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Case Report

Lithium toxicity following initiation of tirzepatide in a patient with bipolar I disorder

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ABSTRACT

Lithium has a narrow therapeutic window, with a therapeutic range for maintenance of 0.6 to 1.2 mmol/l, and toxicity usually occurs at concentrations of 1.3 mmol/l or greater. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have seen a marked rise in use for both diabetes and weight management, and an emerging body of case reports has described lithium toxicity associated with their use, predominantly with semaglutide. A 31-year-old man with a ten-year history of bipolar I disorder. His maintenance psychiatric medications included lithium carbonate ER 900 mg by mouth at bedtime daily. Approximately three months prior to presentation, tirzepatide 10 mg/0.5 ml was initiated subcutaneously once weekly for weight management. His lithium level at the time of initiation was 0.9 mmol/l. Three months after initiation, he began reporting a general sense of not feeling well, along with brain fog, dizziness, and gait disturbance, with good oral fluid and food intake throughout this period and no recent dietary or fluid intake pattern changes. A lithium level obtained at that time was found to be elevated at 1.7 mmol/l. Lithium was reduced to 300 mg daily for two weeks, and tirzepatide was held. A repeat lithium level two weeks later was 0.8 mmol/l. Lithium was then restarted at the original dose of 900 mg daily, and tirzepatide was subsequently discontinued. This case adds to a growing body of literature describing lithium toxicity with GLP-1 RA use, and for occurring in the absence of the gastrointestinal symptoms typically implicated in this interaction. Clinicians should maintain a high index of suspicion for increased lithium levels in patients with GLP-1 RA, with proactive rather than symptom-triggered lithium monitoring.

Keywords: Lithium, GLP-1 receptor agonist, Tirzepatide, Bipolar disorder, Drug interaction, Case report

INTRODUCTION

Lithium is an alkaline metal found naturally as a mineral. It has been used as lithium carbonate in treatment for bipolar disorder for decades, and additionally as an adjunctive option for recurrent or resistant major depressive disorder, with anti-suicidal properties.[1] However, lithium has a narrow therapeutic window, with a therapeutic range for maintenance of 0.6 to 1.2 mmol/l, and toxicity usually occurs at concentrations of 1.3 mmol/l or greater.[2] Both acute and chronic lithium toxicity can arise from inadequate renal excretion, which can stem from intravascular

volume depletion, reduced glomerular filtration rate, low-sodium diets, or the use of drugs like non-steroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs).[2,3] The consequences of excessively high levels of lithium can vary depending on the severity, with mild, moderate, and severe lithium toxicity often correlating with serum concentration. Some adverse effects include gastrointestinal manifestations such as diarrhea, vomiting, stomach pain, and others such as lack of coordination. In more extreme cases, nephrogenic diabetes insipidus, cardiac arrhythmias, seizures, blurred vision, confusion, agitation, and possible coma may occur.[1]

Glucagon-like peptide 1(GLP-1) receptor agonists (RAs) are incretin mimetic medications first approved by the US Food and Drug Administration (FDA) for type 2 diabetes mellitus with semaglutide (Ozempic) initially approved in 2017.[4] Their benefits in aiding weight loss in obese patients has been well known and documented. Several agents subsequently received FDA approval for chronic weight management, including liraglutide in 2014, semaglutide in 2021, and tirzepatide, a dual GLP-1/glucose-dependent insulinotropic peptide (GIP) RA, in 2023.[4,5]

GLP-1 RAs promote weight loss via different mechanisms, including slowing gastric emptying, motility of the small intestine, increasing insulin release, inhibiting glucagon release, and targeting the hypothalamus to reach the intended effect of patients eating less food.[6,7] GLP-1 agonists' side effects mainly reside within the gastrointestinal tract, such as nausea, vomiting, and diarrhea, which could lead to acute kidney injury due to volume contraction. Dizziness, mild tachycardia, infections, headaches, and dyspepsia may also occur. Rarely, pancreatitis, gallbladder problems, and kidney damage may happen to patients.[6]

Lithium clearance is closely related to renal sodium and water handling. Consequently, physiological conditions which promote volume contraction are expected to reduce lithium clearance independent of any change in glomerular filtration.[8] As GLP-1 RA-induced nausea, vomiting, and diarrhea may produce a comparable state of volume contraction, these agents have been hypothesized to elevate serum lithium concentrations through the same mechanism already implicated in other causes of lithium toxicity.[2] Unfortunately, there are no published pharmacokinetic studies directly characterising an interaction between lithium and GLP-1 RAs, and existing literature is limited to a small number of case reports and case series describing clinical association.

We present a case in which a patient, well maintained on lithium, developed elevated lithium levels when starting and continuing a GLP-1 RA. This case adds to the present literature suggesting a clinically significant interaction between lithium and GLP-1 RAs and highlights the need for regular monitoring of lithium levels in patients co-prescribed these agents.

