Successful Treatment of Insulinoma by a Single Daily Dose of Octreotide in Two Elderly Female Patients

HIROFUMI KISHIKAWA, YOSUKE OKADA, AKIKO HIROSE, TAKAHISA TANIKAWA, KAZUKO KANDA AND YOSHIYA TANAKA

First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu 807-8555, Japan

Abstract. We report two cases of insulinoma in advanced age patients considered unsuitable for surgery, in whom single daily doses of octreotide successfully improved hypoglycemia and hyperinsulinemia. The biological half-life of octreotide is about 100 min, hence it is customary to use two or three administrations per day to prevent hypoglycemia in insulinoma patients. The first case was a 76-year-old woman who presented with hyperinsulinemic hypoglycemia. Computed tomography (CT) and magnetic resonance imaging did not identify a tumor in the pancreas but a 1.5-cm tumor was found in the pancreatic body on abdominal angiography and selective arterial calcium stimulation and hepatic venous sampling (ASVS) were compatible with insulinoma. The patient refused surgery, but was successfully treated with octreotide at 50 µg subcutaneous injection once daily. Since the treatment was started (1 year), she has not suffered hypoglycemia. Case 2 was an 85-year-old woman who presented with hyperinsulinemic hypoglycemia. CT identified a 1.5-cm tumor in the pancreatic uncus, but she was considered unsuitable for surgery due to advanced age, obesity and cardiopulmonary dysfunction. Octreotide at 100 µg subcutaneous injection once daily prevented further hypoglycemic attacks, but two months later, postprandial plasma glucose was elevated. Octreotide was gradually reduced to 50 µg once daily. Three years have passed since the treatment without any hypoglycemic attack. Successful treatment with octreotide once daily could be due to old-age-related slow metabolism and could be potentially considered as the treatment of choice for elderly patients with insulinoma especially those considered unsuitable for surgery.

Key words: Insulinoma, Octreotide, Advanced age

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THE treatment of choice of insulinoma, a pancreas endocrinoma, is surgical resection. However, in cases where surgery cannot be conducted, various treatments have been tried. Octreotide, a somatostatin analog that inhibits insulin secretion, has been used for the treatment of insulinoma with successful control of blood glucose in more than 50% of the cases [1]. A number of studies reported that long-term octreotide treatment is suitable for insulinoma [2–5]. However, since octreotide has a biologic half-life of about 100 min, it is customary to administer it two or three times a day in

many cases. We report two cases with insulinoma in whom blood glucose was successfully controlled by once daily administration of 50 µg of octreotide without any complications.

Case Reports

Case 1

A 76-year-old woman was admitted to a peripheral hospital on July 17, 2003, for investigation of hypoglycemia. After 6-hr fasting, the plasma glucose was 39 mg/dl and immunoreactive insulin (IRI) level was 176.3 µU/ml. Thus, insulin secretion was not suppressed in spite of the hypoglycemia. Abdominal ultrasound sonography identified a hypoechoic mass mea-

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Correspondence to: Yosuke OKADA, M.D., First Department of Internal Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan

suring 1.3 cm in diameter in the pancreatic body. She was suspected to have insulinoma and was transferred to our department on July 24.

On admission, height was 145 cm, and body weight 57 kg, with a body mass index of 27.1 kg/m². There were no abnormal findings in the chest and abdomen, and no peripheral edema. Neurological examination was normal. Urinalysis, blood cell counts, and biochemical tests (*e.g.* the liver and kidney function tests) other than plasma glucose concentration were within the normal limits. Although she had hypoglycemia, a high level of C-peptide (CPR) was detected in urine (153 µg/day). Moreover, ST depression was noted in the chest V3-6 leads of the electrocardiogram at the time of a transient episode of palpitation. Although abdominal ultrasound sonography identified a hypo-echoic mass measuring 1.5 cm in diameter in the pancreatic body, no tumor was identified in the pancreas by computed tomography (CT) and magnetic resonance imaging (MRI). In abdominal arteriography, a lightly-stained tumor of 1.5 cm in diameter was detected by selective imaging of the superior mesenteric artery (Fig. 1). As explained above, glycometabolism-related data (Table 1) showed that the IRI level was not suppressed (176.3 µU/ml) when fasting blood glucose was 39 mg/dl. At the same time, ACTH, GH, and cortisol levels were appropriate for hypoglycemia. A standard oral glucose tolerance test (75g-OGTT) showed a high basal level of IRI relative to plasma glucose concentration, before the load. Furthermore, although the rise in plasma glucose concentration after the load was slight, IRI increased to a high level and resulted in hypoglycemia at 180 minutes after the load. Selective arterial calcium stimulation and hepatic venous sampling (ASVS) showed a striking increase in insulin secretion in the superior mesenteric artery, which is the main supplier of the pancreatic body area (calcium injections were performed in order of the superior mesenteric artery, gastroduodenal artery, and splenic artery).

