

Preventing lithium intoxication

Guide for physicians

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ABSTRACT

OBJECTIVE To raise awareness of risk factors for, and symptoms of, lithium intoxication.

QUALITY OF EVIDENCE The literature was searched via MEDLINE from January 1970 to December 1999 using the MeSH headings Lithium, Lithium Carbonate, Drug Toxicity, and Aging. Articles were selected based on clinical relevance and design. Most were case reports, case series, or reviews.

MAIN MESSAGE A case study illustrates both risk factors predisposing patients to lithium intoxication and the symptoms of lithium intoxication. Lithium intoxication can be avoided by conservative dosing, care in combining drug therapies, regular clinical observation, monitoring drug plasma concentrations, and educating patients and caregivers to recognize early signs of intoxication.

CONCLUSION Knowing about lithium intoxication and how to avoid it is most important for family physicians who regularly treat patients receiving lithium.

RÉSUMÉ

OBJECTIF Mieux faire connaître les facteurs de risque d'intoxication au lithium et ses symptômes.

QUALITÉ DES DONNÉES Une recension des ouvrages scientifiques a été effectuée à l'aide de MEDLINE et des rubriques MeSH en anglais pour lithium, carbonate de lithium, toxicité médicamenteuse et vieillissement. Les articles ont été choisis en fonction de leur pertinence clinique et la conception de l'étude. Il s'agissait principalement de rapports de cas, de séries de cas ou d'études.

PRINCIPAL MESSAGE Une étude de cas fait ressortir à la fois les facteurs de risque prédisposant les patients à une intoxication au lithium ainsi que les symptômes d'une telle intoxication. On peut l'éviter en administrant une dose modérée, en usant de prudence dans les pharmacothérapies concomitantes, en veillant à une observation clinique régulière, en vérifiant les concentrations du médicament dans le plasma et en éduquant les patients et les dispensateurs de soins à reconnaître les premiers signes d'une intoxication.

CONCLUSION Il importe fortement pour les médecins de famille qui traitent régulièrement des patients prenant du lithium d'être sensibilisés à l'intoxication à ce produit.

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Cet article a fait l'objet d'une évaluation externe.

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Lithium is one of the most frequently used drugs for treating mood disorders. Because lithium has a narrow therapeutic index and wide therapeutic indications,¹ intoxication continues to be an important issue in lithium therapy. Patients are put at risk of lithium intoxication, the toxicity produced by excessive doses of lithium, when they attend physicians who are unaware of potential interactions with other drugs and of comorbid disorders.

Because early symptoms are often not recognized by patients or caregivers, it is easy for mild-to-moderate lithium intoxication to remain undiagnosed. The toxic effects of lithium might not only threaten the continuation of lithium treatment, but could also irreversibly damage the brain,^{2,3} heart,⁴ and kidneys⁵ and, in some cases, be fatal.⁶

It is easy for physicians to use the therapeutic range for serum lithium concentrations provided on laboratory reports (eg, 0.7 to 1.2 mmol/L; 0.5 to 1.5 mmol/L) as the sole guideline for diagnosing lithium intoxication. Intoxication can occur, however, despite "therapeutic" serum lithium concentrations.⁷ Also, there might be no sign of intoxication when lithium concentrations are above the therapeutic range.⁸ Because lithium tolerance (based in large part on distribution and elimination of lithium) can vary widely from person to person, patients' general state should be monitored as closely as lithium levels themselves.

Patients treated with lithium are usually under the care of family physicians, whom they see regularly for primary care and who are most likely to be in a position to diagnose and prevent lithium intoxication. It is essential that these physicians be aware of conditions and drug interactions that increase the likelihood of lithium intoxication, of the importance of closely monitoring patients receiving lithium, and of signs and symptoms that characterize lithium intoxication. In this article, we present an illustrative case of lithium intoxication and outline both predisposing factors for, and clinical manifestations of, this condition.

Quality of evidence

A MEDLINE search from January 1970 to December 1999 was conducted using the MeSH headings Lithium, Lithium Carbonate, Drug Toxicity, and Aging. The

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search was limited to English-language articles. Bibliographies of these articles were used to identify additional useful papers. Even though the issue of lithium intoxication has frequently been reviewed, intoxication is common, and there is a need to increase awareness and continue to educate doctors and patients about lithium. Articles reviewed were mainly case reports and case series, retrospective studies, and review articles. Few randomized trials were available. To our knowledge, no studies of the effects of education campaigns on the incidence of lithium intoxication have been published.

