Two Patients with Hypoglycaemia

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Recurrent hypoglycaemia is not uncommon in palliative care patients. Ideally, treatment should be targeted at the underlying causes. In palliative care setting, some of the underlying causes may not be reversible and thus hypoglycaemia is treated symptomatically. Treatment can be given via intravenous or oral route. As long term dextrose infusion has the disadvantages of being more invasive and inconvenient for patient, per oral treatment may be a better option. The following cases illustrate two causes of recurrent hypoglycaemia in advanced cancer and their treatment.

Case history 1

Madam X was a 90-year-old, old age home (OAH) resident and was partially dependent in her daily activities. She had history of recurrent hypoglycaemia and suspected to have insulinoma around 15 years ago. She was advised to have more frequent carbohydrate intake at that time. Investigations performed in April 2006 showed an insulin level of 28 H and C-peptide of 1.86 H.

She was admitted to Queen Mary Hospital (QMH) in Dec 2006 for increased frequency of hypoglycemic attacks in OAH, manifested as agitation and irrelevant speech. Her random blood glucose on admission was 1.4mmol/l. Despite dextrose infusion, she continued to have frequent hypoglycemia, ranging from 1.8-2.8mmol/l. Diazoxide was given orally and titrated against clinical response. The dosage was stepped up to 100mg tid and her condition improved. Her agitation and confusion subsided and blood sugar was maintained in the range of 9-15mmol/l.

Case history 2

A 79-year-old woman was diagnosed to have metastatic carcinoma of rectum in May 2007. There was multiple lung and liver metastasis with gross hepatomegaly. She was admitted to QMH for drowsiness and bleeding per rectal. The patient declined chemotherapy and radiotherapy. She developed recurrent hypoglycaemia requiring constant dextrose infusion. She was later transferred to our unit for pain control. As her hypoglycaemia persisted (lowest blood sugar at 1.2mmol/l), finding intravenous (IV) access became difficult with prolonged dextrose infusion. As non-islet cell tumour hypoglycaemia (NICTH) was suspected clinically, dexamethasone 4mg was given orally. Subsequently, there was no recurrence of hypoglycaemia and no further intravenous dextrose solution was needed. She died peacefully eventually.
Insulinoma

Existence of hyperinsulinism was first suggested by the occurrence of episodes of severe hypoglycaemia in a patient with malignant pancreatic islet-cell tumour in 1927. The first cure of hyperinsulinism by removal of insulinoma was reported in 1929. The hypoglycaemia caused by insulinoma is primarily due to reduced hepatic glucose output rather than increased glucose utilization.

The mechanism by which insulinoma maintain high levels of insulin secretion in the presence of hypoglycaemia is unknown. However, one study reported that a variant of insulin mRNA with increased translation efficiency is present in high amounts in insulinoma when compared to normal islets. The incidence was 0.4 per 100,000 person-years (or 4 cases per million per year) in one series.¹

The neuroglycopenic symptoms of insulinoma included confusion, visual change, and unusual behaviour. The sympathoadrenal symptoms included palpitations, diaphoresis, and tremulousness. Amnesia was common. The median duration of symptoms before diagnosis was less than 1.5 years in the Mayo Clinic series. However, a few patients had probably been symptomatic for decades.

Insulinoma can be single or multiple, and benign or malignant. Insulinomas have been reported in pregnant women, in patients with type II diabetes mellitus and those with renal failure. The diagnosis of insulinoma in a patient with fasting hypoglycaemia is established by demonstrating inappropriately high serum insulin concentrations during a spontaneous or induced episode of hypoglycaemia, e.g. 72-hour fast or in the case of the patient with solely postprandial symptoms, the mixed meal test. Imaging techniques are then used to localize the tumour.

Surgical treatment

Surgical removal of the insulinoma is the treatment of choice. Recurrences were found to be more common in the patients with MEN 1; the cumulative 10- and 20-year recurrence rates were 21 percent at both times compared to 5 and 7 percent in those without MEN 1 (p<0.001). Survival was significantly worse in the patients with malignant insulinomas and in older patients.¹

Medical therapy

In controlling symptomatic hypoglycaemia, medical therapy should be considered when surgery is not feasible or not contemplated. The therapeutic choices to prevent symptomatic hypoglycaemia include:

1. Diazoxide diminishes insulin secretion and is given in divided doses of up to 1200 mg/day for controlling hypoglycemia.² However, it can cause marked oedema (which may require high doses of loop diuretics) and hirsutism.

