



Lithium Toxicity with Severe Bradycardia Post Sleeve Gastrectomy: a Case Report and Review of the Literature

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Abstract

Lithium is one of the major treatment options in bipolar disorder. Bariatric surgery can significantly modify the oral bioavailability of drugs, and lithium is no exception; although in most cases drug absorption seems to decrease, in the case of lithium, toxicity is the risk. In this article, we describe a 61-year-old male patient presented with lithium toxicity, including newly diagnosed severe bradycardia requiring a permanent pacemaker, after undergoing sleeve gastrectomy. We discuss the mechanisms behind this case, provide potential solutions for clinicians treating bariatric patients with lithium, and review previous reports of lithium toxicity post bariatric surgery. Awareness of changes in drug absorption, particularly lithium, following bariatric surgery, is prudent and essential for optimal patient care. Close clinical and drug levels monitoring is strongly advised.

Keywords Lithium toxicity · Sleeve gastrectomy · Bipolar disorder · Bradycardia · Drug absorption · Bariatric surgery

Introduction

Obesity has become the epidemic of the western world, with very limited pharmacological options. Bariatric surgery is now the mainstay in the fight against morbid obesity, with impressive long-term health benefits. The different bariatric procedures include gastric banding, Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and the more recent mini-gastric bypass.

Psychiatric conditions are also becoming increasingly prevalent, particularly among morbidly obese patients elected for bariatric surgery [1, 2]. The mood stabilizer lithium is the main treatment choice in bipolar disorder, and it is not unlikely for a bariatric surgery patient to be treated with this drug [3].

Lithium is a very narrow therapeutic index drug. It is administered orally as a carbonate or citrate salt, and is well absorbed from the intestinal tract. It is not metabolized, rather, it is excreted unchanged through the kidneys [4]. The altered gastrointestinal conditions after bariatric surgery can significantly modify the oral bioavailability of drugs, and lithium is no exception [5].

In this case report, we describe a morbidly obese bipolar patient treated with lithium, who presented with serious lithium toxicity after undergoing sleeve gastrectomy. While cases of lithium toxicity after RYGB were reported before, reports dealing with sleeve gastrectomy are scarce. We discuss the mechanisms behind this case, present the potential solutions, and provide a review of previous literature describing lithium toxicity in bariatric patients. Overall, awareness of changes in drug absorption, and lithium in particular, following bariatric surgery, is prudent and essential for optimal patient care.

Arik Dahan and Daniel Porat contributed equally to this work.

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Case Report

We present a case report of a 61-year-old male with medical history prior to bariatric surgery of morbid obesity, dyslipidaemia, sleep apnea, and bipolar affective disorder. BMI before surgery was 37. Medications prior to surgery included venlafaxine CR, clonazepam, risperidone, and lithium 900 mg daily for 9 years. Before surgery, lithium levels were

0.4–0.7 mmol/L (upper normal limit is 1.2 mmol/L). The patient underwent sleeve gastrectomy without significant events in the hospital. Cardiac examination before surgery showed changes in the ECG with T-wave inversion in V3–6, AVL, and slight ST depression in the inferior wall without abnormal conduction changes. No chest pain was described and troponin was negative. The patient was approved for surgery by the cardiologist that did not require further investigation. The patient reported not being able to swallow medications post-surgery and did not crush medications as instructed and thus did not take the recommended vitamins or his chronic medications for 2 weeks until he started taking them in a crushed form. One month after surgery, he started taking vitamins and esomeprazole. Two months post-surgery, the patient arrived at the ED with general weakness, slowing in his behavior and muscle weakness. He has lost 20 kg since the surgery. The patient was given intravenous thiamine and fluids and was discharged. In the ED, laboratory results were not significant with hemoglobin 14.2 g/dL, WBC 9.1 K, glucose 149 mg/dL, sodium 140 mmol/L, potassium 4.22 mmol/L, chloride 108 mmol/L, creatinine 0.9 mg/dL, and CRP 2.17 mg/L. Lithium blood levels were not measured and ECG was not performed. Lithium labs were taken in the ambulatory setting a day before admission and were elevated at 1.6 mmol/L. This lab result was not available at admission and was not taken into account. Pulse was not checked frequently, and the patient was discharged soon after he received fluids and B1. His primary care doctor instructed the patient to miss a dose and then resume. The symptoms were not correlated to the lithium levels but possibly to dehydration and B1 deficiency.

