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Case Report

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Pasireotide: A Novel Treatment for Tumor-Induced Hypoglycemia Due to Insulinoma and Non-Islet Cell Tumor Hypoglycemia

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Abbreviations: COVID-19, 2019 novel coronavirus; GH, growth hormone; HbA_{1c}, glycated hemoglobin; HCC, hepatocellular carcinoma; IGF, insulin-like growth factor; LAR, long-acting release; NICTH, non-islet cell tumor hypoglycemia; SSTR, somatostatin receptor.

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Abstract

Tumor-induced hypoglycemia is a serious disorder most commonly caused by insulinoma or non-islet cell tumor hypoglycemia (NICTH). The hypoglycemia can be severe and refractory to conventional therapy, leading to significant morbidity and mortality. The objective of this work is to describe a series of challenging cases in which refractory, tumor-induced hypoglycemia was shown to respond to the use of pasireotide, a second-generation somatostatin receptor ligand. We describe the clinical and biochemical features of 3 patients with tumor-induced hypoglycemia due to an occult insulinoma, malignant insulinoma, and non-islet cell tumor hypoglycemia. In these 3 individuals, the hypoglycemia remained refractory to guideline-recommended medical therapy, such as diazoxide, nonpasireotide somatostatin analogues, and glucocorticoids. Pasireotide was substituted to attenuate the refractory hypoglycemia for each patient. The addition of pasireotide led to prompt improvement in the frequency and severity of hypoglycemic episodes for each tumor-induced hypoglycemia patient. We demonstrate the successful treatment of 3 individuals with refractory, tumor-induced hypoglycemia with pasireotide. We offer the first reported use of pasireotide for the successful treatment of nonmalignant insulinoma and non-islet cell tumor hypoglycemia.

Key Words: hypoglycemia, insulinoma, insulin-like growth factor II

Hypoglycemia in individuals without diabetes is uncommon and warrants further investigation if the Whipple triad is fulfilled. Insulinoma and non-islet cell tumor hypoglycemia (NICTH) are rare causes of hypoglycemia. They may present with refractory hypoglycemia, and in severe cases, can cause irreversible neurocognitive impairment and death. The medical management of refractory hypoglycemia is challenging because there are limited therapeutic

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options available with unpredictable response and significant adverse effects [1].

The most common cause of hypoglycemia due to endogenous hyperinsulinism is insulinoma, which is generally single and benign [2]. Malignant insulinomas are rare, comprising only 5.8% of all insulinomas [3]. Malignant insulinomas have a poor prognosis, with a 10-year survival of less than 20%, and present with distant metastatic involvement, predominately to the liver and regional lymph nodes [4]. The definitive treatment of solitary insulinomas is surgical, though medical therapy has a role in patients who are poor surgical candidates or who decide against surgery. In cases of malignant insulinomas, however, surgery is not curative; thus, medical therapy has an important role in controlling symptomatic hypoglycemia and reducing tumor burden. Medications indicated for alleviating hypoglycemia in malignant insulinoma include diazoxide, glucocorticoids, and somatostatin analogues, which have shown variable responses [1, 5].

NICTH is a rare paraneoplastic syndrome associated with tumors of epithelial and mesenchymal origin. It is the second-most common cause of tumor-induced hypoglycemia after insulinoma and is most commonly seen in hepatocellular and adrenocortical carcinoma [6]. NICTH is caused by tumor overexpression of insulin-like growth factor (IGF)-2: both mature IGF-2 and incompletely processed "big IGF-2," which promotes hypoglycemia due to insulin-like effects [7]. NICTH should be considered in the presence of hypoinsulinemic hypoglycemia with low growth hormone (GH) and IGF-1 levels, and an IGF-2:IGF-1 ratio greater than 10. There are no commercially available assays for big IGF-2 [8]. Definitive treatment of NICTH involves complete tumor resection. If resection is not feasible, local antitumor therapies are generally pursued, with a trial of glucocorticoids and/or recombinant human GH for refractory hypoglycemia [9].

