Case report

Lanreotide and diazoxide have comparable effects on glucose levels in an elderly Japanese insulinoma patient: a case report

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Abstract

An insulinoma is a pancreatic neuroendocrine tumor that causes hypoglycemia. In the elderly, as surgery is not always possible, drugs are an important alternative. However, the effects of lanreotide on insulinomas have not yet been elucidated. We report the case of an 85-year-old Japanese woman who was admitted for loss of consciousness and hypoglycemia, which was resolved after intravenous glucose infusion. Insulin secretion was not inhibited during hypoglycemia. Enhanced computed tomography and OctreoScan scintigraphy revealed a pancreatic tumor (diameter, 13 mm) with radiotracer accumulation. Thus, clinical insulinoma was confirmed. However, the patient refused further examination and surgery. Diazoxide (150 mg/day) therapy resolved hypoglycemia but caused fluid retention. Consequently, we switched to lanreotide (120 mg/6 weeks). Continuous glucose monitoring revealed that both drugs had comparable effects on interstitial glucose normalization. Furthermore, 447 days after the initiation of lanreotide treatment, the patient had no hypoglycemic symptoms. Therefore, lanreotide may be a useful alternative treatment option for inoperable insulinomas in elderly individuals.

Key words: elderly insulinoma, lanreotide, diazoxide, continuous glucose monitoring

Introduction

An insulinoma is a pancreatic neuroendocrine tumor (p-NET) that causes hypoglycemia via the hypersecretion of insulin. In Japan, the incidence of neuroendocrine tumors is increasing[1]. Approximately three patients per million suffer from insulinoma annually[2]; because Japan is an aging society, the number of elderly patients with insulinoma may increase in the future. This is problematic because, although most insulinomas are benign, curative surgery is the primary treatment[2–4]. In the elderly, surgery is not always possible because of aging, disease progression, and comorbidities[5]. Instead, diazoxide and somatostatin analogs (e.g., octreotide and lanreotide) are sometimes used[2, 4]. Diazoxide, a standard drug for the treatment of insulinomas, acts via ATP-sensitive potassium channels in pancreatic β-cells; however, it often induces fluid retention[4]. Somatostatin analogs act via the somatostatin receptor. Although octreotide has been successfully used[5], it has not yet been approved as a Japanese-insured treatment for p-NETs. After the CLARINET study[6], in July 2017, lanreotide was approved for the treatment of p-NETs in Japan. Therefore, the use of lanreotide for insulinoma may increase in Japan. As a palliative treatment, lanreotide may be important, especially in inoperable elderly insulinomas.

Additionally, the usefulness of continuous glucose monitoring (CGM)[7, 8] and flash glucose monitoring (FGM)[9] in insulinoma has been reported; however, few studies have compared the effects of lanreotide and diazoxide on glucose variations[10, 11]. Thus, the evaluation of 1) the effects of lanreotide and diazoxide on CGM and 2) the long-term effects of lanreotide are crucial issues in the treatment of elderly patients with an inoperable insulinoma.

