremia. Free water through Ryle's tube and Isotonic sodium chloride (0.9%) at 1000ml/day intravenously were administered. Sodium valproate 500mg every 12-hourly was continued for seizure disorder and aspirin 150mg/day and atorvastatin 40mg/day were added in the treatment regime in view of the old infarct detected on NCCT Head. The acute kidney injury was gradually corrected as the hydration was improved. Thereafter, 4 days after presentation, patient was fully conscious (GCS: 15/15) and well oriented to time, place and person.

3. Discussion

Elderly patients are more sensitive to side effects and toxicity of lithium and the consequences of toxicity are comparatively more severe. In addition, the elderly have physical and psychiatric co-morbidities and chronic course of illnesses. Age-related physiologic changes influence both pharmacokinetics and pharmacodynamics of drugs. Hence, dose adjustment of lithium is recommended in elderly.

A serum level between 0.8 mEq/l and 1.2 mEq/l is considered therapeutic for Lithium. This level is usually attained at a dose of 900-1200 mg/day in adults. However, in the elderly, this range can be obtained at lower doses. There have been reports of lithium toxicity that have occurred at moderate blood levels (eg, 0.5–0.8 mEq/L). Factors that increase the risk for chronic toxicity include other concurrent medications, illness, and reduction in potassium or sodium levels. Drugs that alter renal function can increase the risk for chronic lithium toxicity. Among these, ACE inhibitors, NSAID, and thiazide diuretics increase the reabsorption of lithium and result in increased serum lithium concentration. In addition, Forester et al. (2008) found in a study of bipolar patients that serum lithium levels did not correlate with brain lithium levels in older patients. It was noted that even mild delirium or confusion could be directing for toxicity even when older patients are on lower doses and lower target serum level of lithium.

Thus, our case report highlights the following important points. Chronic maintenance therapy with

lithium, in the elderly, may cause lithium intoxication at doses that are well within the therapeutic range for younger adults. Hence in the elderly, dose adjustments and monitoring of serum drug level for lithium are of paramount importance. As noted by Slater et al, elderly patients require a dose which is 31% lower than that of younger adults. Various authors have recommended dosage to be used in the elderly. Menghini et al, in 2000, recommended a dose of 300-600 mg/day for older adults between 65-75 years of age, not exceeding 900 mg/day. While a dose of 150-300 mg/day was recommended for adults above 80 years of age and the frail elderly, upto a maximum of 450 mg/day.

There are three types of Lithium Intoxication: acute, acute on chronic and chronic. Acute intoxication occurs in those who are not being treated with lithium, either by accidental or intentional ingestion. As its elimination half life is shorter in cases of acute ingestion, it generally manifests with milder symptoms than those observed with chronic poisoning. Acute on chronic poisoning occurs due to accidental or intentional overdose in patients being treated with

lithium, especially in patients with depression. This form of poisoning is relatively more severe due to the prolongation of the lithium elimination half-life. Patients receiving chronic lithium therapy develop chronic poisoning usually in the face of increase in the lithium dosage and/or declining renal function, resulting in an increase in serum lithium levels.

Altered mental status is the most frequent presentation of lithium intoxication. When a patient is suspected of lithium intoxication, the drug should be discontinued immediately and drug levels performed. Supportive care by improving the hydration status suffice in most cases. However, in case of severe, renal impairment and inability to eliminate lithium, hemodialysis is the definitive treatment as lithium is readily dialyzable owing to its water solubility and low volume of distribution. Patient and his attendants should be educated about the drug and its potential adverse effects in order to enable them to recognize the signs of toxicity at the earliest.

References

- Alderman CP, Lindsay KSW, 1996 : Increased serum lithium concentration secondary to treatment with tiaprofenic acid and fosinopril. *Ann Pharmacother* 30:1411 -1413.
- Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J: Lithium. 1997. In : *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*, edited by Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J, Baltimore, Williams and Wilkins, p1579
- Forester BP, Finn CT, Berlow YA, Wardrop M, Renshaw PE, Moore CM. Brain lithium, N-acetyl aspartate and myo-inositol levels in older adults with bipolar disorder treated with lithium: a lithium-7 and proton magnetic resonance spectroscopy study. *Bipolar Disord*. 2008 Sep;10;(6):691– 700.
- Goldberger ZD: Sinoatrial block in lithium toxicity. *Am J Psychiatry* 2007, 164:831-832.
- Lehmann K, Ritz E: Angiotensin-converting enzyme inhibitors may cause renal dysfunction in patients on long-term lithium treatment. *Am J Kidney Dis* 25:82 -87, 1995
- Lenox RH, McNamara RK, Papke RL, Manji HK: Neurobiology of lithium: An update. *J Clin Psychiatr* 58:37 - 47, 1998.
- Mamiya K, Sadanaga T, Sekita A, Nabeyama Y, Yao H, Yukawa E: Lithium concentration correlates with QTc in patients with psychosis. *J Electrocardiol* 2005, 38:148-151.
- Menghini VV, Albright RC Jr. Treatment of lithium intoxication with continuous venovenous hemodiafiltration. *Am J Kidney Dis*. 2000 Sep; 36(3):E21.
- Mitchell JE, Mackenzie TB. Cardiac effects of lithium therapy in man: a review. *J Clin Psychiatry* 1982, 43:47-51.
- Slater V, Milanese F, Talcott V, Okafor KC. Influence of age on lithium therapy. *South Med J*. 1984 Feb; 77(2):153-4,158.
- Young RC. Evidence-Based Pharmacological Treatment of Geriatric Bipolar Disorder. *Psychiatr Clin N Am*. 2005 Dec;28(4):837-869.

