Satisfying Glycemic Control Achieved by Adding a Sodium-Glucose Co-transporter 2 Inhibitor to Sensor-Augmented Insulin Pump (MiniMed 640G) Therapy in a type 1 Diabetic Woman

Akiko Nishimura, PhD¹, Yuji Aoki, MD, PhD²

¹Fundamentals of Nursing, Yamanashi Prefectural University, Yamanashi, Japan
²Matsumoto University Graduate School of Health Science, Matsumoto, Japan

Abstract

Beneficial effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors, a new class of oral antidiabetic medications, have been shown in patients with type 2 diabetes and subsequently with type 1 diabetes. Since SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion, insulin doses often need to be reduced to avoid hypoglycemia, leading to increased ketone body formation and, possibly, euglycemic diabetic ketoacidosis. In this case report, we present a type 1 diabetic patient treated with a sensor-augmented insulin pump, who was satisfied with almost normal HbA1c levels and favorable weight loss after adding ipragliflozin, an SGLT2 inhibitor. The insulin pump MiniMed 640G featured with automated suspension and restart of insulin delivery was demonstrated to be effective and useful to prevent severe hypoglycemia and, probably, diabetic ketoacidosis. The extent of ketonemia seemed to vary with changes in pathophysiological factors. Patients and clinicians should be aware of a STICH protocol to mitigate the risk of diabetic ketoacidosis in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors.

Keywords: Type 1 diabetes, sodium-glucose co-transporter 2 inhibitor, diabetic ketoacidosis, MiniMed 640G, STICH protocol.

INTRODUCTION

Beneficial effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors, a new class of oral antidiabetic medications, have been shown in patients with type 2 diabetes [1, 2]. Subsequently, such effects reducing HbA1c, glycemic variability, overall insulin doses and body weight without increasing total hypoglycemia have been shown in patients with type 1 diabetes [3, 4]. However, a concern regarding an increase in the incidence of diabetic ketoacidosis has arisen after the use of SGLT2 inhibitors in type 1 diabetes. Since SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion, insulin doses often need to be reduced to avoid hypoglycemia, leading to increased ketone body formation and, possibly, euglycemic diabetic ketoacidosis [3, 5]. In this case report, we present a type 1 diabetic patient treated with a sensor-augmented Insulin pump, who was satisfied with almost normal HbA1c levels and favorable weight loss after adding an SGLT2 inhibitor.

CASE REPORT

A 61-year-old women with type 1 diabetes (acute onset at age 37 years) had been treated with an insulin pump (continuous subcutaneous insulin infusion) since age 51 years. The insulin pump without continuous glucose monitoring was changed to a sensor-augmented insulin pump at age 56 years, and the insulin pump Medtronic MiniMed 640G was implemented at age 59 years. The personal basal rate of short-acting insulin (insulin lispro) was set (7.13 U/day in total), and personal bolus insulin was displayed by a built-in bolus calculator using the carbohydrate counting method. The insulin pump 640G is featured with automated insulin suspension: basal insulin delivery can be suspended in response to a predictive low glucose value and can resume automatically after 30 minutes if glucose values rise above a preset level (a low limit, 55 mg/dl).

After ipragliflozin, an SGLT2 inhibitor, was approved in Japan to be co-administered with insulin to adult patients with type 1 diabetes, the patient started
taking 50 mg and, subsequently, 100 mg of ipragliflozin daily with the insulin pump therapy. The patient’s clinical course from 3 months to 27 months after the insulin pump 640G was implemented is shown in Figure-1. The patient’s HbA1c level was gradually improved by adding ipragliflozin, and it reached around a level of 6% without severe hypoglycemia. Her body weight was also gradually decreased after adding ipragliflozin, and seemed to be decreased to an unexpected extend in the middle of the course, due probably to some psychological factors.

The patient’s ketone bodies were examined in her serum and urine. Data obtained at the five points of A to E during the patient’s clinical course in Figure 1 are shown in Table-1. There were large differences in serum β-hydroxybutyrate concentrations between two occasions of the fasting state (A and E) and of the postprandial state (B and D). At the point C, the serum β-hydroxybutyrate concentration was measured after the three-day discontinuation of the administration of ipragliflozin, and was much lower than that at the point B but almost the same as that at the point D. The postprandial blood samples were taken 2.5 to 3 hours after breakfast. These results suggest that serum concentrations of ketone bodies can vary with other factors than the effect of an SGLT2 inhibitor. Qualitative tests for urine ketone bodies were negative at all the five points. The patient usually ate 25 to 28 g of carbohydrates and infused 2.0 to 2.8 U of bolus insulin for breakfast. At the point D, there was a record that she ate 20 g of carbohydrates and infused 1.7 U of bolus insulin for breakfast.

At the point E, as shown in Figure 2, the patient’s sensor glucose level measured by continuous glucose monitoring from 0:00 to 13:00 was revealed to be almost well controlled by the function of the insulin pump 640G to automatically suspend and resume basal insulin infusion. The patient felt a mild symptom of hypoglycemia but decided to see how it would go because the basal insulin infusion was suspended, resulting in an increase in the glucose level without treatment. After that, since one unit of bolus insulin was manually infused to correct the glucose level, the patient’s fasting plasma glucose and serum β-hydroxybutyrate levels (109 mg/dl and 391 μmol/l) were lower than those (229 mg/dl and 714 μmol/l) at the point A (Table-1). Basal insulin doses in total were remained to be 7.13 U/day after adding ipragliflozin, and were slightly reduced to 7.08 U/day shortly before the point D.