Here, we report a case of refractory hypoglycemia in an elderly Japanese patient with insulinoma who was successfully treated with lanreotide after initial treatment with diazoxide.
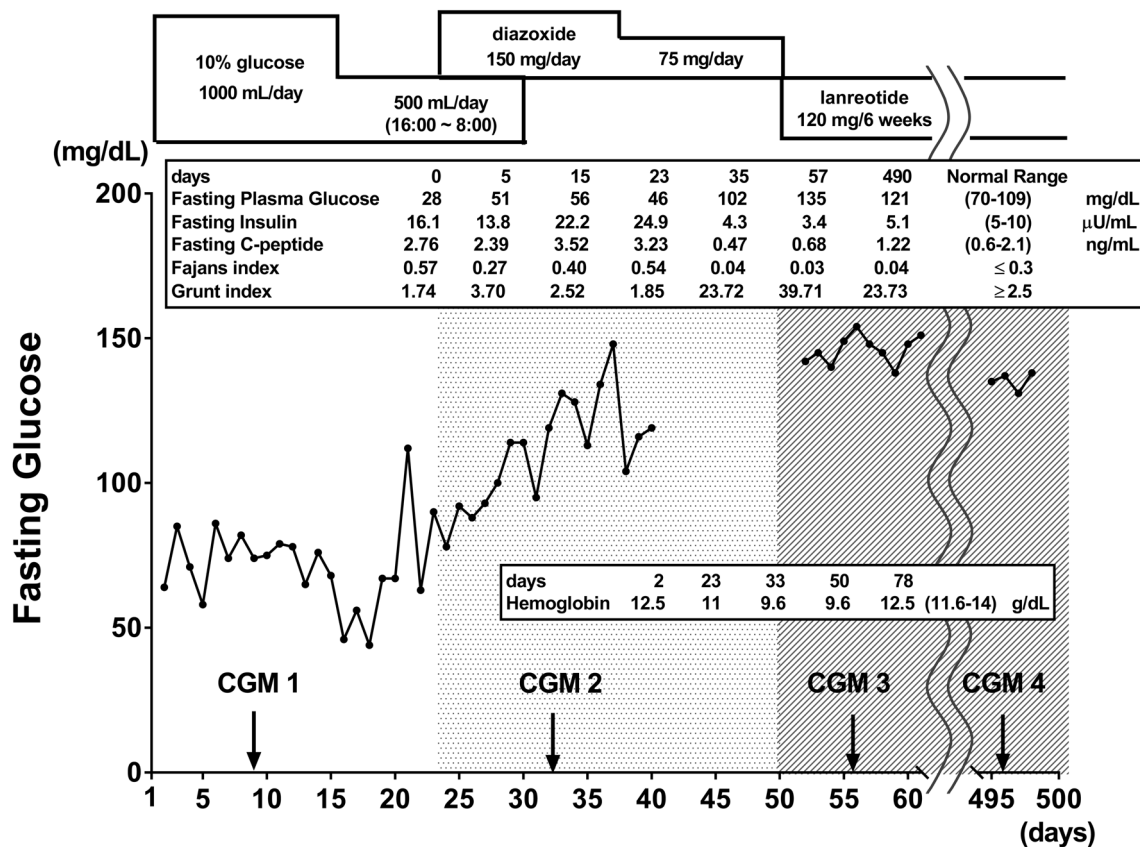
Figure 1 Patient's clinical course.

When the patient was treated with a glucose intravenous drip, her fasting glucose level was low. After the initiation of diazoxide, her glucose levels increased, but she displayed edema and anemia. The patient continued diazoxide at a reduced dose, but was then switched to lanreotide. On the 447th day after the initiation of lanreotide, her glucose levels were comparable to those after the use of diazoxide. On days 9, 32, 56, and 496 after admission, CGM 1, 2, 3, and 4, respectively, were conducted. The CGM results are presented in Figure 3a. CGM, continuous glucose monitoring; FAJAS index: fasting insulin/fasting plasma glucose > 0.3; GRUNT index: fasting plasma glucose/fasting insulin < 2.5.

Case Report

Informed consent for the publication of this report was obtained from the patient. In 2019, an 85-year-old Japanese woman was admitted for hypoglycemia (28 mg/dL) after her family discovered her unconscious at home. Two years prior, she had a similar episode of hypoglycemia. Moreover, during the six months prior to admission, her alertness upon awakening gradually worsened. She had hypertension and was taking nifedipine (40 mg) and candesartan (4 mg). She had no family history of multiple endocrine neoplasia type 1.

The clinical course of the patient is summarized in Figure 1. Physical examination upon admission revealed a height of 148.7 cm, weight of 62.8 kg, body mass index of 28.4 kg/m², and blood pressure of 143/102 mmHg. Although the patient's consciousness levels normalized after the administration of glucose, 100 g/day glucose was continued.

