The Role of Glucagon Administration in the Diagnosis and Treatment of Patients with Tumor Hypoglycemia

Ana Oliveira Hoff, M.D.[1]
Rena Vassilopoulou-Sellin, M.D.[2]

[1] Baylor College of Medicine, Houston, Texas, Section of Endocrine Neoplasia and Hormonal Disorders.

[2] Division of Medicine, the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Presented in part at the Annual Meeting of the Endocrine Society.

The authors thank the clinical staff caring for the patients and Teofila C. Spear for expert preparation of the article.

Address for reprints: Rena Vassilopoulou-Sellin, M.D., Section of Endocrinology, Box 15, the University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

Received July 7, 1997; revision received October 27, 1997; accepted October 27, 1997.

BACKGROUND. Tumor hypoglycemia can be recurrent and severe enough to interfere with definitive antineoplastic treatment. Therefore, rapid commencement of effective therapy is essential. This is best accomplished by identifying which of the hypoglycemic processes is involved, as treatments differ. Some patients present with hypoglycemia and liver metastases; among them, only a few develop hypoglycemia as a result of a failure of hepatic glucose production. Most develop hypoglycemia as a result of an insulin-mediated process—either the secretion of insulin by an islet-cell tumor or the secretion of insulin-like growth factor-II by an extrapancreatic tumor. Administration of glucagon can rapidly make the two groups distinguishable, thus allowing institution of therapy and prompt symptomatic control of hypoglycemia.

METHODS. The charts of seven patients with tumor hypoglycemia and liver metastases who had a glucagon stimulation test (serial glucose measurements after a 1 mg infusion of glucagon) as part of the workup for hypoglycemia were retrospectively reviewed. Those patients whose test revealed a rise in serum glucose of >30 mg/dL were subsequently treated as outpatients, with a continuous glucagon infusion delivered by a portable pump.

RESULTS. Three patients had an insulinoma and four had non-islet cell tumor hypoglycemia (NICTH) due to hepatocellular carcinoma, colon carcinoma, meningeal sarcoma, and hemangiopericytoma, respectively. All of the patients had liver metastateses. Evaluation of these patients included a glucagon stimulation test (1 mg intravenous push), which quickly provided information about the mechanism of tumor hypoglycemia and the direction towards therapy. All patients with insulinoma responded to glucagon with a rise in blood serum glucose levels, indicating adequate glycogen stores. The four patients with NICTH had mixed responses: in two patients, the response suggested that hypoglycemia was due to an insulin-like tumor product; glucose levels did not rise in the other two cases, indicating that hypoglycemia was due to poor hepatic glycogen reserve/liver failure. In all cases, a glycemic response to glucagon predicted good response to long term treatment with glucagon (0.06–0.3 mg/hour, via intravenous infusion pump).

CONCLUSIONS. The glucagon stimulation test is a simple and fast approach that serves to clarify the etiology of hypoglycemia (diagnostic use) and guide effective long term strategies for its control (therapeutic use) in patients with neoplastic diseases and liver metastases. ***Cancer* 1998; 82:1585–92.**
© 1998 American Cancer Society.

KEYWORDS: tumor, hypoclycemia, glucagon, liver, metastasis.

Tumor hypoglycemia often requires fast and efficacious therapeutic intervention. The hypoglycemia is recurrent, severe, and, most important, often interferes with definitive antineoplastic treatment. Therefore, the symptomatic control of hypoglycemia is essential to allow surgical intervention and/or implementation of chemotherapy.

