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CASE REPORT

Rapid and dramatic glucose-lowering effect of bromocriptine in an inadequately controlled type 2 diabetes patient with prolactinoma

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ABSTRACT

Dopamine receptor agonists are typically used to treat Parkinson's disease and certain pituitary tumors, such as prolactinoma or a growth hormone-producing tumor. A 53-year-old woman with a history of prolactinoma was referred to Kumamoto University Hospital (Kumamoto, Japan) with poorly controlled type 2 diabetes. Her glycated hemoglobin and serum prolactin levels were increased (8.8% and 160.3 ng/mL, respectively). Bromocriptine, a dopamine D_2 receptor agonist, was administered to reduce her serum prolactin level. Because bromocriptine-QR (quick release) has been approved for the treatment of type 2 diabetes mellitus in the USA, a continuous glucose monitoring system, FreeStyle Libre Pro, was utilized to examine the effect of bromocriptine on glycemic control. After the initial administration of bromocriptine, glucose levels were rapidly and dramatically ameliorated, and the time in range (70–180 mg/dL) improved from <50% to >90% between 1 week before and after the initial administration of bromocriptine.

INTRODUCTION

Prolactinoma is a common type of functional pituitary tumor, presenting with amenorrhea, loss of libido, galactorrhea and infertility. Dopamine agonists, such as cabergoline and bromocriptine, are used for treatment.

Disorders of dopamine action are related to obesity, metabolic syndrome and type 2 diabetes mellitus[1]. In animal models of insulin resistance, hypothalamic dopamine levels are decreased, and dopamine agonist administration improves their insulin sensitivity[2]. Bromocriptine-QR (quick release; Cycloset®; Salix Pharmaceuticals, Bridgewater, NJ, USA), a dopamine D_2 agonist, was approved in the USA in 2009 to treat type 2 diabetes mellitus. It resets the circadian rhythm and improves glycemic control, but the relationship between these effects remains unelucidated[3].

We describe a 53-year-old woman with prolactinoma and type 2 diabetes treated with bromocriptine. We showed the crucial moment of rapid and dramatic amelioration in blood glucose level after bromocriptine administration using FreeStyle Libre Pro continuous glucose monitoring system.

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CASE REPORT

A 53-year-old Japanese woman underwent surgery for a prolactinoma when she was aged 21 years. At the age of 43 years, she was diagnosed with type 2 diabetes and started taking oral hypoglycemic agents. She was referred to the Department of Metabolic Medicine, Kumamoto University Hospital (Kumamoto, Japan), and hospitalized to improve her glycemic control and assess her pituitary function at the age of 53 years.

The patient's height was 154.7 cm, and weight was 72.4 kg (body mass index 30.3 kg/m^2). She had been previously treated with the oral administration of 50 mg of ipragliflozin, 0.9 mg of voglibose, 1,500 mg of metformin and 2 mg of glimepiride, as well as an injection of 0.9 mg of liraglutide. Her fasting plasma glucose, glycated hemoglobin (HbA1c) and serum prolactin levels were elevated at 176 mg/dL, 8.8% and 160.3 ng/mL, respectively, and her other anterior pituitary hormones were normal. Her fasting plasma insulin and C-peptide levels were 12.7 μU/mL and 2.0 ng/mL, respectively, and homeostatic model assessment for insulin resistance was 5.52, indicating insulin resistance. The patient was instructed to consume a 1,600-kcal diet and walk for 60 min a day. The daily blood glucose profile during hospitalization is presented in Table 1. Magnetic resonance imaging showed a slightly enlarged sella turcica, slightly reduced anterior pituitary lobe and a thick pituitary stalk. A combined anterior pituitary

Table 1 | Seven points of self-measured blood glucose in hospital

	B0	B2	L0	L2	D0	D2	BB	
Day 2	196	256	179	205	149	182	154	Gli 2 mg, I 50 mg, V 0.9 mg, M 1,500 mg, L 0.9 mg
Day 6	114	–	195	143	141	134	149	I 50 mg, V 0.9 mg, M 1,500 mg, L 0.9 mg, Gla 6U
Day 9	109	122	101	158	136	181	145	I 50 mg, V 0.9 mg, M 1,500 mg, L 0.9 mg, Gla 6U, P 15 mg
Day 13	91	162	129	154	106	199	151	I 50 mg, V 0.9 mg, M 1,500 mg, L 0.9 mg, P 15 mg

B0, before breakfast; B2, 2 h after start of breakfast; L0, before lunch; L2, 2 h after start of lunch; D0, before dinner; D2, 2 h after start of dinner; BB, before bed; Gla, insulin glargine; Gli, glimepiride; I, ipragliflozin; L, liraglutide; M, metformin; P, pioglitazone; V, voglibose.

