CLINICAL VIGNETTE

Empagliflozin Contributing to Hyponatremia and Dehydration in an Older Adult

Wendy Zachary, MD and Catherine Lindsay, MD

History

An 83-year-old woman presented to the Emergency Department after a fall. She stated that her walker slid away from her, and both her head and back contacted with the ground. She denied a prodrome but reported recent dizziness while ambulating that resolved with sitting and time. Past medical history includes hypertension, hyperlipidemia, atrial fibrillation status post cardioversion and on anticoagulation, nonobstructive coronary artery disease, heart failure with a recovered ejection fraction of 50%, and restless legs syndrome.

Four months prior to the current presentation, she was readmitted after Holter monitor revealed some episodes of ventricular tachycardia. During that admission, ejection fraction was 30-35%, and she was successfully cardioverted. Empagliflozin and spironolactone were added. Sodium levels during that hospitalization ranged from 127 to 133, without additional evaluation.

Three months prior to the current presentation, an outpatient echocardiogram revealed an ejection fraction of 56%. During that office visit, the patient's sodium was 129 and unspecified weight loss was noted.

On current presentation, the patient's medication list included: apixaban, atorvastatin, cholecalciferol, ropinirole, metoprolol succinate, furosemide, spironolactone, empagliflozin, potassium supplements, pregabalin, and sacubitril-valsartan. There had been no changes to her medications within the previous two months.

Physical exam revealed normal temperature, heart rate ranging from 48 to 72, blood pressures 109-172/59-92, oxygen saturation 96-100%, and respiratory rate of 19. Orthostatic vital signs were not performed prior to IV fluid administration. Five months prior the patient was admitted for heart failure thought to be due to atrial fibrillation. Ejection fraction was 41-45%, and cardiac catheterization revealed nonobstructive disease. Cardioversion was unsuccessful, and amiodarone and furosemide were started, and she was sent home with a Holter monitor. Notably, sodium levels ranged from 128 to 130, without evaluation. Sertraline was started for depression and anxiety later that month. However, the patient reported taking this for only a short period of time.

Her mucous membranes were dry, heart rate was regular, there was no audible murmur, lungs clear, she was alert, attentive, and slowly ambulating independently. Labs were notable for sodium of 122, blood urea nitrogen of 23, and creatinine of 0.99. Urinalysis showed increased glucose but was otherwise unremarkable. Urine lytes showed a urine creatinine of 60.6, urine urea nitrogen of 474, urine sodium of 54, urine osmolality of 506, and fractional excretion of urea was 33.7%. CXR and lumbar spine x-rays and non-contrast CT of the brain were without acute findings.

The patient's diuretics and empagliflozin were held and IV fluids were administered. Her sodium rose to 127, though with further IV fluids, her sodium decreased again, suggesting an underlying syndrome of inappropriate diuretic hormone. Once her sodium normalized, she was discharged on furosemide, with spironolactone and empagliflozin held until outpatient follow up with cardiology.

Discussion

This patient's dehydration and hyponatremia was temporarily related to starting empagliflozin, in the setting of a reduced ejection fraction, along with two other diuretics, contributing to dehydration and hyponatremia.

Empagliflozin (Jardiance) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. This class of drugs blocks the sodium-glucose cotransporter 2 at the proximal tubule, reducing blood glucose (and sodium) by increasing urinary glucose (and sodium) excretion rather than increasing insulin secretion or sensitivity to insulin.[1] Therefore, it was thought to have played a role in the patient's presentation via its diuretic and natriuretic properties.

Empagliflozin has become a treatment choice for a variety of conditions for several reasons. Medications in this class only lower plasma glucose levels by blocking reabsorption of filtered glucose, which falls as plasma levels fall. Therefore, they do not usually cause hypoglycemia. Predominantly via their diuretic properties, SGLT2 inhibitors also modestly decrease blood pressure and weight.[1]

Patients with diabetes on SGLT2 inhibitors have been shown to have both better glucose control when used in conjunction with usual hypoglycemics and a slower decline in glomerular filtration rate.[2] In patients with both diabetes and overt coronary artery disease, atherosclerotic cardiovascular and all-cause

mortality may be reduced with use of empagliflozin, as are hospitalizations due to heart failure.[3]

