

Lithium toxicity following bariatric surgery

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Abstract

A patient with morbid obesity and several psychiatric comorbidities underwent laparoscopic sleeve gastrectomy and experienced success with weight loss. However, she experienced lightheadedness, nausea, and a fall and was admitted to the hospital for encephalopathy due to lithium toxicity. The pharmacokinetics of lithium is altered following bariatric surgery. Due to these factors, adjustments were made to the patient's lithium therapy, her levels were subsequently reduced into the therapeutic range, and she continued with no further issues. Mechanisms of lithium toxicity following bariatric surgery and a monitoring protocol to prevent toxicity are discussed.

Keywords

Psychopharmacology, mental health/psychiatry, bariatric surgery, lithium

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Introduction

Many patients undergoing bariatric surgery have a comorbid psychiatric diagnosis. Lithium is often used in the treatment of patients with mood disorders. The pharmacokinetics of lithium changes following bariatric surgery. It is vital for those involved in the treatment of the bariatric surgery patient with psychiatric conditions to know the changes in the pharmacokinetics of many medications following bariatric surgery and how to make adjustments to achieve therapeutic drug levels while avoiding adverse effects.

We describe a patient with morbid obesity and several psychiatric comorbidities who underwent laparoscopic sleeve gastrectomy and experienced success with weight loss. According to the Centers for Disease Control and Prevention (CDC), prevalence rates of obesity increased by 12% from 1999–2000 to 2017–2018, reaching 42.4%.¹ The American Society of Metabolic and Bariatric Surgery² showed an increase in the number of bariatric surgeries performed, from 158,000 in 2011 to 252,000 in 2018. Studies from several countries show that around 40% of all bariatric surgery patients have at least one psychiatric diagnosis.³ Thus, the case presentation is a typical dilemma that the bariatric surgeon, primary care physician, or psychiatrist might encounter.

The patient experienced encephalopathy due to lithium toxicity on her pre-surgery dose of lithium. Other cases of lithium toxicity after both sleeve gastrectomy and Roux-en-Y have been reported.^{4–9} In this case report, we discuss the mechanisms of lithium toxicity following bariatric surgery and a monitoring protocol to prevent toxicity.

Case presentation

The patient was a 36-year-old female with a history of morbid obesity, major depressive disorder, borderline personality disorder, posttraumatic stress disorder, migraine headaches, and back pain. She possessed the decisional capacity to provide informed consent. She was under the regular care of an internist and a psychiatrist. She had tried numerous weight loss strategies without sustained success. The patient underwent laparoscopic sleeve gastrectomy, after receiving nutrition counseling and psychological clearance for the procedure. An upper gastrointestinal series done prior to the procedure was normal. An x-ray esophagram showed interrupted primary peristalsis with mild stasis, with eventual clearing with secondary peristalsis. The study was otherwise unremarkable. The patient's weight at the time of surgery was 269.6 pounds (body mass index (BMI) = 41.0). The patient underwent the sleeve gastrectomy with no complications. Following surgery, she experienced intermittent nausea and vomiting. She had difficulty with swallowing all of her medications, which

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were liquid, crushable tablets, or capsules whose contents could be emptied into liquid. Medications included promethazine suppositories, ondansetron rapidly dissolving tablet, hydrocodone/acetaminophen solution, acetaminophen-butalbital caffeine tablet, pantoprazole granules, suvorexant tablet, zolpidem tablet, gabapentin capsule, multivitamin tablet, lurasidone tablet, prazosin capsule, duloxetine capsule, trazodone tablet, fexofenadine tablet, propranolol tablet, dicyclomine capsule, sumatriptan injector, and lithium carbonate capsule (300 mg taken in the morning and 600 mg taken in the evening).

Prior to the sleeve gastrectomy, the lithium level had been 0.62 mmol/L. About 4 months after the surgery, the lithium level had increased to 1.47 mmol/L on the same dose of lithium.

Approximately 6 months after the sleeve gastrectomy, the patient presented to the emergency department after a fall. She reported feeling lightheaded and nauseous and felt as though her legs gave out. She denied pain or loss of consciousness. Laboratory evaluation in the emergency department showed a urinalysis that was negative for glucose with a specific gravity of 1.010, negative for blood, positive for nitrite and leukocyte esterase, and was positive for bacteria and many squamous epithelial cells. A basic metabolic panel showed sodium of 138 mmol/L, potassium of 3.6 mmol/L, chloride of 102 mmol/L, urea nitrogen of 8 mg/dL, creatinine of 0.92 mg/dL, glucose of 135 mg/dL, and calcium of 10.1 mg/dL. A complete blood count showed a white blood cell count of 6.7 K/ μ L, hemoglobin of 12.6 g/dL, hematocrit of 38.4%, and platelet count of 299 K/ μ L. A lithium level was elevated at 1.63 mmol/L. The patient had lost approximately 40 pounds (BMI = 34.9; 14.8% body weight lost) since the time of the sleeve gastrectomy.

