A Large Lithium Overdose with Unusual Pharmacokinetics

Justin B Senecal, BMSc MD¹, Zaki Alhashimalsayed, MD¹, Mitchell Levine, MD MSc FRCPC FACP FISPE FCAHS²

¹Internal Medicine Residency Program, McMaster University, Hamilton, Canada; ²Faculty of Health Sciences, McMaster University, Hamilton, Canada

Corresponding author: Justin B Senecal: justin.senecal@medportal.ca

Submitted: 31 May 2023; Accepted: 10 July 2023; Published: 16 September 2023

DOI: https://doi.org/10.22374/cjgim.v18i3.705

Abstract
Lithium has been used in psychiatry for 50 years and remains a first-line option for bipolar depression and mania. Approximately 7% of patients on lithium will develop toxicity at some point during their treatment. This can often be managed with isotonic crystalloid to promote excretion in the urine, but some patients will require hemodialysis. Here we present the case of a 66-year-old female who presented after ingesting 12 grams of immediate-release lithium. Twenty-eight hours after ingestion, her serum lithium began to rise despite adequate urine output and normal renal function. We hypothesized that this was due to delayed absorption from a pharmacobezoar formation, resulting in pharmacokinetics that mimics what was previously described to occur with sustained release formulations. This case exemplifies the importance of monitoring pharmacokinetic parameters in overdoses, as this can bring attention to issues of prolonged absorption. This has the potential to impact clinical decisions regarding hemodialysis or bowel decontamination.

Résumé
Le lithium est utilisé dans le domaine de la psychiatrie depuis 50 ans et demeure une option de première intention contre la dépression et la manie bipolaires. Environ 7 % des patients traités par le lithium manifesteront des effets toxiques à un moment ou à un autre de leur traitement. Souvent, cette intoxication est traitable par l’administration de cristalloïdes isotoniques pour favoriser l’excrétion dans l’urine, mais certains patients devront avoir recours à l’hémodialyse. Le présent article expose le cas d’une femme de 66 ans admise après avoir ingéré 12 grammes de lithium à libération immédiate. Vingt-huit heures après l’ingestion du médicament, le taux sérique de lithium a commencé à augmenter malgré une diurèse suffisante et une fonction rénale normale. Nous avons émis l’hypothèse que cette situation était attribuable à une absorption retardée par la formation d’un pharmacobézoard, entraînant une pharmacocinétique qui reproduit ce qui a déjà été décrit dans le cas des préparations à libération prolongée. Ce cas illustre l’importance de surveiller les paramètres pharmacocinétiques dans les cas de surdosage, car cela peut attirer l’attention sur des problèmes liés à une absorption prolongée. Cela pourrait avoir des répercussions sur les décisions cliniques concernant l’hémodialyse ou la décontamination intestinale.

Keywords: Lithium, Overdose, Pharmacokinetics, Pharmacobezoar
Introduction

First prescribed in the mid-19th century, lithium has been a common treatment for bipolar mania for the last 50 years.\textsuperscript{1} It remains an option for first-line therapy in both bipolar depression and mania, despite a relatively poor understanding of its mechanism of action.\textsuperscript{1} It modifies sodium transport and, in doing so, is theorized to alter neurotransmitter transport and change intracellular signally through secondary messengers.\textsuperscript{2} It is well absorbed from the GI tract, distributed rapidly with a low volume of distribution, and then excreted exclusively in the urine. It has a plasma half-life of 18–36 hours.\textsuperscript{2}

In 2020, more than 6200 cases of lithium overdoses were referred to American Poison Control center.\textsuperscript{3} Approximately 7\% of patients on chronic lithium will have a toxic level at least once while using this medication.\textsuperscript{4}

Predominantly gastrointestinal symptoms characterize acute and acute-on-chronic lithium toxicity, and neurological symptoms are delayed.\textsuperscript{5} This contrasts with chronic intoxications which present with predominantly neurological symptoms.\textsuperscript{2} The most serious neurological complication is the Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) which manifests as permanent brainstem and cerebellar dysfunction.\textsuperscript{5} To avoid this complication, toxic lithium levels are lowered aggressively by promoting excretion in the urine. Patients with lithium concentrations greater than 4–5 mmol/L, renal impairment or severe neurological impairment require dialysis to prevent persistent neurological sequelae.\textsuperscript{5,6}