While this patient had neither diabetes nor overt coronary artery disease, she was started on empagliflozin due to her heart failure with reduced ejection fraction of 30-35%. Benefits for this population were studied in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced). This study included 3730 patients who had an ejection fraction of less than 40%. Approximately 50% of the patients did not have diabetes, and approximately half of them did not have overt CAD. They were randomized to 10mg empagliflozin vs. placebo (added to optimized therapy), with median follow up of sixteen months. The primary outcome was a composite of cardiovascular death and hospitalization for heart failure. Empagliflozin showed a reduction in primary outcome (19.4 versus 24.7 percent; HR 0.75, 95% CI 0.65-0.86), in patients with and without DM. Notably, there was a slightly higher reduction in patients on sacubitril-valsartan, which this patient had also been taking. A secondary outcome was annual rate of decline in eGFR, which was demonstrated in patients on empagliflozin. Furthermore, there was a decrease in risk of serious adverse renal outcomes (composite of dialysis, renal transplant, and sustained reduction in GFR).[4]

Despite the potential benefits of empagliflozin, there is a subset of patients for which its use is not recommended. This includes patients with Type I DM, a history of or predisposition to diabetic ketoacidosis, or an estimated glomerular filtration rate of less than thirty or rapidly declining renal function. It should be used in caution with patients who have volume depletion, symptomatic hypotension, a history of complicated urinary tract or genitourinary infections, presence of risk factors for foot amputation, and bone loss or fracture.[5]

Based on the risk-benefit analysis, this appears to have been an appropriate medication for this patient at the time that it was prescribed. She was, in fact, not rehospitalized for heart failure after starting empagliflozin, though the primary reason for her heart failure was thought to be atrial fibrillation, and she had been successfully cardioverted. However, due to her volume depletion, the empagliflozin should be held at least for the time being.

Whether or not to restart the empagliflozin is a more challenging question. In the Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-Preserved) trial, patients with a preserved ejection fraction (>40%), were studied, again with the primary outcome was composite of cardiovascular death and hospitalization for heart failure. Empagliflozin showed a reduction in primary outcome (HR 0.79, 95% CI, p<0.002), in patients with and without DM. However, patients with previous EF of <40% were not included.[6]

Interestingly, the original protocol for both EMPEROR-Reduced and EMPEROR-Preserved trials included a withdrawal of the study drug (either empagliflozin or placebo) for thirty days after receiving between one and three years of treatment. Data was collected on ninety-three percent of these patients, and more than half completed a Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), which measures symptoms, physical and social limitations, and quality of life in patients with heart failure. When the study drugs were withdrawn, the annualized risk of major heart failure events increased in patients withdrawn from empagliflozin but not in patients withdrawn from placebo (17.0 [95% CI, 12.6–22.1] versus 14.1 [95% CI, 10.1–18.8] events per 100 patient-years, respectively.)[7,8] This suggests that the patient in this scenario may be worse off the medication long term from a heart failure perspective.

In summary, take caution when using empagliflozin with diuretics, as concomitant use is prevalent, and can increase the risk of dehydration due to its diuretic effects. It is reasonable to check creatinine levels three months after initiation of empagliflozin, then annually or as clinically indicated, with special attention to concerns for volume depletion. Empagliflozin should also be held during episodes of acute illness, prolonged fasting, and prior to surgical procedures, when its diuretic effects may be more pronounced.

REFERENCES

1. **Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, Capuano G, Canovatchel W; Canagliflozin DIA 2001 Study Group**. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care*. 2012 Jun;35(6):1232-8. doi: 10.2337/dc11-1926. Epub 2012 Apr 9. PMID: 22492586; PMCID: PMC3357223.
2. **Clar C, Gill JA, Court R, Waugh N**. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open*. 2012 Oct 18;2(5):e001007. doi: 10.1136/bmjopen-2012-001007. PMID: 23087012; PMCID: PMC3488745.
3. **Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators**. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978.
4. **Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators**. Cardiovascular and Renal Outcomes with Empagliflozin in

Heart Failure. *N Engl J Med*. 2020 Oct 8;383(15):1413-1424. doi: 10.1056/NEJMoa2022190. Epub 2020 Aug 28. PMID: 32865377.

5. **DeSantis A**. Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus. Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on November 30, 2023.)
6. **Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators**. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.
7. **Packer M, Butler J, Zeller C, Pocock SJ, Brueckmann M, Ferreira JP, Filippatos G, Usman MS, Zannad F, Anker SD**. Blinded Withdrawal of Long-Term Randomized Treatment With Empagliflozin or Placebo in Patients With Heart Failure. *Circulation*. 2023 Sep 26; 148(13):1011-1022. doi: 10.1161/CIRCULATIONAHA. 123.065748. Epub 2023 Aug 24. PMID: 37621153; PMCID: PMC10516173.
8. **Spertus JA, Jones PG, Sandhu AT, Arnold SV**. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020 Nov 17;76(20):2379-2390. doi: 10.1016/j.jacc.2020.09.542. PMID: 33183512.