We report 3 cases of refractory hypoglycemia due to occult insulinoma, malignant insulinoma, and NICTH that were successfully treated with pasireotide, a second-generation somatostatin receptor ligand. Although not formally approved for use in hypoglycemia, pasireotide has unique features that make it an appealing choice for refractory, tumor-induced hypoglycemia.

Case 1

Pasireotide for the Treatment of Insulinoma in a Poor Surgical Candidate

An 80-year-old woman was referred to our endocrine clinic for recurrent hypoglycemic episodes. She reported a 9-year history of spells of dizziness, tremors, and diaphoresis that improved with eating peanut butter. When symptomatic, the blood glucose levels measured in her assisted living facility were approximately 50 mg/dL. These episodes occurred both in the fasting and postprandial states and were increasing in frequency. Additionally, the patient had gained 12 pounds in the last 6 months.

The patient was admitted to the hospital for a 72-hour fast, which revealed endogenous hyperinsulinism. When the patient's blood glucose measured 43 mg/dL, she had an insulin level of 47 (normal, 2.0-19.6 μIU/mL), C-peptide of 8.2 (normal, 0.80-3.85 ng/mL), proinsulin level of 27.9 (normal, ≤ 18.8 pmol/L), and negative sulfonylurea screen and insulin antibody. Computed tomography (CT) of the abdomen and pelvis showed a subtle 3-mm nodular focus of arterial enhancement within the pancreatic head, suspicious for a small insulinoma, but endoscopic ultrasound failed to localize the tumor. ^{68}Ga DOTATATE positron emission tomography/CT did not reveal any abnormal uptake concerning for neuroendocrine tumor, and a selective arterial calcium stimulation test failed to localize the patient's insulinoma as well.

The patient opted for medical management of her insulinoma as surgery was considered high risk because of her age and significant cardiovascular history. She could not tolerate diazoxide because of edema and was transitioned to short-acting octreotide without improvement in her hypoglycemic episodes. The patient was switched to octreotide long-acting release (LAR) 20 mg every 4 weeks, which was continued for 3 months. During this time, she required 2 hospitalizations for severe hypoglycemia.

Given the patient's inadequate response to octreotide LAR, pasireotide LAR 40 mg intramuscularly (IM) every 4 weeks was initiated, which completely resolved the hypoglycemic episodes within 1 month, with average blood glucose of 200 mg/dL. However, owing to some postural lightheadedness, her dose was decreased to 20 mg IM every 4 weeks. Approximately 1 year later, the patient developed persistent hyperglycemia, with a mean blood glucose of 180 mg/dL and glycated hemoglobin (HbA_{1c}) of 8% (64 mmol/mol). At this time, definitive treatment of her insulinoma was discussed (eg, repeat selective arterial calcium stimulation test followed by surgery), but the patient decided to continue medical management citing concerns with COVID-19 infection risk with an elective radiologic procedure followed by hospitalization for tumor resection. As such, the patient's pasireotide dose was lowered to 10 mg every 4 weeks, and she has maintained glucose levels in the 90- to 120-mg/dL range without any further episodes of hypoglycemia or hyperglycemia.

Case 2

Pasireotide for the Treatment of Malignant Insulinoma

We have published the preliminary details of this case previously [10]. A 53-year-old woman presented with a 2-year history of recurrent hypoglycemia that fulfilled the Whipple triad. Within the first hour of a 72-hour fast, she was found to have a blood glucose of 53 mg/dL, insulin level of 87 mIU/mL (normal, 2.6-24.9 µIU/mL), C-peptide of 13.2 ng/mL (normal, 1.1-4.4ng/mL), and proinsulin of 2822 pmol/L (normal, 3-20 pmol/L), confirming endogenous hyperinsulinism. She was found to have a 3.6 × 2.8 × 2.4-cm pancreatic tail mass with innumerable masses in the liver measuring up to 10 cm. Core biopsy of the hepatic lesions revealed a well-differentiated neuroendocrine tumor (World Health Organization grade 2, Ki-67 4%), and she was diagnosed with stage IV malignant insulinoma with liver metastases.

