A case of hyperinsulinemic hypoglycemia related with a calcimimetic agent

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Abstract

We herein report a case of a 60-year-old female receiving hemodialysis who developed severe hyperinsulinemic hypoglycemia and lost her consciousness. A calcimimetic agent had been administered for the secondary hyperparathyroidism. The calcimimetic agent, mimicking the elevation of the extracellular calcium ion concentration, activates calcium-sensing receptors (CaSR) of the parathyroid cells and inhibits the parathyroid hormone secretions. The previous study suggested that the CaSR are also expressed in both human β cells and insulinoma cells, but the reactivity to change in the extracellular calcium ion concentration is different between normal β cells and insulinoma cells. After cessation of the calcimimetic agent, hypoglycemic symptoms disappeared and endogenous insulin secretion dropped to normal levels. However, the result of a prolonged fasting test indicated that she remained hyperinsulinemic even after its cessation, suggesting that she had insulinoma which could not be detected by the imaging examinations. The previous autopsy data showed that there were many cases of the insulinoma without the symptoms of hypoglycemia. We considered the possibility that she had the insulinoma and the pancreatic tumor was too small to promote the insulin secretion and cause hypoglycemia without activation by the calcimimetic agent. We should know that the calcimimetic agent could cause hyperinsulinemic hypoglycemia with the unidentified insulinoma.

Keywords Hyperinsulinemic hypoglycemia · Calcimimetic agent · Cinacalcet · Calcium-sensing receptor

Introduction

Hypoglycemia is induced by various causes, including insulinoma, insulin autoimmune syndrome, adrenal insufficiency and overuse of anti-diabetic drugs [1]. In addition, many commonly used non-anti-diabetic drugs, such as anti-hypertensive drugs, anti-arrhythmic drugs and anti-bacterial drugs, have also been reported to lower the blood glucose levels [2].

Cinacalcet is a calcimimetic agent that is used for the treatment of secondary hyperparathyroidism (SHPT). The calcimimetic agent mimics the action of calcium ion on tissues, by allosteric activation of the calcium-sensing receptors (CaSR) [3], thereby decreasing the parathyroid hormone (PTH) secretion from the parathyroid glands [4]. Although

the CaSR is also expressed in the pancreatic β cells [5], it is unclear whether the calcimimetic agent influences the insulin secretion. As far as we know, there are no reports previously in which a calcimimetic agent would affect blood glucose levels. We herein report the case of severe hypoglycemia induced by the calcimimetic agent, cinacalcet.

Case report

A 60-year-old female with the chronic renal failure due to glomerulonephritis had been receiving hemodialysis for 23 years. From January 201X, she had been admitted to a hospital in her neighborhood for the treatment of the renal failure. One evening in February, she lost her consciousness suddenly. Her blood glucose levels were 25 mg/dL and an intravenous administration of the glucose recovered her consciousness. After that, hypoglycemic symptoms appeared every day and she was administered the glucose injection each time. To investigate the causes of hypoglycemia, she was admitted to our hospital in April.

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After her admission, hypoglycemia (below 50 mg/dL) occurred in the early morning every day and she received the intravenous administration of the glucose (20 g/h) through a central venous catheter from 21:00 to 8:00. We monitored her glucose levels by the continuous blood glucose monitoring system (CGMS) (Medtronic iPro2®) and the low levels of glucose (below 70 mg/dL) were still observed from night-time to early morning. Hypoglycemia also occurred before lunch and in the afternoon (between 14:00 and 18:00) on both non-dialysis (Fig. 1a) and dialysis day (Fig. 1b). We performed a prolonged fasting test under no administration of glucose. After 10-h fasting, hypoglycemia appeared (plasma glucose levels were 36 mg/dL) without suppression of endogenous insulin secretion (serum insulin and C peptide levels were 13.3 μ U/mL and 5.8 ng/mL, respectively). These findings might indicate that she had an insulinoma inducing hyperinsulinemic hypoglycemia. However, a pancreatic tumor was not detected by the abdominal ultrasonography, the computed tomography (CT) and the magnetic resonance imaging (MRI).

In the clinical laboratory findings, an anti-insulin antibody was negative and the levels of glucoregulatory hormones (such as ACTH, cortisol, growth hormone (GH) and IGF-1) were within the normal ranges (Table 1).

She had been administered anti-hypertensive drugs (an angiotensin II receptor blocker (ARB), a calcium channel blocker and an α blocker), a laxative and cinacalcet. Insulin, oral anti-diabetic drugs, anti-arrhythmic drugs and anti-bacterial drugs had not been administered during this clinical course. She did not receive either angiotensin converting enzyme (ACE) inhibitors or β blockers, which are most commonly reported to cause hypoglycemia among anti-hypertensive drugs [6]. Then, we focused on cinacalcet, which she had been administered for the treatment of SHPT since 201X–3. We suspected that the calcimimetic agent might affect the CaSR of pancreatic β cells or insulinoma cells and tried to cease administration of cinacalcet. Afterwards, the frequencies of hypoglycemia were decreased gradually and finally the blood glucose levels were kept in the normal ranges (above 70 mg/dL) for all night without administration of glucose. We monitored glucose levels by the CGMS, which revealed no hypoglycemia all the day (Fig. 1c, d).