On day 5 after admission, laboratory tests performed during glucose administration revealed: fasting plasma glucose level, 51 mg/dL (70–109 mg/dL); fasting insulin level, 13.8 μU/mL (5–10 μU/mL); fasting-C-peptide level, 2.39 ng/mL (0.6–2.1 ng/mL); hemoglobin A1c level, 4.9% (4.7–6.2%); adrenocorticotropic hormone level, 40.2 pg/mL (7.2–63.3 pg/mL); cortisol level, 12.50 μg/dL (6.2–19.4 μg/dL); thyroid stimulating hormone level, 0.81 μIU/mL (0.35–4.94 μIU/mL); free T3 level, 1.94 pg/mL (2.30–4.30 pg/mL); and free T4 level, 0.97 ng/dL (0.90–1.70 ng/dL). Moreover, plasma catecholamine fractionation showed: adrenaline level, 30 pg/mL (< 100 pg/mL); noradrenaline level, 314 pg/mL (100–450 pg/mL); and dopamine level, 11 pg/mL (< 20 pg/mL). Additional laboratory tests revealed: growth hormone level, 1.35 ng/mL (0.13–9.88 ng/mL); and insulin-like growth factor I level, 155 ng/mL (49–158 ng/mL). Plasma gastrin (100 pg/mL) and glucagon (44 pg/mL) levels were within the normal ranges. The above endocrine examinations suggested that the counterhormone responses were low, even though the patient was hypoglycemic. The
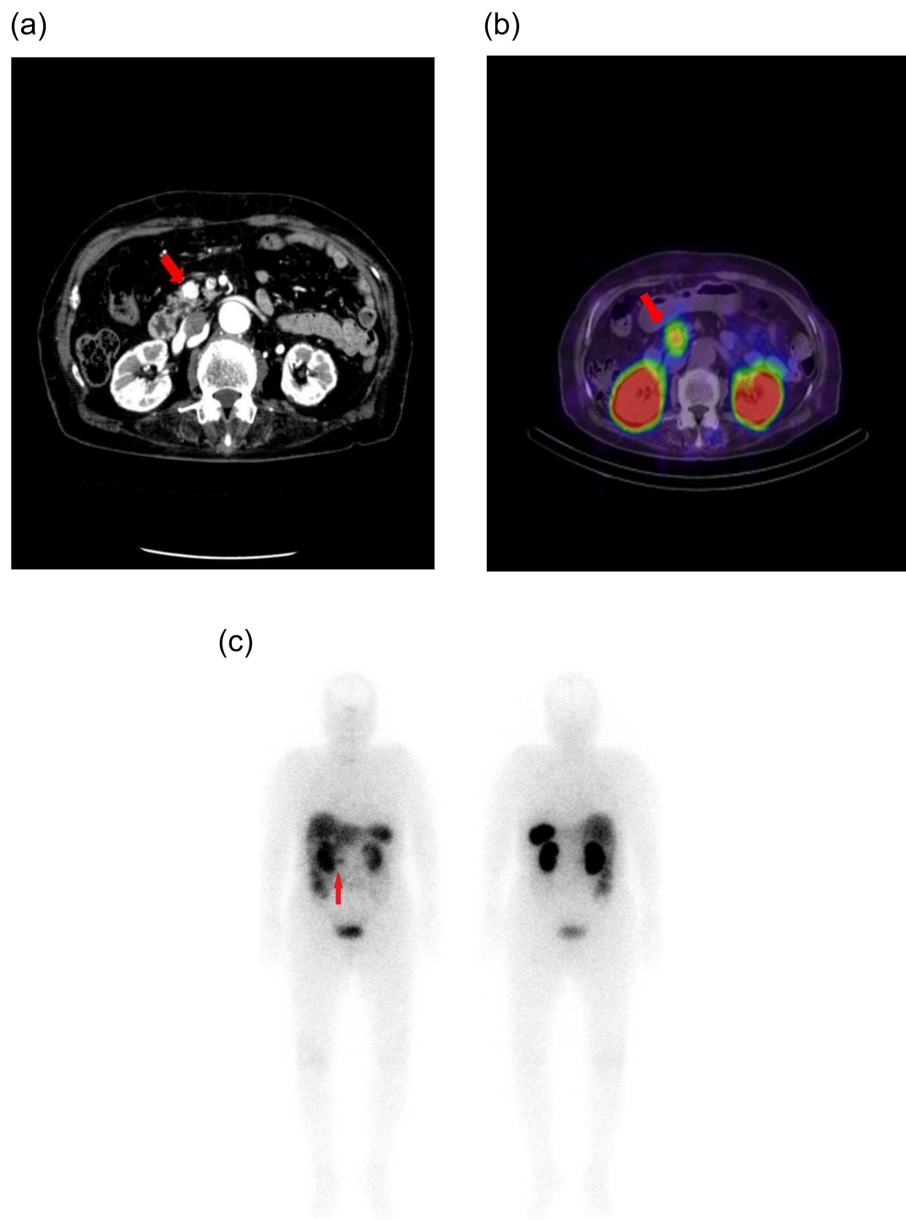
(a)

(b)

(c)

Figure 2 Enhanced computed tomography and OctreoScan scintigraphy images.
(a) Enhanced computed tomography revealed a tumor (13 mm in diameter; red arrow) in the head of the pancreas. (b) OctreoScan scintigraphy showed radiotracer accumulation (red arrow) in the tumor. (c) No other abnormal accumulations were detected in whole-body planar images.

