Semaglutide-Mediated Lithium Toxicity

To the Editors:

Glucagon-like peptide 1 (GLP-1) receptor agonists, such as semaglutide, can alter gastric motility, affecting the absorption of certain medications.[1–6] To date, there is no evidence of the impact of GLP-1 receptor agonists on lithium absorption. Here, we present a case of lithium toxicity following the initiation of semaglutide treatment. The patient provided written informed consent to publish the case.

A 41-year-old woman with a history of major depressive disorder (recurrent, severe, without psychotic features with mixed features of bipolar), posttraumatic stress disorder, generalized anxiety disorder, borderline personality disorder, body dysmorphic disorder, unspecified eating disorder, overweight, and stage 2 chronic kidney disease (CKD) was on long-term lithium therapy. Her CKD, caused by prolonged nonsteroidal anti-inflammatory drug use for joint pain and prior episodes of pyelonephritis, was diagnosed 4 years before lithium initiation and had remained stable prior to semaglutide treatment.

She initially started lithium extended-release therapy at 300 mg oral twice daily and gradually titrated to 600 mg oral twice daily over 7 months by 150-mg increments due to subtherapeutic lithium levels and persistent depressive symptoms with suicidal ideation. Two weeks after the final dose increase, her lithium level was 1.1 mEq/L, and her creatinine was 1.16 mg/dL. After 10 months on this regimen, she delayed routine laboratory testing but was later found to have a stable lithium level of 0.9 mEq/L, a creatinine of 0.89 mg/dL, and an estimated glomerular filtration rate (eGFR) of 84 mL/min. Four months after her most recent laboratory work, nearly 2 years after starting lithium, she initiated semaglutide 0.25 mg/0.5 mL autoinjections for weight management, prescribed due to her body mass index of 28.7 kg/m^2 and worsening eating disorder behaviors following weight gain from psychiatric medications. Her other psychiatric medications included clonazepam, fluoxetine, gabapentin, lurasidone, prazosin, propranolol, and quetiapine.

Roughly 1 week after starting semaglutide, the patient started to develop nausea, tremulousness, gait disturbance, muscle twitching, shakiness, dizziness, and irritability. Despite these symptoms, neither she nor her psychiatrist suspected lithium toxicity, as her lithium dose remained unchanged. She was referred to her primary care provider, where laboratory testing 5 weeks after initiating semaglutide confirmed lithium toxicity. Laboratory results include lithium level of 2.4 mEq/L, creatinine of 1.09 mg/dL, eGFR of 65 mL/min, and thyroid-stimulating hormone of 6.12 μIU/mL with normal free T4. Electrocardiogram findings showed mild T-wave inversions without evidence of atrioventricular block or PR/QTc prolongation.

The patient was managed conservatively by discontinuing lithium and increasing hydration while continuing semaglutide. One day after stopping lithium, laboratory testing showed a lithium level of 2.2 mEq/L, creatinine of 1.2 mg/dL, eGFR of 58 mL/min, and calcium of 11.3 mg/dL, likely secondary to lithium toxicity. Three days after stopping lithium, laboratory testing showed a lithium level of 1.2 mEq/L, creatinine of 0.99 mg/dL, and eGFR of 73 mL/min. Six days after stopping lithium, lithium was subtherapeutic at 0.5 mEq/L.

After resolving her lithium toxicity, the patient was restarted on lithium at half of her original dose, 300 mg twice daily, along with 0.25 mg weekly subcutaneous semaglutide. Follow-up laboratory tests at 6 and 32 days after restart showed stable therapeutic lithium levels of 0.9 and 0.8 mEq/L, respectively, with a creatinine of 0.84 mg/dL. Notably, her lithium dose was reduced from 1200 mg to 600 mg daily to maintain the same therapeutic lithium levels after introducing semaglutide. Her lithium levels and kidney function will continue to be closely monitored, with further adjustments as her semaglutide dose is increased.