Two broad categories of tumors are associated with hypoglycemia: insulin-secreting islet-cell tumors (insulinomas) or non-islet-cell tumors. Non-islet-cell tumor hypoglycemia (NICTH) is associated with mesenchymal tumors, such as hemangiopericytomas, fibrosarcomas, mesotheliomas, and neurofibromas, as well as other tumor types, such as hepatocellular carcinomas, neuroblastomas, and adrenal cortical carcinomas.[1,2] Metastatic involvement of the liver is a common feature of many of these tumors, but the vast majority of patients with liver metastases do not have hypoglycemia.[3] Therefore, the subset of patients with liver metastases who present to the emergency room with hypoglycemia frequently pose a diagnostic and therapeutic dilemma. Liver failure or an insulin-mediated or insulin-like–mediated process are possible causes of the hypoglycemia. Distinguishing which of these processes is involved is of the utmost importance, as management and prognosis differ.[1,3] In our experience, it is possible to distinguish these entities quickly and reliably with a glucagon stimulation test.[4,5] Patients who demonstrate a glycemic response are candidates for short term or, if necessary, long term infusion of glucagon, which controls hypoglycemia while more definitive treatments, such as surgery or systemic chemotherapy, are still being administered.

We retrospectively reviewed seven patients with tumor-associated hypoglycemia and liver metastases who underwent a glucagon test as part of their workup. Those who responded to this test were subsequently treated with continuous glucagon infusions.

MATERIALS AND METHODS

Patients

The charts of seven patients who presented to the University of Texas M. D. Anderson Cancer Center between 1982 and 1996 with tumor hypoglycemia and had a glucagon stimulation test were retrospectively reviewed. Three patients had insulinoma and four had NICTH; all seven patients had liver metastases.

Glucagon Test

Glucagon (1 mg/mL, Eli-Lilly, Indianapolis, IN) was given by intravenous infusion over 2 minutes. Blood was collected with an indwelling catheter at −10, 0, 15, 30, and 45 minutes and checked for serum glucose levels after an overnight fast or during an episode of spontaneous hypoglycemia.

Laboratory Tests

Insulin-like growth factor II (IGF-II) was measured by radioimmunoassay (Endocrine Sciences, Calabasas Hills, CA), insulin-like growth factor I (IGF-I) by radioimmunoassay (Smith Kline Beecham, St. Louis, MO), c-peptide by immunoassay (Smith Kline Beecham, St. Louis, MO), insulin by immunoassay (Smith Kline Beecham, St. Louis, MO), and growth hormone by immunoassay (Smith Kline Beecham, Van Nuys, CA.)

Glucagon Infusion

Glucagon (1 mg/mL, Eli-Lilly, Indianapolis, IN) in a 50 mL solution of D5W was infused by a portable Infumed pump (Medfusion, Inc., Duluth, GA) through a central line at a rate of 0.06–0.30 mg/hour. The glucagon dose was titrated to keep serum glucose levels within the normal range.

Case Histories

Patient 1

A woman age 61 years presented with a several-month history of episodes of confusion, impaired memory, and fainting. The diagnosis of insulin-secreting islet-cell tumor was based on her low serum glucose level (30 mg/dL) and inappropriately high serum insulin (50μU/mL, normal 5–25μU/mL), c-peptide (7.8 ng/mL, normal 0.8–4 ng/mL), and proinsulin levels (6.32 ng/mL, normal $<$0.2ng/mL). Computed tomography (CT) revealed metastatic liver disease, and biopsy results were consistent with metastatic neuroendocrine carcinoma. The patient was treated initially with systemic chemotherapy, which included 5-fluorouracil (5-FU) and leucovorin, but without success. In December 1995, she presented to our institution, where she received three courses of streptozocin and doxorubicin, but her tumor progressed. The recurrent episodes of hypoglycemia were disabling and unresponsive to dietary measurements, diazoxide, and 10% glucose infusion. In January 1996, a glucagon stimulation test was performed to evaluate her hepatic glycogen stores; she responded with a rise in serum glucose (Fig. 1). A continuous infusion of glucagon (0.2 mg/hour, delivered by an infusion pump) in addition to a glucose infusion was then started and resulted in adequate control of her hypoglycemia. In February 1996, the patient developed severe diarrhea, hypokalemia, and metabolic acidosis, which were found to be due to tumor vasoactive intestinal peptide (VIP) hypersecretion. She subsequently underwent three hepatic artery embolizations, which improved the serum glucose level transiently but enough to allow discontinuation of the glucose infusion. The glucagon infusion was maintained at a rate of 0.25 mg/hour until her death in July 1996. Her last visit to the outpatient clinic was in July 1996; home blood glucose monitoring had revealed blood sugars between 76 and 170 mg/dL.