Fajans' and Grunt indices were positive. Other laboratory data were normal, and insulin antibodies were not detected. Antihypertensive drugs were discontinued.

Enhanced computed tomography showed a tumor (diameter, 13 mm) in the head of the pancreas (Figure 2 (a)), an area where OctreoScan scintigraphy showed tracer accumulation (Figure 2 (b)). No other abnormal accumulations were detected in the whole-body planar images (Figure 2 (c)).

On day 9, a retrospective analysis of CGM (iPro®2, Medtronic) data indicated nighttime and pre-dinner hypo-glycemia even with a 10% intravenous glucose drip (Figure 3 (a), CGM 1). With reference to the American Diabetic Association guideline of "time within a given range" (Time in Range)[12], we classified the interstitial glucose levels of CGM as follows: < 54 mg/dL, 54–69 mg/dL, 70–180 mg/dL, 181–250 mg/dL, and > 251 mg/dL. CGM 1 showed that the glucose level was < 70 mg/dL 39.1% of the time (Figure 3 (b)).

On days 13 and 23, laboratory tests showed low glucose and high insulin levels. The Fajans' index was positive on
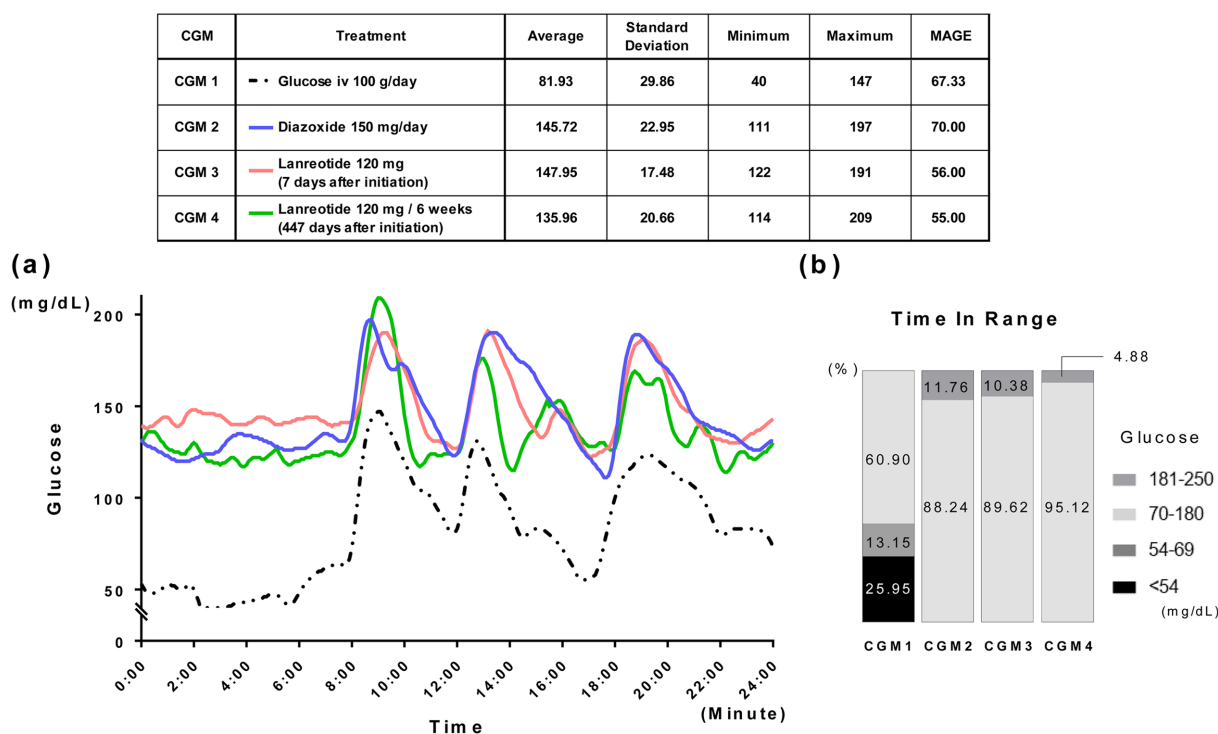
CGM	Treatment	Average	Standard Deviation	Minimum	Maximum	MAGE
CGM 1	·-· Glucose iv 100 g/day	81.93	29.86	40	147	67.33
CGM 2	— Diazoxide 150 mg/day	145.72	22.95	111	197	70.00
CGM 3	— Lanreotide 120 mg (7 days after initiation)	147.95	17.48	122	191	56.00
CGM 4	— Lanreotide 120 mg / 6 weeks (447 days after initiation)	135.96	20.66	114	209	55.00

