INSULINOMA

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ABSTRACT

Insulinomas are rare pancreatic neuroendocrine neoplasms (panNENs - incidence of 1-3 cases per million per year). Most are solitary and do not show signs of malignant spread. Multiple synchronous or metachronous panNENs / insulinomas may occur in multiple endocrine neoplasia type 1 (MEN-1). The diagnosis of an insulinoma requires demonstration of inappropriately high insulin, proinsulin or C-peptide levels for the prevailing hypoglycemia in a 72h fast. Localization of the tumor and exclusion or confirmation of metastatic disease by computed tomography is still the preferred initial option followed by endoscopic ultrasonography (EUS) or MRI. Glucagon-like peptide receptor 1 (GLP-1R) receptor positron emission tomography (PET) CT or MRI is a highly sensitive localization technique for indolent, localized ("benign") insulinomas. For single solitary tumors surgical excision or radiofrequency ablation are the treatments of choice. In aggressive malignant (metastatic) cases, debulking of the panNENs, including locoregional lymph nodes can be considered. If hyperinsulinemia and hypoglycemia persist, diazoxide with a thiazide diuretic relieves hypoglycemia. Liver metastases can be resected, or treated by bland embolization, radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE) depending on local availability. In patients with unresectable low-grade metastatic malignant insulinomas, the long-acting somatostatin analog Lanreotide Autogel is the approved first-line therapy for control of tumor growth and sometimes control of hypoglycemia is achieved with this drug. If indicated, peptide receptor radiotherapy (PRRT) with radiolabeled somatostatin analogs, or Everolimus can be used for tumor, symptom and glucose control. Malignant NENs can also be treated with cytotoxic chemotherapy regimens, particularly those with a high tumor grade.

HISTORY

The pancreatic islet cells were first described by the German medical student Paul Langerhans (1847-1888) in 1869. James R Macleod (1876-1935), Frederick G. Banting (1891-1941), Charles H. Best (1899-1978) and James B. Collip (1892-1965) first isolated insulin in 1922. The US surgeon Seale Harris (1870-1957) was the first to identify a case of endogenous hyperinsulinism. In 1926, the US surgeon William J Mayo (1861-1939) performed an exploratory laparotomy on a patient with recurrent severe hypoglycemia and found an unresectable pancreatic tumor (malignant insulinoma) with multiple liver, lymph node, and mesenteric metastases. In 1927, the US physician Russel M. Wilder (1885-1959) and colleagues reported on the necropsy of this patient. Extracts of a liver metastasis produced marked

lowering of the blood glucose levels when injected into rabbits. It seems also likely that Mayo's & Wilder's patient had multiple endocrine neoplasia type 1 (MEN-1) since he also had renal stones and his cousin had had similar symptoms. In 1954, the US internist Paul Wermer (1898-1975) reported disorders of one or more endocrine glands in five members of one family in 1954. This familial syndrome was once called Wermer syndrome, but is nowadays better known as multiple endocrine neoplasia type 1 (MEN-1).

The first cure of hyperinsulinism by removal of an insulinoma by the Canadian surgeon Roscoe R. Graham (1890-1948) was reported in 1929 by Goldwin Howland (1875-1950) and co-workers. The US surgeon Allen O. Whipple (1881-1963) and pathologist Virginia K. Frantz (1896-1967) identified the diagnostic hallmark of insulinoma better known as "Whipple's triad" (1).

INTRODUCTION

More than 99% of insulinomas are located in the pancreas (2, 3). Extremely rare extra-pancreatic (metastatic) insulinomas have been described in the lung, duodenum, ileum, jejunum, hilum of the spleen, and gastric antrum (4-9). Insulinomas are the most common hormone-producing neuroendocrine neoplasms (NENs) of the pancreas, with an estimated incidence of 1–3 per million per year. Insulinomas are evenly distributed in the pancreas (2, 3). There is an age-specific incidence peak in the fifth decade of life and the incidence is slightly higher in women than in men. Approximately 10% are multiple, 10-15% show malignant spread. As the definitions for malignancy are ambiguous, non-metastatic insulinomas are nowadays referred to as "indolent" and metastatic insulinomas as "aggressive" (3, 10). Patients with aggressive insulinoma have lower survival compared to patients with indolent insulinoma: 5-year-survival has been reported to be 94.5-100% for indolent and 24-66.8% for aggressive disease (3, 11-13).

