

[CASE REPORT]

Bromocriptine as a Potential Glucose-lowering Agent for the Treatment of Prolactinoma with Type 2 Diabetes

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Abstract:

A 22-year-old Japanese woman consulted an endocrinologist due to persistent galactorrhea for the past 10 months. She had hyperprolactinemia and had previously been diagnosed with type 2 diabetes mellitus based on her glycohemoglobin level of 11.6%. After two months, she was admitted to our hospital and finally diagnosed with prolactinoma. For the treatment of prolactinoma, bromocriptine 2.5 mg/day was started. After seven days, her post-prandial blood glucose levels, HOMA-IR and plasma C-peptide levels were significantly improved. These results indicate that traditional bromocriptine can be an effective therapeutic alternative in patients with prolactinoma complicated with type 2 diabetes.

Key words: prolactinoma, type 2 diabetes mellitus, bromocriptine, insulin resistance

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Introduction

Bromocriptine, a dopamine 2 (D2) receptor agonist, is widely used to treat pituitary tumors, such as prolactinoma and acromegaly (1). It is already known that bromocriptine has effects of suppressing glucose production in the liver and improving peripheral insulin resistance by decreasing the plasma free fatty acid (FFA) and triglyceride (TG) levels (2, 3) as well as inducing tumor regression. Quick-release-type bromocriptine, which is an enantiomer of the traditional type, was approved as a glucose-lowering agent by the U.S. Food and Drug Administration in 2010 and has been used to treat type 2 diabetes mellitus in the United States (1).

We herein report a patient with prolactinoma complicated with type 2 diabetes mellitus whose plasma glucose (PG) level was markedly improved by the administration of traditional bromocriptine.

Case Report

A 22-year-old Japanese woman consulted a gynecologic clinic complaining of galactorrhea for 10 months. Although 8 months before her visit to the clinic she had been diagnosed with type 2 diabetes mellitus based on her hemoglobin A1c (HbA1c) level of 8.5% at a periodic medical checkup, she failed to be treated for her diabetes. She had no obvious medical history. Her mother had type 2 diabetes mellitus with insulin therapy, and her maternal grandfather had type 2 diabetes mellitus as well. There was no family history of pituitary diseases. She reported having a normal menstrual cycle since 11 years of age.

Her plasma prolactin (PRL) level was 46.48 ng/mL (normal range <20 ng/mL) at her first visit, and she was referred to an endocrinologist 8 months later. The plasma PRL level had increased to 63.54 ng/mL, and prolactinoma was suspected based on the findings of a pituitary magnetic resonance imaging (MRI) dynamic study. Due to her HbA1c level of 11.6%, she was recommended to undergo diabetes

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treatment while hospitalized. Because she rejected hospitalization, she was prescribed metformin (750 mg/day) and sitagliptin (50 mg/day) for the treatment of her diabetes. Two months later, however, her HbA1c level remained high at 8.5%, not showing any improvement, and her galactorrhea persisted. She was therefore referred to our hospital and admitted for the treatment of galactorrhea as well as hyperglycemia.

Table 1. Laboratory Findings at Admission.

Factor	Value	Normal range
Fasting PG	106 mg/dL	70-110
HbA1c	8.50 %	4.6-6.2
Fasting IRI	9.0 μ U/L	2.0-10.0
HOMA-IR	2.4	\leq 1.6
Urine-Alb	11.2 mg/day	$<$ 30.0
PRL	62.2 ng/mL	1.6-21.9
ACTH	19.5 pg/mL	7.2-63.3
Cortisol	16.1 μ g/dL	6.24-18.0
LH	3.9 mIU/mL	1.76-10.2
FSH	9.6 mIU/mL	3.01-14.7
GH	0.1 ng/mL	\leq 2.10
IGF-1	246 ng/mL	161-425
TSH	2.38 μ IU/mL	0.21-3.85
Free T3	3.0 pg/mL	1.9-3.5
Free T4	1.34 ng/dL	0.88-1.56

PG: Plasma glucose, HbA1c: Hemoglobin A1c, IRI: Immunoreactive insulin, HOMA-IR: Homeostasis model assessment of insulin resistance, Alb: Albumin, PRL: Prolactin, ACTH: adrenocorticotropic hormone, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, GH: Growth hormone, IGF-1: Insulin-like growth factor-1, TSH: Thyroid stimulating hormone, T3: Triiodo thyronine, T4: Thyroxine

On a physical examination, her height was 160.2 cm, body weight was 75.6 kg, body mass index was 29.2 kg/m², blood pressure was 116/74 mmHg, and her pulse rate was 78 /min and regular. No abnormal findings were noted except for galactorrhea from both nipples. Her laboratory data at admission are shown in Table 1. HbA1c was 8.5%, fasting plasma glucose (FPG) level was 106 mg/dL, fasting plasma C-peptide (CPR) level was 2.0 ng/mL, and fasting plasma insulin level was 9.0 μ U/mL, indicating that the capacity for insulin secretion was preserved. Homeostasis model assessment of insulin resistance (HOMA-IR) was 2.4, indicating her insulin sensitivity was somewhat impaired. She had no diabetic microvascular complication. Her plasma PRL level was 62.2 ng/mL, and pituitary MRI showed two microadenomas with diameters of approximately 5 mm (Fig. 1). Based on the disappearance of the PRL response after thyrotropin-releasing hormone loading (Table 2), she was finally diagnosed with prolactinoma.