Patient 2

A woman age 66 years was diagnosed with islet-cell carcinoma in 1984. She underwent a distal pancreatec-

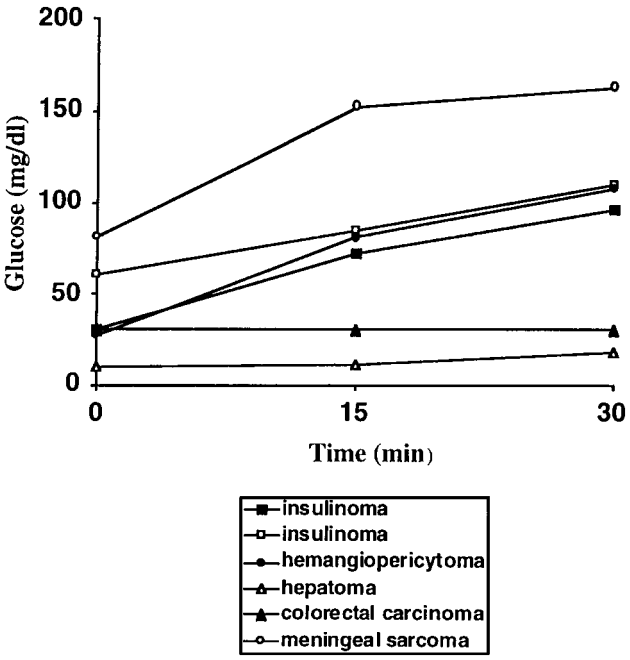

FIGURE 1. Results of a glucagon test are shown for patients with tumor hypoglycemia and liver metastases. A glucose response (a rise of >30 mg/dL) was observed in patients with an insulin-mediated process (insulinoma) and in patients with an insulin-like–mediated process (hemangiopericytoma or meningeal sarcoma). A blunt response to glucagon stimulation indicated poor glycogen stores or an inability to release glycogen (hepatoma or colorectal carcinoma).

tomy and a liver biopsy, which revealed metastatic disease. In 1985, she developed diarrhea and her gastrin and pancreatic polypeptide levels were elevated. A CT scan of the abdomen revealed progression of liver metastases. She underwent hepatic artery embolization in January 1986 and hepatic artery chemoembolizations in February, April, and July of 1986, with transient improvement of diarrhea. When her symptoms recurred, somatostatin (100 μg subcutaneously 3 times a day) was administered, resulting in transient improvement. In 1987, she developed hypoglycemia associated with elevated levels of insulin and c-peptide. Another hepatic artery embolization was performed; diazoxide and hydrochlorothiazide (50 mg orally 3 times a day) were administered. Serum glucose levels were under control until December 1989, when her hypoglycemia became progressively worse despite increasing doses of diazoxide. At that time her serum glucose level was 28 mg/dL, insulin was 82μU/mL, and c-peptide was 3.4 ng/mL. In May 1990 a glucagon test was performed (Fig. 1) and glucagon infusion at 0.3 mg/hour was administered, with good control of glucose levels. The patient received two courses of systemic chemotherapy (streptozotocin and 5-FU); her serum glucose levels improved and the glucagon infusion was decreased to 0.2 mg/hour. She was maintained on the glucagon infusion at home until April 1991, when it was discontinued because of hyperglycemia. At that time, because of progressive metastatic disease and poor oral intake, she was started on central hyperalimentation, which controlled her glucose levels until her death in November 1991.