After initial recognition of the key symptoms, careful laboratory testing, sophisticated imaging and eventually meticulous surgery follows in most cases. It is evident that a multidisciplinary team (MDT) approach is required. The hallmark features of insulinomas resulting from hypoglycemia include neuroglycopenic (e.g., confusion, visual changes, unusual behavior) and sympathetico-adrenal (e.g., palpitations, diaphoresis, tremulousness) symptoms. A firmly established diagnosis of an insulin-secreting lesion of the pancreas is essential for successful management. Therefore, it is critically important to rule out other causes of hypoglycemia associated with fasting (13, 14).

HEREDITARY TUMORS

An overview of the multiple endocrine neoplasia type 1 (MEN1) syndrome can be found in the chapter "MEN1 (15). Fifty percent of MEN-1 patients harbor pancreatic NENs (panNENs) (13, 15, 16). 5–10% of insulinomas are associated with the MEN1 syndrome. MEN1-related NENs / insulinomas may occur as multiple lesions (15). In patients with the multiple endocrine neoplasia type 4 (MEN4) syndrome caused by inactivating mutations in the CDKN1B (*Cyclin Dependent Kinase Inhibitor 1B*) gene, pancreatic NENs can also be found, but it is unclear if insulinomas are more prevalent in MEN4 (17, 18). PanNENs can also be diagnosed in patients with von Hippel Lindau disease (VHL), but also there seems not to be a preponderance of insulinomas in this syndrome (19). Tuberous sclerosis complex (TSC) is a genetic tumor-predisposing syndrome associated with the development of multiple hamartomas among other abnormalities. TSC is caused by mutations of two tumor suppressor genes, TSC1 on chromosome 9q34 and TSC2 on chromosome 16p13.3, which encode for

hamartin and tuberin, respectively. PanNENs are uncommon in TSC, but insulinoma seems to be the predominant panNEN in this genetic disorder (20).

CLINICAL FEATURES

The hallmark of the diagnosis of insulinoma is Whipple's triad: 1) symptoms known or likely to be caused by hypoglycemia, 2) a low plasma glucose measured at the time of the symptoms and 3) relief of symptoms when the glucose is raised back to normal. The principal biochemical feature of an insulinoma is hypoglycemia but there are other malignancies and disorders which can cause hypoglycemia like big-IGF-2-producing tumors, glycogen storage diseases, administration of exogenous insulin or oral glucose-lowering drugs, insulinomatosis, the autoimmune insulin antibody syndrome (Hirata's disease) or insulin receptor (anti-ISR) antibody syndrome (Flier's syndrome) and congenital hyperinsulinism/nesidioblastosis in the pancreas (14, 21-31). While hypoglycemia is a hallmark of insulinoma, the low blood glucose level alone is not diagnostic of insulinoma, nor in general is the absolute insulin level elevated in all cases of organic hyperinsulinism. Hypoglycemia activates the adrenergic and cholinergic nervous systems and depending on the degree of the hypoglycemia presents different levels of impairment of neurologic function (Table 1) (14, 29, 32-35).

Table 1. Distinguishing Signs and Symptoms of Insulinomas

Neurogenic	Neuroglycopenic
· **Adrenergic**	· Blurred Vision
Palpitations	· Cognitive impairments
Tremor	· Behavioral changes
Anxiety/arousal/nervousness	· Psychomotor abnormalities
· **Cholinergic**	· Confusion
Sweating/diaphoresis	· Disorientation
Hunger	· Memory Loss
Paresthesia	· Seizure
Circumpolar tingling	· Stupor