After admission, the administration of metformin (750 mg/day) and sitagliptin (50 mg/day) was continued with concomitant diet therapy (1,600 kcal/day). Although FPG remained stable at around 120 mg/dL, post-prandial PG levels were higher than 200 mg/dL after breakfast and after lunch, remaining around 200 mg/dL even after bedtime (Fig. 2). On the 13th hospital day, bromocriptine (2.5 mg/day after dinner) was started as the treatment for prolactinoma. Subsequently, the plasma PRL concentration decreased to 24.9 ng/mL after 7 days of administration. Furthermore, FPG decreased to 101 mg/dL, and the post-prandial PG levels markedly improved to 130-180 mg/dL after starting bromocriptine therapy (Fig. 2).

We compared the PG levels and M values (based on the glucose level of 100 mg/dL) at the time of admission, before bromocriptine administration (10 days after admission),

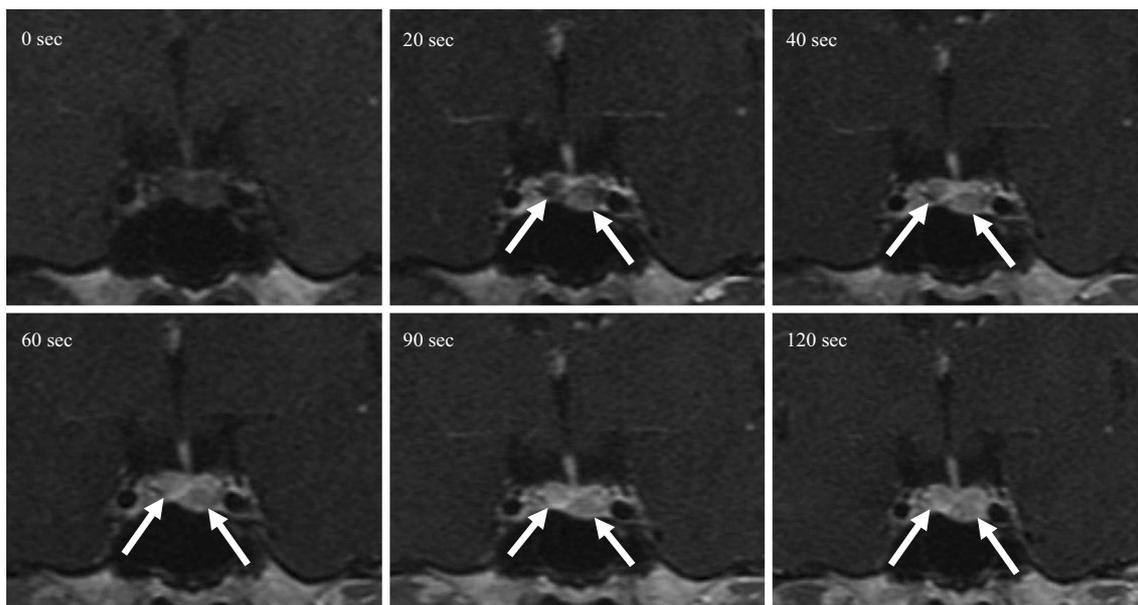


Figure 1. Pituitary MRI (magnetic resonance imaging). There were two microadenomas in the pituitary gland (arrows).

Table 2. TRH Loading Test.

Time (minutes)	0	30	60	90	120
PRL (ng/mL)	55.5	62.5	59.9	56.6	51.4

TRH: thyrotropin-releasing hormone, PRL: Prolactin

and after bromocriptine administration (17 days after admission), using the paired *t*-test. The average daily PG levels at admission, before bromocriptine and after bromocriptine were 189 ± 43 , 182 ± 45 , and 147 ± 26 mg/dL, and the average M values were 25 ± 17.9 , 23 ± 19.9 and 6.3 ± 6.3 mg/dL, respectively. There was no significant difference in the average daily PG and M values between admission and before bromocriptine administration ($p=0.5197$ and $p=0.6881$, respectively). However, a significant difference was observed in the daily PG ($p=0.0097$) and M values ($p=0.0194$) between before and after the administration of bromocriptine.

