CASE REPORT

Hypertensive bipolar: chronic lithium toxicity in patients taking ACE inhibitor

Ruziana Masiran,¹ Mohammad Firdaus Abdul Aziz²

¹Department of Psychiatry, University Putra Malaysia, Serdang, Selangor, Malaysia
²Department of Psychiatry and Mental Health, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Correspondence to
 Dr Ruziana Masiran,
 ruziana78m@yahoo.com

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SUMMARY

A patient with bipolar I disorder has been treated with lithium and haloperidol for the last 20 years and received an ACE inhibitor for his hypertension since 9 years ago. Despite regular clinic follow-ups and blood monitoring, he recently developed tremors and delirium. On hospital admission, serum level of lithium was far above toxic level. Mental state examination revealed an anxious and disorientated man with irrelevant speech. Immediate discontinuation of lithium resulted in slow reduction of serum lithium levels and gradual resolution of tremor but his delirium persisted for 2 weeks. His condition took a turn for the worse when he developed acute renal failure and arm abscess. We discussed about lithium toxicity and the vulnerability factors which have induced delirium and renal failure in this patient.

BACKGROUND

The therapeutic effect of lithium as a monotherapy or combined with other medications in bipolar disorders cannot be argued. However, lithium is associated with a number of adverse events owing to its narrow therapeutic index. Neurotoxicity and nephrotoxicity are two common reported phenomena in lithium toxicity cases. Nevertheless, there are a number of factors intermingled in the development of lithium toxicity, particularly prolonged duration of use, increasing age and drug–drug interaction between lithium and commonly prescribed medications like ACE inhibitors. Despite its well-known lethality, lithium toxicity may still be unrecognised until late.

CASE PRESENTATION

We present a case of a 58-year-old male patient who suffered from bipolar I disorder for the past 30 years with his last manic episode occurring 15 years ago. He has achieved remission with lithium and haloperidol prescribed for at least 20 years. He has been compliant to treatment and attended regular clinic follow-ups with 6 monthly serum lithium assessments. In the last 1 month prior to admission, he occasionally appeared confused and became socially withdrawn. The patient himself reported having had insomnia and tremors for 3 months. He has also experienced auditory and visual hallucinations for at least a month. He became increasingly irritable and has forced his wife to perform indecent sexual acts with him, a behaviour which urged her to bring him to the hospital.

On arrival at the hospital emergency unit, the patient appeared confused, anxious, agitated and

was fidgeting. He was disorientated to time and place and had difficulty focusing and sustaining attention. He was unable to speak relevantly but there was neither pressure nor poverty of speech. Physical examination showed a middle-aged man with an asthenic habitus and pale dry skin. His body temperature was 37.4°C, blood pressure was 150/89 and pulse rate was 103 per min. His lungs were clear to auscultation and cardiovascular examination showed no abnormality. Neurological examination revealed coarse tremor of hands, both intentional and at rest, and mild ataxic gait.

Once the history of lithium therapy has been discovered, lithium toxicity was immediately suspected. At that point in time, lithium level was found to be 2.3 mmol/L. His record showed that he had been on maintenance therapy with a lithium carbonate dosage 300 mg twice daily, which had been unchanged for 10 years. He used to be taking 900 mg of lithium carbonate prior to that. Serum lithium levels were within normal range all these years. However, it was 2.1 mmol/L 2 months prior to this admission—a result which was notified to the doctor but the patient could not be contacted although attempts to call him were made.

The patient also has diabetes mellitus for the past 20 years and hypertension for the past 15 years. Drug history included haloperidol 5 mg/day, lithium carbonate 300 mg twice daily, benzhexol 2 mg thrice daily, perindopril 4 mg/day, simvastatin 10 mg/day, Cardiprin 100 mg/day, metformin 500 mg twice daily, subcutaneous Actrapid 18 units thrice daily, subcutaneous Insulatard 34 units/day.

INVESTIGATIONS

Serial blood investigations were performed throughout his hospital admission.

Renal profile revealed raised urea which ranged from 12.2 to 18.8 mmol/L, raised creatinine (from 352 to 426 μ mol/L) and raised potassium levels (5.3 to 6.2 mmol/L). Creatine kinase (CK) was 581 IU/L.

Full blood counts show anaemia (haemoglobin 10.1–11.4 g/dL). There was thrombocytopenia (platelet 87 000–133 000 /L. Leucocytosis was evident with white cell count ranged from 14.4 to 17.4 $\times 10^9$ /L.

Venous blood gases showed evidence of metabolic acidosis (pH 7.268, pCO₂ 3.88 kPa, pO₂ 14.09 kPa, HCO₃ 13.6 mmol/L, base excess –11.5 mmol/L).

T4 and thyroid-stimulating hormone levels were normal. Alkaline phosphate was mildly raised at 172 U/L.

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and incisional and drainage of the abscess was performed by the orthopaedic team.