DISCUSSION

This is the first reported case of lithium toxicity occurring in a patient on a previously stable lithium dose after initiating semaglutide treatment. We hypothesize that this toxicity resulted from semaglutide's effect on delayed gastric emptying, as existing literature has documented altered drug absorption following the initiation of GLP-1 receptor agonist medications.[1–6] Changes in gastric motility can significantly impact the absorption and serum levels of oral medications, particularly those with narrow therapeutic windows, such as lithium. However, no prior studies have specifically examined the effect of semaglutide on lithium pharmacokinetics.

The patient had maintained stable lithium levels for nearly 2 years and had been on 1200 mg oral daily for 14 months without signs of toxicity. However, following the introduction of semaglutide, she developed lithium toxicity, with her lithium level rising from 0.9 to 2.4 mEq/L despite no change in her lithium dosage. The temporal correlation between semaglutide initiation and the onset of toxicity suggests that its mechanism of delayed gastric emptying altered lithium absorption, leading to increased serum levels and toxicity.

GLP-1 receptor agonists exert their effects by enhancing insulin secretion, suppressing glucagon, and delaying gastric emptying in a dose-dependent manner.[1] This delayed gastric transit can alter the pharmacokinetics of coadministered oral medications, with the most pronounced effects occurring early in treatment, followed by a reduction over time due to tachyphylaxis.[1]

The impact of GLP-1 receptor agonists on drug absorption has been demonstrated in several studies. Oral semaglutide has been shown to increase the area under the curve of metformin, suggesting enhanced and prolonged absorption.[2] Although this change was not considered clinically significant by the authors, it may be relevant for medications with narrow therapeutic indices, such as lithium. One study observed no significant change in area under the curve but reported a delayed C_{max} with subcutaneous semaglutide.[7] A recent review demonstrated that subcutaneous GLP-1 receptor agonists are associated with reduced C_{max} and delayed T_{max}, consistent with delayed gastric emptying.[3]

Further evidence comes from studies on other GLP-1 receptor agonists. Exenatide and liraglutide have both been shown to significantly delay gastric emptying.[4,5] Additionally, the combination GLP-1/GIP receptor agonist tirzepatide modulates gastric motility in a manner similar to GLP-1 receptor agonists.[6] Notably, tirzepatide has a clinically significant impact on drug absorption, particularly reducing the effectiveness of oral hormonal contraceptives. Patients using oral contraceptives are advised to switch to a non-oral method or add a barrier method for 4 weeks after initiating tirzepatide and for 4 weeks following each dose increase.[8] Overall, studies consistently demonstrate that GLP-1 receptor agonists delay gastric emptying, with tirzepatide exhibiting a clinically significant effect that requires treatment adjustments.

In this case, potential contributors including CKD and weight loss to lithium

toxicity were considered. However, the patient's stable history of CKD with normal renal functioning prior to the initiation of treatment with semaglutide, along with gradual weight loss of 5.8 kg over 5 weeks, makes these factors unlikely as the primary cause. Although semaglutide has been linked to acute kidney injury and worsening CKD, our patient's kidney function laboratory results remained close to her baseline throughout the event, and prior to the event, she had normal creatinine and eGFR, suggesting that impaired renal function did not contribute to lithium toxicity.[9] Therefore, the initiation of semaglutide, with its subsequent effect on delayed gastric emptying and enhanced lithium absorption, emerges as the most probable cause for her acute lithium toxicity. Semaglutide's appetite-suppressing effects may have also contributed to reduced fluid, caffeine, and salt intake, which can further increase lithium levels and can be confounding factors to the increase in lithium. Regardless, it is important to be aware of potential changes in lithium levels secondary to initiating treatment with semaglutide.

In conclusion, this case highlights the importance of clinicians being aware of potential interactions between semaglutide and oral medications with narrow therapeutic indices. As the use of GLP-1 receptor agonists continues to expand, careful monitoring and increased vigilance for emerging drug interactions are crucial. Further research is needed to better understand these pharmacokinetic interactions and their impact on patient treatment.

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The authors declare no conflicts of interest.

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