Overdoses with sustained-release formulations have been reported to delay absorption unpredictably.\textsuperscript{7,8} This is proposed to be secondary to a propensity to form pharmacobezoars.\textsuperscript{7,8} This is one reason for recommending GI decontamination with polyethylene glycol in this setting.\textsuperscript{6} This case report of a lithium overdose with unusual pharmacokinetics demonstrates delayed absorption from the GI tract with an immediate-release product which has not previously been described. It suggests that GI decontamination may have a larger role than previously recommended and demonstrates the importance of assessing pharmacokinetic parameters in managing toxic ingestions.

Case

A 66-year-old Caucasian female with a history of type 1 bipolar disorder presented to the ER 17 hours after ingesting 12 g of immediate-release lithium. This was an attempted lethal overdose due to worsening delusions and auditory hallucinations that the patient had been experiencing over the previous 4 weeks. Her past medical history was notable for hypertension, anxiety, well-controlled type 2 diabetes mellitus, and chronic pain for which she intermittently used meloxicam. She was not on any renin-angiotension-aldosterone blockade or diuretics. Her baseline creatinine was between 80 and 90 umol/L (eGFR 60–70 ml/min/1.73m\textsuperscript{2}).

On presentation, the patient was hypertensive with a blood pressure of 183/103. Her vital signs were otherwise stable and her only symptom was nausea. On exam, she was noted to have bilateral intention tremors and an ataxic gait. She had received one litre of lactated ringers before assessment and appeared euvolemic. She had no signs of severe lithium toxicity such as altered mental status, rigidity, or myoclonus. Her blood work demonstrated a sodium of 136 mmol/L, an anion gap of 5 with an albumin of 41 g/L (Table 1). Her initial serum lithium level at 17 hours post ingestion was 2.05 mmol/L (Table 1). Her estimated glomerular filtration rate (eGFR) was 69 mL/min/1.73m\textsuperscript{2}, and her ECG did not show bradycardia, T wave flattening or a prolonged QTc.

A lactated ringers infusion was started at 150 cc/hr rate and a Foley catheter was inserted to measure urine output accurately. After 2 hours of this infusion, the rate was increased to 200 cc/hr to achieve a urine output of 1.5–3 cc/kg/hr. Despite adequate urine output and improvement in her creatinine clearance, the declining lithium levels temporarily plateaued at 28 hours and again at 52 hours (Figure 1).

Table 1. Pertinent Laboratory Findings

<table>
<thead>
<tr>
<th>Pertinent Investigations</th>
<th>Value (Normal Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>7.1 x109/L (3.5–10.5)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>139 g/L (115–155)</td>
</tr>
<tr>
<td>Platelets</td>
<td>149 x 103/L (150–450)</td>
</tr>
<tr>
<td>Sodium</td>
<td>136 mmol/L (135–145)</td>
</tr>
<tr>
<td>Chloride</td>
<td>106 mmol/L (96–106)</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.1 mmol/L (3.5–5.2)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25 mmol/L (22–28)</td>
</tr>
<tr>
<td>Albumin</td>
<td>41 g/L (34–50)</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>5 (8–12)</td>
</tr>
<tr>
<td>Delta Anion Gap</td>
<td>–7</td>
</tr>
<tr>
<td>Lithium</td>
<td>2.05 mmol/L (0.6–1.2)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>81 umol/L (&lt;75)</td>
</tr>
</tbody>
</table>
A large lithium overdose with unusual pharmacokinetics

Consideration was given for GI decontamination with polyethylene glycol (PEG) in light of the concern for ongoing GI absorption, but since her lithium concentration was approaching non-toxic levels and she lacked severe signs or symptoms, management with intravenous fluid was continued. Hemodialysis was not considered for the same reason.