The fasting FFA value after taking bromocriptine for 7 days was almost the same as that before the administration. In the meal tolerance test, the Δ CPR 2 hours value (CPR value 2 hours after meal ingestion minus the value before the meal) improved from 2.3 ng/mL to 5.4 ng/mL with bromocriptine administration. To evaluate the insulin sensitivity of the peripheral tissues, a euglycemic hyperinsulinemic glucose clamp test (4) (insulin infusion rate: 1.25 mU/kg/min) was performed before and after bromocriptine treatment, and the glucose infusion rate (GIR; normal value: >8 mg/kg/min) was not improved by the administration of bromocriptine ($3.58 \rightarrow 2.99$ mg/kg/min). However, the fasting immunoreactive insulin (IRI) decreased from 9.0 μ U/mL to 7.8 μ U/mL, and HOMA-IR, which mainly reflects insulin resistance in the liver (5), decreased from 2.4 to 1.9 after the administration of bromocriptine. Two days after the bromocriptine treatment started, dull headache, malaise and constipation were observed, but those symptoms were tolerated and disappeared after several more days. At the 5-year follow-up, her HbA1c level remained around 6%, and the plasma PRL value remained within the normal range, but the two microadenomas had not disappeared.

The patient has given her informed consent for the publication of her case findings, and the identity of the patient has been protected.

Discussion

Bromocriptine, a D2 receptor agonist, has been recognized to lower the plasma glucose level through the amelioration of insulin resistance (2, 6). Bromocriptine is therefore approved as a therapeutic agent for diabetes in Europe and the United States as a quick-release type (QR) called Cycloset[®] and is categorized as an insulin-sensitizing agent. In the phase III study of bromocriptine QR, it was reported that FPG and post-prandial PG were significantly improved in the bromocriptine QR-treated group compared to the placebo group (1, 2). In Japan, however, only traditional bro-

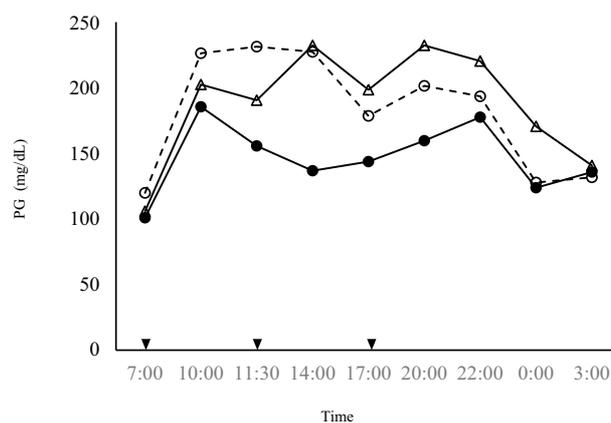


Figure 2. Daily profile of plasma glucose. Open triangles and solid lines indicate the daily profile at admission, open circles and dotted lines indicate that before bromocriptine administration (in 10 days after admission) and closed circles and solid lines indicate that after bromocriptine administration (in 17 days after admission). Closed inverted triangles indicate meal times.

mocriptine, called Parodel[®], is approved, and its applications are limited to pituitary tumors, such as prolactinoma, acromegaly and Parkinson's disease, and not for the treatment of diabetes.

Cabergoline, another kind of D2 receptor agonist, is approved for use in treating these diseases along with traditional bromocriptine in Japan. Cabergoline works about 65 hours after its administration, so it is administered once a week, and the frequency of side effects is lower than with bromocriptine. It has been reported that cabergoline also has glucose-improving effects (7, 8); however, the international approval date of cabergoline is March 1992, about 17 years later than that of traditional bromocriptine. Therefore, there are few reports concerning the glucose-lowering effects of cabergoline, and it is not yet approach as a therapeutic agent for diabetes.

In the present report, we showed for the first time that traditional-type bromocriptine has a glucose-lowering effect in Japanese patients with type 2 diabetes mellitus. In diabetic patients, the hypothalamic dopamine level in the early morning is believed to be low, which leads to increased sympathetic activity and insulin resistance. Following the administration of bromocriptine, the hypothalamic dopamine level increases, resulting in the suppression of PRL and growth hormone (GH) secreted from the pituitary gland and the amelioration of glucose tolerance (2). Bromocriptine improves insulin resistance by suppressing lipolysis and decreasing the production of FFA in the periphery as well as glucose production in the liver (3). These effects of bromocriptine on glucose and lipid metabolisms are brought about through the activation of dopaminergic neurons and suppression of sympathetic nerves without mediating specific receptors (9).