Consensus from our institutional tumor board was to manage the patient medically given her extensive tumor burden. She was initiated on diazoxide and octreotide LAR 30 mg IM every 4 weeks but continued to have persistent hypoglycemia (30% of recorded glucose levels were < 70 mg/dL and 5% < 55 mg/dL) on her Dexcom G4 Platinum continuous glucose monitor (CGM) (Fig. 1A). As such, she was switched to pasireotide LAR 60 mg IM every 4 weeks with marked improvement in her hypoglycemic episodes within 1 month: Only 3% of recorded readings were below 70 mg/dL with no serious hypoglycemia (≤ 55 mg/dL), with mean sensor glucose of 129 mg/dL (Fig. 1B).

The following month, the patient started chemotherapy with capecitabine and temozolomide followed by transarterial chemoembolization of her hepatic metastases. Two months after chemoembolization, the patient developed hyperglycemia, so pasireotide was discontinued. Subsequently, at her 3-month follow-up, the patient was no longer experiencing any hypoglycemic episodes and her average blood glucose was 122 mg/dL. She was started on lanreotide 120 mg IM every 4 weeks for antineoplastic effect and continued on the single chemotherapeutic agent capecitabine by the oncology service.

Two years later, the patient developed type 2 diabetes mellitus with an HbA_{1c} of 9.2% (75 mmol/mol). She was started on empagliflozin and 4 months later, her HbA_{1c} improved to 7.5% (53 mmol/mol). The patient has no evidence of tumor progression 4 years from her initial diagnosis while on capecitabine plus lanreotide therapy, with stable radiographic appearance of her hepatic metastases.

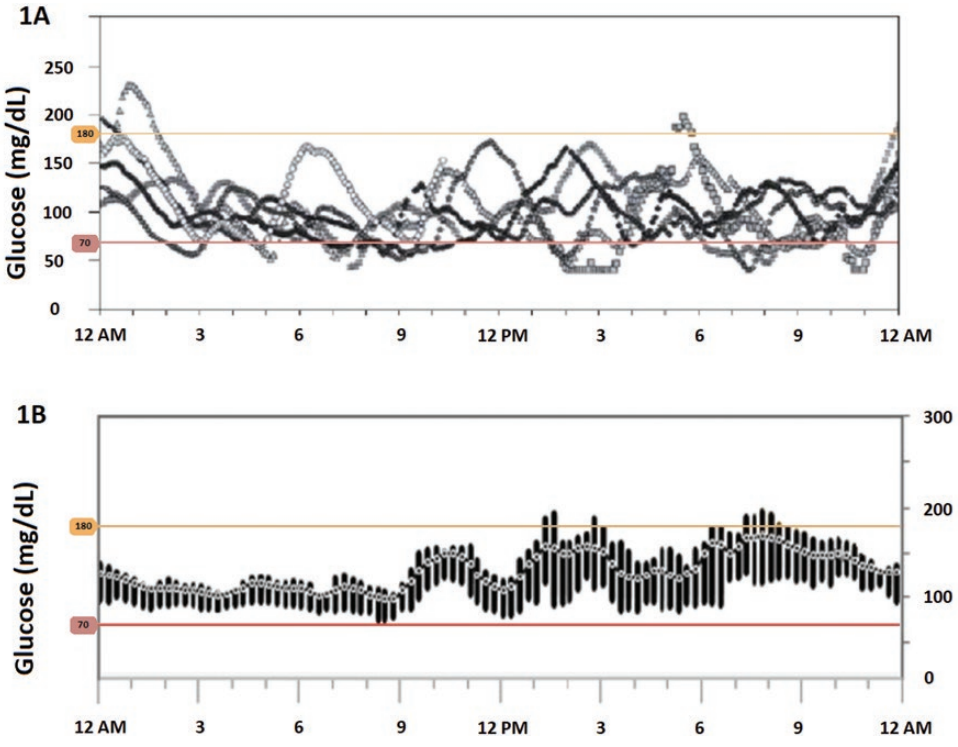

Figure 1. Dexcom G4 Platinum continuous glucose monitor tracings A, before, and B, after pasireotide addition, showing a reduction in glucose readings of less than 70 mg/dL from 30% to 3% of recorded values, respectively.

