CASE REPORT

Therapies for the medical management of persistent hypoglycaemia in two cases of inoperable malignant insulinoma

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Abstract

Objective: Hypoglycaemia poses a significant management challenge in patients with unresectable functional malignant insulinoma. Novel agents such as mammalian target of rapamycin (mTOR) inhibitors and radiolabelled peptides may be effective where there is failure of conventional therapy.

Design: We present the cases of two men diagnosed with inoperable malignant insulinoma and hepatic metastases who developed severe symptomatic hypoglycaemia, and review potential therapies for glycaemic support.

Method: Despite treatment with diazoxide, frequent oral carbohydrate, prednisolone and somatostatin analogue therapy, both men required hospital admission for treatment with continuous i.v. dextrose. Both were treated with Lutetium-177 octreotate. One man was also treated with everolimus, a mTOR inhibitor.

Result: Use of Lutetium-177 octreotate, and in one case everolimus, successfully achieved normoglycaemia, facilitating safe discharge from hospital. Both men also had regression in the size and number of hepatic metastases.

Conclusion: Lutetium-177 octreotate and everolimus are options for managing hypoglycaemia due to unresectable malignant insulinoma when refractory to conventional supportive therapies.

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Introduction

Neuroendocrine tumours of the pancreas occur infrequently, with an incidence of 1–1.5 per 100 000 in the United States (1). Of those, 20–30% are insulinomas (2), the vast majority being benign. Symptomatic hypoglycaemia is the major clinical manifestation of insulinomas. Where possible, surgical resection is the optimal treatment (1, 2) with prior supportive therapy. However, 10–15% of insulinomas are malignant. Patients with significant hypoglycaemia and inoperable metastatic disease can be difficult to manage. We present the cases of two patients with inoperable malignant insulinoma, documenting the steps taken to treat persistent severe hypoglycaemia, and review the literature.

Case reports

Case 1

A previously well 64-year-old man presented with hypoglycaemia, initially manifesting as severe nocturnal hunger. Plasma C-peptide, insulin and glucose levels were consistent with endogenous hyperinsulinaemia (Table 1). There was no evidence of multiple endocrine neoplasia type 1.

Computed tomographic (CT) imaging identified two masses in the body and tail of the pancreas, with multiple hepatic metastases. Endoscopic ultrasound and biopsy confirmed malignant insulinoma. Radiolabelled Indium-111 octreotide scintigraphy demonstrated avidity of the lesions for octreotide. The extent of hepatic involvement precluded resection or ablation.

Hypoglycaemia persisted despite outpatient treatment with diazoxide (up to 200 mg × 3/day), prednisolone (40 mg daily) and s.c. octreotide (up to 500 μg/day in three divided doses). A hypoglycaemic seizure necessitated hospital admission and continuous i.v. 25% dextrose infusion.

The patient was treated with i.v. radiolabelled Lutetium-177 (DOTA⁰,Tyr³) octreotide with concurrent amino acid infusion for nephroprotection. Inpatient support was still required subsequently, with i.v. dextrose (up to 600 g/day), prednisolone, nocturnal nasogastric feeding and a continuous s.c. octreotide infusion (up to 3000 μg/day) necessary to maintain near normoglycaemia.
As it was not possible to safely cease continuous i.v. dextrose therapy, everolimus (2.5 mg × 2/day) – a mammalian target of rapamycin (mTOR) inhibitor – was given, with rapid glucose response (Fig. 1). Complications potentially attributable to everolimus therapy are summarised in Table 2. These conditions resolved without dose reduction of the everolimus. I.v. dextrose infusion was ceased 9 days after the commencement of everolimus therapy, without further episodes of hypoglycaemia, and with decreased serum insulin and C-peptide levels. The patient was discharged from the hospital 45 days after admission.

Imaging at 6 weeks post Lutetium-177 octreotide therapy showed reduction in the size of hepatic metastases. Six cycles of 14 days of capecitabine 1.5 g twice daily, followed by 5 days of temozolomide 400 mg daily were administered over 5 months. Further tumour regression was seen subsequently (Fig. 2). Everolimus, somatostatin analogues and glucocorticoids were discontinued at 3 months post discharge. At 10 months post discharge, the patient has had no recurrence of hypoglycaemia even with strenuous exercise.

**Case 2**

A 67-year-old man presented with biliary obstruction due to a pancreatic mass, with proximity to the superior mesenteric vein preventing surgical resection. Following failure of a biliary stent, a bypass procedure was undertaken. Pathology demonstrated a well-differentiated neuroendocrine tumour in the pancreas with a metastatic deposit in the gastroduodenal node. Indium-111 octreotide scintigraphy demonstrated uptake in the pancreatic mass without evidence of peripheral metastases. There was no hypoglycaemia, nor evidence of multiple endocrine neoplasia type 1, and no further therapy was offered at that time. The patient was then lost to follow-up.