Patient 3

A white woman age 54 years presented with a 3-month history of dizziness and confusion. In September 1996, she was found to be hypoglycemic, and her workup revealed inappropriately high insulin and c-peptide levels. She then underwent a distal pancreatectomy, a splenectomy, a partial omentectomy, and a liver biopsy. The pathologic findings were consistent with a poorly differentiated neuroendocrine carcinoma metastatic to the liver and spleen. She then began receiving somatostatin (100 μg every 6 hours) and regular feedings, but control of the hypoglycemia was poor. In October 1996, she received chemotherapy (5-FU and streptozocin) and was placed on diazoxide in an attempt to control the hypoglycemic episodes. In November 1996, she presented to our institution and reported severe and frequent hypoglycemic episodes. At presentation, her serum glucose level was 41 mg/dL (Fig. 2); glucagon infusion at 0.3 mg/hour was then administered, which controlled serum glucose at a mean level of 151 mg/dL, allowing the right posterior aspect of the liver to be embolized with Gelfoam powder. The glucagon requirement then decreased to the very low dose of 0.06 mg/hour at night, and the patient was sent home. She returned for a second hepatic artery embolization (HAE), again to the right lobe of the liver, a month later. At home, her glucose level ranged from 80 to 182 mg/dL (Accu-Check ADVANTAGE™, Boehringer Mannheim, Indianapolis, IN). In the hospital, glucagon was given at 0.1 mg/hour, left HAE with Gelfoam powder was performed, and again her glucagon requirement dropped to 0.06 mg/hour. In January 1997, she presented to our clinic and received glucagon 0.05 mg/hour at night and frequent feedings during the day; her serum glucose was 60 mg/dL. She was admitted for another HAE (in the remaining part of right lobe) and sent home on glucagon therapy at 0.06 mg/hour. Since then she has had a fourth HAE (left lobe of the liver) and has remained stable on glucagon therapy at 0.06 mg/hour. She was stable at last follow-up in June 1997.

Patient 4

A woman age 26 years was diagnosed with an intrathoracic hemangiopericytoma metastatic to the liver and

