Chronic lithium toxicity

Considerations and systems analysis

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Lithium has been a cornerstone of the treatment of bipolar disorder for decades and remains a first-line agent in Canadian guidelines.[1] Other indications for lithium include acute mania and prevention of manic episodes, and it is used as an adjunct for refractory depression.[2] Lithium has a narrow therapeutic index. Minor changes in serum lithium concentration (SLC) can result in either subtherapeutic or toxic effects. Serum lithium concentration is influenced by treatment adherence, drug interactions, age, and comorbid conditions.[3-7]

We present a case of unintended lithium toxicity, provide current monitoring and toxicity treatment recommendations, and offer a systems analysis approach to reducing the risk of chronic toxicity events. We searched the MEDLINE, EMBASE, and International Pharmaceutical Abstracts databases using the key words *lithium* and *toxicity*, limiting the search to English-language studies of oral formulations in adults. In the presented case, subacute diarrhea and emesis resulted in an acute episode of renal impairment and subsequent reduced lithium excretion.

Case

Emergency medical services brought a 58-year-old woman to the hospital who was confused and unable to follow instructions. She was experiencing tremors, ankle clonus, hyperreflexia, diarrhea, and emesis. Vital signs included a blood pressure of 115/50 mm Hg and a pulse rate of 35 beats/min. Laboratory investigations revealed an SLC of 4.19 mmol/L drawn approximately 16 hours after her last dose (chronic therapy reference range is 0.60 to 1.20 mmol/L),[8] a potassium level of 3.3 mmol/L, and a serum creatinine level of 175 µmol/L. The patient received normal saline supplemented with

Editor's key points

- Unintended lithium toxicity can occur in patients, especially in the elderly, owing to its narrow therapeutic window and numerous drug interactions. Serum lithium concentration should be monitored after initiation of the medication or a change in dosage, and regularly during long-term stable therapy.
- Long-term lithium use increases the risk of nephrogenic diabetes insipidus, which causes loss of renal urine-concentrating ability and increased risk of lithium intoxication. Lithium should be discontinued in patients who develop diabetes insipidus and renal toxicity.
- Despite treatment after lithium toxicity, some patients might experience persistent symptoms, including SILENT (syndrome of irreversible lithium-effectuated neurotoxicity), which manifests as cognitive impairment, sensorimotor peripheral neuropathy, and cerebellar dysfunction.
- A systems review of care structures and processes can reduce the risk of lithium-related morbidity. An analysis of system design, relationships among structures, processes, and outcomes with a no-blame approach can help address problems related to patient safety.

Points de repère du rédacteur

- L'intoxication involontaire au lithium peut se produire chez les patients, surtout les aînés, en raison de son étroite fenêtre thérapeutique et de ses nombreuses interactions médicamenteuses. La concentration de lithium sérique devrait être surveillée après le début de la médication ou un changement dans la dose, de même que régulièrement durant une thérapie stable à long terme.
- Une utilisation à long terme de lithium augmente le risque de diabète insipide néphrogénique, ce qui cause une incapacité rénale de concentrer l'urine et augmente le risque d'une intoxication au lithium. Il faut discontinuer le lithium chez les patients qui développent un diabète insipide et une toxicité rénale.
- En dépit des traitements après une intoxication au lithium, certains patients peuvent avoir des symptômes persistants, y compris le syndrome de neurotoxicité irréversible induite par le lithium (SILENT, selon son acronyme anglais), qui se manifeste sous forme de déficience cognitive, de neuropathie sensorimotrice périphérique et de dysfonction cérébelleuse.
- Un examen systémique des structures et des processus de soins peut réduire le risque de morbidité liée au lithium. Une analyse de la conception du système, des relations entre les structures, des processus et des issues en adoptant une approche dénuée de blâme peut aider à régler les problèmes relatifs à la sécurité des patients.

atropine and 40 mmol/L of potassium chloride. Ten hours later her SLC was 3.83 mmol/L, her potassium level was 2.8 mmol/L, and her serum creatinine level was 141 µmol/L. After hemodialysis, her SLC was 1.53 mmol/L, potassium level was 4.7 mmol/L, and serum creatinine level was 53 µmol/L. Her medications on admission were 900 mg of lithium (immediate release) daily, 100 mg of quetiapine twice daily plus 50 mg at bedtime, 900 mg of gabapentin daily, and 1 mg of clonazepam as needed. Toxicity management included volume replacement for dehydration. In addition, the patient met EXTRIP (Extracorporeal Treatments in Poisoning) criteria for hemodialysis and underwent a single course of hemodialysis. At discharge, the patient was experiencing ongoing neurologic symptoms that might have been pre-existing but were suggestive of SILENT (syndrome of irreversible lithium-effectuated neurotoxicity).

Monitoring considerations

Lithium concentrations are influenced by a number of factors.

- Guidelines suggest SLC should be checked 3 to 5 days after lithium initiation or after a change in dosage and every 3 to 6 months in patients on stable therapy.[1]
- Blood should ideally be drawn at least 12 hours after the previous dose to allow for distribution.[1,6]
- Longitudinal monitoring for patients taking lithium should include electrolyte, urea, and creatinine levels every 3 to 6 months and calcium levels, thyroid-stimulating hormone levels, and weight every 6 to 12 months.[1,6,7]
- A negative anion gap might be observed when lithium concentration is elevated.[9]
- Risk factors for lithium toxicity include age older than 50 years, abnormal thyroid function, and impaired renal function.[3-5]
- Long-term lithium use increases the risk of lithium-induced nephrogenic diabetes insipidus, which causes loss of renal urine-concentrating ability and increased risk of lithium intoxication.[4,9,10]
- Manifestations of chronic lithium toxicity are described in **Table 1**.[1,8,10,11]
- Numerous prescription and over-the-counter products can cause changes in lithium concentrations and are described in **Table 2**.[3,10-13]

Treatment considerations

In the setting of chronic lithium toxicity, sodium polystyrene sulfonate has limited application[14] and there is no role for whole-bowel irrigation. Enhanced elimination strategies include optimizing renal clearance and dialysis. The EXTRIP workgroup recommends dialysis in the following cases[15]:

- if kidney function is impaired and SLC is greater than 4.0 mmol/L; and
- in the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of lithium concentration.