CASE REPORT

Mr Z, a 31-year-old man, with a ten-year history of bipolar I disorder, most recent episode mixed with psychotic features, has been historically treated with lithium 900 mg daily, and different adjuvant antipsychotics such as risperidone and cariprazine among others, with different doses along the years and different degrees of efficacy. Prior to establishing care at our clinic four years ago, he had four psychiatric hospitalisations, related to chronic medication non-compliance and an involuntary commitment due to manic and psychotic behaviour with associated safety concerns. Given this history, he was transitioned to long-acting injectable (LAI) aripiprazole monthly 960 mg therapy and has been symptom free since. Over the four years on LAI antipsychotic therapy, he gained 58 pounds and weighed 230 lbs, with a BMI of 31 kg/m² at the time of his visit 6 months ago, in late 2025.

His maintenance psychiatric medications besides aripiprazole and lithium are divalproex sodium ER 500 mg by mouth at night daily, bupropion HCl ER (XL) 150 mg by mouth each morning daily, propranolol ER 80 mg by mouth daily, and benztropine mesylate 1 mg by mouth daily.

During this visit it was decided to initiate tirzepatide 10 mg/0.5 ml subcutaneously once weekly, even after ruling out Diabetes Mellitus through HbA1c, for weight management. His lithium level at the time of tirzepatide initiation was 0.9 mmol/l.

Over the following three months, the patient lost approximately 25 pounds of weight, down to 205 pounds, and reported no mood symptoms, and considerable improvement on his physical condition. However, around 14 to 15 weeks of this regimen he began reporting a general sense of brain fog, dizziness, gait disturbance along with generalized malaise and persistent nausea. He reported good oral fluid and food intake throughout this period, with no recent dietary or fluid intake pattern changes. A lithium level was immediately requested and it was found to be 1.7 mmol/l with serum creatinine in

normal range (1.0 mg/dl). The patient denied having presented any diarrhea, vomits, profuse sweating, or any drastic change in his habits and diet in the two months previous to this event.

Lithium dose was reduced to 300 mg daily for two weeks, and tirzepatide was held. A repeat lithium level after two weeks reported 0.8 mmol/l, with serum creatinine of 1.10 mg/dl. Lithium was then restarted at the original 900 mg daily and tirzepatide was subsequently discontinued. Further monthly appointments were suggested, along with dietary counselling.

DISCUSSION

This case presents a potential interaction between lithium and GLP-1 RAs, specifically tirzepatide, consistent with recently published case series and some case reports.[2,9-11] These publications described elevated serum lithium concentrations associated with GLP-1 RAs use. Mentioned mechanisms include, altered kidney function, dehydration from reduced oral intake, vomiting, or diarrhea, and delayed gastric emptying.[2,12] So far, there are no published human pharmacokinetic studies directly characterising an interaction between lithium and GLP-1 RAs.

This case provides us additional evidence on the possibility of the occurrence of lithium toxicity. Several mechanisms can have played a role just reinforcing the evidence that a relation might be present, but with no means to confirm how this happens. First, dehydration from reduced oral intake, vomiting, diarrhea, which impair the lithium clearance via increased proximal tubular sodium and water reabsorption.[2] In this case, Mr Z's lithium levels were found to be elevated within 3 months of initiating GLP-1 RAs. However, this occurs without change in oral fluid or food intake, making overt volume depletion less likely in this case. A related but rare possibility is acute kidney injury, which has occasionally been reported in association with GLP-1 RA use, generally in the context of severe dehydration.[13] We consider this mechanism unlikely to explain Mr Z's presentation, as no clinically significant change in renal function was observed. Secondly, delayed gastric emptying, a well-documented pharmacodynamic effect of GLP-1 RA, by slowing gastrointestinal transit.[9,14] However, it is unclear how this might affect lithium levels in the setting of a GLP-1 RA with extended-release lithium. Another contributing element could be weight loss itself.[15]

Reduced sodium intake, secondary to reduced appetite from GLP-1 RAs, offers a further possible mechanism. Because lithium is reabsorbed in the proximal tubule in parallel with sodium, reduced dietary sodium would be expected to increase reabsorption of both ions, without any change in glomerular filtration.[8] Although Mr Z did not report an overall reduction in food intake, a change in dietary sodium content specifically was not reported, and cannot be excluded as a contributing factor.

Finally, a direct pharmacokinetic interaction between lithium and GLP-1 receptor agonists has been hypothesized but remains unconfirmed, and current evidence does not clearly support this over the indirect mechanisms described above. Notably, at least one recent meta-analysis has suggested that GLP-1 RAs are associated with reduced, rather than increased, rates of renal injury.[16] Underscoring how unsettled these mechanisms remain. Lithium elevation can occur following GLP-1 RA initiation even without signs and symptoms of gastrointestinal illness or volume depletion. As lithium has a narrow therapeutic window, reinforcing the need for lithium level monitoring based on the timing of GLP-1 RA initiation or dose change, rather than reliance on symptom-triggered testing alone.[12,17]

Limitations

One case report is not generalized, and the information shared cannot be generalized to any population. Further research must be done to confirm any relationship between Lithium toxicity and GLP-1 agonists. It is not known whether other GLP-1 RAs would yield similar outcomes.

CONCLUSION

This case adds to a growing body of literature describing lithium toxicity when initiating GLP-1 RA, especially tirzepatide, in the absence of the gastrointestinal symptoms typically implicated in this interaction. While exact mechanisms behind this interaction are unknown, clinicians should maintain caution as lithium has a narrow therapeutic index, with potential severe consequences with toxicity levels.

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