Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20184865

Case Report

Accidental chronic lithium toxicity

Vangelis George Kanellis*, Ramila Varendran

Department of General Medicine, The Canberra Hospital, Garran, ACT, Australia

Received: 28 September 2018
Accepted: 26 October 2018

***Correspondence to:**
Dr. Vangelis George Kanellis, Email: vangeliskanellis@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Lithium is an effective first-line mood stabiliser for bipolar disorder, treatment-refractory depression and suicide prevention. Studies have demonstrated its ability to produce neuroprotective benefits. Despite this, Lithium can cause neurotoxicity, cardiotoxicity and endocrine derangement resulting in severe (and potentially permanent) side effects. Lithium toxicity can be precipitated by illness, salt restriction diets, dehydration, nephrogenic diabetes insipidus, impaired creatinine clearance, concomitant drugs. This is particularly true in older patients with altered pharmacodynamics and pharmacokinetics. We present a 52-year-old female who presented with prolonged signs of lithium toxicity post-diarrhoea. Lack of monitoring due to her nomadic life-style resulted in the combination of long-lasting neurotoxicity and thyroid dysfunction. Our patient displayed neurotoxicity that was not present on imaging. This highlights the importance of regular monitoring of renal function, lithium serum levels and neuro-endocrine function to reduce complications associated with lithium toxicity.

Keywords: Bipolar, Chronic, Endocrine, Lithium, Monitoring, Neurotoxicity, Renal, Thyroid, Toxicity

INTRODUCTION

Lithium is a gold standard for the maintenance treatment of bipolar disorder, with demonstrated benefits for depression, mania, reducing the risk of suicide and short-term mortality.[1-3] It also reduces excitatory neurotransmission and demonstrates neuroprotective effects on brain structures involved in emotional regulation.[4] The mood stabilising effects of lithium likely result from its ability to alter glutamate, inositol monophosphate and glycogen synthase kinase transduction, noradrenaline and dopamine and serotonin pathways, induce epigenetic modification and increasing anti-apoptotic pathways.[4,5] At toxic doses however, lithium disturbs renal, thyroid, parathyroid, neurological and metabolic disturbances via mechanisms that have not yet been fully defined.[6,7]

Significant symptoms of neurotoxicity include mental status changes with cognitive and neurological deficits (such as falls, tremor, ataxia, muscle weakness, muscle rigidity, slurred speech, blurred vision and nystagmus).

These may be permanent due to neuronal cell loss and gliosis. Our patient displayed neurotoxicity that was not present on imaging. Whilst the lifetime incidence of bipolar disorder is around 1%, the incidence of lithium intoxication is approximately 1/100 patient-years.[8]

CASE REPORT

History

A 52-year old female presented with 24hrs of diarrhoea, vomiting, resulted in this emergency presentation. Headache was associated with photophobia, neck and shoulder pain, hot flushes, lethargy, blurred vision and dizziness. She reported a 72-hour history of poor co-ordination and dysarthria. Her mental state was consistent with delirium. Two months prior to this her depression was treated with electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMN) and was prescribed lithium 400mg orally twice daily, to complement sertraline and quetiapine. She had no other relevant past medical history and had normal kidney function. The patient was taking ibuprofen 400mg orally daily for the last 2 years but was not taking any other medication.

Table 1: Results of investigations during inpatient stay, from admission (day 0) to discharge (day 20).

Analyte	Reference range	Day 0	Day 3	Day 4	Day 5	Day 11	Day 20
Lithium	0.40-1.00mmol/L	3.5	1.1	0.5		<0.2	<0.2
Na	133-146mmol/L	136	142		142		140
K	3.5-5.3mmol/L	3.4	3.7		3.4		4.5
HCO_3	22-29mmol/L	23	22		13		23
Urea	2.5-7.8mmol/L	4.4	1.9		1.6		5.3
Cr	50-130µmol/L	93	73		72		75
ACa	2.20-2.60mmol/L	2.32			2.33		2.42
FT4	10.0-22.0pmol/L		11.2				
TSH	0.4-4 mIU//L	4.34	4.68		2.19		0.93
Sodium (Na), Potassium (K), Bicarbonate (HCO_3), Creatinine (Cr), Adjusted Calcium (ACa), Free Thyroxine (FT_4), and Thyroid Stimulating Hormone (TSH)							

General examination

Initial examination revealed haemodynamic stability with delirium, tremor, an unstable gait and ataxia. Upper limbs displayed dysdiadochokinesia and dysmetria.

Systemic examination

No significant abnormalities detected.

Investigations

Venous blood analysis during admission is shown in Table 1. Her ECG was normal. Magnetic resonance angiography was unremarkable.

Management

Lithium and ibuprofen were immediately ceased on admission. Lithium toxicity was confirmed with a Naranjo ADR probability scale of 6 (probable) and managed with supportive fluid and electrolyte replacement.[9]

During the first week, the patient's symptoms remained unchanged, despite reduced lithium levels. She developed hypertension 170/90mmHg, ongoing headache and had two falls. Metoprolol was titrated to maintain her blood pressure at 120/80mmHg, and then ceased when her renal function improved. Her mood was managed with sodium valproate and quetiapine.

On the second week her nausea and tremor improved though fatigue, ataxia, severe headache and mild photosensitivity persisted into the third week of admission. Follow-up on the eighth week revealed persistence of the severe ataxia, headache and blurred vision.

