Abstract

Background

Lithium has a narrow therapeutic index and is highly sensitive to changes in renal function, volume status, and concomitant medications. Glucagon-like peptide-1 (GLP-1) agonists, including tirzepatide, are increasingly used for metabolic indications with emerging reports suggesting a possible association with lithium toxicity even in the absence of traditional risk factors.

Case

We present a case of an adult with Bipolar II disorder on chronic lithium therapy with longstanding stability and preserved renal function. Prior to tirzepatide initiation, lithium levels were stable, including a value of 1.3 mEq/L (11 hours post-dose), prompting a preemptive dose reduction, without associated clinical symptoms of toxicity. Following initiation and titration of tirzepatide, dose and time adjusted lithium levels were higher than baseline, with levels of 1.1-1.2 (15-15.5 hours post-dose) associated with neurologic and gastrointestinal symptoms consistent with lithium toxicity. Symptoms persisted despite dose reduction until lithium was decreased to 600 mg daily, with subsequent resolution. Renal function and sodium levels remained stable throughout.

Discussion

Lithium levels are influenced by numerous factors including volume status, renal function and concomitant medications. GLP-1 based therapies promote weight loss, delayed gastric emptying and gastrointestinal effects which may alter lithium pharmacokinetics. In this case, renal function and sodium levels remained stable, making traditional causes of toxicity less likely. Notably, dose- and time-adjusted analysis demonstrated higher observed lithium concentration following tirzepatide initiation, suggesting increased lithium exposure. Symptom resolution following lithium dose reduction, despite continued tirzepatide therapy, supports an effect on lithium exposure rather than a direct adverse drug effect. This finding is consistent with a recent case series reporting similar lithium toxicity in three patients following semaglutide initiation, suggesting this may be a class effect of GLP-1 receptor agonists.

Conclusion

This case demonstrates higher observed lithium concentrations following tirzepatide initiation when accounting for dose and timing of serum level measurement, suggesting increased lithium exposure likely mediated by weight loss related changes in lithium clearance and volume distribution. Clinicians should consider closer monitoring when co-prescribing lithium and GLP-1-based therapies, even in the absence of renal dysfunction.