Case report

A 66-year-old woman hospitalized for treatment of bipolar disorder was prescribed lithium. Her medical problems included chronic renal insufficiency, diabetes, chronic obstructive lung disease, and hypothyroidism. Before and while receiving lithium, she also took haloperidol, carbamazepine, benzodiazepines, enalapril, and thyroxine. Before starting lithium treatment, she had a first-degree atrioventricular (AV) block but a normal sinus rhythm (**Figure 1**).

After 7 days of treatment with 300 mg/d of lithium carbonate, her serum lithium level was 0.47 mmol/L 16 hours after the last dose. An electrocardiograph (ECG) taken on the previous day indicated she had an incomplete right bundle branch block but maintained a normal sinus rhythm (ECG 2, 71 beats per minute [bpm]). On day 8, the dose was increased to 300 mg twice daily, and on day 13 her serum lithium level was 1.14 mmol/L 15 hours after the last dose. The dose was then decreased to 450 mg/d, and on day 15, she had sinus bradycardia in addition to first-degree AV block (ECG 3, 48 bpm). On day 16, she received a final 450-mg dose of lithium and 40 hours later her serum lithium level was 1.4 mmol/L. A junctional rhythm with a prolonged QT interval developed (ECG 4, 31 bpm) on day 18, and she was drowsy, tremulous, diaphoretic, and hypotensive, and had several syncopal episodes. Cardiac conduction disturbances and other symptoms diminished over the next few days (ECG 5, 57 bpm). A pacemaker was placed in her right ventricle and she was then treated successfully with lithium at a dose of 300 mg/d to maintain a serum level of 0.41 mmol/L.

Predisposing factors

This case illustrates some of the important factors that lead to lithium intoxication. To assess a patient's risk of developing lithium intoxication, a detailed medical history and baseline measurements of thyroid, cardiac, and renal function can provide physicians

Figure 1. Electrocardiograms (ECG) recorded before lithium treatment and on days 6, 15, 18, and 20: ECG 1 revealed first-degree atrioventricular (AV) block but normal sinus rhythm (75 beats per minute [bpm]); ECG 2 (71 bpm) indicated incomplete right bundle branch block and possible left atrial enlargement; ECG 3 (48 bpm) showed a sinus bradycardia in addition to first-degree AV block; ECG 4 (31 bpm) showed development of a junctional rhythm with a prolonged QT interval; ECG 5 (57 bpm) showed improvement in cardiac function after discontinuation of lithium treatment.



with much of the information they need to identify factors, such as advanced age, comorbid diseases, and concurrent drug therapy, that lower lithium tolerance (Table 1⁹⁻¹¹).

Because the clinical indications for lithium therapy continue to broaden and as the population ages, clinicians will encounter more older patients either commencing or continuing lithium therapy. It is now generally accepted that elderly patients do not tolerate lithium as well as younger patients and can develop serious adverse effects more rapidly while taking lower doses or at lower serum levels.¹²⁻¹⁵ Elderly people are at a greater risk of intoxication for two reasons: normal age-related decreases in general brain,¹⁶⁻¹⁸ cardiac,^{19,20} and renal²¹⁻²³ function; and an increased prevalence of disease.

Physiologic and electrochemical changes. Histologic changes in the kidneys, for example, correlate with age and are associated with decreased glomerular filtration rate, which results in reduced renal clearance of lithium.^{21,22} Physiologic and

electrochemical changes in the heart that lead to cell loss in the conductive tissue also occur with age, predisposing elderly people to conductive disorders²⁴

Table 1. Predisposing factors for lithium intoxication

History of lithium intoxication

Advanced age

Overdose

Diet or gastrointestinal disturbances: anorexia, diarrhea, vomiting, decreased dietary sodium intake, dehydration

Comorbid medical conditions: heart disease, hypertension, atherosclerosis, renal damage, renal insufficiency or renal failure, brain disorders, hypothyroidism

Drug therapies: angiotensin-converting enzyme inhibitors, diuretics, nonsteroidal anti-inflammatory drugs, neuroleptics, antiepileptics, calcium antagonists

Adapted from Groleau,⁹ Okusa and Crystal,¹⁰ and Timmer and Sands.¹¹

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Table 2. Guidelines for monitoring lithium carbonate

TEST	BASLINE	STABILIZATION	MAINTENANCE EVERY 3-12 MONTHS
Complete blood count	✓		✓
Electrolytes (sodium and potassium)	✓		✓
Thyroid-stimulating hormone	✓		✓
Creatinine	✓		✓
Urinalysis	✓		✓
Pregnancy test*	✓	Contraception recommended	Contraception recommended
Electrocardiogram if ≥ 40 years†	✓	As clinically indicated	As clinically indicated
Lithium level‡		5 days after dose change and 1 month later	Every 3 months

*Lithium is a teratogen. Vitamin K and folic acid supplements are believed to substantially reduce risk of teratogenicity.⁴²

†Electrocardiographic testing can vary from a single follow-up test to regular monitoring for patients with heart disease.

