Acute Renal Failure after Dapagliflozin Treatment: A Case Report

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Abstract

Sodium glucose Cotransporter-2 (SGLT2) inhibitors lower serum glucose through reductions in glucose reabsorption by the kidney. Dapagliflozin is one of the first members of the SGLT2 group of drugs. In this paper, we report a case of acute renal failure secondary to dapagliflozin use. A 75-year-old woman with diabetes and hypertension presented with weakness, nausea and vomiting. Dapagliflozin had been added to her treatment due to the high blood sugar a week ago. Acute renal failure secondary to tubulointerstitial nephritis was diagnosed. The patient was hydrated. Dapagliflozin was discontinued. With hydration, urine output increased. BUN and creatinine levels and clinical status returned to normal after five days. Patients receiving dapagliflozin have an increased risk for developing renal failure due to the high amount of diuresis and dehydration. Therefore, renal functions should be closely monitored in these patients.

Key words: Acute Renal Failure, Dapagliflozin, side effect

1. Introduction

Sodium glucose Cotransporter-2 (SGLT2) inhibitors are a new class of drug approved for the treatment of type-2 diabetes. Through reductions in glucose reabsorption by the kidney, SGLT2 inhibitors lower serum glucose in patients with type 2 diabetes and they improve glucose control whether used alone or in combination with other drugs. They have various advantages as oral antidiabetic agents such as reduction in visceral fat, long durability of action, weight loss, and reduction of systolic blood pressure in addition to the low risk of hypoglycaemia (1,2).

Dapagliflozin (DPG) is one of the first members of the SGLT2 group of drugs. It is an orally bioavailable, selective and reversible inhibitor of SGLT2 that has been demonstrated to improve parameters of glycaemic control and promote weight loss in patients with T2DM and normal kidney function (3).

The most frequently reported adverse events with SGLT2 inhibitors are female genital mycotic infections, urinary tract infections and increased urination (4). Their middle and long term side effects are of importance. In this paper, we report a case of acute renal failure secondary to dapagliflozin use.

2. Case

A 75-year-old obese woman, normally living abroad and with a 15-year history of type 2 diabetes mellitus, presented to the emergency room with weakness, nausea and vomiting. In addition to type 2 diabetes, she had also...
hypothesis, hypertension and heart failure. She had been receiving metformin, valsartan, exenatide and L thyroxine for the last 2 years. Laboratory studies performed 1 month before revealed microalbuminuria, normal BUN and creatinine. Dapagliflozin added to her treatment a week ago. She had no history of fever, diarrhea, vomiting, NSAID use or exposure to contrast material. Her physical examination demonstrated an obese patient, clear consciousness, temperature 37°C, blood pressure: 120/80mmHg, pulse: 96/min and rythmic, minimal pretibial edema and a tongue with a rusty and dry appearance. All other system examinations were normal.

Her laboratory tests revealed WBC 20.500/mm³ (4.800-10.800), hemoglobin: 12.2g/dL (12.0-16.0), platelet: 149000/µL (130000-400000), CRP 56 mg/dL (0-3), glucose 187 mg/dL (74-106), urea: 127mg/dL(17-43), creatinine 2.59 mg/dL (0.51-0.95), potassium 5.6mmol/L (3.5-5.1), sodium 134mmol/L (136-146), INR 1.23 (0.8-1.2) and blood gasess pH 7.28 (7.35-7.45). Her urine analysis revealed density of 1015, leucocytes, trace protein and ketones. The patient was admitted with the diagnosis of acute renal failure. Renal ultrasonography was within normal ranges. Echocardiography was performed and revealed EF: 55%, no valvular disease and normal pulmonary pressures. Urine culture was negative. The patient’s body mass index (BMI) was 45 kg/m². Protein excretion in 24-hour urine was 478 mg. The patient was consulted to the infectious diseases and nephrology departments. Acute renal failure secondary to tubulointerstitial nephritis was diagnosed. The patient was hydrated. Dialysis requirement did not arise. Dapagliflozin, valsartan, spironolactone and exenatide were discontinued. Glycaemic control was managed with insulin and blood pressure with amlodypin. With hydration, urine output increased from 500cc/day on admission to 3000cc/day. BUN and creatinine levels and clinical status returned to normal.