Differential diagnosis included dehydration and gastrointestinal infection in addition to lithium toxicity.

At this emergency department, the patient was instructed to hold her lithium for 2 days, which the patient did. The patient's primary physician and a clinical pharmacist reviewed the patient's record and made the decision to decrease the patient's lithium dose to 300 mg twice daily.

The patient returned to the emergency department approximately 10 days after the first emergency department visit with difficulty walking and one fall, as well as somnolence. A family friend who brought the patient to the emergency department stated that there was no suspicion of overdose. The emergency department workup revealed a urine toxicology screen that was negative for amphetamine, barbiturate, benzodiazepine, cannabinoid, cocaine, opiates, phencyclidine, and oxycodone. Computed tomography scan of the head showed no acute intracranial abnormalities. Lithium level at that time was 1.10 mmol/L. She was admitted to the hospital for encephalopathy. A differential diagnosis, in addition to lithium toxicity, of dehydration, acute kidney injury, and infection were considered. Psychiatry consultation was obtained, and in collaboration with the primary physician, the decision was made to reduce the patient's lithium dose to 150 mg bid. The patient has had no further episodes of somnolence, falls, or supratherapeutic lithium level since this dose reduction. A lithium level obtained several months later on the 150 mg bid dose was 1.02 mmol/L. One year following surgery, the patient's lithium level was 0.53 mmol/L at a weight of 199 pounds (BMI = 30.26; 26.2% body weight lost).

The following table summarizes the patient's weight loss, creatinine, lithium dosing, and lithium level at baseline, at her presentations to the emergency department, and at follow-up.

| | BMI (kg/m ²) | Creatinine (mg/dL) | Daily lithium dose (mg) | Lithium level (mmol/L) |
|-------------------------------|--------------------------|--------------------|-------------------------|------------------------|
| Baseline | 41 | 1.08 | 900 | 0.62 |
| 4 months post-surgery | 36.8 | 0.72 | 900 | 1.47 |
| 6 months post-surgery | 34.9 | 0.92 | 900 | 1.63 |
| 6 months 10 days post-surgery | 34.2 | 0.64 | 600 | 1.10 |
| 9 months post-surgery | 33.3 | 0.68 | 300 | 1.02 |
| 1 year post-surgery | 31.6 | 0.79 | 300 | 0.53 |

Discussion

In a sleeve gastrectomy procedure, the stomach is divided and stapled vertically, removing more than 85% of the stomach, creating a tube- or banana-shaped pouch that restricts the amount of food that can be consumed and absorbed by the body. Risks of sleeve gastrectomy include gastritis, heartburn, stomach ulcers, injury to the stomach, intestines, or other organs during surgery, leaking from the line where the parts of the stomach have been stapled together, poor nutrition, scarring inside the belly that could lead to a future blockage in the bowel, and vomiting.¹⁰

Furthermore, the Roux-en-Y and sleeve gastrectomy procedures affect gastric pH and surface area, but the way these changes affect drug dissolution and absorption is not fully elucidated.⁶⁻¹¹

The Roux-en-Y and sleeve gastrectomy procedures affect absorption within the gut. It may be presumed that in addition to a decreased absorption of nutrients, we would expect a decrease in absorption of medications. However, with lithium, the opposite is the case. Increases in gastric pH can actually increase the deprotonated form of lithium and lead to increased absorption.^{8,10}

The elimination and distribution of lithium throughout the body is multifactorial. Renal blood flow, glomerular filtration rate (GFR), lean tissue mass, and total body water can affect the pharmacokinetics of the medication. All of these factors are affected during weight loss. In a weight loss situation, there is a decrease in renal blood flow and GFR. This is secondary to a decrease in total body water.⁷

Lithium follows sodium's path in the kidney, so in instances of dehydration or gastrointestinal fluid loss, lithium would be avidly reabsorbed. Given that our patient experienced inadequate hydration and nutrition postoperatively, her renal absorption of lithium was increased. This may have also contributed to her lithium toxicity.