The patient was considered to have hyperinsulinemic hypoglycemia. Although CT and MRI did not identify a pancreatic tumor, she was diagnosed with insulinoma of the pancreatic body based on ASVS studies. Though we explained the surgical treatment of insulinoma, she refused surgical resection because of advanced age and cardiac disease. Based on suppression of insulin secretion in the octreotide loading test, she was treated with subcutaneous injection of 50 µg of octreotide once daily before sleep (Table 2). Fortu-

Fig. 1. Case 1. Light staining of a tumor measuring 1.5 cm in diameter in the superior mesenteric arteriography.

Table 1. Glucose-related studies (Case 1)

Hormones at hypoglycemia					
Fasting blood glucose (mg/dl)	39	IRI (μU/ml)	176.3		
ACTH (pg/ml)	71.7	Cortisol (mg/dl)	21.8		
TSH (μU/ml)	2.83	fT4 (ng/dl)	1.18		
GH (ng/ml)	6.0		148		
75g-OGTT					
Time (min)	0	30	60	120	180
Blood glucose (mg/dl)	66	112	68	73	47
IRI (μU/ml)	19.2	1115	468	163	54.7
Arterial stimulation and venous sampling					
Ca stimulation			before	1 minute after	
IRI (μU/ml)	gastroduodenal artery		445	369	
	superior mesenteric artery		16.7	542	
	splenic artery		102	342	

nately, she has never had hypoglycemic attacks for 1 year since the commencement of octreotide treatment. One year after the commencement of treatment, she had an impaired glucose tolerance (IGT) pattern in 75g-OGTT (Table 3), and a gallstone that was not observed in abdominal ultrasound sonography.

Case 2

An 85-year-old woman was admitted to a peripheral hospital on December 8, 2000, in a hypoglycemic coma. Although she received an intravenous drip of dextrose and consciousness level improved, she developed

Table 2. Effect of octreotide (Case 1)

Somatostatin loading test (octreotide 100 µg subcutaneous injection)				
Time (min)	0	60	120	180
Blood glucose (mg/dl)	61	59	133	186
IRI (µU/ml)	13.5	1.4	1.4	1.7
Daily profile (octreotide 50 µg × 1 subcutaneous injection)				
Time	7:30	11:30	17:30	21:00
Before therapy				
Blood glucose (mg/dl)	70	67	52	54
After therapy				
Blood glucose (mg/dl)	171	110	98	138

Table 3. 75g-OGTT: 1 year after start of octreotide therapy (Case 1)

75g-OGTT				
Time (min)	0	30	60	120
Blood glucose (mg/dl)	98	171	149	167
IRI (µU/ml)	11.1	132	190	109

frequent episodes of hypoglycemia after that attack. Blood glucose was 39 mg/dl while IRI level 37.0 µU/ml. Abdominal CT identified a tumor measuring 1.5 cm in diameter in the pancreatic uncus. Based on these findings, the provisional diagnosis was insulinoma.

She was transferred and admitted to our hospital on December 19. Medical history indicated frequent hypoglycemic attacks for the last five years. She also indicated that her weight had increased by 10 kg during the last one year though she admitted little physical activity in daily life. Height was 151 cm and body weight was 71 kg, with a body mass index of 31.1 kg/m². Auscultation of the chest revealed wheeze in the upper lung area. Abdominal examination and neurological tests were normal. Urinalysis was normal and blood cell count showed mild leukocytosis (10700/µl). Biochemical tests showed low serum levels of albumin (3.4 mg/dl), and elevated total cholesterol (235 mg/dl) and triglyceride (167 mg/dl). Blood gas analysis showed low PaO₂ (76 mmHg) and elevated PaCO₂ (47.7 mmHg). Urinary CPR level was high (116 µg/day) in spite of the hypoglycemia. Chest X-ray showed marked cardiomegaly with a cardiothoracic ratio of 63.8%, and the presence of an esophageal hiatus hernia. Abdominal CT showed an enhanced tumor of 1.5 cm in diameter in the pancreatic uncus (Fig. 2). Abdominal arteriography showed tumor staining with

Fig. 2. Case 2. An enhanced tumor measuring 1.5 cm in diameter was detected in the pancreatic uncus on abdominal CT. **Fig. 3.** Case 2. Arteriography of the dorsal pancreatic artery showed a tumor measuring 1.5 cm in diameter in the pancreatic uncus.