BIOCHEMICAL DIAGNOSIS

The first step in the diagnosis of an insulinoma is to demonstrate hyperinsulinemic hypoglycemia (this is also called "organic hyperinsulinism"). This can potentially be achieved during a spontaneous hypoglycemia. However, most frequently a 72-hour fast is needed, which is currently the standard test to diagnose an insulinoma. The patient is closely clinically observed while serial glucose and insulin levels are obtained over the 72 hours until the patient becomes symptomatic, or a hypoglycemia is demonstrated. More than 95% of cases can be diagnosed based on responses to this easy test. Because the absolute insulin level is not elevated in all patients with insulinomas, a nondetectable or nonelevated insulin level does not rule out the disease. Values of insulin equal to or greater than 3 μU/mL (using modern insulin assays) in the presence of a blood glucose less than 3 mmol/l (55 mg/dl) are highly suggestive. Most specialists prefer more stringent cut-off glucose values amounting to 2.2 – 2.5 mmol/L (40 - 45 mg/dL) or less to increase the diagnostic specificity. Because of the potential increased proinsulin secretion, which is not detected using the currently used insulin assays, it is generally

recommended also to measure proinsulin and/or C-peptide levels, particularly in those cases with low to undetectable insulin levels in the blood. In the past these elevated proinsulin levels were also detected using the insulin RIAs, whereas nowadays these tumors are inadvertently addressed as pro-insulinomas. In these cases, concomitant C-peptide levels equal to or greater than 0.2 nmol/l and/or concomitant pro-insulin levels equal to or greater than 5 pmol/l (in the presence of a hypoglycemia) are also suggestive of an insulinoma. Commercial insulin preparations do not contain C-peptide and low C-peptide levels combined with high insulin levels confirm the diagnosis of factitious hyperinsulinemia (14, 21, 29, 36, 37).

Furthermore, absence of sulfonylurea (metabolites) in the plasma or urine has also been used to exclude factitious hypoglycemia's in (von) Munchhausen syndrome / (von) Munchausen by proxy. Patients who take sulfonylureas surreptitiously may have raised insulin and C-peptide values soon after ingestion, but chronic use will result in hypoglycemia without raised insulin or C-peptide levels. Only a high index of suspicion and measurement of plasma or urine sulfonylureas will lead to the correct diagnosis. (14, 21, 29, 37).

Finally, the demonstration of ß-hydroxy-butyrate levels equal to or less than 2.7 mmol/l at end of fast is used by some to confirm the hyperinsulinemic state. Some experts require the demonstration of a glucose response to 1 mg glucagon of more than 1.4 mmol/l (25 mg/dl) at end of fast. This increase of glucose is illustrative for the hyperinsulinemic state, because hyperinsulinemia preserves the liver glycogen storage despite (14, 21, 24, 29, 32-37).

TUMOR LOCALIZATION

Once the diagnosis of insulinoma is confirmed, every effort should be made to localize the tumor. Preoperative localization is important because approximately 30% of insulinomas are less than 1 cm in diameter and 10% are multiple, the latter particularly is present in MEN-1 patients (16). In addition, 10 to 15% are aggressive, malignant (metastatic), and very few patients will have either islet cell hyperplasia, or congenital hyperinsulinism/nesidioblastosis and no visible tumor at all. The anatomical localization of nonmetastatic (benign) insulinomas is also important for the choice between laparoscopic, robot-assisted, and open pancreatic surgery and between enucleation or resection – partial pancreatectomy and radiofrequency ablation (RFA) (37). Techniques most commonly used to demonstrate tumors in the pancreas include 3 phase CT and MRI, and endoscopic ultrasound (EUS). Each modality has variable reported abilities to identify insulinomas, likely reflecting institutional or operator-dependent (like in EUS) expertise (Table 2) (37).

Table 2. Imaging Strategies in Insulinoma Patients	
	Sensitivity
Transabdominal ultrasound	9 -65%
Three phase CT	60-80%
MRI (T1 +T2 weighted images + fat suppression)	85-90%
Endoscopic Ultrasound (EUS)	75-90%
Arterial Calcium Stimulation - Venous Sampling	80-90%
Intraoperative Localizing Techniques	
Palpation	70%
Intraoperative ultrasound (IOUS)	75-90%
Palpation plus IOUS	85-95%
Nuclear Medicine	
Somatostatin receptor scintigraphy SPECT / PET*	46-50% / 50-86%
^{18}F-DOPA PET	50%
Glucagon-Like Peptide-1 (Exendin-4) Receptor Imaging SPECT / PET**	75 / 95%

*, preferably used in patients with aggressive – malignant – metastatic insulinomas
**, preferably used in patients with indolent – ("benign") – localized insulinomas