A month later (that is, 3 months post-surgery), the patient arrived at the ED again, describing that in the past 2 weeks, he was not able to go to work due to severe weakness. He also described severe general tremor. He exhibited slow slurred speech and occasional confusion. In the morning of his admission, he could not rise from his bed due to weakness. Vital signs in the ED included blood pressure 108/75, heart rate of 70 bpm with events of bradycardia to 36 bpm, and events of asystole for 2–3 s. He was also found to have abnormal breath sounds. Upon admission, laboratory tests included WBC 17 K with normal electrolytes and renal function and negative troponin. Abnormal laboratories included CRP 132.78, folic acid 4.6 ng/ml, transferrin 156 mg/dL; ECG in the ED showed inverted T waves in V4–5, biphasic T wave at V2–3, without QT prolongation. Head CT was without evidence of new events of bleed or ischemic stroke. He was admitted and received antibiotics in addition to chronic medications. Throughout his admission, his heart rate was between 40 and 60 bpm. In chest CT, pneumonia was ruled out as the patient was asymptomatic with no plural effusion, and it was determined that he had small aspirations due to the surgery.

The patient did not take lithium during this hospital admission. One day after admission, his lithium level was 1.2 mmol/L, and decreased to 0.7 mmol/L 2 days later.

The patient was hospitalized for 6 days due to recurrent events of bradycardia to 36 bpm (demonstrated with cardiac holter) and many pulse pauses of up to 10 s, mostly while awake. Other causes of bradycardia such as electrolyte abnormalities, other cardiac disease or event, other medications, and neurologic events were all ruled out. It was suggested by the hospital cardiologist to be a rare adverse event of sick sinus syndrome due to lithium, as the patient had supratherapeutic levels (1.2 mmol/L the day after admission after several days of patient reporting not taking the medication consistently) and other symptoms consistent with lithium toxicity. As the patient needed to maintain the lithium therapy and as it has been reported in the past that lithium could cause sinus node disease even at therapeutic levels [6].

It was decided to insert a permanent pacemaker, as it seemed that it would benefit the patient's condition, and he was discharged in good condition. No other measures (such as dialysis or reversal drug) besides fluids and holding lithium treatment were conducted during hospitalization. His lithium daily dosage was decreased from 900 to 600 mg in divided doses. Six months after the sleeve gastrectomy, the patient was stable on the current lithium dose with blood levels of 0.9 mmol/L.

Discussion

Bariatric surgery affects anatomical and physiological parameters that may alter oral drug absorption. Gastrointestinal tract characteristics that change after bariatric surgery include decreased gastric acidity (i.e., increased pH), reduced gastric volume and motility, and faster gastric emptying and gastrointestinal transit time [5].

Drug dissolution, which is a prerequisite for absorption, was reported to decrease in 10/22 psychiatric medications studied in vitro, whereas for two drugs, including lithium, dissolution actually increased [7]. This enhanced dissolution may be an important element in post-surgery lithium toxicity; decreased gastric acidity may deprotonate the carbonate salt, resulting in increased dissolution. This mechanism was suggested in a previous report of lithium toxicity 5 weeks after laparoscopic sleeve gastrectomy. The authors proposed two additional mechanisms of lithium toxicity after bariatric surgery: sleeve gastrectomy led to limited fluid intake and dehydration, resulting in kidney damage and decreased lithium clearance and lithium toxicity. The other pathway is based on lithium clearance being greater in the obese population. Thus, the bariatric surgery, which caused significant weight loss (70 lbs), could lead to decreased lithium clearance and toxicity [8].

