CLINICAL VIGNETTE

The Use of SGLT2 Inhibitors in Heart Failure: Two Cases of Patients with Low Blood Pressure

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Case 1

A 61-year-old female with type 2 diabetes mellitus (T2DM) presented to endocrinology with hypotension. She reported shortness of breath and episode of atypical chest pain of 1-hour duration with associated lightheadedness and dizziness. Her medical history is remarkable for non-obstructive coronary disease, non-ischemic cardiomyopathy NYHA class 3 with an ejection fraction of 25-30%, chronic obstructive pulmonary disease, dyslipidemia, hypertension, and prolonged QT syndrome.

She was taking carvedilol 3.125 mg twice daily, Furosemide 40 mg daily, Benazepril 2.5 mg daily, Spironolactone 12.5 mg daily, Lantus 18 units at bedtime, Humalog 3 units with meals, metformin 1000 mg twice daily, and Dapagliflozin (Farxiga®) 5 mg daily which was the only new medication since her last visit.

Physical examination showed a well-nourished, well-developed obese female in no distress. Vital Signs, Blood pressure (BP) 70/48, heart rate (HR) 95/min (bpm); respiratory rate 14 and afebrile; Weight 187 lbs. (84.8 kg), BMI 34.2 kg/m2. Physical examination of lungs, heart and abdomen were within normal limits.

Patient was given two cups of water and repeat manual BP was 68/48 mmHg. Dapagliflozin was stopped and she was referred to the emergency department for further evaluation and management.

In the emergency department, laboratory testing including CBC, BMP, troponin, bacterial cultures, lactate, COVID 19 PCR, ck total and urinalysis were unremarkable. Imaging revealed a normal chest x-ray and EKG. Patient was given 1-liter IV fluids with improvement in BP to 88/53 mmHg. She felt clinically improved and was discharged home with close follow-up.

Two days later at her cardiology follow-up visit, her BP was 99/58 mmHg. Furosemide was reduced to 20 mg daily and Dapagliflozin 5 mg daily was resumed.

One week later, her BP was 71/54 with HR 102. Patient was given 1 liter of normal saline. BP improved to 83/50 mmHg. She was continued on the same medicines and encouraged to maintain hydration. She remained hemodynamically stable.

Case 2

A 62-year-old female with nonischemic cardiomyopathy NYHA class II with an ejection fraction of 30-35% presented for follow-up. Her previous medical history was remarkable for Graves' disease s/p radioactive iodine ablation in 1983, colon cancer s/p right hemicolectomy and chemotherapy (Nivolumab, Oxaliplatin) in 2018 now in remission and ventricular tachycardia. The patient did not have a history of T2DM.

She has been taking aspirin 81 mg daily, levothyroxine 88 mcg daily, metoprolol 50 mg XL daily, rosuvastatin 5 mg daily, spironolactone 25 mg daily and sacubitril-valsartan 24-26 mg 0.5 mg tablets twice daily.

Physical examination showed a well-nourished, well-developed female in no distress or discomfort. Vital Signs; BP was 89/69 and HR76 bpm; respiratory rate 14 and afebrile; Weight 140 lbs. (63.7 kg), BMI 20.7 kg/m2. Physical examination of lungs, heart, abdomen, and extremities were within normal limits.

Patient was started on dapagliflozin 5 mg daily and successfully uptitrated to 10 mg over a period of one month without any side effects. Her repeat vital signs at her 3-month follow-up visit were BP 109/80; HR65 bpm; respiratory rate 14 and afebrile. She did not require any changes in her other medications and remained hemodynamically stable.

Discussion

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are quickly becoming one of the preferred oral diabetic medications for patients with heart failure (HF) with T2DM. There is increasing evidence that SGLT2 inhibitors exert cardioprotective and renoprotective effects in patients with T2DM that are far greater than expected based on their effects on glycemia or glycosuria. In multiple large-scale randomized controlled trials, SGLT2 inhibitors reduced risk for hospitalizations for HF and often decreased risk of cardiovascular death.[1-3] More recently, the SGLT2 inhibitor dapagliflozin has been shown to cause a reduction in death and HF hospitalization in patients with HF with reduced ejection fraction without T2DM.[4] Additionally, SGLT2 inhibitors also reduce the risk of end-stage renal events in diabetic patients, including the occurrence of renal death and the need for dialysis or renal transplantation by ~30%.[5] As the list of benefits broaden for the use of SGLT2 inhibitors in

patients with and without T2DM, it is important for physicians to understand potential hemodynamic adverse effects that SGLT2 inhibitors may induce in medically complex individuals.

The SGLT2 receptor is localized to the renal proximal convoluted tubules, acting to reabsorb ~80-90% of the filtered glucose, coupled with sodium. Inhibition of SGLT2 therefore results in glycosuria, and the ensuing osmotic diuresis may be beneficial particularly for those with T2DM, hypertension, and HF.[6] It is likely through a diuretic effect that SGLT2 inhibitors reduce systolic BP in both hypertensive and normotensive patients, usually by 3-6 mmHg.[1-3,7] Individuals on additional diuretics, particularly loop diuretics, may experience larger reductions in blood pressure.

In the RECEDE CHF-Trial, the combined diuretic and natriuretic effects of empagliflozin in combination with loop diuretics was evaluated. This randomized control trial showed that within six weeks empagliflozin caused a significant increase in total urine volume without a significant increase in urinary sodium or fraction excretion of sodium compared with placebo. Given the diuretic effect with empagliflozin, 5 of 24 patients required a 50% reduction in their furosemide dose by day three. These 5 patients also experienced a mean weight loss at day three of 2.22±1.19 kg. When empagliflozin was stopped at the end of the study, participants required the uptitration of furosemide to their pre-study dose.[8]

Our patient in case 1 demonstrates the pronounced diuretic effect an SGLT2 inhibitor can have in combination with a loop diuretic and likely explains her sudden drop in blood pressure after dapagliflozin was initiated. The patient in case 2 was not on a loop diuretic and did not experience the extreme drop in BP when dapagliflozin was initiated despite having a low baseline BP. The comparison of these two cases illustrated the need for caution when initiating SGLT2 inhibitors in individuals with or without diabetes who are using loop diuretics. Patients not on loop diuretics may or may not experience a drop in BP with the introduction of an SGLT2 inhibitor. Additionally, the second case demonstrates that patients with HF and low baseline BP not on loop diuretics may be able to safely use an SGLT2 inhibitor without a significant change in their hemodynamic status.

The use of SGLT2 inhibitors will continue to grow in popularity for patients with T2DM, HF, and/or renal disease given their compelling cardioprotective and renoprotective effects. These agents are known to have a diuretic and BP lowering effect. Extreme caution should be taken when prescribing an SGLT2 inhibitor to a patient with tenuous fluid status, low BP, or with concurrent use of a loop diuretic. Daily monitoring through patient- initiated BP checks and weight checks may help detect whether medicines affecting BP or diuresis need to be adjusted, particularly during the first three days after an SGLT2 inhibitor is initiated. Awareness of the hemodynamic effects of SGLT-2 inhibitors and monitoring patients closely during initiation of therapy will maximize the safety of these agents while allowing patients to benefit from their cardioprotective, glucose lowering, and renoprotective effects.

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