Clinical Management Issues

45

INTRODUCTION

Lithium is the most effective long-term therapy for bipolar and schizoaffective disorders. Despite its efficacy, lithium has a narrow therapeutic index and adverse effects are frequent. Lithium intoxication (LI) generally affects brain, but less frequently can affect kidneys, thyroid, and parathyroid. Here, we report the case of a patient with lithium neurotoxic effects complicated by parathyroid and renal adverse effects. The patient was a 52-year-old woman treated with lithium, who was recently diagnosed with hypercalcemia and hyperparathyroidism. She was admitted for severe agitation, confusion, and diffuse tremor. Despite serum lithium and calcium normalization, laboratory tests revealed a life-threatening hypernatremia caused by nephrogenic diabetes insipidus (NDI). Hemodialysis was started, but after the first treatment the patient died for cardiac arrest. Neurological symptoms of LI may occur even if the dosage is close to the normal therapeutic range. Hypercalcemia and NDI are rare, but should be promptly diagnosed and treated. In case of poor clinical outcome, hemodialysis should be performed independently of lithium serum level.

Keywords: Lithium Toxicity; Hypercalcemia; Nephrogenic Diabetes Insipidus; Hypernatremia

CMI 2020; 14(1): 45–49
http://dx.doi.org/10.7175/cmi.v14i1.1461

Why Do We Describe This Case

Lithium is an effective medication but has a narrow therapeutic index and, thus, toxicity is frequent. Intoxication commonly involves central nervous system, but less frequently can cause rare and life-threatening adverse effects such as hypercalcemia and nephrogenic diabetes insipidus. These adverse effects should be promptly recognized and treated.

Abstract

Lithium is the most effective therapy for bipolar and schizoaffective disorders. Despite its efficacy, lithium has a narrow therapeutic index and adverse effects are frequent. Lithium intoxication (LI) generally affects brain, but less frequently can affect kidneys, thyroid, and parathyroid. Here, we report the case of a patient with lithium neurotoxic effects complicated by parathyroid and renal adverse effects. The patient was a 52-year-old woman treated with lithium, who was recently diagnosed with hypercalcemia and hyperparathyroidism. She was admitted for severe agitation, confusion, and diffuse tremor. Despite serum lithium and calcium normalization, laboratory tests revealed a life-threatening hypernatremia caused by nephrogenic diabetes insipidus (NDI). Hemodialysis was started, but after the first treatment the patient died for cardiac arrest. Neurological symptoms of LI may occur even if the dosage is close to the normal therapeutic range. Hypercalcemia and NDI are rare, but should be promptly diagnosed and treated. In case of poor clinical outcome, hemodialysis should be performed independently of lithium serum level.

Keywords: Lithium Toxicity; Hypercalcemia; Nephrogenic Diabetes Insipidus; Hypernatremia

CMI 2020; 14(1): 45–49
http://dx.doi.org/10.7175/cmi.v14i1.1461

INTRODUCTION

Lithium is the most effective long-term therapy for bipolar and schizoaffective disorder, protecting against both depression and mania and reducing the risk of suicide and short-term mortality. It is also used as add-on therapy in patients with treatment-resistant unipolar and recurrent major depression and in cluster headache prophylaxis [1]. Although its efficacy, lithium has a narrow therapeutic window and a clearance variability due to several individual and environmental factors. Therefore, lithium toxicity is frequent and routine monitoring of serum concentrations is required. Lithium intoxication (LI), whether intentional or unintentional, can be a severe occurrence carrying a significant risk for permanent sequelae, mainly neurologic, and can even lead to death. LI is categorized as:

- acute intoxication in lithium-naïve patients;
- acute-on-chronic intoxication in patients taking long-term lithium treatment; or
- chronic intoxication due to the gradual accumulation of lithium during chronic exposure [2].