‡Special circumstances can alter the relationship between dose and blood level: medical illness especially with diarrhea, vomiting, or anorexia; advanced age; strenuous exercise; pregnancy and delivery; very hot climate; crash dieting; and surgery.

and increased vulnerability to lithium's toxic effects on the heart. Also, as people age, neurodegeneration and neurochemical and neurophysiologic changes occur in the brain that can sensitize it to lithium and lead to neurotoxicity at lower doses.^{16,25}

Comorbid diseases. Older patients are also more at risk of developing lithium intoxication because they have more comorbid medical conditions. Diseases of the heart,²⁶ kidneys,^{5,23} and brain⁷ place patients at increased risk of developing lithium intoxication in these organs. Because renal mechanisms are the only means of eliminating lithium, any impairment of renal function increases the risk of lithium intoxication.^{27,28} Conditions including atherosclerosis, hypertension, heart failure, or even prior intoxication^{22,23} can adversely affect renal function²⁹ and reduce clearance of lithium. Heart disease (and diseases affecting heart function, such as hypothyroidism^{30,31}) and brain disorders (eg, tardive dyskinesia,³² epilepsy,³³ Parkinson's disease,³² dementia,^{15,34} schizophrenia,³⁵ and stroke³⁶) lower the threshold for cardiotoxicity and neurotoxicity. Lithium often exacerbates current cardiac, renal, and neurologic disturbances. Our patient's renal insufficiency reduced her clearance of lithium and increased her vulnerability, as evidenced by a first-degree AV block, to lithium-induced cardiotoxicity.

Concurrent medications. Patients treated with lithium are often concurrently treated with other medications. Drug interactions can raise the risk of lithium intoxication. Concomitant drug therapies that inter-

fere with elimination of lithium increase the risk of intoxication. Diuretics, some neuroleptics, some anticonvulsants (eg, carbamazepine), angiotensin-converting enzyme inhibitors, and many nonsteroidal anti-inflammatory drugs (NSAIDs) interact with and can cause toxicity if administered with lithium.³⁷ Acetylsalicylic acid and sulindac might be safer than other NSAIDs,³⁷ but caution is still warranted. Carbamazepine, a potentially cardiotoxic drug, might have contributed to our patient's cardiotoxicity.³⁸⁻⁴¹

Predisposing factors should not inhibit use of lithium for at-risk patients. With caution, these patients can be treated safely and effectively with lithium. Patients should not, of course, be treated with lithium if intoxication is unavoidable. Physicians sometimes make the mistake of giving patients with reduced lithium tolerance a high starting dose. To avoid intoxication, elderly people should be started on low doses, especially if they have comorbid conditions affecting brain, heart, or kidneys and if they are receiving drug therapies that increase risk of intoxication.

Our patient's dose of lithium was increased excessively rapidly. If lithium is well tolerated, dosage can be increased gradually while patients are closely monitored for signs of intoxication. Lithium concentrations must be measured about 12 hours after the last dose because therapeutic ranges for lithium were developed using this interval.

When treating elderly and at-risk patients, physicians should not rely on the therapeutic range as the sole indicator of intoxication. As our case demon-

strates, a high serum lithium concentration might not be observed until intoxication is well established. Monitoring for signs and symptoms of intoxication is most important. Guidelines developed by the Pharmacy and Therapeutics Committee at the Kingston Psychiatric Hospital for monitoring lithium patients are presented in **Table 2**⁴². As a final precaution against intoxication, physicians and pharmacists should educate both patients and their caregivers about potential risk factors for intoxication (eg, diet, over-the-counter NSAIDs) and about its early signs and symptoms.

Symptoms of lithium intoxication

Our patient's lithium intoxication developed fairly rapidly, manifesting itself as a cardiac conduction disturbance. Lithium poisoning often occurs more gradually, sometimes after years of treatment, with symptoms that are wide ranging and that often masquerade as physical illnesses seemingly unrelated to lithium therapy and mood disorder. Lithium intoxication can manifest as neurotoxicity, cardiotoxicity, or nephrotoxicity (**Table 3**⁹⁻¹¹). Gastrointestinal side effects frequently occur during commencement of therapy and might or might not occur with lithium intoxication.