Five years later, the patient presented with hypoglycaemia. CT imaging demonstrated hepatic metastases. Despite treatment with prednisolone (up to 60 mg daily) and octreotide 100 μg twice daily (later changed to Sandostatin LAR (Novartis) 20 mg monthly) the patient required frequent meals (as often as 2 hourly overnight) to maintain normoglycaemia. Diazoxide was both ineffective and poorly tolerated. Progression of hypoglycaemia resulted in hospitalisation for i.v. 25% dextrose infusion. He was entered into a Phase IIa trial of capecitabine (2 g in the morning and 1.5 g in the evening) with Lutetium-177 octreotide. Glycaemic control improved rapidly, and i.v. dextrose was safely ceased within 24 h of Lutetium-177 octreotide administration. All supportive therapies were discontinued over 3 months with maintenance of normoglycaemia on a normal diet. Four cycles of 7.8 GBq Lutetium-177 octreotide and capecitabine were administered over an 8-month period. Reduction in the size of hepatic metastases was seen on imaging and post-treatment scintigraphy (Fig. 3). Chromogranin A levels reached a nadir of 81 U/l at 9 months after initial Lutetium-177 octreotide therapy, from a peak > 800 U/l at diagnosis (reference range <18).

Two years after initial radiopeptide therapy, recurrence of hypoglycaemia required further admission for continuous i.v. dextrose therapy. Repeat administration of an identical activity of Lutetium-177 octreotide was commenced, with immediate glycaemic improvement. Unfortunately, post-treatment scintigraphy identified progressive disease. Chemotherapy with capecitabine and temozolomide is under consideration in view of progressive disease burden and high risk for further hypoglycaemia.

**Discussion**

These two cases demonstrate the difficulty in controlling hypoglycaemia in patients with inoperable functional malignant insulinoma. In these patients, conventional hyperglycaemic agents lacked efficacy, and potentially life-threatening hypoglycaemia necessitated inpatient...
i.v. dextrose infusion. Novel medical therapies proved successful in amelioration of hypoglycaemia. A review of potential therapies in this context is presented below, with a summary of therapies utilised in our patients being presented in Table 3.

**Somatostatin analogues**

Somatostatin is an inhibitor of pancreatic insulin and glucagon release mediated through G-protein transmembrane receptors (3). Synthetic analogues, such as octreotide, have affinity for sst2A and sst5 receptors, and have been used for glycaemic support in insulinoma patients.

Short-term (<6 months) use of octreotide at a mean final dose of 621 mg/day (range 50–2000 mg/day) abolished hypoglycaemia in 12 of 16 patients with endogenous hyperinsulinaemia mostly due to insulinoma (4). In the same trial, all 11 patients who proceeded to long-term use (mean duration 67 months) of octreotide had ongoing benefit with similar doses. However, only one of the four patients with malignant insulinoma treated with octreotide achieved glycaemic control. Octreotide may be less effective, or require higher doses, in malignant insulinomas compared with benign insulinomas.

Four case reports have shown that Sandostatin LAR 10–20 mg monthly can improve fasting blood glucose and serum insulin in both benign and metastatic malignant insulinomas for up to 3 years (5). However, a separate report described a patient with malignant insulinoma and hepatic metastases who failed to respond to fortnightly lanreotide 30 mg (6). Pasireotide (SOM230), a new long-acting somatostatin analogue with high affinity for almost all somatostatin receptors except sst4 (7), might have a future role in this area.

Octreotide may additionally have tumour-stabilising effects. In patients with metastatic, well-differentiated functioning midgut neuroendocrine tumours. Sandostatin LAR 30 mg monthly increased median time to tumour progression compared with placebo (10.35 vs 5.45 months) (8). However, this study was done predominantly in patients with carcinoid tumour.

Predicting therapeutic success for somatostatin analogues remains difficult. Octreotide test doses were unhelpful in malignant insulinoma, and Indium-111
Octreotide scintigraphy was also inconsistent at predicting response (4). However, identifying specific sst2A receptor expression may be helpful (3).

The glycaemic efficacy of somatostatin analogues in malignant insulinoma therefore remains uncertain due to limited published evidence and variable outcomes. Nevertheless, with the knowledge that it is both well tolerated (4, 8) and may have tumour-stabilising effects, a trial of octreotide seems reasonable for all patients. High doses may be required.