Corresponding author
Arturo de Falco
arturodefalco@tin.it

Received: 7 March 2020
Accepted: 11 May 2020
Published: 30 September 2020
The effective therapeutic range of lithium is 0.6–1.0 mmol/L, but in long-term therapy levels equal or greater than 1.2 mmol/L are considered toxic. Several factors are associated with increased risk for LI:

- medications (i.e., neuroleptics, SSRIs, and amiodarone);
- dehydration;
- renal failure;
- infections;
- fever.

Further potential causes are intentional or accidental overdoses [3]. LI is associated with a variety of clinical manifestations depending on pathologic lithium accumulation in different organs including neurological, gastrointestinal, endocrine, and renal disorders. Acute LI is most often associated with gastrointestinal symptoms, cardiotoxic effects, and late developing neurological signs, whereas chronic forms are predominantly characterized by neurological symptoms including tremor, extrapyramidal and/or cerebellar signs, hyperreflexia, agitation, confusion, myoclonus, seizures, and consciousness impairment [3].

Lithium therapy is also associated with renal impairment [2,4,5]. Young women had higher hazard ratios than other groups, suggesting that they are at greatest risk of renal disorder [5]. A patient receiving lithium is at high risk of developing at least stage 3 chronic kidney disease. A subset of these patients might develop end-stage renal failure with an absolute risk of approximately 0.5–2% [4,5]. Increased serum lithium concentrations and young age in women seem to be associated with increased risk of decline in renal function [5].

Nephrogenic diabetes insipidus (NDI) is a rare adverse effect of LI: tubular cells lose their ability to respond to antidiuretic hormone (ADH). This effect is initially reversible, but can progress to structural and irreversible changes [2,6]. In this setting, the risk of hypernatremia increases and may lead to serious or even life-threatening conditions if not promptly and properly treated [7].

Antithyroid effects of lithium are well established and more evident in young women [4,5]. Multiple mechanisms are probably involved. The most important is the inhibition of thyroid hormone release from the thyroid gland. However, lithium may also decrease iodine trapping within the gland and inhibit thyroid hormones synthesis [8]. Although thyroid dysfunction is the most common endocrine adverse effect, patients receiving lithium have an absolute risk of 10% (vs. 0.1% of the general population) of developing primary hyperparathyroidism. This is probably caused by lithium inactivation of the calcium-sensing receptor leading to an increased release of parathyroid hormone, which raises calcium concentration in blood [9,10]. Moreover, in a review of 88 case reports of lithium-induced hyperparathyroidism, 42 cases were found to have parathyroid adenomas and 29 were found to have hyperplasia [9,10]. Lithium treatment is also associated with cardiac conduction abnormalities and electrocardiographic changes such as transient ST depression, bradycardia, sinus node dysfunction, and inverted T-waves in lateral precordial leads [2,11]. Lithium-treated patients who have hypercalcemia have been reported to have higher prevalence of cardiac conduction disturbances compared with lithium-treated patients with normal calcium levels [9,11].

The standard treatment strategy of lithium toxicity generally begins with cessation of lithium administration and medications that may reduce lithium elimination, hydration, and gastrointestinal decontamination. Because of its favorable pharmacokinetic parameters, the most effective treatment to remove lithium from serum is intermittent hemodialysis [12,13]. The prognosis of patients with LI varies, ranging from full recovery to long-lasting neurologic deficits. The most concerning long-term deficit or dysfunction of lithium toxicity is the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). SILENT is characterized by a broad spectrum of neuropsychiatric symptoms that follows lithium toxicity and may persist long after serum lithium normalization. Clinical features may include brainstem and/or cerebellar dysfunction, extrapyramidal features, and cognitive impairment [14]. Prognosis is worst when symptoms persist for a longer period. Recent data suggest a low mortality (less than 1%) [3].