We performed the prolonged fasting test again 24 days after discontinuing administration of cinacalcet. Unexpectedly, 18-h fasting induced hypoglycemia (blood glucose levels were 37 mg/dL) without suppression of endogenous insulin secretion (serum insulin and C peptide levels were 4.1 μ U/mL and 1.9 ng/mL, respectively). After finishing the prolonged fasting test, we injected 1 mg of glucagon to her and her blood glucose levels rose to 100 mg/dL in 30 min. These results suggested that the cause of hypoglycemia was not glycogen depletion but endogenous hyperinsulinemic state and the patient might have insulinoma. The reactive

hypoglycemia and excess secretion of insulin were not observed in the 75 g oral glucose tolerance test (OGTT) (The level of blood glucose, serum insulin and C peptide at 0, 30, 60, 90 and 120 min were 66, 130, 129, 121 and 109 mg/dL; 2.8, 38, 30.5, 27.2 and 20.7 μ U/mL; 2.37, 5.78, 7.6, 8.54, and 9.19 ng/mL, respectively). To confirm the existence of insulinoma in her pancreas, we proposed an arterial stimulation with simultaneous venous sampling (ASVS) to the patient, but she refused further examinations.

After cessation of cinacalcet, although intact PTH levels were elevated from 147 to 326 pg/mL, the serum calcium maintained almost the same levels (corrected calcium levels changed from 10.5 to 10.3 mg/dL). Afterwards, hypoglycemia did not occur under taking three meals a day. However, considering the result of the prolonged fasting test after the cessation of cinacalcet, the hypoglycemia may possibly occur in fasting state. Therefore, we decided to keep observing her blood glucose and insulin levels periodically after discharging from the hospital.

Discussion

It is reported that various diseases and factors, such as sepsis, hepatic, renal or cardiac failure and hormone deficiencies, cause hypoglycemia [1]. A non-islet cell tumor secreting IGF-II and endogenous hyperinsulinism (such as insulinoma, noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) and autoimmune hypoglycemia), which are rare cases, induce hypoglycemia [7]. The drugs are the most common cause of hypoglycemia. In addition to glucose-lowering drugs, commonly used non-anti-diabetic drugs have been reported to cause or contribute to hypoglycemia, even in individuals without diabetes. The anti-hypertensive drugs (e.g., ACE inhibitors and β blockers), the anti-arrhythmic drugs (e.g., cibenzorin and disopyramide) and the anti-bacterial drugs (e.g., quinolone and pentamidine) are reported to lower the blood glucose levels in a systemic review [6]. Our patient had continued to take ARB and other anti-hypertensive drugs for several years. At first, we suspected the influence of anti-hypertensive drugs. However, it is reported that the association between ARB use and hypoglycemia is negative in anti-diabetic drug users [8].

Next, we suspected the calcimimetic agent might affect secretion of insulin because the CaSR is expressed in both human β cells and insulinoma cells [5, 9, 10]. Cinacalcet is a calcimimetic agent that has been used for the treatment of SHPT among patients undergoing dialysis since 2004 [11, 12]. The prescription of cinacalcet increased and about 20% of hemodialysis patients have come to use cinacalcet in Europe, North America and Japan [13]. The calcimimetic agent activates the CaSR of parathyroid cells and inhibits PTH secretions. The parathyroid glands sharply perceive the

Fig. 1 Changes of glucose levels observed by continuous glucose monitoring system (CGMS) under administration of cinacalcet on non-dialysis day (a) and dialysis day (b). The patient received intravenous (i.v.) administration of glucose (20 g/h) through a central venous catheter from 21:00 to 8:00. After discontinuing administration of cinacalcet, glucose levels were maintained within a normal range on both non-dialysis day (c) and dialysis day (d). An area of gray color shows 70–140 mg/dL of glucose levels

Table 1 Laboratory data on admission

TP	5.4 g/dL	Cortisol	18.9 µg/dL
Albumin	3.1 g/dL	ACTH	104 pg/mL
BUN	29.6 mg/dL	Free T3	2.4 pg/mL
Creatinine	7.04 mg/dL	Free T4	1.0 ng/dL
Calcium	9.6 mg/dL	TSH	7.03 µIU/mL
Phosphate	2.4 mg/dL	Glycoalbumin	17.5%
Adrenalin	0.38 ng/mL	HbA1c	3.7%
Noradrenalin	0.5 ng/mL	Glucose	36 mg/dL
Dopamine	0.03 ng/mL	C peptide	5.8 ng/mL
GH	3.62 ng/mL	Insulin	13.3 µU/mL
IGF-1	159 ng/mL	Insulin antibodies	Negative

TP total protein, BUN blood urea nitrogen, GH growth hormone, IGF-1 insulin-like growth factor-1, ACTH adrenocorticotrophic hormone, TSH thyroid stimulating hormone

slight change of calcium ion concentration in the extracellular fluid ($[Ca^{2+}]_e$) by CaSR, which regulates PTH secretion and maintain homeostasis of $[Ca^{2+}]_e$. The calcimimetic agent is the compounds that act on CaSR on the parathyroid cells as a positive allosteric modulator and that have the pharmacologic action that strongly suppresses PTH secretion in the same way as a rise in $[Ca^{2+}]_e$. The most frequent adverse effects of cinacalcet are the digestive symptoms such as nausea, vomiting and stomach discomfort [14]. We ceased administration of cinacalcet and confirmed marked improvement of the blood glucose levels in the patient. This result suggested that cinacalcet promoted insulin secretion and induced hypoglycemia.

