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Case Report

Lithium Toxicity Due to Concomitant Thiazide Diuretic and Non-Steroidal Anti-Inflammatory Drug Therapy

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Abstract

Background and Objective: Lithium has been used effectively in the treatment of Bipolar Affective Disorder since seven decades. Despite its remarkable efficacy in this condition, lithium treatment leads to various side effects and often toxicity involving various organ systems of our body. The risk of toxicity is higher in elderly patients with compromised renal function and receiving other concomitant medications such as loop or thiazide diuretics, non-steroidal anti inflammatory drugs (NSAIDS), or others. We aim to present a case of lithium toxicity in an elderly lady with concomitant thiazide diuretic and NSAID therapy.
Case description: An elderly lady suffering from Bipolar Affective Disorder and maintaining well on lithium and quetiapine prophylaxis was prescribed an NSAID (aceclofenac and paracetamol) and a thiazide diuretic (hydrochlorthiazide) for comorbid knee joint osteoarthritis and hypertension, respectively. She developed signs and symptoms of lithium toxicity after a week and was treated with hemodialysis in an emergency setup.
Conclusion: The index case suggests patients receiving lithium should be prescribed NSAID and thiazide diuretic with great caution if at all with proper monitoring of serum lithium level (German J Psychiatry 2012; 15 (2) : 66-68).

Keywords: lithium, drug-drug interaction, toxicity

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Introduction

Lithium, a monovalent cation, first used for the treatment of mania in the 1940s, continues to be the preeminent choice for bipolar disorder with antimanic, antidepressant and antisuicidal properties (Mohandas & Rajmohan, 2007). Lithium is minimally protein-bound and has an apparent volume of distribution of 0.6 L/kg. The therapeutic dose is 300–2700 mg/d, with desired serum levels of 0.7-1.2 mEq/L (Jefferson & Griest, 2005). The plasma elimination half-life of a single dose of lithium is from 12 to 27 hours (varying with age) and increases to approximately 36 hours in elderly persons. Toxicity associated with lithium treatment is prevalent, and 75–90% of patients treated with lithium have symptoms and signs of toxicity at some point during their treatment. Around 15% are rated moderate-to-severe toxicity, but mortality is less than 1% (Groleau, 1994). Lithium toxicity can be of two types, acute and chronic. Acute lithium intoxication occurs when the patient ingests it as a suicide attempt or overdoses accidentally. Chronic lithium intoxication occurs when the patient's lithium dosage has been increased, or when their renal function has been impaired, resulting in an increase in serum lithium levels. Other factors that might increase the risk of chronic lithium intoxication in previously stable patients include drug-drug interactions, concurrent illness resulting in decreased circulating volume and alternations in electrolyte concentrations (especially potassium, calcium and sodium)

(McKnight et al., 2012). Concomitant use of diuretics, angiotensin-converting enzyme inhibitors, calcium channel antagonists or NSAIDS has been associated with lithium toxicity through pharmacokinetic interactions (McKnight et al., 2012). Diuretics reduce renal clearance of lithium, the magnitude of this effect being greater with thiazide than with loop diuretics. Lithium level usually rises within 10 days of a thiazide diuretic being prescribed; the magnitude of this rise is unpredictable and can vary from 25% to 400% (Juurlink et al., 2004; Hines & Murphy, 2011). NSAIDS inhibit the synthesis of renal prostaglandins, thereby reducing renal blood flow and possibly increasing renal re-absorption of sodium and therefore lithium. The magnitude of this rise is unpredictable and vary from around 10% to 400%. The onset of effect also varies from few days to several months (Juurlink et al., 2004; Hines & Murphy, 2011). Hemodialysis is the cornerstone of therapy for lithium toxicity and should be considered early in treatment, when serum lithium levels are elevated, regardless of symptoms. Guidelines recommend that the following patients receive hemodialysis: those whose lithium levels exceed 6 mEq/L; those receiving long-term lithium therapy whose lithium levels exceed 4 mEq/L; those with severe neurologic symptoms, renal insufficiency or unstable hemodynamic status with lithium levels ranging from 2.5 to 4.0 mEq/L; and those with end-stage renal disease or an increasing lithium level after hospital admission and whose levels range from 1.0 to 2.5 mEq/L (Timmer & Sands, 1999).

We describe a case of 58-year-old patient suffering from Bipolar Affective Disorder and on lithium prophylaxis who developed lithium toxicity after being concomitantly prescribed NSAIDS and thiazide diuretics for co-morbid physical conditions. This case emphasizes the need for patient education regarding the symptoms of toxicity and common risk factors before lithium treatment is being initiated.