selective imaging of the dorsal pancreatic artery (Fig. 3). Glycometabolism-related studies (Table 4) showed no suppression of the IRI (50.8 µU/ml) and CPR (6.10 mg/ml) at the time of hypoglycemia (blood glucose: 37 mg/dl). Moreover, at the time of hypoglycemia, ACTH, GH, and cortisol levels were low. A standard 75g-OGTT revealed hypoglycemia and hyperinsulinemia at baseline and a brisk rise in IRI with

Table 4. Glucose-related studies (Case 2)

Hormones at hypoglycemia					
fasting blood glucose (mg/dl)	37				
IRI (μ U/ml)	50.8	CPR (pg/ml)	6.1		
ACTH (pg/ml)	39.0	Cortisol (μ g/dl)	11.4		
GH (ng/ml)	2.6	Glucagon (pg/ml)	148		
75g-OGTT					
Time (min)	0	30	60	120	180
Blood glucose (mg/dl)	34	115	109	122	55
IRI (μ U/ml)	68.7	249.8	258.4	182.9	52.9
Arterial stimulation and venous sampling					
Ca stimulation			before	1 minute after	
IRI (μ U/ml)	dorsal pancreatic artery	169.7	6,396		
	superior mesenteric artery	160.8	200.9		
	splenic artery	474.0	444.0		

increased plasma glucose concentration after loading, followed by persistent post-test hyperinsulinemia at 240 minutes after the load despite the hypoglycemia. ASVS showed a striking increase in insulin secretion in the dorsal pancreatic artery, the supplier of the pancreatic uncus area (calcium injections were performed in the order of the dorsal pancreatic artery, splenic artery, and superior mesenteric artery).

She was diagnosed with insulinoma of the pancreatic uncus based on the hyperinsulinemic hypoglycemia and CT and ASVS findings. Since five years had passed since the first hypoglycemic attack, we considered that the malignant potential of the insulinoma was low. She was also considered unsuitable for immediate surgery because of old age, heart failure and pulmonary insufficiency caused probably by obesity and old pulmonary tuberculosis. Since suppression of insulin secretion was noted in the octreotide loading test, she was treated with subcutaneous injection of 100 μ g octreotide once daily before sleep. Table 5 compares the daily changes in blood glucose in the day before and after treatment with octreotide. After discharge from our hospital in January 2001, she did not develop any hypoglycemic symptoms. Furthermore, in March 2001, she was noted to be hyperglycemic with high HbA1c to 6.0%. A standard 75g-OGTT indicated normal insulin secretion before the load and a fall in insulin secretion after the load, suggestive of type 2 diabetes status caused by insulin resistance (Table 6). Accordingly, octreotide treatment was gradually decreased from 100 to 75, 62.5 and finally to 50 μ g once daily, along with diet therapy, which resulted in a re-

Table 5. Effect of octreotide (Case 2)

Somatostatin loading test (octreotide 100 μ g subcutaneous injection)				
Time (min)	0	60	120	180
Blood glucose (mg/dl)	61	51	108	160
IRI (μ U/ml)	51.8	3.1	3.8	6.2
Daily profile (octreotide 100 μ g $\times$ 1 subcutaneous injection)				
Time	7:30	11:30	17:30	21:00
Before therapy				
Blood glucose (mg/dl)	42	65	34	157
After therapy				
Blood glucose (mg/dl)	166	192	132	161

Table 6. 75g-OGTT: 7 months after start of octreotide therapy (Case 2)

75g-OGTT				
Time (min)	0	30	60	120
Blood glucose (mg/dl)	120	214	234	242
IRI (μ U/ml)	8.8	38.3	68.6	96.5

duction of body weight to 59 kg in December 2001. During the last three years, administration of a minimal dose of octreotide once daily has resulted in successful control of blood glucose and body weight, without any complications such as cholelithiasis.

Discussion

Insulinoma is a pancreas endocrinoma that causes hypoglycemia, and the first choice treatment is surgical resection. However, in patients regarded as unsuitable candidates for surgery or those who refuse surgery, various pharmacotherapies have been used. Such medications are divided roughly into insulin frenosecretory or antagonism agents such as octreotide [6] and diazoxide [7], and antitumor agents such as streptozotocin [8]. Octreotide is a synthetic long-acting somatostatin analog, and shows wide-spectrum inhibitory effects on the anterior pituitary function, pancreas and gut endocrine secretions, and gastrointestinal functions [9]. Octreotide suppresses pancreatic secretions by blocking the influx of calcium ions. However, the exact mechanism(s) of the inhibitory actions of octreotide on insulin, glucagon, and GH release and prevention of hypoglycemia remains elusive [6]. In addition, octreotide affects glycometabolism by delaying intestinal

secretion, prolonging orocecum transit time, and/or inhibiting absorption of nutrients [10, 11].