Figure 3 Continuous glucose monitoring and Time in Range of no drug (glucose infusion), diazoxide, lanreotide, and 447 days after lanreotide initiation.

The upper table shows the average, standard deviation, minimum and maximum glucose level, and mean amplitude of glycemic excursions (MAGE) in each CGM. On days 9, 32, 56, and 496 after admission, CGM 1, 2, 3, and 4, respectively, were conducted. (a) Continuous glucose monitoring graph comparing the effects of no drug (glucose infusion), diazoxide, lanreotide, and 447 days after lanreotide initiation. The dashed line (no drug; patient treated only with 10% glucose continuous intravenous drip) shows exceptionally low glucose levels at night and before dinner. The blue line (150 mg diazoxide/day), red line (7 days after initiating 120 mg lanreotide), and green line (120 mg lanreotide/6 weeks, 447 days after initiating lanreotide) show comparable glucose levels and the resolution of hypoglycemia. (b) Time in Range of no drug (glucose infusion), diazoxide, lanreotide, and 447 days after lanreotide initiation. We classified the interstitial glucose levels of each CGM as follows: < 54 mg/dL, 54–69 mg/dL, 70–180 mg/dL, 181–250 mg/dL, and > 251 mg/dL. Both diazoxide and lanreotide prevented glucose levels of < 70 mg/dL.

days 13 and 23, and the Grunt index was positive on day 23.

Because the patient had hypoglycemia without inhibited insulin secretion and an OctreoScan-positive tumor in the pancreas, we diagnosed her with a clinical insulinoma.

Surgery and a selective arterial secretin injection test were recommended, but the patient refused invasive procedures, citing increasing age-related weakness. Consequently, diazoxide (150 mg/day) was administered as an alternative palliative drug therapy.

Fasting glucose levels were elevated, and both the Fajans' and Grunt indices were improved (Figure 1). On day 32, CGM showed that diazoxide elevated fasting glucose levels and eliminated hypoglycemia by the eighth day after initiation (Figure 3 (a), CGM 2). CGM 2 showed that the glucose level was < 70 mg/dL 0% of the time and 70–180 mg/dL 88.24% of the time (Figure 3 (b)).

However, as the patient had edema and anemia owing to fluid retention, we reduced the dose of diazoxide. Because the insulinoma was OctreoScan-positive, diazoxide was discontinued and lanreotide (120 mg) was administered, after which the patient's edema and anemia improved.

On day 56, CGM showed that lanreotide also elevated fasting glucose levels and eliminated hypoglycemia (Figure 3 (a), CGM 3). CGM 3 showed that the glucose level was < 70 mg/dL and 70–180 mg/dL 0% and 89.62% of the time, respectively (Figure 3 (b)). The mean amplitude of glycemic excursions (MAGE) was improved. Lanreotide (120 mg/6 weeks) was continued.

One year after starting lanreotide therapy, the patient had generally good health with no hypoglycemia and no lanreotide-related side effects. On day 496 after the first admission, CGM indicated controlled glucose levels without hypoglycemia (Figure 3 (a), CGM 4). CGM 4 showed that the glucose level was < 70 mg/dL and 70–180 mg/dL 0% and 95.12% of the time, respectively (Figure 3 (b)). Moreover, the MAGE was improved. On day 494, enhanced computed

tomography showed a tumor (diameter, 12 mm) in the head of the pancreas; thus, the size of the tumor was unchanged. On day 613, the fasting glucose level was 99 mg/dL, and the HbA1c level was 6.4%, which was slightly elevated.

Discussion

In this study, we demonstrated that lanreotide is a useful alternative treatment for insulinomas by observing glucose variations and side effects in an elderly patient.