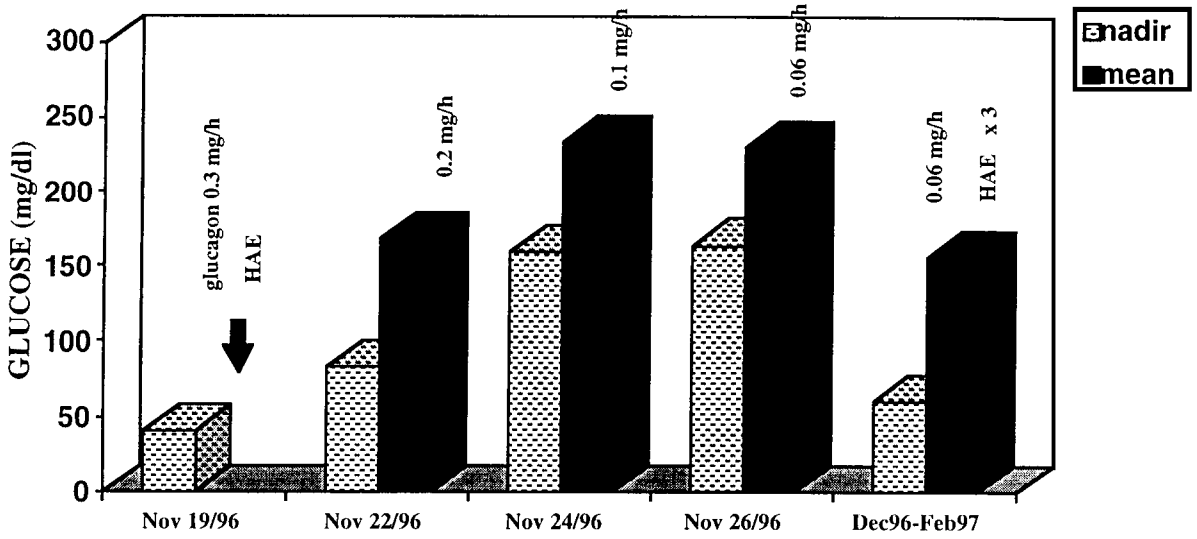

FIGURE 2. Serum glucose levels are shown for Patient 3, who had insulinoma before and after treatment with glucagon and hepatic artery embolization (HAE). At presentation, serum glucose was 41 mg/dL; the hypoglycemia had been unresponsive to somatostatin, diazoxide, frequent meals, and systemic chemotherapy. The patient began to receive glucagon (0.3 mg/hour), and HAE was performed, which resulted in decreased requirement of glucagon. She has undergone three more HAEs and has been stable on glucagon 0.06 mg/hour overnight (serum glucose levels from March and April are not shown).

kidney in 1980. She received neoadjuvant chemotherapy, which included cyclophosphamide, doxorubicin, and dacarbazine, followed by resection of the mass and postoperative chemotherapy and radiation therapy. The patient was free of disease until October 1994, when she presented with severe hypoglycemia. Her serum glucose level was 28 mg/dL. Insulin, c-peptide, growth hormone, and IGF-I levels were suppressed: <3 μU/mL, <0.1 ng/mL, 1.2 mg/mL, and $<$ 10 ng/mL, respectively (normal IGF-I, 116–270 ng/mL). IGF-II level was normal (518 ng/ml; range, 358–854 ng/ml; normal, 288–736 ng/mL). A CT scan of the abdomen revealed a large mass replacing the right lobe of the liver. A glucagon test resulted in a rise of serum glucose from 28 mg/dL to 108 mg/dL (Fig. 1). She then began receiving a continuous infusion of glucagon (0.3 mg/hour), which achieved good control of serum glucose levels. Interferon and *cis*-retinoic acid were given without success. Because of progressive disease, she underwent hepatic chemoembolization with ivalon and cisplatin in January 1995. At that time (3 months after the initiation of glucagon) she was also found to have a rash, which resolved when glucagon was discontinued; thereafter, a 10% glucose infusion at 100 mL/hour was started and maintained for several months in an outpatient setting. A second chemoembolization as well as systemic chemotherapy (7 courses of doxorubicin and ifosfamide) resulted in complete normalization of serum glucose levels, and the glucose infusion was discontinued. The patient has been euglycemic with stable disease since then. She was last seen in the outpatient clinic in January 1997; her serum glucose level was 103 mg/dL.

Patient 5

A man age 38 years[6] was diagnosed with meningeal sarcoma in 1978. He was treated with surgery in 1978, and again in 1984, when the sarcoma recurred. In 1986, he was found to have metastases to the right hip, which were treated with intra-arterial cisplatin plus radiation therapy. In 1988, he developed liver metastases and underwent 12 courses of systemic chemotherapy consisting of ifosfamide. In 1989, he presented with hypoglycemia. His serum glucose level was 23 mg/dL. Insulin, c-peptide, and IGF-I levels were subnormal: 2 μU/mL, <0.3 ng/mL, and 135 ng/mL (normal from 20 controls, 384 $\pm$ 196 ng/mL [mean $\pm$ standard deviation]). His IGF-II level was elevated (2373 ng/mL compared with 634 $\pm$ 190 ng/mL found in 20 normal controls). The patient was treated with human growth hormone administered intramuscularly at 0.1 mg/kg in 2 divided doses daily for 8 weeks. There was a transient improvement of the hypoglycemia, but then the growth hormone injections were discontinued due to progressively worse hypoglycemic episodes and arthritic symptoms. Intravenous administration of 1 mg of glucagon produced a rise in the serum glucose level from 82 mg/dL to 163 mg/dL (Fig. 1). The patient then began to receive continuous-infusion glucagon at 0.3 mg/hour; this abated the hypogly-

cemic episodes and permitted another trial of chemotherapy with interferon-α and vinblastine sulfate. This treatment controlled the hypoglycemia, and glucagon was discontinued 6 months after its initiation. The patient remained euglycemic until his death from progressive metastatic disease in 1991.