2. Octreotide, an analogue of somatostatin (growth hormone-inhibitory hormone), inhibits GH secretion, but in large doses, it also inhibits the secretion of TSH, insulin, and glucagons.³ While octreotide is highly effective in controlling the symptoms associated with glucagonomas, VIPomas, and carcinoid tumours, efficacy is less predictable for symptomatic patients with insulinoma. Nevertheless, it is a reasonable choice for patients with persistent hypoglycaemia that is refractory to diazoxide.

3. Lanreotide is another somatostatin analogue which appears to have similar clinical efficacy as octreotide.

4. Others: Verapamil and phenytoin have also been used with some success.

Non-islet cell tumour hypoglycaemia (NICTH)

Non-islet-cell tumour-induced hypoglycemia (NICTH) is a syndrome which is attributable to the production of insulin-like growth factor II (IGF-II) by the tumour although in these patients the levels of circulating IGF-II are usually in the normal range. This syndrome has attracted more attention in recent years, with better elucidation of the underlying pathophysiology and increasing identification by application of appropriate tests.⁶

Diagnosis is characterized by the clinical picture of constant or frequent hypoglycaemia; findings of suppressed serum insulin, C peptide and growth hormone (GH); low serum insulin-like growth factor-I (IGF-I); but apparently normal, or even elevated, serum levels of immunoreactive IGF-II.⁷
Various tumours have been associated with this syndrome. Table 1:

Table 1: Non-islet cell neoplasms associated with hypoglycaemia

<table>
<thead>
<tr>
<th>Mesenchymal</th>
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<tbody>
<tr>
<td>Mesothelioma</td>
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<tr>
<td>Fibrosarcoma</td>
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<tr>
<td>Rhabdomyosarcoma</td>
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<tr>
<td>Leiomyosarcoma</td>
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<td>Haemangioipercytofoma</td>
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<tr>
<th>Carcinoma</th>
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<tr>
<td>Hepatic: hepatoma, biliary carcinoma</td>
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<tr>
<td>Adrenocortical carcinoma</td>
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<tr>
<td>Hypernephroma, Wilms' tumour, prostate</td>
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<tr>
<td>Reproductive: cervical or breast carcinoma</td>
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<th>Neurologic / Neuroendocrine</th>
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<tr>
<td>Pheochromocytoma</td>
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<td>Carcinoid</td>
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<td>Neurofibroma</td>
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| Haematological                  |

In one series of 68 consecutive tumours investigated, histological classification showed 31 carcinomas and 23 sarcomas of tissues mainly in the thorax or retroperitoneal space. Another 14 tumours included hepatomas, carcinoid tumours and 10 tumours of unknown type. In cases subjected to detailed examination, over-expression of the IGF-II gene has been reported. The serum contained an abnormal (big) form of IGF-II which was incompletely sequestered in high molecular weight IGF binding protein (IGFBP) complexes and therefore capable of exerting potent insulin-like activity resulting in severe hypoglycaemia.

Identification of NICHT in palliative care patients should not be difficult. When a patient with known tumour burden develops hypoglycaemia, a search for other causes of hypoglycaemia is generally unwarranted and fruitless, especially if the tumour type is known to be associated with hypoglycaemia.

Treatment

1. **Glucocorticoid** is the most effective group of drugs in symptomatic relief of NICHT when surgery is not an option. The glucocorticoid can be given as prednisolone 20-60mg/day or dexamethasone 4mg/day. There is variable efficacy, which is also dose dependent and reversible. Moderate to high doses of steroids may cause shrinkage of the tumour and suppression of IGF-mediated tissue growth.

2. **Glucagon** has been shown to be effective for the treatment of patients with hypoglycaemia due to tumor overproduction of IGF-II.

3. **Growth hormone, intrahepatic adriamycin and percutaneous ethanol injection** were shown to have beneficial effects in hepatoma with hypoglycaemia and overproduction of IGF-II (E-21).

Summary

Recurrent hypoglycaemia is not uncommon in palliative care. Treatment should be directed to underlying cause whenever possible. Long term dextrose infusion may not be appropriate or feasible.

Medical treatment for insulinoma includes diazoxide and octreotide. Palliative treatment of NICHT include use of counter-regulatory hormones such as glucocorticoid and glucagon. For hepatoma, growth hormone, intrahepatic adriamycin and percutaneous ethanol injection may be treatment options.

References