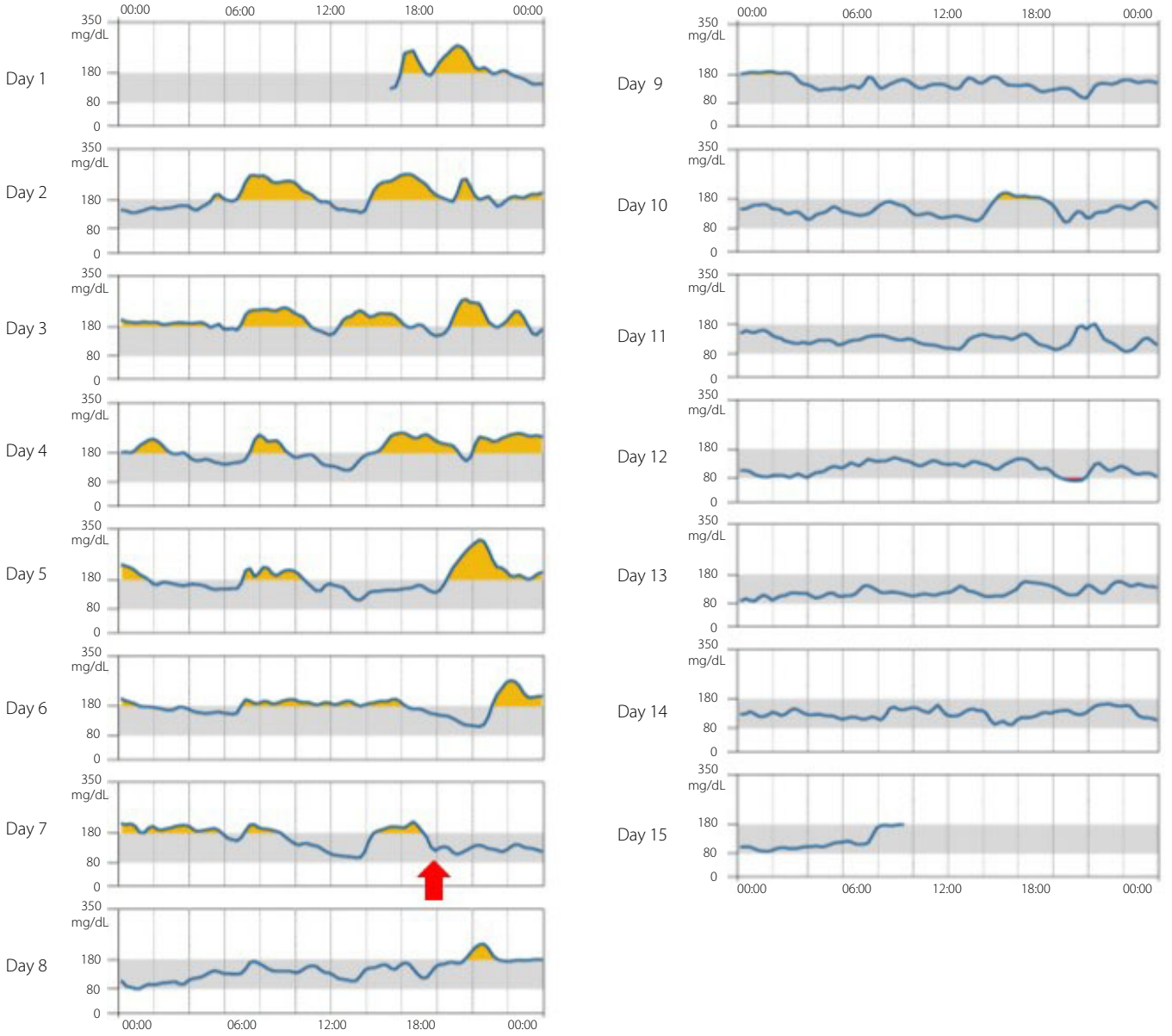

Figure 1 | Continuous glucose monitoring system. The areas of time above range (>180 mg/dL, shown in yellow) almost disappeared immediately after bromocriptine administration. The arrow shows the moment when oral administration of bromocriptine commenced.

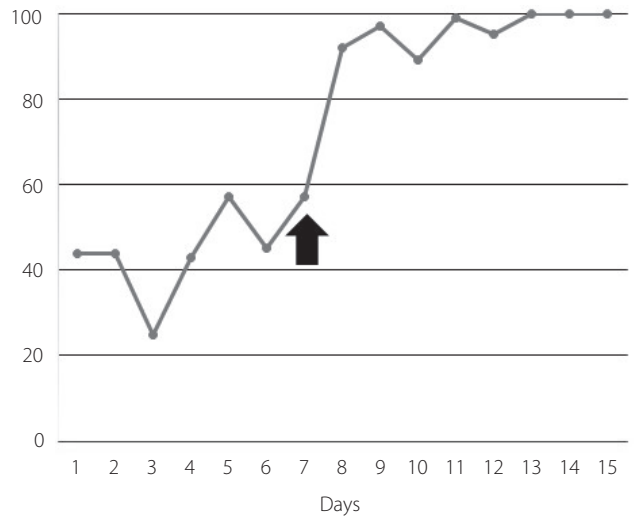

Figure 2 | Changes in percentages of time in range before and after bromocriptine administration. The arrow shows the day when oral administration of bromocriptine commenced.

function test using thyrotropin-releasing hormone, corticotropin-releasing hormone and gonadotropin-releasing hormone was carried out. Serum prolactin levels remained high and unchanged by thyrotropin-releasing hormone stimulation. The other anterior pituitary hormones had normal responses. Finally, the patient was diagnosed with residual prolactinoma and type 2 diabetes mellitus. Insulin glargine was used transiently during hospitalization, and pioglitazone was started just before discharge.