Table-1: Fasting or postprandial plasma glucose and serum ketone concentrations with qualitative tests for urine ketones

|                | A     | B     | C     | D     | E     |
|----------------|-------|-------|-------|-------|-------|
| Fasting plasma glucose (mg/dl) | 229   |       |       | 109   |       |
| Postprandial plasma glucose (mg/dl) |       | 61    | 84    | 81    |       |
| Serum acetacetate (μmol/l) | 193   | 111   | 14    | 21    | 112   |
| Serum β-hydroxybutyrate (μmol/l) | 714   | 319   | 20    | 22    | 391   |
| Urine ketones (qualitative) | (-)   | (-)   | (-)   | (-)   | (-)   |

Figure-1 Clinical course of the present type 1 patient treated with a sensor-augmented insulin pump (MiniMed 640G). Plasma glucose and serum ketone bodies were measured at the five points of A to E (data are shown in Table-1). The administration of ipragliflozin was discontinued for three days before the point C.
**DISCUSSION**

Increased risk of diabetic ketoacidosis is a concern for type 1 diabetic patients treated with SGLT2 inhibitors [3-5]. Ketosis (increased levels of β-hydroxybutyrate and acetoacetate) and ketoacidosis are likely to occur in individuals with type 1 diabetes whose total insulin or basal insulin doses are reduced after SGLT2 inhibitor therapy, particularly when physiological stress is present. Reduced basal insulin by more than 10-20 % and reduced carbohydrate intake are moderate to high risk factors for diabetic ketoacidosis associated with SGLT2 inhibitor therapy, which can cause a pharmacologic push toward ketosis by increasing urinary glucose loss [6]. In the present case, the basal insulin was slightly reduced by 0.7 % after adding ipragliflozin, an SGLT2 inhibitor. The patient lost her weight from 53 kg to 48 kg in the middle of the course after the administration of ipragliflozin, suggesting excessive energy or carbohydrate restriction that led to increased production of ketone bodies. However, the highest level of serum β-hydroxybutyrate was measured to be 714 μmol/l, which is mild ketonemia (normal, less than 600 μmol/l) [6]. For reference, 500 to 3,000 μmol/l range for β-hydroxybutyrate occurs during nutritional ketosis [7].

The insulin pump 640G featured with automated suspension and restart of insulin delivery was demonstrated to be effective and useful to prevent hypoglycemia and, probably, diabetic ketoacidosis, as shown in the present case. Diabetic ketoacidosis was reported to occur in combined use of an SGLT2 inhibitor and the hybrid closed-loop insulin delivery system (MiniMed 670G) [8]. It needs to be kept in mind that insulin pump use or insulin pump failure is in general regarded as a low to moderate or moderate to high risk factor for diabetic ketoacidosis associated with SGLT inhibitor therapy [6]. It was actually a beneficial effect of adding ipragliflozin that the present patient treated with the sensor-augmented insulin pump (MiniMed 640G) was satisfied with improved glycemic control without increased risk of severe hypoglycemia and finally favorable weight loss. Since the extent of ketonemia can vary with changes in pathophysiological factors as seen in the present case, patients and clinicians should be aware of the risk of diabetic ketoacidosis associated with SGLT inhibitor therapy. A STICH protocol is recommended to mitigate the risk of diabetic ketoacidosis: STop the SGLT inhibitor + Injection bolus insulin + Consume 30g carbohydrates + Hydrate [5, 6].

**CONCLUSION**

Satisfying glycemic control and weight loss were achieved by adding an SGLT2 inhibitor in the present type 1 diabetic patient treated with a sensor-augmented insulin pump. The insulin pump 640G featured with automated suspension and restart of insulin delivery was demonstrated to be effective and useful to prevent hypoglycemia and, probably, diabetic ketoacidosis. Patients and clinicians should be aware of a STICH protocol to mitigate the risk of diabetic ketoacidosis in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors.

**ACKNOWLEDGMENT**

We appreciate the patient’s written consent to the publication as a case report in Scholars Journal of Medical Case Reports.

**Conflict of Interest**

The authors declare that they have no conflicts of interest regarding the publication of this case report.

**REFERENCES**

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Erik Johansen O, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373 (22): 2117-2128.

2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular
and renal events in type 2 diabetes. N Engl J Med. 2017; 377 (7): 644-657.

3. Janssens B, Caerels S, Mathieu C. SGLT inhibitors in type 1 diabetes: weighing efficacy and side effects. Ther Adv Endocrinol Metab. 2020; 11: 1-10.

4. Evans M, Hicks D, Patel D, Patel V, McEwan P, Dashora U. Optimising the benefits of SGLT2 inhibitors for type 1 diabetes. Diabetes Ther. 2020; 11: 37-52.

5. Garg SK, Peters AL, Buse JB, Danne T. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. Diabetes Technol Ther. 2018; 20 (9): 571-575.

6. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, Alexander CM, Battelino T, Ampudia-Blasco FJ, Bode BW, Cariou B, Close KL, Dandona P, Dutta S, Ferrannini E, Fourlanos S, Grunberger G, Heller SR, Henry RR, Kurian MJ, Kushner JA, Oron T, Parkin CG, Pieber TR, Rodbard HW, Schatz D, Skyler JS, Tamborlane WV, Yokote K, Phillip M. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care. 2019; 42(6): 1147-1154.

7. Miller VJ, Villamena FA, Volek JS. Nutritional ketosis and mitohormesis: potential implications for mitochondrial function and human health. J Nutr Metab. 2018: Article ID 5157645.

8. Singh S, Rushakoff RJ, Neinstein AB. A case report of diabetic ketoacidosis with combined use of a sodium glucose transporter 2 inhibitor and hybrid closed-loop insulin delivery. J Diabetes Sci Technol. 2019;13(3): 605-606.