Following lithium poisoning, a small proportion of patients with neurotoxicity have an incomplete recovery and are at risk of developing SILENT. This manifests as cognitive impairment, sensorimotor peripheral neuropathy, and cerebellar dysfunction. Currently, little is known about the syndrome, including cause, epidemiology, or risk factors.[11,16]

Discussion

Chronic lithium toxicity can occur in patients who are dependent on the medication. The risk of events such as the one described here can be minimized through modifying the systems we use to provide care. An analysis of system design, relationships among structures, processes, and outcomes with a no-blame approach can help address problems related to patient safety.[17-19]

Structures include organizational characteristics, such as individuals and their education, skills, and knowledge; how work is organized; technologies and tools used; and the environment. Considerations related to this case include the following.

Table 1. Clinical and laboratory manifestations of chronic lithium toxicity

VARIABLE	MANIFESTATION
Laboratory value	
Serum lithium concentration	Mild toxicity: 1.5 to 2.5 mmol/L Moderate toxicity: > 2.5 to 3.5 mmol/L Severe toxicity: > 3.5 mmol/L
Clinical findings	
Central nervous system	Early onset of symptoms
• Mild toxicity	Weakness, light-headedness, fine tremor, nystagmus
• Moderate toxicity	Muscle twitching, fasciculation, tinnitus, drowsiness, hyperreflexia, slurred speech, apathy
• Severe toxicity	Parkinsonism, psychosis, memory deficits, pseudotumour cerebri
Renal	Nephrogenic diabetes insipidus, interstitial nephritis, renal failure
Cardiovascular	Nonspecific electrocardiography changes, Ebstein anomaly*
Gastrointestinal	Nonspecific
Dermatologic	Dermatitis, ulcers, localized edema
Endocrine	Hypothyroidism or hyperthyroidism, hyperparathyroidism
Hematologic	Aplastic anemia

*Found in infants born to those with lithium toxicity.
Data from Yatham et al,[1] Greller,[8] Grandjean and Aubry,[10] and Uldall et al.[11]

Table 2. Drug interactions

INTERACTION	DRUG OR DRUG CLASS
Pharmacokinetic	
Increase in SLC*	Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers β-blockers Cisplatin Cyclooxygenase-2 inhibitors Cyclosporine A Methyldopa Metronidazole Nonsteroidal anti-inflammatory drugs† Phenytoin Tetracycline Thiazide diuretics Verapamil
Decrease in SLC	Acetazolamide Aminophylline Theophylline Topiramate Caffeine Nifedipine Osmotic diuretics Sodium bicarbonate Bulk-forming laxatives
Pharmacodynamic	
Might worsen neurotoxicity	Antidepressants Antipsychotics Carbamazepine Diltiazem Verapamil Serotonin receptor agonists Piroxicam Phenytoin‡
Might worsen thyroid changes	Iodide salts or iodine Phenytoin Carbamazepine
Might increase polyuria	Antidepressants Phenytoin
Might contribute to sinus node dysfunction	Carbamazepine

SLC—serum lithium concentration.
*An increase in SLC can also be caused by reduced sodium intake.
†Other than acetylsalicylic acid.
‡Can cause tremor.
Data from Juurlink et al,[3] Grandjean and Aubry,[10] Uldall et al,[11] Langlois and Paquette,[12] and the American Geriatrics Society 2012 Beers Criteria Update Expert Panel.[13]

- Identify patients at risk of dehydration and support them with strategies to maintain hydration.
- Educate patients and the health care team to prevent toxicity by being aware of when it is necessary to reduce or discontinue the medication. For example, patients who develop diabetes insipidus and renal toxicity should probably discontinue lithium therapy, as it is primarily excreted by the kidneys.
- Ensure patients and health care providers are aware of medications and substances that might affect SLC.

Analysis of the practice site might include identifying technologies (eg, electronic reminders, electronic health records) that help identify, monitor, and educate patients at risk of lithium toxicity.

Work processes have a direct effect on the outcomes of care.[17] Evaluate work flow processes to understand how activities of care are currently performed. This might identify opportunities for increasing use of available tools and technologies. Information flow as a care process directly influences decision making. Considerations related to this care include the following:

- Consider how we manage communication flow to identify patients with recent hospitalizations to make decisions related to adjusting lithium doses or discontinuing the drug altogether.
- Consider how we communicate with patients to ensure regular laboratory assessment and follow-up to identify patients early who might need to discontinue lithium or reduce their doses.
- Consider how we identify patients who might be experiencing adverse effects from long-term lithium use that warrant a change in therapy.

Family practice is a system within a system and not all elements that influence patient outcomes can be managed at the community level. However, a willingness to learn about systems and how to improve them can have a meaningful effect on outcomes.

Conclusion

Unintended lithium toxicity can occur, especially in the elderly, owing to its narrow therapeutic window and numerous drug interactions. Lithium can be neurotoxic; despite treatment after lithium toxicity, some patients might experience persistent symptoms, including SILENT. A systems review of care structures and processes can reduce the risk of lithium-related morbidity.

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Competing interests
None declared

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