ORIGINAL RESEARCH PAPER

Internal Medicine

LITHIUM AND NSAIDS: LIFE THREATENING TOXICITY OF LITHIUM PRECIPITATED BY A COMMON OVER THE COUNTER MEDICATION

KEY WORDS: Lithium, NSAIDs, toxicity, drug interaction

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ABSTRACT

Lithium though a pivotal drug in treatment of several neuropsychiatric conditions, it needs to be maintained within a very narrow therapeutic range by frequent therapeutic drug level monitoring as excessive Lithium levels can cause toxicity with severe side effects involving multiple organ systems and can even be fatal. Lithium is also notorious for several drug-drug interaction with many frequently used medications, some of which are available as over the counter medications. Here we present a case of Lithium toxicity precipitated by its interaction with NSAIDS. It highlights the importance of careful prescribing of drugs and avoiding over the counter medication while on Lithium.

INTRODUCTION

Lithium is used as a first line maintenance therapy in treatment of bipolar disorder and as a mood stabiliser (Hassan, 2013). However, Lithium has a narrow therapeutic index which means that the dose at which it is clinically effective is only slightly lower than the dose at which it becomes toxic. Excessive Lithium levels can lead to toxicity with severe side effects involving multiple organ system which can be fatal if not recognised. Lithium toxicity is a clinical diagnosis which can be confirmed with serum Lithium levels. The likelihood of Lithium intoxication is increased with underlying renal insufficiency, effective circulating volume depletion and older patients with low glomerular filtration rate. Drug-drug interactions is another important risk factor for Lithium toxicity, the propensity for which increases in geriatric age group as there is often use of polypharmacy. The narrow therapeutic index combined with broad side effect profile makes it difficult for the clinician to manage the drug and needs constant serial blood concentration monitoring (Mark D. Okusa MD, 1994).

Case Summary

61-year-old gentleman who is a known case of bipolar disorder and rheumatoid arthritis presented to the Emergency Department with progressively worsening altered mental status (drowsy, delirious, not oriented to time place and person) for the last 1-2 days. His regular medications included Lithium, Olanzapine, Prednisolone. Methotrexate, Folic Acid and Tofacitinib. On taking detailed history of the patient, the care giver who accompanied the patient stated that he underwent root canal treatment 3 days ago, and since then he has been taking self-medication TAB. Ketorolac (analgesic) twice daily for pain which he purchased over the counter without prescription.

In the Emergency Department the patient was found to be drowsy, delirious, not oriented to time, place or person. There was no focal neurological deficit but he had laboured breathing with decreased oxygen saturation and unstable haemodynamics. He was afebrile and no other significant findings were found on clinical examination of other systems. Urine toxicology screening was done to rule out any toxicological causes of altered sensorium (barbiturates, benzodiazepines, amphetamine, cocaine, cannabinoids and opiate poisoning was ruled out). The laboratory values showed mild renal impairment (Sr. Creatinine 1.4 mg/dL, Sr. Potassium level 5.6 mEq/L). He was initially treated at ER with intravenous hydration, oropharyngeal airway, non-invasive ventilation along with other supportive care and was shifted to critical care unit for further management. As the patient had an history of Lithium intake along with recent intake of NSAIDs, the possibility of Lithium toxicity was considered and Serum Lithium level measurement was sent along with discontinuation of Lithium and NSAIDs. Infective and metabolic causes of altered sensorium were subsequently ruled out. Serum Lithium level was found to be significantly elevated at 2.16 mmol/l. Nephrologist opinion was taken and haemodialysis was not initiated as the patient's renal function and sensorium gradually improved with conservative management. He was subsequently discharged from the hospital and is currently being followed up by his primary Care Physician with reinitiation of Lithium and regular monitoring of drug levels.