In the past, selective pancreatic angiography and elective intra-arterial injection of calcium with sampling of hepatic vein insulin were used on a regular basis in high volume centers (38, 39). These invasive regionalization (an exact localization will be never given) procedures became less used because of the improved imaging procedures mentioned above and the introduction of glucagon-like peptide 1 (GLP-1) receptor imaging. The glucagon-like peptide 1 receptor (GLP-1R) is mainly expressed on the pancreatic beta cells and is therefore an interesting target for imaging of (previously occult) indolent ("benign") localized insulinomas. However, as opposed to localized, indolent ("benign") insulinomas, aggressive malignant (metastatic) insulinomas often lack the GLP-1R. Conversely, malignant (metastatic) aggressive insulinomas often do express the somatostatin receptor subtype 2 (SST2), which can be targeted using PET/CT or PET/MRI using ^{68}Ga-DOTA-labeled somatostatin analogs (SSAs) or in the past with somatostatin receptor scintigraphy and SPECT (40) (11, 41). In various studies, the GLP-1 receptor agonists ^{111}In-DOTA-exendin-4 and/or ^{68}Ga-DOTA-exendin-4 PET/CT successfully detected localized indolent ("benign") insulinomas. ^{68}Ga-DOTA-exendin-4 PET/CT seems more sensitive than ^{111}In-DOTA-exendin-4 SPECT/CT (41, 42). Replacing DOTA by NODAGA for ^{68}Ga-NODAGA-exendin-4 PET/CT ensures higher specific activities (Figure 1).

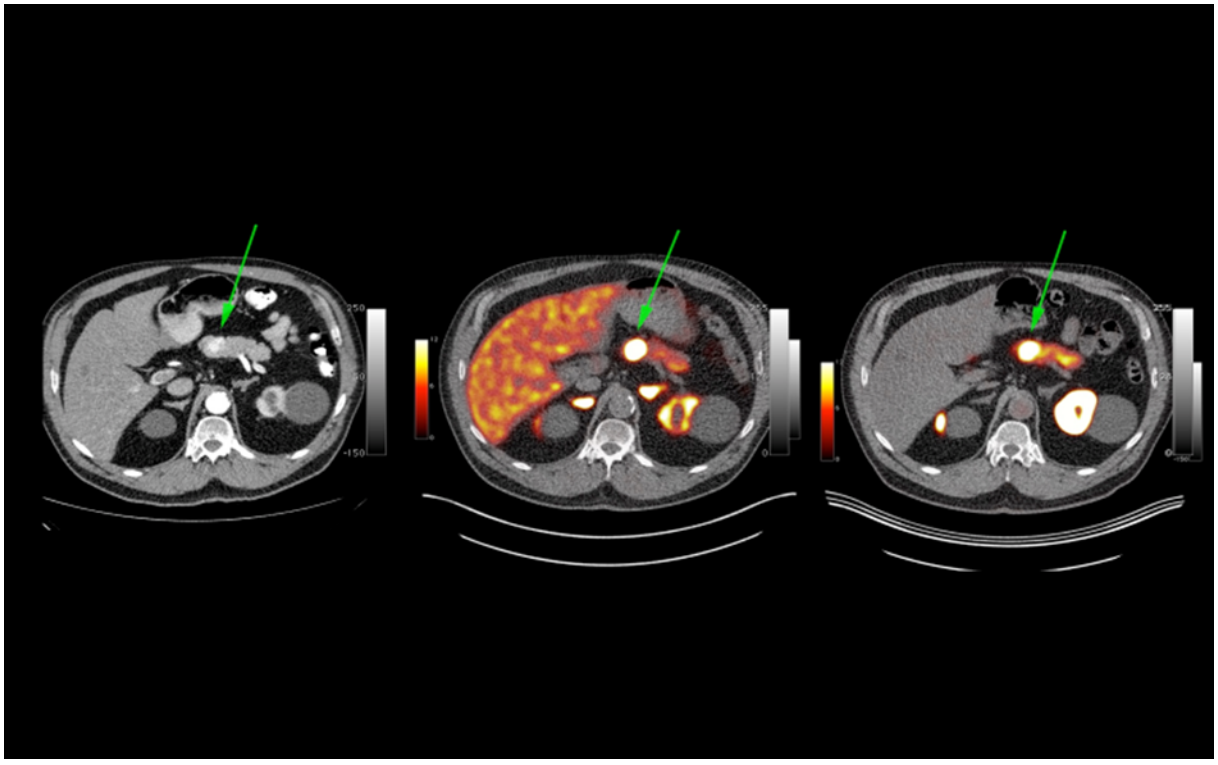

Figure 1. Localization studies demonstrating a localized insulinoma. From left to right: arterial-phase contrast-enhanced CT, ^{68}Ga-DOTATATE PET-CT, ^{68}Ga-NODAGA-exendin PET-CT (Courtesy: Drs. Marti Boss and Martin Gotthardt, Radboud University Medical Centre, Nijmegen, the Netherlands).

