CASE REPORT

Do not treat the numbers: lithium toxicity

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Accepted 20 May 2017

SUMMARY

We describe the case of a 62-year-old man with a history of bipolar disorder, previously stable on lithium for over 20 years, who presented with a manic relapse and signs of lithium toxicity in the form of a coarse tremor. Serum lithium levels were in the normal range, and the patient had stage 3 chronic kidney disease. He was admitted for treatment under Section 2 of the Mental Health Act, and after stopping lithium was started on olanzapine. Signs of lithium toxicity improved after withdrawal of lithium. This case highlights the need to treat normal serum lithium levels with caution in patients showing signs of clinical lithium toxicity.

BACKGROUND

Lithium is an effective medication for the treatment of bipolar disorder, and National Institute for Health and Care Excellence (NICE) guidelines recommend it as the first-line pharmacological treatment for long-term management.¹ However, lithium's narrow therapeutic range (0.6–1.0 mmol/L) requires monitoring to prevent toxicity.¹ The clinical manifestations of lithium toxicity are manifold, involve multiple systems and can be classed as acute, acute-on-chronic, or chronic.² There has been much debate surrounding the long-term effects of lithium on renal function. It is well recognised that lithium can induce nephrogenic diabetes insipidus;^{3–5} however, evidence of a causal relationship with chronic kidney disease is mixed.^{5 6}

We describe the case of a manic relapse of bipolar disorder with clinical lithium toxicity in a patient who was previously stable on lithium for over 20 years.

CASE PRESENTATION

A 62-year-old man with bipolar disorder and prostate cancer was admitted to our psychiatric unit following concerns of a relapse in the community. His bipolar disorder was first diagnosed 25 years ago, and he was reported to be stable on lithium for the majority of this time. He was last admitted to psychiatric services in early 2015 following a stress-related hypomanic relapse, and on admission had not been seen by the community team for 1 year.

His mania was characterised by hyperactivity, lack of sleep, agitation and grandiosity in his thinking. Psychiatric services were alerted to a possible relapse after he was taken to the accident and emergency department (A&E). The police had found him sheltering in a train station in the early morning after he had been disinhibited in the

community, partaking uninvited in a charity dance class. He was disorganised, having lost his bag containing keys, mobile phone and medication.

While in the A&E, he was elated in mood and overfamiliar with patients and staff. He was easily agitated and used the floor of the department to perform exercises. Review by the liaison psychiatry service noted pressured speech, flight of ideas and grandiose delusions. He had not slept in three nights, was not eating well and had poor concentration. It was not possible to determine when he had last taken his medications, nor the pattern of his medication usage as this was not supervised prior to admission. He had a labile affect, appearing euphoric and joking but then becoming anxious, pacing around worrying about his belongings. He described himself as 'jolly' and 'the only way is up'. He denied feeling depressed, but spoke about seeing someone suffering in A&E and started to cry. He was felt to lack insight into his current relapse and was admitted for inpatient care under Section 2 of the Mental Health Act, which enables patients to be detained in hospital for a period of assessment and treatment.

His medical history included a low-risk prostate cancer, which was being managed conservatively with regular prostate-specific antigen (PSA) monitoring.

He also had a long-standing tremor which records report had started unilaterally and later became a bilateral fine tremor. Initially, he was investigated for Parkinson's disease but a treatment trial with selegiline was stopped after lack of efficacy. He was later trialled with propranolol for essential tremor; however, this was also stopped after no improvement. He had no allergies, and on admission regular medications were lithium 800 mg nocte, trazodone 50 mg nocte and tadalafil 20 mg as required.

There was no family history of mental health disorders. He was living in sheltered accommodation and retired early from his job due to his bipolar disorder. He denied smoking, use of alcohol or illicit drugs.

On examination, his heart rate was 91 bpm, blood pressure 135/79 mmHg, temperature 36.5 and oxygen saturations 96% on room air. He was thin, had a coarse, bilateral, postural tremor at approximately 5 Hz and slurred speech. The system examinations were otherwise unremarkable.

Full blood count, electrolytes and liver function tests were normal (WCC $7.5 \times 10^9/L$, Hb 123 g/L, neutrophils $5.2 \times 10^9/L$, platelets $196 \times 10^9/L$, Na 142 mmol/L, K 4.7 mmol/L, cCa 2.24 mmol/L, thyroid-stimulating hormone 2.9 mIU/L, aminotransferase 23 IU/L, alkaline phosphatase 48 IU/L,

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To cite: Foulser P, Abbasi Y, Mathilakath A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220079

total bilirubin 14 $\mu\text{mol/L}$, albumin 41 g/L). His creatine was elevated at 123 $\mu\text{mol/L}$, with urea 10.1 mmol/L and an estimated glomerular filtration rate (eGFR) of 52 mL/min. PSA was 6.82 $\mu\text{g/L}$ and serum lithium levels were at the high end of the normal range at 0.95 mmol/L. It was felt that the lithium levels were taken >12 hours post dose due to the circumstances surrounding his presentation. Urine dip was negative for nitrites and leucocytes, and a urine drug screen was negative.

The renal impairment was largely unchanged from 2014, during which time the eGFR had ranged between 46 and 56 mL/min. The patient was rehydrated with oral fluids, and the urea fell to a normal range. Lithium was initially stopped, replaced by olanzapine 10 mg nocte for its mood stabilising and sedative effects. During 2 weeks of observation, his mania worsened. Lithium was, therefore, restarted as a trial, but signs of toxicity in the form of a coarse tremor returned. It was felt that due to the evidence of chronic renal impairment, manic relapse and predisposition for toxicity, lithium should be stopped completely. We started treatment with sodium valproate (Depakote), a second-line medication for bipolar disorder. Stopping lithium caused a marked improvement in his tremor within a further 2 weeks.