DISCUSSION

Lithium is used to treat acute mania, hypomania, bipolar and monopolar depression as well as for the maintenance treatment of bipolar disorders but it has a very narrow therapeutic index. The target Sr. Level of Lithium for acute phase management and maintenance treatment is between 0.8-1.2 mEq/L (0.8-1.2 mmol per L). Acutely mild toxicity usually does not occur at levels < 1.5 mEq/L. Levels > 2.5 mEq/L is a medical emergency even in patients who appeared relatively asymptomatic. Acute and acute on chronic toxicity often presents with gastrointestinal symptoms of nausea, vomiting and diarrhoea with late development of neurological findings. Chronic toxicity often presents with neurological symptoms including ataxia, confusion, agitation, delirium and/or neuromuscular excitability. Severe toxicity can cause seizures, non-convulsive status epilepticus, encephalopathy, hypotension, rigidity, hypertonia, myoclonus, cardiopulmonary collapse. Cardiac toxicity can cause dangerous dysrhythmias, flattened T waves, prolonged QTc intervals and bradycardia. In chronic toxicity symptoms like increased tremor, slurred speech and mild lethargy generally occur with Sr. Lithium

Concentration between 1.5-2.5 mEq/L. Worsening lethargy, coarse tremor, clonus can be seen when Lithium concentrations between 2.5-3.5 mEq/L. Severe toxicity generally occurs at Lithium concentration more than 3.5 mg/L (Jeanmarie Perrone, 2022).

Drug interactions especially with medications that change renal function or salt balance can alter Lithium excretion thus changing in Sr. Lithium concentrations. Thiazide diuretics, NSAIDs except Aspirin (KM Phelan, 2003), ACE inhibitors, Tetracyclines, Metronidazole increases Sr. Lithium level. Potassium sparing diuretic, SGLT2 inhibitors decrease Sr. Lithium level (Labbate, 2010). Loop diuretics and Calcium channel blockers may increase or decrease Lithium level. These medications are not contraindicated with Lithium but close monitoring of Sr. Lithium levels must be undertaken while taking these medications. It is recommended that Sr. Lithium levels be checked every 5-7 days after a dose of Lithium is changed or any new drugs is added which can cause interaction with Lithium excretion.

Lithium levels are helpful in the primary diagnosis of toxicity but the symptoms loosely correlate with the serum concentration. The management of toxicity must be guided by clinical symptoms and not by serum concentration. Lithium is mainly an extracellular water-soluble ion which can be cleared rapidly by intravenous hydration or haemodialysis in case of acute toxicity. However, following chronic Lithium ingestion intracerebral and intercellular concentrations are high which can result in clinical decompensation even after correction of Sr. Lithium level as Lithium equilibrate slowly between both compartments.

Laboratory studies that should be performed in patients with suspected Lithium toxicity includes Sr. Lithium concentration, complete blood count, Sr. Electrolytes, blood urea nitrogen, creatinine and TSH. Acid based disorders do not typically occur with Lithium toxicity and if present should raise suspicion of other ingestions foods like Aspirin or alcohol.

Differential diagnosis of Lithium toxicity includes Benzodiazepine toxicity and withdrawal, acute Ethanol withdrawal, hypoglycaemia, CNS infection, head trauma, stroke, myxoedema coma thyrotoxicosis, non-toxicologic cause of seizures and other medications and intoxication that can cause seizures.

For patients presenting with Lithium toxicity resulting from drug interaction with NSAIDs initial management include stopping of the offending drug, supportive care (airway, breathing and circulation), IV fluids with isotonic saline with a target to maintain adequate urine output (> 1.5-3 mL per kg/hour) but depends on fluid status and cardiac function. Sr. Sodium should be monitored very closely in patients with concern for Sr. Lithium induced nephrogenic diabetes insipidus. In severe cases the management of choice is haemodialysis (Juan Carlos Lopez, 2012).

Inference

In a patient who comes with altered mental status at emergency department with a history of Lithium intake as a part of daily treatment regime Sr. Lithium levels must be obtained and Lithium toxicity should be one of the differentials for altered sensorium. Detailed history of other drugs intake (both prescribed and over-the-counter medications) must be carefully documented. Clinicians should be aware of the fact that Lithium toxicity can be induced by NSAIDs which is commonly available over the counter medication.

Consent: Informed consent was obtained from the patient for publication of this case report.

Conflicts of Interest: The authors declare there is no conflicts of interest regarding publication of this article.

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