The elimination of lithium approached a normal rate 90 hours after ingestion. The lithium concentration was less than 1 mmol/L at that time. The patient was then transferred to psychiatry to manage her mood disorder further.

Discussion

A conservative estimate of the half-life of lithium is 36 hours\(^2\), although there are reports of reduced clearance in the setting of chronic intoxication.\(^6\) In this case, after a 12 gm ingestion of immediate-release lithium carbonate, the decline in lithium concentration plateaued temporarily on two occasions despite an increasing CrCl and adequate urine output (Figure 1). We believe this reflects delayed absorption from the GI tract, likely due to the formation of a pharmacobezoar. This phenomenon has been described previously in case reports but only with sustained relations formulations.\(^6\)–\(^8\) A “rebound” in serum lithium levels was also previously reported after the initiation of hemodialysis and was thought to be due to the same mechanism.\(^5\)

There is disagreement in the literature regarding indications for extracorporeal treatments and GI decontamination. This is due to the lack of evidence as most information is from case series and case reports. Generally, hemodialysis is recommended with severe neurological symptoms on presentation, a lithium level > 5.0, or serum lithium levels of 2.5–4 mmol/L plus reduced renal clearance.\(^6\) The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) also recommends that hemodialysis should be

Figure 1. Serum lithium concentration. (A) Creatinine clearance over course of admission. Estimated by Cockroft-Gault equation. (B) Serum lithium concentrations. Grey line denotes expected clearance assuming an elimination half-life of 36 hours. Dotted line shows the time at which serum lithium is recommended to be <1mmol/L.
initiated if it is predicted that it will take longer than 36 hours from presentation to obtain a serum lithium concentration of less than 1 mmol/L by other means. A recent retrospective study has shown that this guideline does select additional patients with more severe neurological sequelae that were not selected for dialysis otherwise.

The latter recommendation relies on clinicians’ prediction of lithium elimination and this case exemplifies how this can be challenging. From the beginning of this case, it was clear that the elimination rate was less than reported in the literature (Figure 1) by the difference in the observed and expected curves. We hypothesize that this was due to ongoing absorption from the GI tract instead of a problem with the renal clearance of lithium.

In retrospective studies, GI decontamination has been shown to significantly reduce serum lithium levels when initiated early in the course. In this setting, GI decontamination (or whole bowel irrigation) consists of polyethylene glycol until stools are clear. Charcoal is not effective for lithium intoxication and kayexalate is generally not recommended. GI decontamination is only recommended for sustained-release formulations in patients that present less than four hours from consumption. This case report calls into question the limitation of the recommendation to only controlled released formulation and presentations within four hours of ingestion. We have shown evidence of GI absorption more than 60 hours after ingesting an immediate-release product. This is far longer than the 1–6 hour time to achieve the maximum serum concentration reported in the literature. While we did not use GI decontamination in this instance if the patient’s lithium levels were higher at the time of the stalled serum concentration decline or she had presented with more severe clinical features, then GI decontamination may have helped forgo dialysis or temporized the patient until it could have been arranged.

This case report illustrates the importance of pharmacokinetics in managing acute ingestions, such as determining if the lithium levels are declining in a manner that is expected. It also suggests that GI decontamination may be beneficial in large overdoses of immediate-release lithium. Further study could help elicit the indications for this intervention in this setting.

Conclusions

In this case of a large immediate-release lithium overdose, there was evidence of prolonged absorption from the GI tract, potentially as late as 60 hours. This is far later than previously described in the literature and suggests a potential role for GI decontamination in the settings predisposed to pharmacobezoar formation.

Informed Consent

Written informed consent was obtained for publication of case report and is available for review upon request. No identifying information outside of age and sex are reported.

Contributions

- Conception – ZA, ML
- Procurement of Data – JS, ZA
- Analysis of Data – JS, ZA, ML
- Drafting of Original Manuscript – JS, ZA
- Critical Review of Original Manuscript – JS, ZA, ML

Sources of Funding

The case report did not receive any funding or grants from public or commercial agencies.

Conflict of Interest

All authors declare that they do not have any competing interests in regard to the case report.

References

A large lithium overdose with unusual pharmacokinetics