The efficacy of fluorine-18-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) PET/CT is based on co-secretion of dopamine and hormones or peptides by NEN cells. In these cells, L-DOPA is converted by the enzyme L-DOPA decarboxylase to dopamine. Next to ^{68}Ga-NODAGA-exendin-4 PET/CT (43), ^{18}F-DOPA PET/CT (with carbidopa premedication) plays an important role in the differential diagnosis of congenital hyperinsulinism (nesidioblastosis), especially for the identification of focal forms (28, 43-45).

If all localization and regionalization techniques fail to localize a tumor, intraoperative palpation of the pancreas and intraoperative ultrasound might prove to be successful (46).

In addition to the assessment of insulin hypersecretion, the metastatic spread, as reflected by the (ENETS/AJCC-UICC) staging, also determines the clinical manifestations and contribute to the prognosis (Figure 2 and Table 3) (28-31). Secondary, or metachronous insulin secretion by pancreatic neuroendocrine tumors which previously were non-secreting, or secreted other peptide hormones can also occur and is generally associated with poor survival (47, 48).

	ENETS	AJCC -UICC
	(T) Primary Tumor	(T) Primary Tumor
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed
T0	No evidence of primary tumor	No evidence of primary tumor
T1	Tumor limited to the pancreas and size <2 cm	Tumor limited to the pancreas, ≤2 cm in greatest dimension
T2	Tumor limited to the pancreas and size 2 - 4 cm	Tumor limited to the pancreas, >2 cm in greatest dimension
T3	Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of celiac axis or superior mesenteric artery	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
	(N) Regional Lymph Nodes	(N) Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis
	(M) Distant Metastases	(M) Distant Metastasis
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis

Figure 2. TNM staging system for pancreatic neuroendocrine tumors including insulinomas.

Table 3. TNM Staging System for Pancreatic Neuroendocrine Tumors including Insulinomas

Stage	T	N	M
I	T1	N0	M0
IIa	T2	N0	M0
IIb	T3	N0	M0
IIIa	T4	N0	M0
IIIb	Any T	N1	M0
IV	Any T	Any N	M1

HISTOPATHOLOGY

The WHO classification and grading of panNENs separates these tumors using the Ki67 index (MIB-1 antibody staining) into 4 broad categories: grade 1-2 (G1-2) well-differentiated pancreatic NETs (panNETs), poorly differentiated pancreatic neuroendocrine carcinomas (NECs – panNECs) and well-differentiated grade 3 (G3) NET. Helpful for the distinction of NECs from G3 NETs is their overexpression of p53 and loss of expression of Rb1 (Table 4). Insulin staining is not obligatory positive in insulinomas and is usually not necessarily required once the clinical diagnosis is made (3, 10, 49, 50).

Table 4. WHO 2017/2023 Classification for Neuroendocrine Neoplasms (NENs) of the Pancreas

Differentiation	Name	Grade	Ki 67 (% of ≥500 cells)	Mitotic count (2 mm2)
Well differentiated	NET	G1	<3	<2
		G2	3-20	2-20
		G3	>20	>20
Poorly differentiated	NEC	(G3)	>20	>20
	Small cell type			
	Large cell type			

Indolent and aggressive insulinoma are different entities. Aggressive insulinomas are characterized by rapid onset of symptoms, larger size, expression of ARX and alpha-1-antitrypsin; and decreased or absent immunohistochemical expression of insulin, PDX1 and GLP-1R. Moreover, aggressive insulinomas often harbor *Alpha-Thalassemia/mental Retardation, X-linked* (*ATRX*) and *Death Domain Associated Protein* (DAXX) mutations, the alternative lengthening of telomeres phenotype (ALT) and chromosomal instability (CIN). Tumor grade and MEN1 and YY1 mutations are less useful for predicting behavior. Aggressive insulinomas have similarities to normal alpha-cells and nonfunctional pancreatic neuroendocrine tumors, while indolent insulinomas remain closely related to normal beta-cells (11, 51),

