

Lithium toxicity following Roux-en-Y gastric bypass: Mini review and illustrative case

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Abstract

Lithium is among the mainstays of treatment for bipolar disorder. Bariatric surgery can considerably change the oral bioavailability of drugs, particularly lithium. In this review, a 36-year-old male patient is described, who presented with lithium toxicity, including neurologic and gastric symptoms after undergoing Roux-en-Y gastric bypass. The mechanism of lithium toxicity is discussed; recommendations for clinicians regarding lithium use in postsurgical patients are provided; and previous case reports of lithium toxicity post-gastric bypass surgery are analyzed. Awareness and education of lithium absorption changes postbariatric surgery is essential for optimal patient care. Close clinical and drug concentration level monitoring is warranted.

Keywords: lithium toxicity, bipolar disorder, bariatric surgery, obesity, malabsorption

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Approximately 70% of bipolar patients taking psychotropic medications are overweight or obese.³

Medications, such as lithium, second-generation antipsychotics, and in some cases, antidepressants, contribute to obesity in these patients.² Furthermore, other contributing factors for higher prevalence of obesity in patients are unhealthy eating habits to regulate mood and decreased self-care behaviors.²

Introduction

Bipolar disorder is a severe affective disorder, characterized by rapid shifts in mood, concentration, and energy levels, affecting 2.4% of US adults.¹ Multiple studies show that bipolar disorder is associated with obesity, defined as a BMI ≥ 30 kg/m².¹ Obesity in patients with bipolar disorder is associated with greater severity of the disease and comorbid medical conditions.² In comparison with the general population, patients with bipolar disorder are at higher risk of cardiovascular morbidity and mortality.³

Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy are the 2 most commonly performed bariatric surgery procedures in the United States.⁴ Approximately 3% of bariatric surgery candidates have a diagnosis of bipolar disorder.⁵ RYGB is associated with perioperative pharmacokinetic changes in psychotropic medications that can result in subtherapeutic or supratherapeutic drug concentration levels.⁴ Altered absorption, changes in volume of distribution, metabolism, and rapid weight loss can all affect pharmacokinetics.^{4,6}

Lithium (Li) is one of the medications that require special care perioperatively. Li is recommended as a first-line



treatment option in bipolar disorder and has been the mainstay of treatment for acute manic episodes, suicide prevention, and prophylactic treatment for the last 6 decades.^{7,8} Li is infamous for its narrow therapeutic range of 0.6 to 1.2 mmol/L, with levels >1.5 mmol/L considered toxic.⁷ Li is well absorbed in the intestinal tract, remains unchanged, and is renally excreted.⁷ Therefore, differences in volume of distribution owing to age and weight, renal clearance, and drug-drug interactions severely affect the pharmacokinetics and bioavailability of Li.^{7,9}

Patients undergoing RYGB are at higher risk of Li toxicity because of preoperative dietary modifications to fluid and sodium intake, gastrointestinal tract manipulation from the surgical procedure altering drug absorption, and increased dissolution of Li causing increased absorption.^{4,6} Stomach pH increases significantly following both RYGB and sleeve gastrectomy, facilitating the deprotonation of carbonate salt.⁶ The increase of the deprotonated form of Li leads to an increased dissolution of Li ions.⁶

With the growing number of bariatric surgeries performed on patients with mood disorders, it is necessary that health care professionals be cautious while prescribing and monitoring medications with a narrow therapeutic window, particularly Li.⁷ Close therapeutic drug monitoring to assess the serum concentration of Li remains an important part of clinical surveillance.

We present an illustrative case of Li toxicity following RYGB in a patient with bipolar disorder. We discuss the mechanisms behind the case, present optimal solutions, and provide a review of the literature relating to Li toxicity in such patients. The purpose of this review is to highlight the significance of monitoring for safety and efficacy of Li in such patients.

Case Report

A 36-year-old male (Mr A) with morbid obesity (weight, 113 kg; BMI, 43 kg/m²), concomitant bipolar II disorder, hypertension, migraine, and a history of pulmonary embolism underwent RYGB. His medications prior to surgery included Li extended-release (ER) 300 mg 3 times a day, venlafaxine ER 75 mg daily, nifedipine XL 30 mg daily, and propranolol 10 mg daily. The patient was seeing a psychiatrist every 2 months and a psychologist biweekly for bipolar depression. His trough level of Li before surgery, taken 12 hours before the last dose, was 0.63 mmol/L, and baseline serum creatinine was 0.65 mg/dL. His cardiac examination was normal with nonsignificant changes in the ECG. The patient underwent an RYGB procedure without any complications. The patient was advised to crush his lithium ER post-surgery for 4 to 6 weeks owing to difficulty swallowing tablets post-surgery

and was discharged on postoperative day 2 with the preadmission medication regimen. On his first follow-up visit, 28 days post-surgery, his trough level of Li and serum creatinine were 0.93 mmol/L and 0.67 mg/dL, respectively. The patient was compliant with the crushed Li dose. His Li level was within the therapeutic range, and therefore, no dose adjustments were made. Ten days later, on postoperative day 38, the patient developed diffuse cramping abdominal pain, nausea, vomiting, polydipsia, and decreased tolerance for solid food intake. Three days later, he presented to the emergency department with mental status changes, increased anxiety, diaphoresis, bradycardia, slurred speech, and unsteady gait.