Reiss et al.¹⁰ compared the clearance of lithium in obese subjects with that of normal-weight subjects. They found that the steady-state volume of distribution for the obese group was significantly less than that for the control group. The steady-state volume of distribution was significantly correlated with ideal body weight and fat-free mass, but not creatinine clearance. The clearance of lithium was significantly correlated with total body weight, but not with creatinine clearance. These results suggest that obese patients may require larger lithium maintenance doses than non-obese patients.

Gong et al.¹² report that short-term courses of a low dose of lithium may ameliorate kidney injury. Furthermore, this pathway may explain lithium's mechanism of action.¹³ However, this patient required a lifelong treatment course with lithium for antidepressant augmentation and mood stability. The patient maintained a consistent response to the lowered dose of lithium following bariatric surgery.

In evaluating the patient's variable response to lithium, we did consider the role of pharmacogenetics.¹⁴ However, her response to lithium had been consistent prior to bariatric surgery, and her lithium level remained in the therapeutic range on the same dose prior to the surgery. Her variation in response appeared to vary with her BMI and GFR following surgery. She responded to a typical dose of lithium before the surgery and achieved a similar therapeutic level with a much smaller dose when her stomach surface was smaller, gastric pH was higher, and her GFR and BMI were lower.

Early signs of lithium toxicity include nausea, tremor, diarrhea, blurred vision, vertigo, confusion, and a decrease in deep tendon reflexes. These can occur at a level of 1.2 mmol/L or greater. As toxicity worsens, typically when lithium levels are greater than 2.5 mmol/L, patients may experience seizures, coma, cardiac dysrhythmias, and potentially permanent neurologic impairment. Our patient experienced lightheadedness and nausea, suggesting that some component of volume depletion was at play. This, in addition to the pharmacokinetic changes associated with lithium distribution and elimination seen with weight loss, created a perfect storm for lithium toxicity.

There is one case of lithium toxicity after sleeve gastrectomy reported in the literature.⁶ The patient, who was on 900 mg of lithium daily, had a level of 2.6 mmol/L and required hemodialysis. That patient also was suffering from

acute kidney injury. The authors propose both decreased lithium clearance with resolution of obesity and increased lithium absorption as mechanisms by which lithium toxicity may have ensued. Stomach pH increases after both Roux-en-Y and sleeve gastrectomy, leading to increased deprotonation of carbonate salt and increased dissolution of lithium ions.⁸ Walsh et al.⁷ suggest that crushing medications to facilitate dissolution in a gastric environment with a higher pH also affects absorption. Walsh et al.⁷ cite evidence that lithium dissolution is increased after Roux-en-Y gastric bypass, which is concerning given its narrow therapeutic window. The effect of a gastric sleeve bypass on lithium dissolution is not known, but it is reasonable to assume that it is similar, given the evidence presented in this case study and the other of lithium toxicity following gastric sleeve bypass.⁶

Many patients undergoing bariatric surgery have a comorbid psychiatric diagnosis. About two-thirds of patients presenting for bariatric surgery have a psychiatric disorder,^{6,11} and 34% of patients undergoing psychological evaluation for gastric bypass are on a psychotropic medication.⁹ Given the narrow therapeutic window of lithium and the fact that its pharmacokinetics changes with body weight, it behooves physicians who treat bariatric surgery patients to appreciate the risk of lithium toxicity and make dose adjustments in order to prevent it. Walsh et al.⁷ further suggest that one clinician be responsible for ordering and evaluating the lithium level and making dose adjustments. Our patient's lithium level more than doubled in the 2 months following surgery, and further increase was observed less than 2 months after that. Bariatric surgery physiology and the prescribed diet and diet-related complications all predispose to alterations in lithium pharmacokinetics. Therefore, a lithium level should be monitored frequently, with dose changes made accordingly. The half-life of lithium in normal patients is 18–36 h. In the presence of rapid weight loss (where lithium clearance would decrease), the elimination half-life of lithium dictates that it would be prudent to monitor the lithium level every 2–4 weeks until weight loss is stable.

In conclusion, this case illustrates the importance of monitoring lithium levels soon after bariatric procedures. Due to reduction in stomach surface area and increase in gastric pH, along with increases in lithium distribution and decreased elimination, significant increases in plasma concentration of this drug with a narrow therapeutic window could cause toxicity to ensue. Therefore, we recommend monitoring of lithium levels every 2–4 weeks after bariatric surgery. This requires collaboration among bariatric surgeons, primary physicians, and psychiatrists, preferably with the involvement of a clinical pharmacist to guide lithium dose changes based on pharmacokinetics.

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