Empagliflozin-Mediated Lithium Excretion: A Case Study and Clinical Applications

Guy Philip Armstrong

Corresponding Author: Guy Philip Armstrong, e-mail: ArmstrongG@ramsayhealth.com.au

Conflict of interest: None declared

Patient: Male, 30-year-old
Final Diagnosis: Schizoaffective disorder
Symptoms: Renal excretion of lithium
Medication: Empagliflozin
Clinical Procedure: Nephrology • Psychiatry

Objective: Unusual or unexpected effect of treatment

Background: Empagliflozin selectively reduces apical sodium-glucose co-transporter 2 function in the proximal convoluted tubules, increasing sodium and glucose excretion in the urine, ultimately reducing glucose reabsorption in the kidneys for diabetic management. Lithium, the gold-standard treatment for bipolar disorder, also utilizes sodium transporters in the proximal convoluted tubules.

Case Report: Presenting with a manic relapse of refractory schizoaffective disorder, our patient was found to have subtherapeutic levels of lithium on admission due to poor outpatient medication compliance. Restoration to therapeutic lithium levels allowed inpatient blood glucose measurements, which led to a new diagnosis of type 2 diabetes mellitus. Given his comorbid severe hepatic impairment, obesity, and prior pancreatitis, the patient was started on empagliflozin to safely manage this new diagnosis without collateral organ injury. Routine monitoring found reproducible and clinically significant decreases in serum lithium levels in the presence of empagliflozin therapy, without obvious confounding factors. Subsequent discussion with specialist teams resulted in trialling metformin, which adequately controlled the new diabetic diagnosis without inpatient complications.

Conclusions: We suspect that empagliflozin reduced sodium-glucose and lithium-glucose reabsorption in the proximal connecting tubules, thereby increasing the renal excretion of sodium, glucose, and lithium. Applications include awareness of the interaction between these medications, support for the role of physiological SGLT-2-mediated lithium transport, and the possibility of using empagliflozin and other SGLT-2 inhibitors to treat life-threatening lithium toxicity.

MeSH Keywords: Drug Interactions • Lithium • Renal Excretion • Sodium-Glucose Transporter 2

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/923311
Background

Approved by both the US Federal Drugs Administration and the Australian Therapeutic Goods Administration in 2014 for the control of type 2 diabetes mellitus (T2DM), empagliflozin and other sodium-glucose co-transporter 2 (SGLT2) inhibitors are now frequently used in the evidence-based treatment of T2DM [1]. This clinical success stems from satisfactory diabetic control, marked cardiovascular and renal benefits, and manageable adverse effects, including increased predisposition to urinary tract infections (a consequence of glycosuria) and eu-glycemic ketosis [1–3]. Pharmacologically, empagliflozin is a reversible, highly potent, and highly selective competitive inhibitor of SGLT2, a co-transporter found predominantly in the S1 segment of the proximal convoluted tubule (PCT) and responsible for approximately 90% of renal glucose reabsorption in healthy individuals [1–4]. However, evidence suggests that 25 mg empagliflozin daily linearly reduces excess glucose reabsorption by less than 40%, perhaps due to the capacity of the normally redundant spared SGLT1 (found more distally in the PCT) [2,4].

Even more clinically successful is lithium; by virtue of its history, efficacy, availability, reduction in suicide rate, and purported role in neuroprotection, it remains the gold-standard mood stabilizer in those able to tolerate it [5]. However, the utility of lithium is limited by a narrow therapeutic index, highly variable clearance rates between individuals, and lethal toxicity, teratogenicity, and nephrotoxicity [5]. Since initial human trials in 1949, and FDA approval in 1970 for the treatment of mania, the renal clearance lithium has been extensively studied [5,6]. Like sodium and glucose, the majority (>60%) of filtered lithium is reabsorbed in the PCT, with distal epithelial sodium channels also contributing [7,8]. Established apical lithium transporters in proximal epithelial cells include the amiloride-sensitive sodium channel, the amiloride-sensitive sodium-proton exchanger, and, to a seemingly far lesser extent, the sodium-glucose and sodium-phosphate co-transporters (in typical human physiological conditions) [7–9]. Such utilization of sodium transporters by lithium is presumed to stem from their atomic similarities.

The following case report identifies a novel drug–drug interaction between empagliflozin and lithium.