SURGICAL AND INTERVENTIONAL TREATMENT

The treatment of pancreatic localized insulinoma usually is surgical; in the great majority of cases, it will provide a complete cure. It should be performed only when the diagnosis is certain, however, and by a surgeon who is skilled in pancreatic surgery. The surgical approach to an insulinoma is straightforward when the tumor is localized. Localized insulinomas are typically removed by enucleation of the tumor and rarely do tumors at the head of the pancreas require a pancreaticoduodenectomy (Whipple's procedure). Precise localization obviates blind pancreatic resection. EUS with special focus on the relationship between the tumor and the pancreatic duct is an excellent tool to guide the surgical decision. Laparoscopic, or robot-assisted enucleation of an insulinoma has been shown to be feasible, particularly if the lesion is visualized pre-operatively on CT scan or by EUS. In patients who have been unresponsive to medical therapy and in whom ^{18}F-DOPA PET/CT, PTHVS, or intra-arterial calcium stimulation with venous sampling suggests diffuse or multiple sources, such as adenomatosis, nesidioblastosis/congenital hyperinsulinemia, or hyperplasia, a resection of at least 80% of the distal pancreas can be indicated. In selected cases curative endoscopic ultrasound-

guided radiofrequency ablation (EUS-RFA) of a localized insulinoma can be feasible (2, 46, 52-54).

Malignant aggressive (metastatic) insulinomas can occasionally be surgically cured when there is localized or oligometastatic disease. Also, liver metastases can be resected, or treated by bland or chemo-embolization (TACE), radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE) depending on availability at the institution (55). If more than 90% of tumor load can be resected, palliative surgery can also be considered. However, most aggressive malignant metastatic insulinomas cannot be cured by surgery only and require medical antihormonal and antitumor treatment (46).

MEDICAL MANAGEMENT

When hypoglycemia can be controlled with diet alone or with small, well-tolerated doses of diazoxide, and/or when the medical condition of the patient increases the hazard of surgery sufficiently, medical management alone may be considered. Patients with diffuse hyperinsulinism for whom an operation is planned first should have a trial of treatment with diazoxide and a natriuretic benzothiadiazide. Medical treatment is required for the great majority of malignant insulinomas because only occasionally are they cured by operation. Medical treatment for localized, indolent ("benign") insulinomas includes a change in meals to include "lente carbohydrate" or unrefined carbohydrate given as frequently as required to prevent hypoglycemia. The management of malignant insulinoma is antihormonal and antitumor therapy (14, 46).

DIETARY MANAGEMENT

The cornerstone of medical management of insulinoma and other forms of hyperinsulinism is the diet. Not uncommonly, patients may avoid symptoms of hypoglycemia for variable periods of time by shortening the number of hours between meals. For some, the inclusion of a bedtime (11:00 pm) feeding is sufficient; for others, a midmorning, midafternoon, and/or a 3:00 pm snack is necessary. More slowly absorbable forms of carbohydrates (e.g., starches, bread, potatoes, rice) generally are preferred. During hypoglycemic episodes, rapidly absorbable forms (e.g., fruit juices with added glucose or sucrose) are indicated. In patients with severe refractory hypoglycemia, use of a continuous nasogastric tube feeding or intravenous infusion of glucose, coupled with increased dietary intake of carbohydrate, frequently alleviates hypoglycemia long enough to institute additional therapy (14).