Case 3

Pasireotide for the Treatment of Non-Islet Cell Tumor Hypoglycemia

A 72-year-old man with history of cirrhosis from hepatitis C and recently diagnosed hepatocellular carcinoma (HCC) presented to our institution with refractory hypoglycemia. The patient's HCC was diagnosed 2 months prior to admission in the setting of severe hypoglycemia and seizure. The patient noted lightheadedness and diaphoresis occurring at 2-hour intervals during the day and night with fingerstick glucose readings of approximately 40 mg/dL during these episodes. His symptoms resolved on consuming carbohydrates. The patient was not taking any medications associated with glucose-lowering and denied alcohol consumption. He had normal renal and hepatic function. A download of his Dexcom G6 CGM revealed that 48% of his recorded blood glucose readings were below 70 mg/dL with multiple episodes (28%) of severe nocturnal hypoglycemia with blood glucose below 54 mg/dL (Fig. 2A).

A 72-hour fast was initiated, and within 1 hour, the patient had a blood glucose measurement of 30 mg/dL, with an insulin level of 2.2 mcIU/mL (normal, 2.6-24.9 mcIU/mL), C-peptide of 0.17 ng/mL (normal, 0.80-3.85 ng/mL), β-hydroxybutyrate less than 0.1 mmol/L (normal, 0.0-0.3 mmol/L), and proinsulin less than 0.4 pmol/L (normal, ≤ 18.8pmol/L). The patient had a negative insulin antibody (< 0.4 U/mL) and negative serum hypoglycemic agent screen. Further evaluation of his noninsulin-mediated hypoglycemia excluded adrenal insufficiency via cosyntropin stimulation testing. His GH level was 0.06 ng/mL (normal, 0.01-0.97 ng/mL), IGF-1 was less than 10 ng/mL (normal, 32-200 ng/ml), and IGF-2 level was 780 ng/mL (normal, 333-967 ng/mL). Owing to the patient's hypoinsulinemic hypoglycemia with low IGF-1 level and an IGF-2:IGF-1 ratio greater than 10, the patient was diagnosed with NICTH.

CT abdomen/pelvis revealed a cirrhotic liver with a 7-cm lesion involving the right hepatic lobe; biopsy confirmed the diagnosis of well-differentiated hepatocellular carcinoma. The tumor was unresectable because of portal vein thrombosis, so the patient was started on an immunotherapy clinical trial with pembrolizumab and bavituximab. He was not a candidate for yttrium-90 radioembolization because of an anterioportal shunt that could not be adequately embolized, so he received palliative external beam radiotherapy. However, the patient continued to experience refractory hypoglycemic episodes, which necessitated hourly waking by his family to encourage him to eat carbohydrates, despite the addition of prednisone 30 mg daily, 1 month after the diagnosis of HCC. He was readmitted to the hospital for glucose optimization.

During hospitalization, the patient required a titratable dextrose 50% infusion, 37.5 g of dextrose gel orally every 3 hours, and frequent meals for management of his hypoglycemia. He was started on combination medical therapy with diazoxide, prednisolone 20 mg twice daily, and short-acting octreotide 100 mg subcutaneously every 8 hours. Despite that, the patient remained in the hospital for 3 weeks, as he promptly developed hypoglycemia when the dextrose infusion was discontinued. Pasireotide LAR was ordered for the patient but could not be given inpatient, so he was discharged to a long-term assisted care facility while remaining on the dextrose infusion.