**CASE PRESENTATION**

The patient was a 52-year-old woman admitted to the Neurology Unit for severe agitation and mental confusion. She had a history of schizoaffective disorder and was on chronic treatment with lithium carbonate 300 mg bid, olanzapine 10 mg qd, and clonazepam 0.5 mg qd during the last 2 years. Moreover, she had a history of hypertension and dyslipidemia. Hyperparathyroid-
intake of glucose 5% solutions and free water by naso-gastric tube, laboratory tests showed a progressive rise of Na\(^+\) up to 184 mmol/L and an acute renal failure with increased serum creatinine and blood urea nitrogen (Table I). Urine specific weight was low. Ultrasound showed slight reduced kidney dimension and parenchyma hyperechogenicity. Diagnosis of nephrogenic diabetes insipidus (NDI) was made and hemodialysis was started. After the first treatment, Na\(^+\) serum level decreased to 164 mmol/L without clinical improvement and patient died the day after for cardiac arrest.

**DISCUSSION**

Lithium is the first-line therapy for bipolar disorder and is also widely used in refractory depression and in cluster headache prevention. Lithium has a narrow therapeutic index and toxicity is frequent in patients taking this agent [1,2,4,5]. Long-term lithium use may lead to episodes of intoxication, that represent a considerable risk for long-term morbidity and even mortality. In our patient, who was on long-

| Parameter          | At admission | 3 days after admission | 7 days after admission | Normal range |
|--------------------|--------------|------------------------|------------------------|--------------|
| Lithium (mmol/L)   | 1.3          | 0.8                    | -                      | 0.6-1.2      |
| Calcium (mg/dL)    | 11.9         | 9.4                    | -                      | 8.6-10.2     |
| Creatinine (mg/dL) | 1.33         | 1.97                   | 2.49                   | 0.57-1.11    |
| BUN (mg/dL)        | 45           | 89                     | 145                    | 10-50        |
| Sodium (mmol/L)    | 138          | 173                    | 184                    | 136-145      |
| PTH (pg/mL)        | 427          | -                      | -                      | 12-75        |
| Calcitonin (pg/mL) | 4            | -                      | -                      | 0-10         |
| USG (n)            | -            | 1004                   | -                      | 1005-1035    |
| Potassium (mmol/L) | -            | -                      | 4.5                    | 3.5-5.1      |

**Table I. Laboratory findings at admission, 3, and 7 days after the admission**

BUN = Blood Urea Nitrogen; PTH = Parathyroid hormone; USG = Urine Specific Gravity

---

**What should the clinician ask him/herself or the patient?**

- **Is the patient in therapy with neuroleptics, selective serotonin reuptake inhibitors (SSRIs), or amiodarone?**
- **Has the patient a history of thyroid or parathyroid dysfunction?**
- **Has the patient a history of renal failure?**
- **Does the patient report a recent condition of dehydration, such as fever or diarrhea?**
- **Are the clinical features attributable to central nervous system lithium intoxication, hypercalcemia, or hypernatremia?**
- **Is hemodialysis indicated for lithium intoxication?**
- **When should hemodialysis be started?**
Hypercalcemia and Nephrogenic Diabetes Insipidus: Rare and Life-Threatening Effects of Lithium Intoxication

In patient with LI, clinicians should recognize common neurotoxic symptoms, but also rare and life-threatening adverse effects such as hypercalcemia and NDI. The serum lithium concentrations should be only a guide to avoid toxicity and should always be considered in the context of patient history and clinical findings. Therefore, any patient suspected of LI requires immediate and appropriate care. In most cases, renal failure, hypernatremia, and hypercalcemia can be safely managed without needing intensive care. Hemodialysis is indicated for lithium serum level > 4 mmol/L, but, in case of severe adverse effects or poor clinical outcome, it should be promptly performed regardless of lithium serum level. In conclusion, recommendations for the safe use of lithium include correct patient selection and periodic laboratory and clinical monitoring. This may contribute to prevent the potentially harmful intoxication of this effective and widespread medication.