3. Discussion

Dapagliflozin is a competitive, reversible and selective inhibitor of SGLT2. After oral intake, it reaches maximum plasma concentration within 2 hours and has a half-life of 17 hours. Preclinical trials have shown that its oral absorption is good, it is tolerated well with foods, can be sufficiently excreted through the kidneys at doses between 2.5 – 500 mg without leaving behind an active metabolite and that a single daily dose is adequate. Dapagliflozin does not have an effect on p450 cytochrome system and is excreted primarily by glucuronidation, hydroxylation and O-deethylation (5). SGLT2 inhibitors inhibit the reabsorption of renal glucose therefore leading to glycaemic control and weight loss. Decrease in blood pressure and uric acid levels are another important and positive effect of these drugs. However, osmotic diuresis caused by glucose excretion via urine and an increase in genitourinary infections, cancer and liver toxicity are the reported negative effects of them (3,5). Many studies have reported good results with the addition of SGLT2 inhibitors to metformin or metformin with sulfonylurea treatment in diabetic patients with refractory glyceamic control. A study by Neal et al evaluated the effect of adding canagliflozin to insulin in type 2 diabetes. In this double blinded placebo controlled CANVAS study, blood glucose, body weight and blood pressure was significantly reduced, while on the other hand, hypoglycemia, genital micotic infections and hypovolemia was more frequently observed (6). In another study, Henry et al evaluated the effect and safety of dapagliflozin in type 1 diabetic patients during a 2 weeks’ study period (7). Positive results were reported for both effect and short-term safety.

The most frequently reported side effect of SGLT2 inhibitors are genital micotic infections and urinary tract infections (4). Dapagliflozin, which is a competitive, reversible and highly selective inhibitor of SGLT2, is the first drug in this group to receive approval for use in USA and EU (8).

Dapagliflozin is not advised in patients with bladder cancer as DPG has been shown to increase the incidence of bladder cancer when compared to placebo. Studies are continuing on the cardiovascular safety of DPG, with results yet to be published.

Glomerular filtration rate initially decreases and then returns to normal in patients taking dapagliflozin. Patients receiving dapagliflozin have an increase in amount of diuresis that can lead to dehydration resulting in increases in urea and hematocrit levels (9), with reports of patients further developing renal failure (10).

Our patient’s eGFR was calculated to be 80 mL/min before DPG was commenced. However, she had a history of grade 4 diabetic nephropathy and use of RAS blocker. The patient, who was already taking metformin and exanatide,
had been started on DPG due to its weight loss promoting effect. There are several studies demonstrating weight loss without hypoglycaemia in patients undergoing metformin with DPG therapy (8).

SGLT2 inhibitors produce osmotic diuresis due to glycosuria. The common osmotic diuresis-related adverse effects reported were pollakiuria, nocturia, micturition frequency, and thirst related (increased thirst, dry mouth, polydipsia, throat dry, or tongue dry). Volume depletion-related adverse effects were captured in trials of SGLT2 inhibitors: reduced blood pressure, dehydration, postural dizziness, orthostatic hypotension, and reduced urine output (11). Renal failure in this case might also develop due to the volume depletion-related adverse effects.

The patient reported in this case also used exenatide which is a short acting GLP-1 analogue. Its most unsettling side effect is pancreatitis. Other side effects include (>10%) nausea, diarrhea and hypoglycemia (especially when combined with sulphonurea). Acute renal failure is seen in <1% and may be seen together with urinary tract infections. It is not recommended for use in severe renal impairment (creatinine clearance < 30 ml/min) (12). Our patient had been on exenatide for the last 2 years. Renal failure was due to tubulointerstitial nephritis that occurred after dapagliflozin use, therefore the responsible agent was believed not to be exenatide.

Through its various mechanisms of effect, dapagliflozin promising new agent for the treatment of diabetes. Case reports are important for reporting side effects so the effect and safety of this drug can be properly evaluated. As seen in our report, renal functions should be closely monitored when DPG is commenced, especially in morbidly obese patients and those that have diabetic nephropaty.

4. References