Shortly after discharge, the patient was started on pasireotide 40 mg IM every 4 weeks. Within 1 week, he was weaned off the dextrose infusion. Three weeks later, at his endocrine follow-up appointment, his Dexcom G6

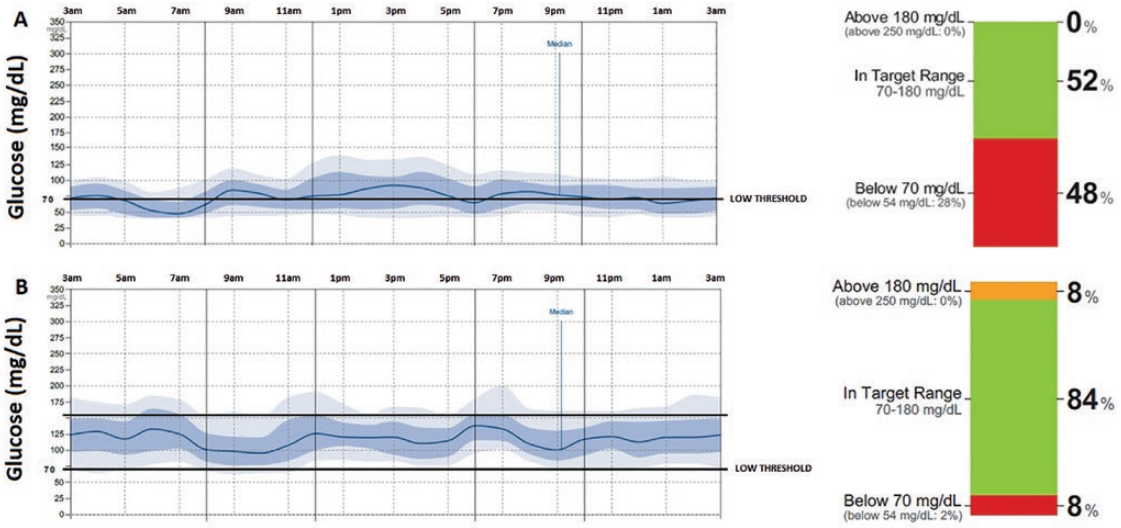

Figure 2. Dexcom G6 continuous glucose monitor tracings A, before, and B, after pasireotide addition, showing a reduction in glucose readings of less than 70 mg/dL from 48% to 8% of recorded values, respectively.

CGM data revealed markedly improved glycemic control, with a mean sensor glucose of 121 mg/dL, 8% of readings below 70 mg/dL, and only 2% of readings below 54 mg/dL (Fig. 2B). Unfortunately, the patient's HCC progressed despite the use of sorafenib and later nivolumab, and he died of shock and decompensated liver failure 5 months after his initial HCC diagnosis.

Discussion

Medications that are currently approved for refractory, tumor-induced hypoglycemia are generally of limited efficacy and tolerability [5]. In the cases described here, each patient with tumor-induced hypoglycemia was started on guideline-recommended medications for the treatment of hypoglycemia (ie, diazoxide, glucocorticoids, and/or octreotide) without attenuation of their refractory hypoglycemia. Then, pasireotide was substituted with marked improvement of hypoglycemia in all cases within 1 month of administration.

Pasireotide, like other somatostatin analogues, exerts its biologic effect by binding to somatostatin receptors (SSTRs). There are 5 somatostatin receptor subtypes ($SSTR_1$, $SSTR_2$, $SSTR_3$, $SSTR_4$, and $SSTR_5$) distributed heterogeneously throughout the body. Once stimulated, somatostatin is a potent inhibitor of endocrine and exocrine hormonal release in humans [11]. Inhibition of insulin and glucagon secretion is primarily mediated by $SSTR_2$, whereas insulin secretion is predominantly mediated via $SSTR_5$ [12]. Neuroendocrine tumors largely express somatostatin receptors, with $SSTR_2$ and $SSTR_5$ expression shown in 70% of insulinomas [13]. Pasireotide, a second-generation SSTR ligand, has a 30- to 40-fold higher binding affinity for $SSTR_5$ than the first-generation SSTR ligand octreotide, which accounts for the former's advantage in treating hypoglycemia [14]. The hyperglycemia effect of pasireotide is related to a decrease in insulin secretion and incretin hormone response without change to hepatic or peripheral insulin sensitivity [15]. Although octreotide has been shown to improve hypoglycemia in two-thirds of insulinoma patients in one study [16], there are insufficient data for the use of pasireotide in insulinoma patients to calculate a treatment response. However, pasireotide induces a potent hyperglycemic effect in its currently indicated uses for Cushing disease and acromegaly: Seventy-three percent of Cushing disease patients [17] and 57% of acromegaly patients [18] developed hyperglycemia-related adverse events while on pasireotide. Pasireotide-induced hyperglycemia has been shown to respond to vildagliptin and liraglutide therapy [19].