DISCUSSION

Nausea, vomiting and diarrhoea, are common side effects of lithium at therapeutic and toxic doses. It has a narrow therapeutic index with the potential to cause a wide range of symptoms including renal dysfunction, neurological dysfunction, gastrointestinal symptoms, cardiac manifestations and endocrine derangements. Lithium's most commonly encountered side effect is nephrogenic diabetes insipidus. This occurs by reducing the ability of the kidney to concentrate urine by 15%, resulting in polydipsia and polyuria.[6] In addition, further renal dysfunction can occur through the induction of tubule-interstitial nephropathy.[5] Cardiotoxicity may manifest itself clinically during overdoses as atrial fibrillation and ventricular (non-sustained ventricular tachycardia) or as non-specific electrocardiogram changes such as T-wave flattening, prolonged QT intervals, sinus node dysfunction, ventricular tachycardia and ventricular fibrillation.[10] At therapeutic doses, 25% of patients have thyroid and parathyroid derangements that may not fully recover after lithium cession.[6] Additionally, when compared to those not on lithium, there is a six-fold increase rate in hypothyroidism, 10% absolute risk of

primary hyperparathyroidism. These hormonal changes can also cause cardiac dysfunction. Other common side effects include alopecia, sexual dysfunction, and weight gain (due to insulin derangements).[11] Interestingly, although there was mild elevation of thyroid-stimulating hormone (TSH) in the initial assessment, there was no other significant endocrine toxicity noted in this patient. The reported increase in TSH and nephrogenic diabetes insipidus in patients with lithium toxicity reflect the drug's ability to alter intracellular signalling mechanisms of vasopressin and TSH receptor, respectively.[12] The patient involved in this study, displayed persistent neurological symptoms, most notably cerebellar dysfunction, despite normalisation of serum lithium levels within the first week of ceasing the medication during admission as shown in Table 1. This highlights the idea that neurological symptoms likely arise from long-lasting accumulation of lithium within the brain's parenchyma, neuronal cell loss and gliosis, or a combination of both lithium accumulation and persistent cellular changes. Importantly, such changes may occur with various causes of dehydration, in the elderly, or patients with pharmacokinetics and pharmacodynamics.

Because there is a poor correlation between lithium serum concentrations and the severity of clinical toxicity, treatment should be guided both by clinical signs and lithium serum levels rather than serum levels alone.[13] Treatment of lithium toxicity involves the use of IV normal saline, forced diuresis (concomitant infusion with sodium chloride 0.9% and frusemide), haemodialysis, and whole bowel irrigation with polyethylene glycol solution (especially for sustained-release lithium formulations).[5] Concomitant medications to avoid include tricyclic antidepressants, those that decrease the glomerular filtration rate, nonsteroidal anti-inflammatory drugs, renin-angiotensin converting-enzyme inhibitors and diuretics.[8] Intensive care unit admission with intubation may also be required during times that clinically suggest an impending central nervous system failure such as impaired consciousness, seizures and coma.[14]

CONCLUSION

The patient developed long-standing treatment-resistant neurotoxicity due to chronic lithium toxicity despite being maintained at therapeutic doses. Hence, we recommend regular monitoring of renal function, lithium serum levels and neuro-endocrine function in patients on lithium. Using this drug in patients who are not able to engage in regular monitoring should be avoided as the risk may outweigh the benefit.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trialls. Am J Psychiatry. 2004;161:2:217-22.
2. Geddes JR, Goodwin G, Rendell J, Azorin JM, Cipriani A, Ostacher M, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010;375:385-95.
3. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry. 2005;162:10:1805-19.
4. Malhi GS, Tanious M, Das P, Coulston CM, Berk M. Potential Mechanisms of Action of Lithium in Bipolar Disorder. CNS Drugs. 2013;27:2:135.
5. Baird-Gunning J, Lea-Henry T, Hoegberg LCG, Gosselin S, Roberts DM. Lithium poisoning. J Intensive Care Med. 2017;32:249-63.
6. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379:721-8.
7. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. The Lancet. 2015;386:9992:461-8.
8. Ott M, Bernd S, Ellinor SR, Ursula W. Lithium intoxication: incidence, clinical course and renal function- a population-based retrospective cohort study. J Psychopharmacol 2016;30:1008-19.
9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:2:239-45.
10. Menegueti MG, Basile-Filho A, Martins-Filho OA, Auxiliadora-Martins M. Severe arrhythmia after lithium intoxication in a patient with bipolar disorder admitted to the intensive care unit. Indian J Crit Care Med. 2012;16:109-11.
11. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord 2016;4:27.
12. Livingstone C, Rampes H. Lithium: a review of its metabolic adverse effects. J Psychopharmacol 2006;20:3:347-55.
13. Vermeire S, Vanbrabant P, Van Boxstael P, Sabbe M. Severity (and treatment) ofchronic lithium poisoning: clinical signs or lab results as a criterion? Acta Clinica Belgica. 2010;65:2:27-8.
14. Zaworski J, Delannoy PY, Boussekey N, Thellier D, Georges H, Leroy O. Lithium. one drug, five complications. J Intensive Care 2017;5:1:70.

Cite this article as: Kanellis VG, Varendran R, Accidental chronic lithium toxicity. Int J Basic Clin Pharmacol 2018;7:2456-8.