Case Report

Mrs. AD, 58 years old, has been a known case of Bipolar Affective Disorder (as per DSM-IV) for the last 30 years. She was also receiving treatment for hypertension and hypothyroidism and was maintaining well on telmisartane (40 mg/d) and levothyroxine (50 mcg/d), respectively. Mrs. AD was prescribed lithium (600 mg/day) and quetiapine (200 mg/day) after her last breakthrough episode 8 months back, and she was maintaining well on the same before she came for a routine check up in the second week of January 2012. At that time her serum lithium level was found to be 0.82 mmol/l; serum TSH and serum creatinine was 4.05 μIU/ml and 0.9 mg/dl respectively. Her electrocardiogram was within normal limits. She was euthymic on presentation but complained of severe pain in both knee joints, with difficulty increasing while walking. Her blood pressure was recorded to be 160/100 mmHg. Therefore, she was asked to take an orthopedic and cardiology consultation and to continue the previous psychotropic medications. Her husband called up the therapist two weeks later to inform that patient has been appearing drowsy with slurred speech and unsteady gait. She was examined by the therapist very next day. On examination she was found to be drowsy, ataxic, having slurred speech and coarse tremor of upper extremities. Her blood pressure and pulse rate was within normal limit. Her hydration was well maintained as measured by skin turgor. There was no history of fever, headache or vomiting. On careful enquiry from husband, she was also found to be receiving telmisartane (80 mg) and hydrochlorthiazide (12.5 mg) combination and aceclofenac (100 mg) and paracetamol (500 mg) combination for high blood pressure and knee joint pain respectively which were initiated about seven days back. A case of lithium toxicity was suspected and patient was admitted in the Emergency Department of a state-run tertiary care hospital. On admission (i.e., on 30.01.12) her serum lithium level was found to be 4.78 mmol/l, serum urea 62 mg/dl, serum creatinine 1.3 mg/dl, hemoglobin 10.4 gm%, total leukocyte count was 10600/cumm, liver function test was within normal limits, serum Na+ and K+ was 142 meq/l and 5.1 meq/l, respectively. Routine urine examination revealed high albumin content. Ultrasonography of the kidney, ureter and bladder did not reveal any abnormalities. Her psychotropics and pain medications were stopped immediately. Antihypertensive medication was changed to telmisartane 80 mg/d and amlodipine 5 mg/d, while levothyroxine (50 mcg.d) was continued. She was taken up for hemodialysis, and two dialyses were given over next 7 days. Serial serum lithium monitoring was done; results being 2.84 mmol/l (on 04.02.12) and 1.16 mmol/l (on 07.02.12). Before discharge from the hospital her serum urea and creatinine level also normalized. Her neurological and overall physical status was improved. She came for follow up after one week. She was euthymic on presentation with complaints of early insomnia. Considering her longitudinal history of frequent relapses and recurrences she was started on a titrating dose of sodium valproate-chrono preparation up to 500 mg twice daily along with nitrazepam 10 mg at night. The serum valproate level was checked after 5 days and it was found to be 83 meq/l. She has been following up regularly and maintaining well till date.

Discussion

In the index case, the patient was receiving lithium for the last 25 years, with serum lithium monitoring being done at regular intervals. Her other physical parameters related to lithium therapy were also checked periodically. She was started on levothyroxine six years back after she was diagnosed as a case of lithium-induced hypothyroidism by the endocrinologist. She was maintaining well on lithium and quetiapine prophylaxis, when NSAID and thiazide diuretic was introduced in her treatment regimen because of knee joint osteoarthritis and uncontrolled hypertension, respectively. On both occasions the treating doctors were not shown the psychiatric prescriptions and were told that the patient was having some 'chronic mental illness'. Signs and symptoms of lithium toxicity started appearing around seven days later, which is usual for such cases (Juurlink et al., 2004; Hines & Murphy, 2011). In the index case, signs and symptoms of lithium toxicity were predominantly neurological

(e.g. drowsiness, coarse tremor, ataxic gait, slurring of speech etc.), which iscommon at a serum lithium level > 2.5 mmol/l and indicative of cerebellar involvement (Oakley et al., 2001). No time was wasted in this case to institute hemodialysis, which remains the cornerstone of therapy for such cases (Timmer & Sands, 1999). The patient showed signs of improvement after two sessions of hemodialysis and serum lithium level was also decreased. Considering her past psychiatric history and the presence of hypothyroidism, the patient was started on sodium valproate maintenance therapy. This case amply demonstrates the importance of patient education regarding symptoms of lithium toxicity and common risk factors before initiating lithium treatment. The information should be repeated at appropriate intervals so that it is clearly understood. Our colleagues in other branches of medicine should also exercise appropriate caution while dealing with an elderly patient suffering from longstanding psychiatric disorder and should make in depth enquiry about illness and medication before prescribing their own. Family members need to inform their doctor regarding the psychiatric medications patient has been receiving and should not be casual in their approach so as to avoid such potential life threatening condition.

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