MEDICAL THERAPY

Diazoxide (Proglycem) owes its potent hyperglycemic properties to two effects: it directly inhibits the release of insulin by β cells through stimulation of α-adrenergic receptors. It also has an extra-pancreatic hyperglycemic effect, probably by inhibiting cyclic adenosine monophosphate phosphodiesterase (cyclic AMP), resulting in higher plasma levels of cyclic AMP and enhanced glycogenolysis. Because diazoxide induces the retention of sodium, edema is troublesome at higher dosages. The addition of a diuretic benzothiadiazine (e.g., hydrochlorothiazide) not only corrects or prevents edema but synergizes the hyperglycemic effect of diazoxide. At the doses needed to counteract the higher doses of diazoxide (e.g., 450-600 mg/d), natriuretic benzothiadiazines frequently induce hypokalemia. Nausea is an additional complication at higher dosages of diazoxide, and hypertrichosis may complicate long-

term treatment. These compounds have been useful to elevate blood levels of glucose into the euglycemic range if an operation must be delayed for weeks or months. If they can be tolerated, higher doses may be used in patients with malignant insulinomas (56).

Theoretically, calcium channel blockers are capable of inhibiting insulin secretion. Verapamil and diltiazem have been used with variable results in patients with organic hyperinsulinism (57, 58).

β-Adrenergic-receptor blocking drugs inhibit insulin secretion and therefore may be of value in treating organic hyperinsulinism. The use of propranolol has been associated with the reduction of plasma insulin levels and with the relief of hypoglycemic attacks in patients with localized, indolent ("benign"), or aggressive malignant (metastatic) insulinoma. Because this drug can also mask the adrenergic symptoms of hypoglycemia and inhibit muscle glycogenolysis, however, there is a risk of aggravating the clinical syndrome. The drug should be used with extreme caution and careful monitoring (59).

The anticonvulsive diphenylhydantoin has been shown to inhibit the in vitro release of insulin from both the labile and storage β-cell pools. In only one-third or less of patients with localized, indolent ("benign") insulinoma, however, is the hyperglycemic effect of diphenylhydantoin of any clinical significance (60, 61). Furthermore, adverse effects usually occur with the dosages required. Maintenance doses range from 300 to 600 mg/d. The concurrent administration of diazoxide lowers measurable blood levels of diphenylhydantoin, and their concurrent use is not recommended.

Several reports exist on the successful use of intermediate acting subcutaneous octreotide injections (100-500 µg t.i.d.) in prolonging the ability to fast in a patient with localized, indolent ("benign") and aggressive malignant (metastatic) insulinomas. However, long-term administration of depot octreotide (Sandostatin LAR 30 mg / 4wks IM) or lanreotide (Somatuline Autogel 120 mg / 4 wks deep SC) may give only short-term relief of hypoglycemia. SSAs may also actually worsen plasma glucose levels probably by inhibiting the counterregulatory glucagon response. SSA treatment in insulinoma and nesidioblastosis patients should, therefore, always be preceded by a clinical trial with intermediate acting subcutaneous octreotide. In a limited number of cases, the second generation pan-SSA pasireotide has been successfully used to control hypoglycemias in patients with malignant insulinomas (62-65).

Targeting the pathway of the mammalian target of rapamycin (mTOR) has been shown in several trials to be effective in the management of low grade metastatic inoperable neuroendocrine tumors (66). Several studies have recently shown that everolimus (10mg/day) can normalize blood glucose levels in insulinoma patients. mTOR inhibitors like everolimus can reduce the insulin secretion and increase insulin resistance (62, 67-72). The multi-kinase inhibitor sunitinib (25mg/day) has only been occasionally reported to improve symptoms of hypoglycemia (62, 68, 73). Tyrosine kinase inhibitors (TKIs) do not have the capacity to suppress insulin, as well as inducing insulin resistance, like everolimus.

The use of glucocorticoids, which increase gluconeogenesis and cause insulin resistance, also can help to stabilize blood glucose at an acceptable level. Pharmacologic doses (Prednisone, approximately 1 mg/kg) must be used (74). Glucagon may help to raise blood glucose concentrations, but it may simultaneously directly stimulate the release of insulin (55).

ANTI-TUMOR TREATMENT IN MALIGNANT INSULINOMAS

Like in the other panNEN subtypes, anti-tumor treatments can consist of peptide receptor radiotherapy (PRRT) with radiolabeled beta radiation emitting somatostatin analogs (SSAs), several chemotherapy schedules (For a review see ref (75)) and targeted treatment with everolimus and sunitinib. PRRT with radiolabeled beta radiation emitting SSAs and, as mentioned above, mTOR inhibitors like everolimus, are frequently able to successfully control the hypoglycemias in patients with inoperable metastatic insulinomas (66-69, 75-79).

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