Patient 6

A man age 70 years was diagnosed with adenocarcinoma of the colon in 1995. He underwent sigmoidectomy in April of 1995, and examination of his liver revealed metastatic disease. He was treated with 5-fluouracil and leucovorin, with progression of disease, and was also treated with cyclohexylchloroethylnitrosourea (CCNU), which resulted in severe myelosuppression. In May 1996, he presented to the emergency room with a serum glucose level of 16 mg/dL; he was given a 50% glucose infusion and his serum glucose level rose to 93 mg/dL. At a serum glucose level of 33 mg/dL, his insulin, c-peptide, and growth hormone levels were suppressed (3 μU/mL, 0.1 ng/mL, and 0.1 ng/mL, respectively). A 10% glucose infusion at 80mL/hour overnight was administered, but his serum glucose level dropped to 40 mg/dL. A 1-mg stimulation glucagon test failed to raise the patient's serum glucose level (Fig. 1), indicating poor glycogen stores or impaired gluconeogenesis. In fact, there was evidence of hepatic insufficiency, as liver function tests values were abnormal (lactate dehydrogenase, 1144 IU/L; total bilirubin, 2.1 mg/dL; albumin, 2.6 g/dL; alkaline phosphatase, 587 IU/L; alanine aminotransferase, $<$16 IU/L). The patient was treated with a 20% glucose infusion and methylprednisolone (40 mg daily) until his death 24 days after hospital admission.

Patient 7

A man age 34 years was diagnosed with hepatocellular carcinoma in 1981. Despite four courses of systemic chemotherapy (5-flourodeoxyuridine, doxorubicin, and mitomycin C), his disease progressed with pulmonary metastases. In December 1981, he underwent hepatic artery embolization. In March 1982, he presented to the emergency room and was diaphoretic, tachycardic, and semicomatose. His serum glucose level was 10 mg/dL and his insulin level was suppressed at 3 μU/mL. A chest X-ray and ultrasound scan of his abdomen revealed progression of disease. No response to the glucagon stimulation test was elicited (Fig. 1). He failed to respond to diazoxide treatment and was given a 50% glucose infusion via a pump until his death in April 1982.

DISCUSSION

We describe our experience with seven patients (Table 2) who had severe tumor hypoglycemia and liver metastases. We utilized the 1-mg glucagon stimulation test as a strategy to define better the differential diagnosis and develop a treatment plan. The patients who responded were then treated with continuous-infusion glucagon for several months, which allowed good glycemic control in the outpatient setting and implementation of more definitive treatment. The three patients who had insulinoma presented with elevated insulin and c-peptide levels as well as pathologic evidence of pancreatic neuroendocrine carcinoma. The triad of hypoglycemia, a non-islet-cell tumor, and hypoinsulinemia, in addition to low IGF-I and growth hormone levels, and normal or elevated IGF-II levels were indicative of non-islet-cell tumor hypoglycemia in Patients 4–7. Patients 4 and 5 (who had hemangiopericytoma and meningeal sarcoma, respectively) responded to glucagon, supporting the diagnosis of paraneoplastic insulin-like secretion. However, Patients 6 and 7 (who had adenocarcinoma of the colon and hepatocellular carcinoma, respectively) also presented with hypoglycemia and hypoinsulinemia that was consistent with non-islet-cell tumor hypoglycemia but did not respond to the glucagon stimulation test, indicating a diagnosis of liver failure or hepatic fuel depletion.

The glucagon test [7–9] has been used to distinguish between an insulin-mediated or insulin-like–mediated hypoglycemia and hypoglycemia induced by liver failure. After an overnight fast, the former responds with a rise in serum glucose levels, which is the result of increased hepatic glucose production and indicates adequate hepatic glycogen stores. The latter shows no rise in serum glucose levels, indicating poor hepatic glycogen stores or inability to release them.