**Radiolabelled somatostatin analogues**

Radiolabelled somatostatin analogue therapy is a novel treatment for inoperable neuroendocrine tumours. [DOTA0,Tyr3] octreotate has nine times higher affinity for sst2 receptors than [DOTA0,Tyr3] octreotide with high tumour uptake. With respect to radionuclides, tumour uptake of radioactivity is up to 3–4 times higher after the administration of Lutetium-177 octreotate compared with Indium-111 octreotide despite similar renal uptake. Indium-111 also has short tissue penetration, making it suboptimal for radiopeptide therapy (9). Yttrium-90 octreotide has also been studied with at least partial response in 7–33% (7, 9). To maximise radiopeptide uptake, it is necessary to discontinue the use of short-acting somatostatin analogues 1 day before treatment, and long-acting analogues 6 weeks prior to treatment (9).

In a Dutch study (9), 59 of 131 patients (47%) with inoperable gastroenteropancreatic neuroendocrine tumours (mostly carcinoid) had at least minor response in tumour size and 44 (33%) had stable disease over 16 months median follow-up when treated with Lutetium-177 octreotate (cumulative activity of 27.8–29.6 GBq). Predictors of remission included Indium-111 octreotide uptake on scintigraphy and low number of hepatic metastases. There was no description of effect on symptoms due to hormone secretion.

Adverse events included minor gastrointestinal symptoms, transient bone marrow toxicity (particularly in patients aged >70 years, but much less frequently than with Indium-111- or Yttrium-90-labelled peptides) and transient male primary hypogonadism. Hypopituitarism due to potential Lutetium-177 octreotate uptake by the pituitary was not seen. Severe renal impairment occurred in two patients. A large burden of hepatic disease, and lower hepatic reserve, is associated with a higher risk of hepatic failure from Lutetium-177 octreotate, Indium-111 [DTPA0] octreotide or Yttrium-90 [DOTA0,Tyr3] octreotide therapy (9). In seven patients treated concurrently with capecitabine, there was one case each of severe anaemia, thrombocytopenia and mild stomatitis (10).

In our two patients, glycaemic response occurred within hours of octreotate administration, persisting in case 1 for 24 h, but contributing to complete abolition of hypoglycaemia for 2 years in case 2. Hence, Lutetium-177 octreotate proved useful in achieving and maintaining euglycaemia after failure of other supportive therapies. The benefits are probably due to a combination of somatostatin receptor activation in the early phase with later anti-tumour effect. No adverse effects were reported by our two patients.
who had intact hepatic function despite hepatic metastases. Lutetium-177 octreotate may also have potential for treatment of recurrent disease, as demonstrated in our second case.

**mTOR receptor inhibitors: rapamycin (sirolimus) and everolimus**

Rapamycin (sirolimus) or its derivative everolimus are mTOR receptor antagonists used to prevent organ transplant rejection and cellular proliferation in drug-eluting coronary stents. These agents cause hyperglycaemia through complex mechanisms inducing hepatic and peripheral resistance to insulin and β-islet cell toxicity (11).

A case series has described four patients with metastatic insulinoma on multiple hyperglycaemic agents who were able to cease, or significantly reduce, other glycaemic supports after the introduction of everolimus. Two patients had evidence of regression in the size of tumours (12). Successful use of sirolimus (rapamycin) 2 mg daily for glycaemic support in an elderly man with metastatic insulinoma has also been reported, allowing withdrawal of diazoxide, octreotide and i.v. dextrose therapy (13).

mTOR is a key intracellular component of signalling pathways responsible for cell survival, growth and angiogenesis (12–15). Dysregulation of upstream components can upregulate mTOR, making it a potential target for anti-tumour therapy (14). A recent open label Phase II study demonstrated that everolimus 10 mg daily has radiological anti-tumour effect in patients with progressive metastatic pancreatic neuroendocrine tumours despite chemotherapy (16). Concurrent mTOR inhibition with long-acting depot octreotide is also under investigation (15). One of our patients received both everolimus and Lutetium-177 octreotate with tumour regression and glycaemic improvement.

mTOR inhibitors are associated with a variety of adverse effects. In a Phase I dose escalation study in cancer patients, dose limitation due to stomatitis and fatigue occurred at 50 mg/week and due to hyperglycaemia occurred at 10 mg/day (14). In a Phase II study in low-grade neuroendocrine tumours, use of
everolimus 5 mg daily with long-acting depot octreotide was well tolerated, with mild aphthous ulceration being the most common toxicity of everolimus (15). When used for cardiac transplantation, the most common adverse effects were fluid retention and infection (17).

Our experience with everolimus suggests efficacy after failure of conventional therapy. Early use of mTOR inhibitors in hypoglycaemia refractory to conventional therapy could be considered, but there is no current published experience for use as first-line agents.