Case Report

Presenting with a recurrence of insightless disinhibition, disorganization, uncontrollable drive, pressured speech, and exacerbated grandiose and religious delusions, an obese, 29-year-old man of Central American descent was admitted with a manic relapse of schizoaffective disorder. Since diagnosis in his late teens, various mood stabilizers and antipsychotics had been administered in the context of intellectual impairment and poor outpatient oral medication compliance; a severe, treatment-refractory schizoaffective illness; the gradual development of obesity and non-alcoholic fatty liver disease; and various adverse drug reactions, including valproate-induced pancreatitis, olanzapine-induced acute liver injury, and dose-related haloperidol-induced acute liver injury. The patient had been frequently treated by inpatient services, historically re-presenting following a reduction in the level of supervision by his supportive family and/or community outpatient supports, with subsequent non-compliance to oral lithium. The patient and family denied any smoking, alcohol, or illicit substances, yet poor appetite control had led to a body mass index (BMI) approaching 42 kg/m². In addition to 1350 mg modified-release oral lithium daily, the patient’s regular medications on admission were 300 mg (long-acting injectable) aripiprazole monthly, 50 mg pregabalin at night, 5 mg haloperidol at night, 3 mg clonazepam daily, vitamin D supplementation, and melatonin.

Initial difficulty in managing his drive, delusions, disinhibition, and disorganization led to administration of an intramuscular zuclopenthixol acetate course (125 mg, 150 mg, 150 mg every second day) and intramuscular benzodiazepines on a secure ward, with some settling effect. However, as in previous admissions, the restoration of therapeutic lithium levels (<0.2 mM to 1.1 mM by Day 4) with his regular dose of modified-release lithium (1350 mg daily) was found to markedly improve his manic and psychotic features.

This settling allowed the collection of routine nursing observations on Day 9, including blood sugar levels (BSLs), which were found to be 26.2 mM (without ketosis). Subsequent investigation found an HbA1c of 7.3%, leading to a new diagnosis of T2DM. Further exploration of the patient’s medical history found the previous use of metformin for pre-diabetes 1 year ago, which was ceased in the context of acute-on-chronic hepatic injury during trials of oral olanzapine and high-dose oral haloperidol. Consultation with medical staff, diabetic educator staff, and diabetic guidelines led to a mutual decision to trial empagliflozin over acarbose due to the relative safety profile, as all other oral diabetic medications were considered contraindicated in the context of previous pancreatitis and severe liver impairment. Empagliflozin was commenced on Day 10 and uptitrated to 25 mg every morning over the following days, with excellent diabetic control (BSLs 6–11 mM throughout the day) and without physiological adverse effects. However, on Day 13, routine blood tests identified a subtherapeutic lithium level (0.4 mM). Repeat testing (Day 14) confirmed the subtherapeutic levels. Following a suspicion of empagliflozin-mediated lithium excretion, empagliflozin was withheld, and 10 units of covering Lantus at night ensured euglycemia. By Day 20 of admission, lithium levels had returned to therapeutic
range (1.3 mM). A willingness of our patient and his family to re-trial empagliflozin at 25 mg every morning led to another subtherapeutic lithium level (0.5 mM) by Day 22 (confirmed on Day 23). No ketosis was detected on routine nursing bedside testing, the patient remained well hydrated, plasma sodium and potassium were preserved within the normal range, and an eGFR >90 ml/min/1.73 m² was maintained throughout the admission.

Following endocrinology consultation and recommendation, empagliflozin was ceased and instant-release metformin 500 mg was first re-triailed on Day 24 of admission. Euglycemia was then maintained without adverse effects such as LFT derangement, precipitation of lactic acidosis, or pancreatitis. With progressive stabilization and concurrent re-implementation of outpatient community supports, the patient was discharged home at baseline function and therapeutic lithium level (0.9 mM) a few days later. The sole change to regular medication throughout the admission was the re-introduction of metformin.

Discussion

Despite the unexpected and previously undocumented strong negative correlation between a SGLT-2 inhibitor and serum lithium levels in this case, the connection between lithium (mostly absorbed by sodium transporters in the PCT) and empagliflozin (which impairs an apical sodium-glucose co-transporter in the PCT) is theoretically unsurprising. This parallels the discovery of how amiloride, through inhibition of the amiloride-sensitive sodium channel, reduces lithium reabsorption and subsequently manages nephrogenic diabetes insipidus (alongside a complex reversal of aquaporin downregulation) [9]. With a Naranjo Adverse Drug Reaction Probability Scale score of +8, further cases and/or prospective scientific enquiry are necessary to validate this case’s probable drug–drug interaction.