It is known that an elevated prolactin level causes insulin resistance (7) in patients with prolactinoma. In our case, we

selected conservative therapy using traditional-type bromocriptine to treat prolactinoma complicated by type 2 diabetes mellitus due to the presence of microadenomas of about 5 mm in diameter. Following this treatment, the FPG and post-prandial PG were improved, similar to the results obtained with bromocriptine QR. Although there was no change in the GIR, which mainly reflects peripheral insulin sensitivity, the HOMA-IR, which mainly reflects the hepatic insulin resistance, was improved by the administration of traditional bromocriptine. There was almost no change in the fasting FFA by traditional bromocriptine treatment, which is consistent with the fact that the insulin sensitivity in the peripheral tissues did not change.

When taken within two hours after waking up, bromocriptine QR increases the hypothalamic dopamine tone in the early morning, which leads to the suppression of glucose release from the liver and FFA release from the adipose tissue, thus helping improve the insulin resistance. However, traditional-type bromocriptine has a lower bioavailability than the QR type (28% vs. 65%-95%) (1), so this agent might not have sufficiently suppressed the FFA release throughout the day had it been taken in this manner. Traditional bromocriptine was taken after dinner in the present patient, explaining the sufficient supply of this agent in the early morning and the improvement of hepatic insulin resistance. These may explain the partial improvement of insulin resistance using this traditional agent. The improvement in insulin secretion observed in this case is presumed to be due to the mitigation of glucose toxicity by the effects of traditional bromocriptine on the amelioration of hepatic insulin resistance.

As mentioned above, because the traditional agent provides peak concentrations about three hours after administration, it works more slowly than the QR type (1) and has a relatively low bioavailability by comparison (1). Therefore, it is less suitable for the treatment of diabetes than the QR type. Bromocriptine QR is administered in the early morning, and the blood concentration of this drug increases to the maximum within one hour after ingestion, with a half-life of around six hours. Because 98% of metabolites are excreted into bile acid, the QR type can be used in patients with an impaired renal function (10, 11). The administration of bromocriptine QR alone reduced the HbA1c by 0.65% without increasing hypoglycemia compared to placebo administration (2). Furthermore, in a randomized clinical trial, the QR type significantly suppressed the cardiovascular outcomes among patients with type 2 diabetes mellitus (12). While there is no report on the long-term safety and efficacy of the QR type and it is not yet approved in Japan, it is expected to be a viable alternative for the management of type 2 diabetes mellitus, which is becoming more and more complicated as time goes on.

Conclusion

Although the glucose-lowering effect of bromocriptine is well known in Europe and the United States, few cases have been reported so far in Japan. While other therapeutic strategies, such as cabergoline administration and surgery, should also be considered for the treatment of prolactinoma, traditional-type bromocriptine may be an effective therapeutic alternative in Japanese patients with prolactinoma complicated with type 2 diabetes mellitus.

The authors state that they have no Conflict of Interest (COI).

References

- Holt RI, Barnett AH, Bailey CJ. Bromocriptine: old drug, new formulation and new indication. *Diabetes Obes Metab* **12**: 1048-1057, 2010.
- DeFronzo RA. Bromocriptine: a sympatholytic, d2-dopamine agonist for the treatment of type 2 diabetes. *Diabetes Care* **34**: 789-794, 2011.
- Cincotta AH, Meier AH. Bromocriptine inhibits in vivo free fatty acid oxidation and hepatic glucose output in seasonally obese hamsters (*Mesocricetus auratus*). *Metabolism* **44**: 1349-1355, 1995.
- DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* **237**: 214-223, 1979.
- Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**: 412-419, 1985.
- Barnett AH, Chapman C, Gailer K, Hayter CJ. Effect of bromocriptine on maturity onset diabetes. *Postgrad Med J* **56**: 11-14, 1980.
- Gibson CD, Karmally W, McMahon DJ, Wardlaw SL, Korner J. Randomized pilot study of cabergoline, a dopamine receptor agonist: effects on body weight and glucose tolerance in obese adults. *Diabetes Obes Metab* **14**: 335-340, 2012.
- Adele B, Zahra K, Ezzatossadat D, Ozra A, Shahram A. Effects of cabergoline on blood glucose levels in type 2 diabetic patients. A double-blind controlled clinical trial. *Medicine (Baltimore)* **95**: e4818, 2016.
- Cincotta AH. Hypothalamic role in the insulin resistance syndrome. In: *Insulin resistance syndrome*. Hansen B, Shaffrir E, Eds. London, Taylor and Francis, 2002: 271-312.
- Hahr AJ, Molitch ME. Management of diabetes mellitus in patients with chronic kidney disease. *Clin Diabetes Endocrinol* **1**: 2, 2015.
- Mejia-Rodriguez O, Herrera-Abarca JE, Ceballos-Reyes G, Avila-Diaz M, Prado-Urbe C, et al. Cardiovascular and renal effects of bromocriptine in diabetic patients with stage 4 chronic kidney disease. *Biomed Res Int* 104059, 2013.
- Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* **33**: 1503-1508, 2010.

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