CASE REPORT

Successful Withdrawal from Dobutamine by Canagliflozin in a Diabetic Patient with Stage D Heart Failure

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Summary

Patients with stage D heart failure (HF) frequently become dependent on high doses of diuretics and inotropic agents. Recently, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), an oral antidiabetic agent, has been demonstrated to have favorable effects in preventing HF. However, it remains unknown whether SGLT2i is reliable for patients with decompensated HF. We experienced a case of a patient with stage D HF for whom attempting intravenous dobutamine withdrawal was difficult even after the administration of all conventional pharmacological treatment. Administration of canagliflozin produced an additive diuretic action and correction of volume overload in combination with azosemide and tolvaptan, and resulted in successful withdrawal of dobutamine. Thus, SGLT2i might be promising for the treatment of patients with congestive HF who are refractory to conventional diuretic treatment.

Key words: Diabetes mellitus, Sodium-glucose cotransporter 2 inhibitor, Diuretics, Inotropic agents

Sodium-glucose cotransporter 2 inhibitors (SGLT2i-s) are novel antidiabetic agents with multiple effects such as a glucose-lowering effect, osmotic diuretic action, and others. Recently, empagliflozin, an SGLT2i, has been demonstrated to reduce death from cardiovascular causes and hospitalization for heart failure (HF) in the EMPA-REG OUTCOME trial. Importantly, this significant reduction of both mortality and HF emerged after only a couple of months of treatment, which might be attributable to the favorable effects of SGLT2i on hemodynamics, such as osmotic diuretic action, reduction of preload and afterload, and inhibitions of neurohumoral system. The EMPA-REG OUTCOME study supports the concept that SGLT2i is also effective for decompensated HF, but it remains unknown whether SGLT2i is actually effective in such patients. Here we describe a case of successful HF treatment with canagliflozin, one of the SGLT2i-s, in a patient with stage D HF and diabetes mellitus. Administration of canagliflozin produced an additive diuretic action and correction of volume overload in combination with azosemide and tolvaptan, and resulted in successful withdrawal of dobutamine.

Case Report

The patient was a 67-year-old woman with ischemic cardiomyopathy (Table) who had received coronary artery bypass in October 2015. In the patient, signs of HF worsened even after introduction of standard medical therapy, and the patient needed pimobendan with high doses of loop diuretics and tolvaptan. The patient soon became dependent upon intravenous infusion of inotropes, including dobutamine and olprinone and received intra-aortic balloon pumping (IABP). The patient was transferred to our hospital in January 2016. On admission, serum levels of creatinine 0.99 mg/dL, total bilirubin 0.8 mg/dL, and HbA1c 7.4% were assayed, and the plasma B-type natriuretic peptide (BNP) was 2,679 pg/mL. Transthoracic echocardiography showed left ventricular ejection fraction of 15% along with dilatation of left ventricle (diastolic diameter: 65 mm). Blood pressure and pulse rate were 135/82 mmHg and 109 per minute and right catheterization showed that mean right atrial pressure was 9 mmHg, mean pulmonary capillary wedge pressure was 31 mmHg, and cardiac index was 2.3 L/minute/m² under continuous infusion of carperitide (0.06 μg/kg/minute), dobutamine (5 μg/kg/minute), olprinone (0.3 μg/kg/minute) and IABP. IABP and intravenous infusion of olprinone were removed nine and 16 days after admission, respectively. However, in the process of tapering of dobutamine, the patient’s body weight and BNP level were gradually increased and signs of HF were again worsened. The dose of dobutamine was increased again even in the incremental combination with pimobendan, denopamine, and docarpamine (Figure).

Therefore, we decided to initiate canagliflozin of 100 mg/day to control the patient’s body fluid balance expecting a diuretic effect. Urinary glucose excretion and urine

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volume were significantly increased after canagliflozin administration (Table). Hemoglobin and hematocrit were also elevated after one week of canagliflozin administration. Dobutamine could be tapered and finally discontinued after eight weeks of canagliflozin without any sign of worsening HF. The patient was discharged from our hospital on treatment with canagliflozin, and was stable for months on an outpatient basis. The patient’s HbA1c level improved to 6.3% after treatment.

**Discussion**

We describe a case of successful treatment with canagliflozin in a patient with stage D HF and diabetes mellitus. Although it was difficult to withdraw dobutamine even after all conventional pharmacological treatment in this case, the administration of canagliflozin facilitated correction of volume overload and withdrawal from dobutamine. We will discuss the mechanisms of how SGLT2i was effective in the treatment of advanced HF.

We consider that diuretic action is the most important mechanism of SGLT2i in patients with symptomatic HF. SGLT2i suppresses the cotransport of glucose and sodium from the tubular lumen of the proximal tubules to the blood, which results in osmotic aquaresis and natriuresis. Patients with stage D HF often depend on high doses of loop diuretics. The necessity of high doses of loop diuretics in patients with HF almost always associates the activation of the renin-angiotensin-aldosterone system along with the sympathetic nervous system and eventually results in increased mortality and hospitalizations, as well as diuretic resistance. Because SGLT2i acts on a different site to loop diuretics and thiazides, SGLT2i may be helpful in restoring diuresis even in patients with diuretic resistance. Urine volume was significantly increased after canagliflozin administration in the studied case of a patient who was resistant to conventional diuretics and tolvaptan.