Upon arrival in the emergency department, Mr A's weight was 85.7 kg (total weight loss of 27 kg since RYGB). His electrolyte panel revealed hyponatremia and hypokalemia (Na, 131 mmol/L; K, 3.3 mmol/L). His BUN and creatinine were within normal range. His trough level of Li was at 2.2 mmol/L. His ECG revealed a prolonged QTc interval of 605 milliseconds using the Bazett formula, with normal being equal to or less than 0.40 s (≤ 400 milliseconds).

Psychosomatic liaison team was consulted for elevated levels of Li and for medication adjustments. Nifedipine was continued, but Li, venlafaxine, and propranolol were stopped; and he was placed on telemetry to monitor for arrhythmias. Frequent Li levels were obtained, and IV hydration was provided aggressively. On his sixth day of admission, the Li level reached 0.21 mmol/L, and his serum creatinine was 0.66 mg/dL. Li was restarted at a lower dose (300 mg once daily); other medications were restarted at previous dosages. Subsequently, the patient's acute mental status improved, and he was deemed appropriate for discharge. At the time of discharge, he was alert, oriented to time, place, and person, cooperative, engaging, and pleasant on approach; his mood was stable, and his thought process was linear and goal directed, without any paranoia, delusions, or perceptual disturbances. He was instructed to follow-up with a psychiatrist. Within 2 weeks after discharge, Li (non-crushed) was titrated up to 300 mg twice a day, which was later increased to 300 mg 3 times a day on subsequent follow-up visits, and he remained stable on the same dose for the next 6 months. No subsequent Li levels were reported.

Discussion

In addition to our patient (Mr A), 11 cases of Li toxicity following RYGB were found in the literature (Table). These cases assisted us in understanding the potential mechanisms underlying Li toxicity following RYGB.

TABLE: Case reports on lithium (Li) toxicity after Roux-en-Y gastric bypass surgery (RYGB)

Study	Age and Sex	Preop Li Level/ Toxic Li Levels Postop (mmol/L)	Weight Loss (kg)	Timeline of Symptoms	Surgery	Toxicity Signs	Treatments	
							Changes to Li	Other
Alam et al ¹¹ (2016)	18 F	NK/2.7	31.75	5 wk	Vertical sleeve gastrectomy	Diarrhea, dehydration, tremors, lethargy, confusion	Dosage at discharge: NM Preop dose: Li, 900 mg OD (300 mg AM, 600 mg PM)	IV fluids, olanzapine, hemodialysis
Dahan et al ¹⁴ (2019)	61 M	0.4-0.7/1.6	20	2 mo	Sleeve gastrectomy	Slurred speech, muscle weakness, tremors, confusion, bradycardia, asystole, inverted T Waves on ECG	Discharged at 600 mg divided doses Preop dose: Li, 900 mg OD before surgery	IV fluids, permanent pacemaker
Jamison et al ¹⁸ (2020)	36 F	0.62/1.63	18.14	6 mo	Laparoscopic sleeve gastrectomy	Drowsiness, light- headedness, nausea, vomiting, dehydration	Li carbonate dose decreased to 150 mg bid Preop dose: Li carbonate capsule, 300 mg AM; 600 mg PM	NM
Lin et al ¹⁶ (2020)	38 M	NK/3.42	17	3 wk	Laparoscopic sleeve gastrectomy	Diarrhea, dehydration, weakness, drowsiness, polyneuropathy, AKI	Replaced Li with lamotrigine	IV fluids, hemodialysis
Marques et al ¹⁹ (2019)	44 F	0.7/ 2.1	NM	1 mo	RYGB	Confusion, muscle weakness, tremors, nausea, diarrhea	Suspension of Li Preop dose: ER Li carbonate, 600 mg OD	Hydration by IV fluids, halting medication
Musfeldt et al ¹⁰ (2016)	61 F	0.61/ 1.51	NM	12 d	RYGB	Light-headedness, dizziness, weakness, dehydration, bradycardia, hypotension	Upon discharge, maintained at 450 mg ER Li carbonate OD Preop dose: Li, 600 mg bid	IV fluids, dopamine, IV vancomycin and piperacillin/ tazobactam, supportive care
Niessen et al ²⁴ (2018)	40 F	NK/2.1	NM	17 d	Sleeve gastrectomy	Drowsiness, confusion, dehydration, prerenal ARF	Li discontinued at discharge Preop dose: Li, 1250 bid	IV fluids, thiamine, hemodiafiltration
Nykiel et al ¹⁷ (2014)	61 F	NK/1.51	NM	10 d	RYGB	Light-headedness, weakness, fatigue, dizziness, bradycardia, hypotension	NM	Atropine, IV fluids, pacemaker, dopamine
Shah et al ⁹ (2018)	59 F	NK/1.42	NM	9 d	Sleeve gastrectomy	No clinical signs	Dose reduction to 300 mg bid	NM
Tripp ¹² (2011)	51 M	NK/2.14	NM	14 d	Laparoscopic RYGB	Dehydration, confusion	Li discontinued at discharge; aripiprazole increased to 30 mg OD Preop dose: ER Li carbonate, 450 mg every AM; 600 mg PM	IV fluids
Walsh et al ¹⁵ (2014)	53 F	0.63/3.22	NM	25 d	RYGB	Nausea, vomiting, diarrhea, hypotension, AKI	Li started at lower dose, 300 mg OD Preop dose: immediate release Li carbonate, 1200 mg PM	IV fluids