After 24 days, the patient was discharged in a stable condition. He responded to and tolerated sodium valproate 600 mg thrice daily and haloperidol 5 mg twice daily. Serum level of sodium valproate was acceptable that is, 500.79 $\mu\text{mol/L}$. Renal profile has improved tremendously although urea and creatinine is still raised at 16 mmol/L and 296 $\mu\text{mol/L}$, respectively. The nephrology team will review him further in their outpatient clinic.

DISCUSSION

The narrow therapeutic index of lithium is associated with a number of adverse events, especially in elderly and those on chronic lithium maintenance therapy. This is aggravated by an increasing practice of polypharmacy worldwide and comorbid medical or psychiatric conditions in this group of patients. In the early stage of lithium intoxication, clinical findings such as ataxia, coarse tremor, dysarthria, hyper-reflexia and myopathy are common, and could further deteriorate into a stage of encephalopathy, cerebellar dysfunction and seizures.¹ In the syndrome of irreversible lithium-effectuated neurotoxicity, these neurological dysfunction may even persist for a long period after the discontinuations of lithium.²

To make the situation worse, there is a widespread increasing trend of polypharmacy practice in bipolar disorders,³ with almost half of patients receiving at least three concurrent medications.⁴ To be specific, coadministration of lithium and neuroleptic drugs has been an ongoing issue as this was found to cause neurotoxicity. A study suggested that the combination of lithium and neuroleptic agents, especially haloperidol may cause greater neurotoxicity.⁵ Another form of polypharmacy would include the concomitant use of drugs indicated for various medical illnesses like hypertension, diabetes mellitus or myalgia. This is significant to a country like Malaysia where the prevalence of hypertension shows an increasing trend. Thiazide diuretics, ACE inhibitors and non-steroidal anti-inflammatory drugs have been known to alter the serum lithium concentrations, escalating the risk for lithium toxicity.⁶

It is important to understand the pharmacokinetics of lithium in elderly. Degenerative processes in older persons contribute to functional decline in all systems including the kidneys,⁷ within which sclerotic changes becomes the culprit in causing renal failure⁸ and chronic kidney disease.⁹ Apart from advanced age, duration of lithium treatment is an added risk factor for reduced glomerular filtration rate (GFR) and the subsequent deterioration of renal function.¹⁰ Studies showed that patients on long-term lithium had significantly lower GFR values¹¹ and renal failure tends to 'appear after decades of treatment and gradually progresses irrespective of lithium continuation'.¹² Nephrogenic diabetes insipidus, tubulointerstitial nephritis and nephrotic syndrome are among the manifestations of lithium nephrotoxicity. Other than nephrotoxicity, elderly patients are also more predisposed to neurotoxicity of lithium even at normal serum levels because their serum lithium levels may not correlate with the brain lithium levels (Forester *et al*).¹³

Another vital aspect in managing this case is establishing the causal relationship between lithium taken by the patient and the onset of signs and symptoms of lithium toxicity in him. In the field of pharmacovigilance, such causality assessment of a medication's adverse effects has become customary.^{14 15} Among the widely used drug reaction measurement scales is the Naranjo

Algorithm, also known as the Adverse Drug Reaction Probability Scale.¹⁴ This algorithmic scale basically use a simple questionnaire to assign probability scores to estimate whether the adverse effect of a medication certainly, probably, possibly or unlikely to have taken place. With a score of 6 with Naranjo algorithm for causality assessment, lithium prescribed for the illustrated patient had a 'probable' causal association with the adverse drug event.

The role of lithium in the production of acute renal failure in this patient was generally contributed by dehydration and the subsequent volume depletion due to the combination of natrium-water diuresis accompanied by elevated lithium levels, altered mental status and subsequent poor oral intake. In this patient, long duration of lithium and concomitant use of haloperidol were precipitated by the prescription of ACE inhibitors culminating in lithium toxicity. Although the available record showed that his toxicity might have persisted for about 2 months, it could have actually occurred longer. Chronic toxicity is associated with persistent cognitive and neurological impairment, during which mental status is often altered and coma may ensue if the diagnosis is unrecognised.¹² In conclusion, changed pharmacokinetics and pharmacodynamics of drugs caused by ageing act together with comorbidity and polypharmacy have all posed this patient to lithium toxicity. Like most severe cases of lithium toxicity, withdrawing lithium as well as augmenting lithium elimination¹⁶ through fluid therapy were the primary steps taken.

Learning points

This case emphasises some important points:

- Psychiatrists should remain vigilant in treating bipolar patients with lithium, especially the elderly group and those on chronic maintenance treatment.
- Physicians and patients must be aware of the risk of concomitant administration of ACE inhibitors among hypertensive patients taking lithium.
- Regular clinical assessments, serum level and renal function monitoring must be carried out on patients taking lithium.
- An active patient tracing must be practised once serum lithium is found to reach a toxic level.
- Delirium in lithium neurotoxicity can be prolonged.

Contributors MFAA and his team managed the case from inpatient to outpatient setting. RM managed the patient during her on-call working hours and drafted the manuscript. Both MFAA and RM critically revised the manuscript.

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