In this case, heart rate and urinary excretion of norepinephrine were decreased one week after the administration of canagliflozin under significant diuresis, which suggested lower activation of the sympathetic nervous system. Similarly, no increases in heart rate were observed in the EMPA-REG OUTCOME study. Elevated levels in hemoglobin and hematocrit after the administration of SGLT2i in the patient were also consistent with the several studies posed, the increases in hemoglobin and hematocrit within a week may be primarily attributable to plasma volume reduction by glycosuria-induced osmotic diuresis. In this regard, SGLT2i should increase urine osmolality along with an increment in urinary glucose excretion. However, urine osmolality was curiously unchanged even after the administration of SGLT2i in the patient. This unexpected response to SGLT2i might be due to the combined treatment of a vasopressin receptor antagonist in this case. Urine osmolality is invariably decreased after the administration of tolvaptan in patients with HF who respond to tolvaptan, and the depressed osmolality sustains for over 24 hours since blood concentration of tolvaptan is often detectable at the trough, especially in cases with renal

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**Table.** Clinical Parameters at Baseline (Day 0) and 7 Days After Canagliflozin Treatment

| Parameter                      | Canagliflozin treatment Day 0 | Canagliflozin treatment Day 7 |
|--------------------------------|-------------------------------|-------------------------------|
| Vital signs                    |                               |                               |
| Systolic blood pressure, mmHg  | 82                            | 76                            |
| Diastolic blood pressure, mmHg | 54                            | 48                            |
| Heart rate, bpm                | 99                            | 93                            |
| Body weight, kg                | 45.0                          | 44.2                          |
| Blood test results             |                               |                               |
| White blood cell count, × 10^9/μL | 7610                       | 8350                          |
| Hemoglobin, g/dL               | 9.6                           | 10.6                          |
| Hematocrit, %                  | 28.6                          | 32.2                          |
| Albumin, g/dL                  | 3.5                           | 4                             |
| Sodium, mEq/L                  | 133                           | 132                           |
| Potassium, mEq/L               | 4.6                           | 4.8                           |
| Total bilirubin, mg/dL         | 0.5                           | 0.6                           |
| Urea nitrogen, mg/dL           | 32                            | 36                            |
| Creatinine, mg/dL              | 1.16                          | 1.23                          |
| Estimated GFR, mL/minute/1.73m² | 36.5                         | 34.2                          |
| Fasting blood glucose, mg/dL   | 112                           | 115                           |
| BNP, pg/mL                     | 537.4                         | 498.5                         |
| Renin activity, ng/mL/hour     | 12.8                          | 15.1                          |
| 24-hour urine test             |                               |                               |
| Urine volume, mL/day           | 1823                          | 2093                          |
| Urine glucose, g/day           | 0.04                          | 12.08                         |
| Urine sodium, mEq/day          | 128                           | 147                           |
| Urine potassium, mEq/day       | 36                            | 40                            |
| Urine urea nitrogen, mg/dL     | 312                           | 245                           |
| Urine osmolality, mOsm/kg H₂O  | 314                           | 317                           |
| Urine norepinephrine, μg/day   | 150.2                         | 102.8                         |
Figure. Clinical course of this case before and after the administration of canagliflozin. DOB indicates dobutamine; BW, body weight; and BNP, plasma B-type natriuretic peptide.

dysfunction. Therefore, the level of urine osmolality was not changed by marked aquarexis of tolvaptan, even under the significant existence of glycosuria induced by SGLT2i. In other words, diuretic benefit by SGLT2i cannot be simply attributable to glycosuria but also to ameliorating resistance to other diuretic/aquaretic agents, possibly by way of improving renal congestion.

Although canagliflozin is approved for the treatment of patients with eGFR ≥45 mL/minute/1.73 m² in the United States, a previous study has indicated the validity and safety of canagliflozin in patients with stage 3 chronic kidney disease (eGFR ≥ 30 to < 60 mL/minute/1.73 m²). We confirmed marked glycosuria without hypoglycemia after the administration of the drug and considered that the efficacy and safety of the drug were undeniable in this patient with eGFR of 36.5 mL/minute/1.73 m².

Renoprotective action is also an important mechanism of SGLT2i in HF. In the EMPA-REG OUTCOME trial, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically-relevant renal events than placebo. Acute impairment of renal function and long-term preservation after drug administration are explained by increased afferent arteriolar resistance and alleviation of glomerular hydraulic pressure through tubuloglomerular feedback. Such feedback is normally accompanied by the decreased renin production in the juxtaglomerular apparatus, but the level of plasma renin activity was even increased after the administration of canagliflozin in this case. An apparently contradictory finding of the renin activity was similarly reported in the previous study. Tubuloglomerular feedback may be reconsidered in terms of the renin-angiotensin system after SGLT2i treatment, and further studies are definitely needed.

In conclusion, although no previous report has demonstrated an advantage of SGLT2i in patients with advanced HF, the present findings suggest that SGLT2i is definitely useful for correcting volume overload and recovery from decompensation state. Further studies are needed to specify the factors that might contribute to the effectiveness of SGLT2i therapy in HF patients with diabetes mellitus.

Disclosures

Conflicts of interest: None.

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