Gorden *et al.* [1] reported the effects of octreotide treatment in 20 patients with insulinoma. Octreotide reduced plasma insulin concentration by more than 25% in 12 (60%) patients and improved hypoglycemia in 10 (50%) patients [1]. The diverse biological effects of somatostatin are mediated through a family of G protein-coupled receptors of which five members have been recently identified by molecular cloning. It is reported that octreotide binds with high affinity to somatostatin-receptor (SSTR) subtypes 2 and 5 and with a moderate affinity subtype 3 but does not bind to subtypes 1 and 4 [12, 13]. The SSTRs have also been detected in various tumors such as pituitary adenomas and gut neuroendocrine tumors [14]. In analysis of 20 insulinomas, semiquantitative RT-PCR of SSTR mRNAs showed the expression of SSTR 2 and 5 in 70% of the tumors [15]. In another study, it is reported that the efficacy of octreotide may depend on the expression of SSTR 2 in endocrine tumors [16], and that the expression of SSTR 2 was extremely positive in a specimen from a patient with pancreatic endocrine tumors in whom octreotide treatment had proven very effective [17]. Furthermore, the expression of a *gsp* oncogene was suggested for the efficacy of octreotide in GH-secreting adenomas [18]. We could not analyze the expression of SSTRs in our two cases because surgery was not performed in either case. However, we suspect the expression of SSTR 2 and/or 5 in our two cases, because plasma glucose levels were maintained near normal by administration of a minimal dose of octreotide.

On the other hand, other studies have reported that the half-life of octreotide varies from 72 to 113 min in healthy subjects, and that the serum levels are not dependent on the dose [19, 20]. Accordingly, octreotide administration 2 or 3 times per day is usually used for prevention of hypoglycemia in insulinoma cases. In our two cases, the insulin secretion was inhibited by once daily octreotide administration. As hypoglycemia appeared at night in our cases, it caused anxiety and sleepless. Therefore, we used octreotide before sleeping. Their hypoglycemia was thus avoided all day though we did not measure their IRI. A careful search of the 1980–2004 Medline database identified only a single reported case of an 80-year-old woman with insulinoma in whom hypoglycemia was controlled for seven months prior to surgery by once daily adminis-

tration of octreotide [4]. Thus, our two cases are considered very rare.

When considering the factor that facilitated the control of insulin by once daily administration of octreotide, it is interesting that our 2 cases and the previously reported case [4] were elderly patients. Another case of endogenous hyperinsulinism caused by a benign β -cell disorder but not insulinoma, in which hypoglycemia was successfully controlled by 50 μ g of octreotide once daily, was also an 80-year-old man [21]. Although the metabolism and excretion of octreotide has not been investigated in detail, a preliminary study reported that hepatic extraction of octreotide was estimated to be between 30 and 40% in healthy volunteers [20]. In another study of healthy volunteers, octreotide was excreted unchanged in urine and bile and the rates of urinary excretion after subcutaneous single administration of octreotide at 50 μ g and 100 μ g were 36.3% and 42.1%, respectively, and urinary excretion was almost complete by 8 hours after administration [22]. Furthermore, in patients with severe renal impairment, plasma octreotide clearance was significantly reduced to about half of that of healthy subjects, reflecting the presence of a renal component in the disposition of this substance [23]. Neither of our two cases had liver or renal dysfunction. However, we suspect that the successful control of plasma glucose by once daily administration of octreotide is due to slow metabolism associated with generalized low physiological activity of old age.

Although there are several reports of tachyphylaxis to octreotide in patients with VIPoma or acromegaly [24, 25], our two cases with insulinoma were controllable over long periods of time with octreotide and we could reduce the octreotide dose. It is suggested that the appearance of an antibody to octreotide may cause the tachyphylaxis [25]. Although the reason for the lack of tachyphylaxis in our cases is not clear, we suspect diabetic diathesis in case 2.

One report has described octreotide-induced suppression of secretion of insulin as well as counter-regulatory hormones and aggravation of hypoglycemia in patients with insulinoma [26]. Therefore, in the octreotide loading test, careful observation is necessary and close monitoring of blood sugar is advisable.

In conclusion, we reported two rare cases of elderly female patients with insulinoma who were well controlled with a small once daily administration of octreotide. Since octreotide has little adverse drug reactions

and is well tolerated during long-term therapy as seen in our patients, treatment with octreotide once daily could be potentially considered as the treatment of

choice for elderly patients with insulinoma especially those considered unsuitable for surgery.

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