**Diazoxide**

Diazoxide is an antihypertensive benzothiadiazine derivative (18) without diuretic activity, but it is capable of inducing hyperglycaemia. Potential glycaemic mechanisms include suppression of glucose and adrenergically mediated insulin release (19), or increasing hepatic gluconeogenesis and reducing glucose uptake by cells (20).

Early case series found that over 50% achieved amelioration of hypoglycaemia (21), and higher response rates have been described with efficacy being reported even after use for over 10 years (18, 22). Although doses as high as 1500 mg/day have been reported (18), usually 200–600 mg/day orally is used in divided doses. While patients with malignant insulinomas were included in these studies, their outcomes were not separately reported from benign insulinomas.

Adverse effects are common. Fluid retention may be controlled with thiazide diuretics, which may also accentuate the hyperglycaemic effects of diazoxide (21–23). Rare, but severe complications include myelosuppression and cardiomyopathy. Stevens–Johnson syndrome has also been described (18).

In our patients, diazoxide was either ineffective at controlling hyperglycaemia or not tolerated. Despite our experience, existing literature supports the use of diazoxide as a first-line agent in inoperable functional insulinomas, albeit without specific information for malignant disease.

**Glucocorticoids**

Glucocorticoids induce hyperglycaemia by both inhibiting insulin production and increasing peripheral insulin resistance (24). An early review yielded poor results with only one-third of insulinoma patients achieving symptomatic control (21). Little is published with regard to malignant insulinomas. Novotny et al. (6) reported a case with metastatic insulinoma where hypoglycaemia responded to prednisone (peak dose 60 mg/day) despite failure of chemotherapy, radiotherapy and treatment with interferon-α-2b and lanreotide. Our patients did not derive clear benefit from prednisolone therapy at doses up to 60 mg orally per day. The use of glucocorticoids for chronic glycaemic support should be balanced against adverse effects.

**Chemotherapy and biological anti-tumour therapy**

Conventional chemotherapy for well-differentiated pancreatic neuroendocrine tumours consists of streptozocin in combination with doxorubicin or 5-fluorouracil (5-FU). Combination therapy response rates are highest with streptozocin–doxorubicin (69%) therapy compared with streptozocin–5-FU (35–63%) therapy. However, median survival remained poor (up to 2.2 years). Poorly differentiated tumours and carcinoids have lower response rates (7).

Capecitabine, an oral agent which is metabolised to 5-FU, has shown promising results when used in combination with temozolomide. Of 17 patients with metastatic pancreatic neuroendocrine tumours refractory to octreotide, one had complete pathological response, while nine achieved partial pathological response. Although doses as high as 1500 mg/day have been reported (18), usually 200–600 mg/day orally is used in divided doses. While patients with malignant insulinoma were included in these studies, their outcomes were not separately reported from benign insulinomas.

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**Invasive therapies**

Reduction in hepatic metastatic tumour burden to control symptoms was not feasible in our two patients, but it remains an important option. Surgical resection can be considered if more than 90% of hepatic disease can be removed (28). Other techniques include arterial embolisation with or without local chemotherapy and
ablation with radiofrequency or cryotherapy (7, 29). Chemoembolisation may achieve symptomatic and biochemical control in metastatic neuroendocrine tumours (7), with reported mortality of around 2–5% (29). Concurrent somatostatin analogue therapy can prevent hormonal crises. Post-embolisation syndrome (nausea, fever, tachycardia, abdominal pain and elevated transaminases) is the most common adverse event (7). Another invasive option, hepatic transplantation, has been associated with poor survival (29).

Conclusion

In the cases we have presented, conventional medical therapies for glycaemic control in unresectable malignant insulinoma were unsuccessful. Despite prednisolone, diazoxide and octreotide treatment, recurrent hypoglycaemia persisted and required frequent enteral feeding and i.v. dextrose infusion. The availability of new methods of combating hypoglycaemia enabled us to maintain a good quality of life in these two patients.

Hypoglycaemia due to malignant insulinoma is less responsive to diazoxide, prednisolone and octreotide than that due to benign disease. But, until improved clinical evidence becomes available, conventional therapies still have an initial role. Consideration should be given to earlier use of novel therapies for refractory hypoglycaemia in unresectable disease. mTOR inhibition can be an effective option in this situation, with local availability of specialised therapies (such as chemoembolisation or radiopeptide therapy) determining their utility. Chemotherapy or interferon-α can be considered after failure of other modalities. We have shown the effectiveness of Lutetium-177 octreotide and mTOR inhibition. Further research is required to determine their role in the treatment of functional malignant insulinoma.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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