Gastric emptying is the rate limiting step of many drugs from immediate release oral dosage forms. The operated stomach is incapable of keeping the drug dose for long, resulting in a surge of drug levels in the blood, which may be toxic. This notion was shown in animals using the anticholinergic agent propantheline bromide to delay lithium's gastric emptying. In the group treated with lithium and propantheline bromide, C_{\max} was significantly lower and T_{\max} was significantly longer, whereas AUC values were unchanged [9].

Another proposed mechanism was suggested in a case report of lithium toxicity 4 weeks after RYGB: surgery preparation may require liver shrinkage, achieved by liquid meal replacement diet, with altered fluid and sodium intake, which influences lithium levels. The authors also proposed that tablet crushing, which increased the surface area, may further enhance the dissolution of lithium [10].

In another RYGB lithium toxicity case, the authors associated the increased serum lithium concentrations with the significant weight loss, which in turn decreased GFR, resulting in lower lithium clearance. They added that lithium clearance is 20–30% of GFR, and mentioned that changes in lithium dissolution/absorption contributed to the toxicity [11]. In that case, the patient was moved to liquid dosage form before surgery, which may further enhance lithium absorption. While liquid formulations should successfully overcome dissolution problems after bariatric surgery, for lithium, whose dissolution may be enhanced, liquid formulations may result in toxic systemic drug levels. In that particular case, lithium treatment was stopped and changed to aripiprazole [11].

In the last reported case of lithium toxicity after RYGB, lithium dose was reduced during hospitalization, but upon discharge, lithium was again changed to aripiprazole [12]. The author remarked that the extended release preparation actually dissolved better in post bypass GI environment, which is yet another possible explanation for the result of enhanced lithium dissolution after surgery. In this case, clinicians should check if the formulation is immediate-release or modified-release and adjust the dosage accordingly.

In a case report of lithium toxicity after gastric banding, the patient experienced lithium-induced nephrogenic diabetes

insipidus, which manifested as hypernatremia and hyperosmolarity, long after lithium termination. The authors explained that long-term lithium administration may irreversibly compromise urinary-concentration capacity and reversibly reduce GFR. These outcomes may be triggered after gastric banding, because this procedure requires limitation in water intake by the patient [13].

Overall, seven case reports of lithium toxicity after bariatric surgeries were found in the literature, six of which involved a female patient (Table 1). The symptoms of toxicity were similar among the different cases, and included the following: nausea, vomiting, and diarrhea, which resulted in dehydration, mental manifestations of fatigue, confusion, and agitation. Our patient also presented with these symptoms, along with severe cardiovascular events. Previous reports, not in bariatric surgery, suggest that lithium toxicity may manifest as cardiovascular events, which may be asymptomatic, and include complete heart block, atrial fibrillation, and sinus bradycardia [15]. In one case report, the patient developed asymptomatic severe bradycardia upon acute lithium treatment at therapeutic level [16]. In another case, lithium intoxication was exhibited in ECG changes, including sinus bradycardia, rapid atrial fibrillation, second-degree atrioventricular block, and T wave changes [17]. Sinus bradycardia may also present along with other non-cardiac adverse conditions, such as hypercalcemia, hyperparathyroidism, nephrogenic diabetes insipidus, and thyroid dysfunction [18]. Several conclusions may be drawn from our case and previous ones: older patients may be more susceptible to lithium-induced bradycardia; this condition may be asymptomatic and result from either chronic or acute lithium dosing, and even at non-toxic drug blood levels.

The specific lithium dosage form may be important, as liquid formulation seems more likely to result in toxic plasma drug levels. After handling lithium toxicity, formulation change should be considered, as well as dose reduction.

Clinical staff education is warranted, in order to raise the awareness of the fact that bariatric surgery may not affect the systemic exposure of all drugs in a similar fashion [5, 19]. Lithium levels, in particular, should be closely monitored, given its narrow therapeutic index and high risk.