CONCLUSIONS

In patient with LI, clinicians should recognize common neurotoxic symptoms, but also rare and life-threatening adverse effects such as hypercalcemia and NDI. The serum lithium concentrations should be only a guide to avoid toxicity and should always be considered in the context of patient history and clinical findings. Therefore, any patient suspected of LI requires immediate and appropriate care. In most cases, renal failure, hypernatremia, and hypercalcemia can be safely managed without needing intensive care. Hemodialysis is indicated for lithium serum level > 4 mmol/L, but, in case of severe adverse effects or poor clinical outcome, it should be promptly performed regardless of lithium serum level. In conclusion, recommendations for the safe use of lithium include correct patient selection and periodic laboratory and clinical monitoring. This may contribute to prevent the potentially harmful intoxication of this effective and widespread medication.
Consent to publication
The consent to publication was obtained from a relative of the patient here described.

Funding
No funding has been obtained for this article.

Conflicts of Interests
The authors declare that they have no conflicts of interests concerning the topics of this article.

REFERENCES

1. Oruch M, Elderbi MA, Khattab HA, et al. Lithium: a review of pharmacology, clinical uses, and toxicity. *Eur J Pharmacol* 2014; 740: 464-73; https://doi.org/10.1016/j.ejphar.2014.06.042

2. Ott M, Stegmayr B, Salander Renberg E, et al. Lithium intoxication: Incidence, clinical course and renal function – a population-based retrospective cohort study. *J Psychopharmacol* 2016; 30: 1008-19; https://doi.org/10.1177/0269881116652577

3. Baird-Gunning J, Lea-Henry T, Hoegberg LCG, et al. Lithium Poisoning. *J Intensive Care Med* 2017; 32: 249-63; https://doi.org/10.1177/0885066616651582

4. McKnight RF, Adida M, Budge K, et al. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* 2012; 379: 721-8; https://doi.org/10.1016/S0140-6736(11)61516-X

5. Shine B, McKnight RF, Leaver L, et al. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet* 2015; 386: 461-8; https://doi.org/10.1016/S0140-6736(14)61842-0

6. Erden A, Karagöz H, Başak M, et al. Lithium intoxication and nephrogenic diabetes insipidus: a case report and review of literature. *Int J Gen Med* 2013; 6: 535-9; https://doi.org/10.2147/IJGM.S46383

7. Ott M, Forssen B, Werneke U. Lithium treatment, nephrogenic diabetes insipidus and the risk of hypernatraemia: a retrospective cohort study. *Ther Adv Psychopharmacol* 2019; 9: 2045125319836563; https://doi.org/10.1177/2045125319836563

8. Lazarus JH. Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 723-33; https://doi.org/10.1016/j.beem.2009.06.002

9. Lehmann SW, Lee J. Lithium-associated hypercalcemia and hyperparathyroidism in the elderly: what do we know? *J Affect Disord* 2013; 146: 151-7; https://doi.org/10.1016/j.jad.2012.08.028

10. Shapiro HI, Davis KA. Hypercalcemia and “primary” hyperparathyroidism during lithium therapy. *Am J Psychiatry* 2015; 172: 12-5; https://doi.org/10.1176/appi.ajp.2013.13081057

11. Kayrak M, Duman C, Gul EE, et al. A bizarre electrocardiographic pattern due to chronic lithium therapy. *Ann Noninvasive Electrocardiol* 2010; 15: 289-92; https://doi.org/10.1111/j.1542-474X.2010.00366.x

12. Haussmann R, Bauer M, von Bonin S, et al. Treatment of lithium intoxication: facing the need for evidence. *Int J Bipolar Disord* 2015; 3: 23; https://doi.org/10.1186/s40345-015-0040-2

13. Decker BS, Goldfarb DS, Dargan PI, et al. Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. *Clin J Am Soc Nephrol* 2015; 10: 875-87; https://doi.org/10.2215/CJN.10021014

14. Adityanjee, Munshi KR, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005; 28: 38-49; https://doi.org/10.1097/01.wnf.0000150871.52253.b7