DIFFERENTIAL DIAGNOSIS

Manic/hypomanic relapse of bipolar disorder

Acute hyperactive delirium

Lithium toxicity

Intoxication

Electrolyte disturbance

Cerebrovascular accident

Central nervous system (CNS) infection

OUTCOME AND FOLLOW-UP

The patient remained an inpatient for 3 months and was managed under Section 3 of the Mental Health Act. He lacked insight in the reason for admission, however remained aware of his diagnosis and agreed to continued medical management. There was a gradual but labile improvement to his mental state and integration into the ward. Olanzapine was increased to 20 mg nocte, and he subsequently developed rigidity and lip smacking. These were felt to be extrapyramidal side effects, for which procyclidine was introduced. The sodium valproate (Depakote) was titrated up to 500 mg mane and 1000 mg nocte. Repeated blood tests revealed no deterioration in his chronic kidney disease. He was discharged from hospital on olanzapine and sodium valproate and is receiving community mental health follow-up. A repeat dopamine transporter scan has shown no signs of Parkinson's disease.

DISCUSSION

Lithium as a cause of nephrogenic diabetes insipidus is well documented; however, evidence of a causal association between chronic lithium use and renal dysfunction is mixed. A 2015 population-based cohort study refutes previous data suggesting that long-term lithium use in itself can cause deterioration in eGFR.⁶ The study found that baseline eGFR, age, comorbidities, coprescription of nephrotoxic drugs and episodes of lithium toxicity (defined as serum levels >0.80 mmol/L) predict reductions in eGFR, rather than duration of lithium exposure or average lithium level. Furthermore, a recent systematic review and meta-analysis found little evidence of a clinically significant reduction in renal function in most patients taking long-term lithium.⁷ We postulate that our patient developed chronic renal impairment during periods of toxicity.

With the therapeutic range defined as 0.6–1.0 mmol/L, and evidence of renal dysfunction occurring with serum levels >0.8 mmol/L, questions have been raised as to whether we should reconsider the desired levels in some patients.⁸ We feel that in elderly patients, especially those taking medications known to increase lithium levels (nonsteroidal anti-inflammatory drugs, ACE inhibitors, angiotensin receptor blockers, thiazides, spironolactone, diltiazem and verapamil),² and those with risk factors for chronic kidney disease, lithium levels in the lower therapeutic range should be targeted.

Acute lithium toxicity is characterised by nausea, vomiting, diarrhoea, dysrhythmia and neurological manifestations such as coarse tremor, muscle weakness, cerebellar signs and delirium. Severe lithium toxicity can cause seizures, coma and permanent neurological effects such as dementia.⁵ Neurological side effects are the most common in chronic toxicity, as it takes time for lithium to distribute into the central nervous system.² The risk of chronic lithium toxicity is increased during times of sodium or volume depletion.⁹

A recent review highlights the physiological basis behind which lithium more readily causes neurotoxicity in chronic users.² With chronic lithium use, lithium distributes to a steady-state concentration in the brain and serum, and it is noted that there can be interindividual variation between the relative concentrations.² In patients taking chronically high doses, lithium will accumulate at a level in CNS tissue that induces toxicity. If subsequent doses are missed, the serum levels may be normal despite neurological toxicity. This highlights the need to interpret lithium levels in the context of the time since the last dose (12 hours post-ingestion).² For our case, it is likely the lithium level was taken >12 hours since the last dose as it is unlikely he was well enough to remember to take his medications. Serum levels may therefore have fallen into therapeutic range, despite elevated concentrations in the CNS. We therefore feel that although serum lithium level monitoring is important, the levels must be taken in the context of the clinical history and examination, along with the time since last dose and length of lithium therapy.

This case highlights the need to read the lithium level in the context of the patient as a whole. The serum lithium level gives a snapshot of the blood lithium concentration, but does not always reflect the lithium levels in the other body compartments. Given that patients can take lithium for many years, we feel that monitoring of lithium levels and renal function should occur alongside clinical review for signs of toxicity. Equally, we feel that targeting a lower lithium level in elderly patients is preferable, due to the risks of toxicity associated with polypharmacy and declining renal function. Finally, while we believe that checking lithium levels will remain important and common practice, when clinical toxicity is suspected, lithium levels in the low or normal range should be treated with caution.

Learning points

- ▶ Lithium has diverse side effects—in all patients presenting to hospital with a clinical suspicion of lithium toxicity, measure a serum level 12 hours post dose.
- ▶ In patients in whom clinical lithium toxicity is suspected, treat the lithium level in the normal range with caution, especially when the timing of the last dose is unknown.
- ▶ In elderly patients taking lithium for long term, consider targeting a lithium level in the low end of the normal range.

Contributors PF wrote the article and conducted literature review, sending it for review to the other authors. He also collated information from the patient's notes.

YA helped with the written content and editing of the article, and also assisted with the literature review. She also researched the patient's prognosis and long-term follow-up. AM was involved in the initial planning of the article. RN gave advice regarding the content and direction of the article, particularly the discussion. He edited the article and reviewed the article prior to submission. PF and YA are guarantors for the content.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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