Neurologic manifestations of toxicity are diverse and appear to be the most frequent. Early lithium neurotoxicity can be accompanied by nonspecific neurologic and psychologic symptoms, such as decreased alertness, weakness, slurred speech, tremor,

Table 3. Symptoms of lithium intoxication

GASTROINTESTINAL

Vomiting, diarrhea

RENAL

Renal insufficiency, polyuria, polydipsia, acute renal failure

CARDIOVASCULAR

Syncope, dizziness, worsening of cardiac function, bradycardia, sick sinus syndrome, atrial or ventricular arrhythmias, sinoatrial block, atrioventricular block, junctional rhythms, bundle branch block, ventricular tachycardia, ventricular fibrillation, myocarditis, death

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

Drowsiness, fatigue, apathy, lethargy, altered state of consciousness (confusion, delirium, coma), cerebellar symptoms (ataxia, dysarthria, unsteady gait, lack of coordination), seizures, coarse tremors, hyperreflexia, nystagmus, muscle fasciculation, death

Adapted from Groleau,⁹ Okusa and Crystal,¹⁰ and Timmer and Sands.¹¹

Editor's key points

- Lithium intoxication, especially mild to moderate intoxication, is more common than most family physicians realize.
- Lithium intoxication can occur even at concentrations within the published therapeutic range.
- In addition to monitoring levels of lithium in patients' blood, physicians should also monitor cardiac, renal, thyroid, and overall status. Predisposing factors, such as advanced age, comorbid conditions, and concurrent medications, should be taken into account.
- Signs and symptoms of lithium toxicity include vomiting and diarrhea, deteriorating renal function, cardiac arrhythmias, and central and peripheral nervous system changes.

Points de repère du rédacteur

- L'intoxication au lithium, en particulier de faible à modérée, est beaucoup plus fréquente que la plupart des médecins de famille peuvent s'imaginer.
- L'intoxication au lithium peut se produire même à des concentrations qui se situent dans les normes thérapeutiques acceptables publiées.
- En plus de surveiller les taux de lithium dans le sang, les médecins de famille devraient aussi examiner l'état général des patients, la fonction cardiaque, rénale et thyroïdienne. Les facteurs de prédisposition comme l'âge avancé, la comorbidité et une médication concomitante devraient être pris en compte.
- Au nombre des signes et des symptômes de l'intoxication au lithium figurent les vomissements et la diarrhée, une détérioration de la fonction rénale, une arythmie cardiaque et des modifications au système nerveux central et périphérique.

restlessness, apathy, and muscular rigidity and fasciculation.^{9,43} Early indicators of cardiotoxicity include dizziness and syncope,⁴⁴ changes in cardiac function,⁹ or general worsening of cardiac symptoms.⁴⁵ Nephrotoxicity can manifest as impairment of urinary concentrating ability and polyuria or polydipsia.⁴⁶ Even subtle changes in mental status or central nervous system, cardiac, or renal functioning should be investigated to identify or rule out lithium intoxication.

Symptoms of early toxicity might gradually worsen into severe intoxication. In severe neurotoxicity, confusion worsens into stupor; tremor can become more severe; spontaneous or latent twitching movements of the limbs, body, and head can appear; and seizures and coma sometimes develop.⁴³ Worsening cardiotoxicity can manifest itself as bradycardia,⁴⁷ sick sinus syndrome,⁴⁵ ventricular and atrial arrhythmias,^{13,44} bundle branch block, or myocarditis.⁴⁸ Severe cardiotoxicity can result in death or necessitate cardiac pacing.

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Severe nephrotoxicity presents as renal insufficiency or renal failure^{9,46} and can result in renal damage or even death. As soon as symptoms of intoxication appear, lithium should be reduced or discontinued. If intoxication is severe, steps should be taken to expedite clearance of lithium.^{8,10,11,49,50}

Conclusion

Identification of patients at risk and prescription of appropriate doses of lithium will help avoid intoxication, but physicians should remember that intoxication can occur in the apparent absence of predisposing conditions. All patients treated with lithium should be monitored regularly for signs of intoxication. Lithium intoxication is a common problem, and physicians need to be aware of its manifestations and risk factors in order to prevent as many cases as possible. ❁

Competing interests

None declared

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