Two months after discharge, the patient revisited our hospital with her weight reduced to 68.3 kg. She was prescribed 50 mg of ipragliflozin, 0.9 mg of voglibose, 1,500 mg of metformin and 15 mg of pioglitazone, as well as 0.9 mg of liraglutide injection. Her random plasma glucose, HbA1c and serum prolactin levels were 150 mg/dL, 8.3% and 86.6 ng/mL, respectively. We had prescribed bromocriptine, expecting improvement in both prolactin levels and glycemic control; although, bromocriptine was different from bromocriptine-QR, which was unavailable in Japan. The FreeStyle Libre Pro continuous glucose monitoring (CGM) system examined the effect of bromocriptine on glycemic control. Seven days after the start of the FreeStyle Libre Pro CGM system, bromocriptine treatment (2.5 mg/day; once daily) was initiated. Immediately after the initial bromocriptine administration, the patient's blood glucose level decreased dramatically, and there was almost no time above the range (>180 mg/dL; Figure 1). Before bromocriptine administration, the time in range (70–180 mg/dL) was approximately 50%, which came up to >90% after bromocriptine administration (Figure 2). There was no time below the target range, either before or after bromocriptine administration. After bromocriptine administration, the patient's serum prolactin levels decreased to the normal range, and no adverse effects were observed.

DISCUSSION

We showed the crucial moment of rapid and dramatic blood glucose amelioration after bromocriptine administration using a CGM system in a patient with prolactinoma and type 2 diabetes. The use of CGM systems has rapidly increased in daily medical practice. CGM is useful to observe glycemic excursions and daily profiles, which can provide information on immediate therapy decisions and lifestyle modifications. In August 2019, clinical targets for CGM data interpretation were proposed[4], recommending a target range of 70–180 mg/dL for individuals with type 1 and type 2 diabetes, and a set of targets according to the time of day (% of CGM readings or min/h). In the present patient, the percentage of time in range dramatically increased immediately after bromocriptine administration. This extraordinarily rapid and dramatic effect prompted us to consider some interesting mechanisms whereby bromocriptine lowers glucose.

There are some explanations about the mechanism by which dopamine agonist improves glycemic control. The circadian rhythm of dopamine release at the hypothalamic suprachiasmatic nucleus (SCN), the body's master clock, regulates peripheral insulin sensitivity and appears to be disrupted in insulin-resistant states[5]. The decreased circadian peak of dopaminergic activity in the SCN increases noradrenergic input activity to the ventromedial hypothalamus and the paraventricular nuclei[6]. It also increases neuropeptide Y and corticotropin-releasing hormone at the paraventricular nuclei[7]. Increased sympathetic nervous system activity and hypothalamic–pituitary–adrenal axis induce glucagon secretion, hepatic glucose production, lipid synthase, adipose lipolysis and hyperinsulinemia, and decrease peripheral glucose uptake[5]. For example, dopamine neurotoxin administration to the SCN of lean mice resulted in insulin resistance without any change in food consumption[8]. Circadian-timed daily dopamine administration to the SCN of insulin-resistant animals ameliorated insulin resistance and obesity[9]. Restoration of circadian dopaminergic peak activity at the SCN decreased noradrenergic activity at the ventromedial hypothalamus[6], and decreased the levels of neuropeptide Y and corticotropin-releasing hormone at the paraventricular nuclei[7].

Recently, bromocriptine was shown to improve glycemic control in a type 2 diabetes patient with prolactinoma[10]. The study showed that insulin resistance was improved by an elevated hypothalamic dopamine level in the early morning. In the present case, bromocriptine reduced blood glucose levels immediately after the initial treatment in the evening. It seems to show that bromocriptine has some effects different from the reset of the circadian rhythm. As for the rapid glucose-lowering effect, it is common to think that bromocriptine inhibited hepatic glucose production, because this effect lasted all through the night after the initial treatment. We speculate that the direct suppression of the sympathetic nervous system or hypothalamic–pituitary–adrenal axis was involved, although we could not show it. Another possibility is that reduced prolactin levels by

bromocriptine ameliorated glycemic control, because elevated prolactin levels are associated with insulin resistance[11].

The present report had several limitations, such as no data on insulin sensitivity and secretion after bromocriptine treatment. Further studies should investigate the mechanism underlying rapid bromocriptine effects on glycemic control.

This is the first report showing the crucial moment of the glucose-lowering effect of bromocriptine using a CGM system. Although the bromocriptine used for this patient was different from bromocriptine-QR, it showed excellent glucose-lowering effects. Bromocriptine is not well known as a glucose-lowering agent in Japan, and might be an alternative treatment for Japanese patients with insulin resistance or type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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