After cessation of cinacalcet, the result of the prolonged fasting test revealed hyperinsulinemic hypoglycemia, which might indicate existence of insulinoma or post-gastric bypass hypoglycemia (PGBH) [7]. She had no history of gastrectomy and 75 g OGTT did not reveal hyperinsulinemic hypoglycemia, which ruled out PGBH. The pancreatic tumor was not detected by the abdominal ultrasonography, CT and MRI. It is reported that imaging studies are successful in identifying approximately 75% of insulinomas [15]. However, insulinomas are often too small (less than 1.0 cm) to be detected; therefore, negative imaging does not exclude the diagnosis [16].

The CaSR is also expressed in the β cells of rodent and human pancreatic islets [10]. The previous study revealed that the CaSR is expressed in insulin-secreting β -cells in human islet of Langerhans and the CaSR activation by Ca^{2+} might act as a local regulator of insulin secretion [17]. Clinically, ASVS is often used for localization of insulinoma. When the calcium is injected in the insulinoma-feeding artery in ASVS, the hepatic venous insulin level becomes elevated. Kato and colleagues demonstrated that human insulinoma cells expresses the CaSR and that the CaSR expression of insulinoma might be related to its insulin

secretion [9]. Although both insulinoma cells and islets express the CaSR, the reactivity to changes in the $[Ca^{2+}]_e$ concentration was different between them. Komoto and colleagues suggested that insulinoma cells had a pathway that evoked the elevated calcium ion concentration in the intracellular fluid ($[Ca^{2+}]_i$) level via PI 3-kinase in response to stimulation by CaSR. In contrast, in normal rat β cells, calcium-stimulated elevation in the $[Ca^{2+}]_i$ level is not mediated by PI 3-kinase [5]. Therefore, there is a possibility that the reactivity to the calcimimetic agent is also different between insulinoma cells and normal β cells.

The insulinoma typically causes hypoglycemic symptoms; however, it is considered that there are many asymptomatic cases of the insulinoma. Although the annual incidence of neuroendocrine pancreatic tumors, including insulinoma, is about 3.5–4 per million population, there is a discrepancy between the clinical incidence and that found post-mortem. In clinicopathological analysis of autopsy, the incidence of endocrine tumors of the pancreas was 10% (6/60) in individuals having histological studies of all sections of the pancreas. In the immunohistochemical analysis of those pancreatic endocrine tumors, insulin-positive cells were found in 5 of 6 lesions. None of those cases with the tumors showed symptoms of hormone production [18]. This result suggested that there are many cases of the insulinoma without the symptoms of hypoglycemia. We considered the possibility that our patient had the insulinoma and the pancreatic tumor was too small to promote the insulin secretion and cause hypoglycemia without activation by the calcimimetic agent.

It is reported that 7.4% of the insulinomas are associated with the multiple endocrine neoplasia type 1 (MEN-1) [19]. A pituitary tumor was not detected by MRI in her brain and none of her family have the symptoms of the MEN-1 including hyperparathyroidism, the pancreatic tumor and the pituitary tumor. However, we did not perform her genetic test of *MEN1* and could not rule out the possibility of the MEN-1. The patients with MEN-1 often have a gastrinoma and the hypercalcemia sometimes increases the secretion of the gastrin from the gastrinoma [20]. To our knowledge, the hypercalcemia did not induce the insulin secretions from the insulinoma. After discontinuing administration of cinacalcet, the levels of serum calcium did not change significantly. Therefore, increasing the insulin secretion by the calcimimetic agent seems to be independent of the serum calcium levels.

It is also reported that the CaSR regulates the cell proliferation, including pancreatic ductal cells, glomerular mesangial cells and vascular smooth muscle cells [21–23]. Hills and colleagues demonstrated that activation by the calcimimetic agent enhances MAPK-mediated β cell proliferation at physiologically appropriate concentrations of extracellular calcium [24]. These findings may indicate that the

stimulation of the CaSR affects the proliferation of the insulinoma cells. Our patient had been administrated cinacalcet for about 3 years. It is possible that activating the CaSR of insulinoma cells by the calcimimetic agent for a long time could have promoted proliferation of the insulinoma cells and increasing secretion of insulin.

In conclusion, we reported a case who suffered severe hyperinsulinemic hypoglycemia related with cinacalcet use. There is a possibility that the calcimimetic agent stimulates insulin secretion of the insulinoma cells. From our findings, physicians should consider the possibility that the calcimimetic agent affects the insulin secretion and lowers the blood glucose levels.

Compliance with ethical standards

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

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or a substitute for it was obtained from the patient for being included in the study.

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