The reproducibility in this case also questions the consensus, founded on a heavily-referenced paper by Holstein-Rathlou in 1990 [10], about the theoretically-limited role of the sodium-glucose co-transporter in lithium reabsorption [7]. We suggest that a large amount of lithium must be transported by SGLT-2 for empagliflozin to have so markedly impaired our patient’s serum lithium levels, given the reported maximal 40% reduction of empagliflozin in clinical SGLT-2 function. Similarly, Uwai et al. [11] found (in rat studies) that two-thirds of lithium reabsorption occurred through the sodium-phosphate co-transporter, opposing the consensus that these transporters negligibly contribute. Given new empirical and recent investigative evidence opposing the existing theoretical model, further research should identify and/or confirm the relative efficacy of different apical PCT transporters and channels on lithium reabsorption.

Finally, if lithium is substantially reabsorbed by SGLT-2 as empirically observed, and empagliflozin markedly reduces SGLT-2 function with a tolerable adverse effect profile, empagliflozin could improve the management of lithium toxicity. Lithium toxicity is life-threatening and can cause cardiac arrest, hyperthermia, seizures, and potentially irreversible tremor, ataxia, and nystagmus [12]. Due to a lengthy physiological half-life of 24 hours, lithium toxicity is currently managed through non-specific measures such gastric lavage, intravenous dilution, and/or haemodialysis to expedite clearance [12]. As oral empagliflozin reaches peak plasma concentrations within 1.5 hours, empagliflozin (and other SGLT-2 inhibitors) could improve best practice management of lithium toxicity by expediting renal excretion of lithium in a more cost-effective, convenient, and safe manner. Further research should seek to validate this hypothesis.

Conclusions

Our unique case report of trialling empagliflozin in an inpatient with frequent lithium-monitoring empirically identified a reproducible effect of empagliflozin use on lithium levels. This Naranjo-probable suspected association is only partially supported by the current understanding of lithium and SGLT-2 inhibitor pharmacology; therefore, our experience in treating this patient raises questions about the previously proposed theoretical models, which possibly minimize the role of the SGLT in lithium reabsorption. With further research to validate the findings of this case study, subsequent research could assess the relative cost-efficacy, convenience, and safety of using SGLT-2 inhibitors to manage lithium toxicity over existing best practice.

Acknowledgements

Dr Amatul Uzma, Supervising Consultant Psychiatrist (Joondalup Health Campus Mental Health Services) and the Joondalup Health Campus Human Resource Ethics Committee, for their general supervision and permission to publish this case report.

Our patient and his family, for their willingness to share this previously undocumented outcome with the world.

Conflicts of interest
None.
References:

1. Therapeutic Goods Administration (AUS). Australian Register of Therapeutic Goods – Empagliflozin [Internet]. Australia, 2013, https://www.ebs.tga.gov.au/
2. Ferrannini E: Sodium-glucose co-transporters and their inhibition: Clinical physiology. Cell Metab, 2017; 26(1): 27–38
3. Thomson SC, Vallon V: Renal effects of sodium-glucose co-transporter inhibitors. Am J Cardiol, 2019; 124(1): 528–35
4. Al-Jobori H, Daniele G, Cersosimo E et al: Empagliflozin and kinetics of renal glucose transport in healthy individuals and individuals with type 2 diabetes. Diabetes, 2017; 66(7): 1999–2006
5. Malhi GS, Outhred T, Morris G et al: Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary. Med J Aust, 2018; 208(5): 219–25
6. Oliveira JL, Silva Júnior GB, Abreu KL et al: Lithium nephrotoxicity. Rev Assoc Med Bras, 2010; 56(5): 600–6
7. Timmer RT, Sands JM: Lithium intoxication. J Am Soc Nephrol, 1999; 10: 666–74
8. Schneider A, Azab AN: Lithium-induced nephrogenic diabetes insipidus – a case report and discussion on the pathophysiological mechanism. Int J Nephrol Kidney Failure, 2015; 1(3): 1–4
9. Kortenoeven ML, Li Y, Shaw S et al: Amiloride blocks lithium entry through the sodium channel thereby attenuating the resultant nephrogenic diabetes insipidus. Kidney Int, 2009; 76(1): 44–53
10. Holstein-Rathlou NH: Lithium transport across biological membranes. Kidney Int Supp, 1990; 28: 4–9
11. Uwai Y, Arima R, Takatsu C et al: Sodium-phosphate cotransporter mediates reabsorption of lithium in rat kidney. Pharmacol Res, 2014; 87: 94–98
12. Grandjean EM, Aubry JM: Lithium: Updated human knowledge using an evidence-based approach. Part II: Clinical pharmacology and therapeutic monitoring. CNS Drugs, 2009; 23(4): 331–49