Table 1 Literature data of lithium toxicity after bariatric surgery

Bariatric procedure	Time after surgery	Toxicity manifestations	Lithium dosage	Lithium levels (mmol/L)	Reference
LSG	5 weeks	GI problems, agitation, thyroid storm, nephrogenic diabetes insipidus	300 mg morning, 600 mg night	2.7	[8]
RYGB	20 days	Dizziness and GI problems	1200 mg	3.22	[10]
RYGB	12 days	Dehydration and septic shock, weakness and fatigue, lightheadedness	600 mg twice daily	1.51	[11]
RYGB	2 weeks	Dehydration and delirium	450 mg morning, 600 mg night	2.14	[12]
RYGB	Few days	Tremulousness, dizziness, and GI problems	1800 mg	1.53	[14]

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Statement Informed consent was obtained from all individual participants included in the study.

Studies with Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

- Dawes AJ, Maggard-Gibbons M, Maher AR, et al. Mental health conditions among patients seeking and undergoing bariatric surgery: a meta-analysis. *JAMA*. 2016;315(2):150–63.
- Fisher D, Coleman KJ, Arterburn DE, et al. Mental illness in bariatric surgery: a cohort study from the PORTAL network. *Obesity (Silver Spring)*. 2017;25(5):850–6.
- Hensel J, Selvadurai M, Anvari M, et al. Mental illness and psychotropic medication use among people assessed for bariatric surgery in Ontario, Canada. *Obes Surg*. 2016;26(7):1531–6.
- Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med*. 1994;331(9):591–8.
- Azran C, Wolk O, Zur M, et al. Oral drug therapy following bariatric surgery: an overview of fundamentals, literature and clinical recommendations. *Obes Rev*. 2016;17(11):1050–66.
- Oudit GY, Korley V, Backx PH, et al. Lithium-induced sinus node disease at therapeutic concentrations: linking lithium-induced blockade of sodium channels to impaired pacemaker activity. *Can J Cardiol*. 2007;23(3):229–32.
- Seaman JS, Bowers SP, Dixon P, et al. Dissolution of common psychiatric medications in a Roux-en-Y gastric bypass model. *Psychosomatics*. 2005;46(3):250–3.
- Alam A, Raouf S, Recio FO. Lithium toxicity following vertical sleeve gastrectomy: a case report. *Clin Psychopharmacol Neurosci*. 2016;14(3):318–20.
- Bellibas SE, Tuglular I, Kayali A. The effect of delayed gastric emptying and absorption on pharmacokinetic parameters of lithium. *Eur J Drug Metab Pharmacokinet*. 1995;20(2):129–33.
- Walsh K, Volling J. Lithium toxicity following Roux-en-Y gastric bypass. *Bariatric Surg Practice Patient Care*. 2014;9(2):77–80.
- Musfeldt D, Levinson A, Nykiel J, Carino G. Lithium toxicity after Roux-en-Y bariatric surgery. *BMJ Case Rep* 2016;2016.
- Tripp AC. Lithium toxicity after Roux-en-Y gastric bypass surgery. *J Clin Psychopharmacol*. 2011;31(2):261–2.
- Leo JR, Farrell HM, Friedman R. Lithium-induced nephrogenic diabetes insipidus after gastric banding. *Psychosomatics*. 2013;54(2):200–4.
- Bingham KS, Thoma J, Hawa R, et al. Perioperative lithium use in bariatric surgery: a case series and literature review. *Psychosomatics*. 2016;57(6):638–44.
- Maddala RNM, Ashwal AJ, Rao MS, et al. Chronic lithium intoxication: varying electrocardiogram manifestations. *Indian J Pharmacol*. 2017;49(1):127–9.
- Nakamura M, Nakatsu K, Nagamine T. Sinus node dysfunction after acute lithium treatment at therapeutic levels. *Innov Clin Neurosci*. 2015;12(11–12):18–20.
- Chen Y, Zheng L, Liu W, et al. Electrocardiographic changes caused by lithium intoxication in an elderly patient. *Springerplus*. 2016;5:10.
- Demirtas L, Akbas EM, Degirmenci H, et al. Multisystemic side effects of an indispensable old drug: a case report of chronic lithium use (a patient with multiple side effects of lithium). *Case Rep Med*. 2015;2015:473931.
- Azran C, Langguth P, Dahan A. Impaired oral absorption of methylphenidate after Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2017;13(7):1245–7.