Regarding glycemic control, CGM indicated that diazoxide and lanreotide (both initially and 447 days after) had comparable effects on hypoglycemia (Figure 3). Both drugs reduced fasting insulin and c-peptide levels (Figure 1). Fasting hypoglycemia is a characteristic of insulinomas[2]; our patient also had hypoglycemia before dinner. As postprandial hypoglycemia is a complication accompanying insulinoma[2], CGM-based evaluation is important.

Recently, CGM and FGM have been reported as useful tools in diabetes management, and the American Diabetic Association recommends that the glucose level be evaluated based on the "Time in Range"[12]. In a recent case-control study, Ma *et al.* reported that because the characteristics of the glucose pattern in CGM between patients with an insulinoma and those without are different, CGM is a valuable tool in differential diagnosis[8]. However, research on insulinomas using CGM/FGM is still limited, and further study may be needed.

Vezzosi *et al.* recently reported that CGM can diagnose hyper- and hypo-glycemia unawareness in patients with a drug-treated insulinoma[13]. In this study, lanreotide and diazoxide had comparable effects on interstitial glucose levels in CGM. In our case, both drugs caused no hypoglycemia unawareness. However, to clarify the detailed differences between lanreotide and diazoxide using CGM/FGM, further clinical studies are needed.

Although the tumor inhibitory effect of lanreotide in p-NET was reported in the CLARINET study[6, 14] and CLARINET open-label extension study[15], in our case, the tumor size was almost the same after approximately 1.2 years of lanreotide treatment. However, because the curative treatment for an insulinoma is surgery, the long-term effect of lanreotide on local tumors remains unclear; a longer observational period may be needed in a future study.

Regarding side effects, diazoxide induces fluid retention and thrombocytopenia[2, 4], especially in females[4], which is consistent with our findings. In contrast, somatostatin analogs can cause malabsorption, cholelithiasis, and hypoglycemia[2], and inhibit the secretion of counterregulatory hormones, such as glucagon, paradoxically inducing hypoglycemia[2]. One year after lanreotide therapy, the patient experienced no such effects.

In our case, after approximately 1.6 years of lanreotide use, the HbA1c level was 6.4%, which was slightly high. Lanreotide has been reported to inhibit the secretion of both glucagon and insulin[2, 14]. Therefore, both hypo- and hyperglycemia can occur as a result of the balance in hormone inhibition. Similarly, in a recent meta-analysis, Cozzolino et al. reported that somatostatin analogs induce the elevation of HbA1c levels in acromegaly[16]. However, whether lanreotide induces the elevation in HbA1c levels in insulinoma is still unclear, and careful observation is needed.

If somatostatin receptor type 2 is expressed, such as in our case, lanreotide may be a first-line drug. Consequently, OctreoScan scintigraphy was useful to determine the selective drugs in our case. Currently, the standard technique to localize insulinomas is the selective arterial secretin injection test[2]. Our patient refused this invasive procedure; thus, we used OctreoScan scintigraphy, which proved to be a useful alternative. Somatostatin receptor scintigraphy can detect only 50% of insulinomas[2], owing to low somatostatin receptor type 2 expression[2, 17]. Nevertheless, OctreoScan-positive results can help guide treatment. For example, lanreotide was recently effective in a young patient with an OctreoScan-positive insulinoma who had suffered from a diazoxide-induced side effect[11]. This concurs with our results.

This study had several limitations. First, we could not obtain specimens or conduct a pathological evaluation because our patient refused all invasive procedures. Although we could not exclude nesidioblastosis (a major differential diagnosis of insulinoma[2, 18]), the patient's clinical course was not inconsistent with an insulinoma. Second, the observational period was approximately one year; a longer period was preferable. Third, although the counterhormone responses were low, even though hypoglycemia was confirmed in this case, we could not adequately examine the hypothalamic–pituitary–adrenal axis. Tang *et al.* hypothesized that repeated hypoglycemia exhausts counterregulatory mechanisms. As a result, the glucose level threshold for counterhormone release was at a very low level[19]. However, the detailed mechanism remains unclear, and further studies are needed.

In summary, this is the first CGM-based comparison of glucose variations caused by lanreotide and diazoxide in an elderly patient with insulinoma. Our results suggest that lanreotide is a useful alternative treatment for insulinomas in elderly patients.

Conflicts of interest: The authors have no conflicts of interest to disclose.

Acknowledgment

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