AKI = acute kidney injury; ARF = acute renal failure; bid = twice a day; NK = not known; NM = not mentioned; OD = once a day; postop = postoperative; preop = preoperative.

After RYGB surgery, patients lose a significant amount of weight, leading to decreased total body water, thus decreasing renal blood flow and glomerular filtration rate (GFR).¹⁰ Since Li is exclusively excreted by the kidneys at a rate of 20% to 30% of the GFR, a decreased GFR can result in Li toxicity.¹⁰ Furthermore, published case studies^{9,11,12} indicate that patients undergoing RYGB may develop Li toxicity due to decreased food intake and dehydration. On postoperative day 38, our patient reported decreased fluid intake and multiple episodes of vomiting, which resulted in severe dehydration and eventually Li toxicity. This explains the observed findings in several cases listed in the Table.

Patients undergoing RYGB may also experience cardiac complications such as QT prolongation, but the hypothesis that has gained the most traction suggests a delay in myocardial conduction velocity owing to intracellular hypokalemia secondary to the Na/K pump inhibition.¹³⁻¹⁷ Because Li and Na⁺ share the same attachment site on the Na/K pump, such fatal side effects may also occur in patients with Li toxicity. Mr A's ECG showed bradycardia and QTc interval prolongation 5 weeks after RYGB. A similar observation was made in other case reports.¹⁴⁻¹⁷

Toxic Li levels result in neurotoxicity, ranging from temporary altered mental status to permanent neurologic sequelae such as cerebellar impairment, brain stem syndromes, and peripheral neuropathies.¹⁶ This is explained by Li's extensive diffusion within the central and peripheral nervous systems following its thorough absorption.^{16,18} Mr A developed altered mental status, slurred speech, and an unsteady gait owing to Li toxicity. He received fluids and appropriate treatment. Similar findings were reported by Marques et al,¹⁹ where the patient developed drowsiness, muscle weakness, extremity tremors, and difficulties in motor coordination after treatment with Li. In general, when treatment is discontinued, and the patient is hemodialyzed, the neurologic symptoms subside and the patient's consciousness returns to normal.²⁰ However, in some cases, those symptoms may persist for a long time despite hemodialysis, resulting in neurologic sequelae such as extrapyramidal symptoms or blindness.²⁰ Mr A did not receive hemodialysis because the neurologic symptoms developed acutely, and his symptoms were treated sufficiently with aggressive IV hydration upon arrival in the emergency department. Apart from IV hydration and hemodialysis, other treatment regimens for Li toxicity are gastric lavage and intestinal irrigation to limit the gastrointestinal absorption of lithium. Other successful treatments also include sodium polystyrene sulfonate, arteriovenous and venovenous hemodiafiltration.^{21,22}

Usually, it takes 6 to 12 months to recover from bariatric surgery, and the body is stable for normal diet and

physical activity.²³ There are currently no clearly established guidelines for clinical Li monitoring or a predefined ideal Li level during the perioperative period in RYGB surgery.⁴ However, experts have made the following recommendations to avoid Li toxicity post-RYGB:

1. Collaboration between a bariatric surgeon, a psychiatrist, a primary care physician, and a clinical pharmacist in the pre- and postoperative phases.
2. Determine the patient's preoperative Li baseline value and perform a scale-based clinical assessment of mood.²⁴
3. Educate the patient preoperatively on the importance of drinking at least 2 to 3 L of water per day.⁴
4. Postoperatively, assess for Li toxicity by performing weekly assessments of the patient's Li level and GFR for 6 weeks, then every 2 weeks until 6 months postoperative. After that, monthly levels should be obtained until 1-year post-surgery.²⁵
5. Consider decreasing the dosage if the Li level exceeds more than 25% of the patient's preoperative baseline value.^{4,24}
6. To prevent dehydration, counsel the patient to alert their physician or psychiatrist in case of any changes in food or fluid intake or severe vomiting.

Conclusion

This review emphasizes the significance of monitoring Li levels after RYGB. Following surgery, the pharmacokinetics of Li are affected by the decrease in stomach surface area and increase in gastric pH, as well as changes in weight and GFR, which may result in Li toxicity. Due to the lack of consensus guidelines to address Li toxicity, physicians must closely monitor Li levels after RYGB surgery every week for at least 6 weeks, every 2 weeks until 6 months postoperative, and later monthly until 1-year post-surgery.

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