Additionally, pasireotide has been shown to have antiproliferative effects comparable to the more conventionally used somatostatin analogues octreotide and lanreotide in the treatment of advanced neuroendocrine tumors [20].

Treatment of NICTH involves tumor resection or the use of alternate antitumor modalities when resection is not possible. While the use of pasireotide in the management of NICTH has not been previously described, high-dosed octreotide given as continuous infusion following uptake of ^{111}In-labeled octreotide by a solitary fibrous, pleural tumor was not effective in suppressing big IGF-2 production or improving hypoglycemia [21]. In a separate case, the mechanism of refractory hypoglycemia due to NICTH from an intra-abdominal hemagiopericytoma was attributed to muscle tissue uptake of glucose mediated by IGF-2; during somatostatin treatment, big IGF-2 levels decreased modestly but could not adequately control hypoglycemia without the simultaneous infusion of exogenous glucose [22]. The effect of pasireotide therapy on big IGF-2 levels has not been described previously, though a potent lowering of big IGF-2 levels, potentially through $SSTR_5$ interaction, could account for the hyperglycemic effect noted in our patient with hepatocellular carcinoma. Hepatocellular carcinoma tumor cells have been shown previously to express a high proportion of $SSTR_5$ [23]. However, the treatment of advanced hepatocellular carcinoma with somatostatin analogues has shown variable response [24]. A recent phase 2 trial of pasireotide LAR in patients with unresectable HCC showed limited antitumor benefit; however, 30% of participants developed grade 3 hyperglycemia, and 5% of participants developed grade 4 hyperglycemia [25].

Despite the presumed advantage of pasireotide in treating tumor-induced hypoglycemia, only a single case, besides our own, has been published using pasireotide for the treatment of malignant insulinoma. Tirosh et al found that pasireotide LAR was more effective in treating refractory hypoglycemia compared with lanreotide in a patient with malignant insulinoma with hepatic metastases [26]. This manuscript adds to the literature by outlining 3 cases of refractory, tumor-induced hypoglycemia—due to an occult insulinoma, malignant insulinoma, and NICTH from HCC—that all failed to respond to conventional medical therapy, and for which pasireotide caused rapid, dramatic improvement in glucose levels (resolving the hypoglycemia completely in the first 2 cases). Two of our cases—pasireotide for treating hypoglycemia in occult insulinoma and NICTH—are not previously reported in the literature.

In conclusion, we recommend that pasireotide be considered for the treatment of tumor-induced hypoglycemia in 3 settings. First, in a patient with insulinoma who is either not a surgical candidate or who decides against surgery, and in whom hypoglycemia persists despite conventional medical therapy. Second, in the patient with NICTH for whom tumor resection is not possible and

adjunctive medical therapy is unhelpful. Third, during the COVID-19 pandemic, there is added concern on the part of providers and patients, both from an infectious disease and resource use standpoint, in terms of admitting tumor-induced hypoglycemia patients for the purposes of diagnosis, localization, and/or surgical management. In such case, there may be a role for temporary pasireotide therapy as a "bridging" technique until definitive diagnostic and therapeutic strategies can be implemented. In summary, given its potent antihypoglycemic and antitumor properties, pasireotide is a reasonable choice for the treatment of tumor-induced hypoglycemia, though additional investigation is warranted.

Additional Information

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Data Availability: Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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