The glucagon stimulation test has scarcely been discussed in the recent literature. In the 1960s, an exacerbated insulin response to intravenous administration of glucagon was a strategy to define better the diagnosis of insulinoma.[10] In tumor hypoglycemia, it has been used mainly in the differential diagnosis and, more specifically, in the identification of the mechanism of hypoglycemia.[9] In our experience, this test is not only helpful in determining the differential diagnosis, but is also an easy and fast way to help us decide on an effective treatment, as all patients who responded to it also responded to prolonged glucagon infusion.

In oncology the most common cause of chronic hypoglycemia is an insulin-secreting islet-cell tumor; the next most common cause is a tumor producing IGF-II.[4] Liver failure and increased glucose consumption by the tumor are less common and may be additional factors contributing to the development of hypoglycemia. Nadler and Wolfer[11] described the first case of non-islet-cell tumor hypoglycemia (NICTH) in

TABLE 1
Patient Characteristics

Patient no.	Diagnosis	Age/gender	Liver metastases	Response to glucagon test	Duration of glucagon treatment	Survival after diagnosis of hypoglycemia
1	Insulinoma	61/F	Yes	Yes	6 mos	10 mos
2	Insulinoma	65/F	Yes	Yes	11 mos	4 yrs
3	Insulinoma	54/F	Yes		6 mos	6 mos
4	Hemangiopericytoma	26/F	Yes	Yes	4 mos	$2^{1/2}$ yrs
5	Meningeal sarcoma	38/F	Yes	Yes	6 mos	2 yrs
6	Colorectal carcinoma	70/M	Yes	No	—	24 days
7	Hepatoma	34/M		No	—	25 days

TABLE 2
Laboratory Values at Diagnosis at Hypoglycemia[a]

Patient no.	Diagnosis	Glucose (mg/dL)	Insulin (μU/mL)	c-peptide (ng/mL)	IGF-II	GH
1	Insulinoma	30	50	7.8		
2	Insulinoma	28	82	3.4		
3	Insulinoma	41	207	10.8		
4	Hemangiopericytoma	28	<3	<0.1	518	1.2
5	Meningeal sarcoma	23	2	<0.3	2373	
6	Colorectal carcinoma	16	3			0.1
7	Hepatocellular carcinoma	10	3			

IGF-II: insulin-like growth factor II; GH: growth hormone.
[a] Normal levels: glucose, 70–110 mg/dL; insulin, 5–25 μU/mL; c-peptide, 0.8–4 ng/mL; IGF-2, 288–736 ng/mL.

a man age 30 years with a hepatocellular carcinoma involving 80% of his liver; the hypoglycemia was thought to be secondary to hepatic destruction. In 1930 Doege et al.[12] were the first to speculate that ''hyperinsulinism'' was responsible for NICTH, as tumor extract injected into rabbits caused hypoglycemia. Since then, the pathophysiology of NICTH has been extensively studied,[8,13] but only recently has it been better understood. Insulin levels in patients with NICTH are not high but are appropriately suppressed to the low glucose level. It is now known that IGF-II mediates the hypoglycemia in these patients. It is noteworthy that the serum level of IGF-II is normal in most cases,[2] and the reason is that the tumor produces an increased amount of IGF-II, which is poorly processed. Therefore, a high-molecular-weight form of IGF-II that cannot be detected by routine IGF-II assays is released into the circulation. To overcome this difficulty, Daughaday et al. have developed an assay able to detect the first 21 amino acids of the E-domain (E-21) of pro-insulin-like growth factor II (''big'' IGF-II).[14] As a protective mechanism against hypoglycemia, IGFs are carried in the circulation by two protein complexes: 150-KDa complex (inactive), which consists of IGF-I or II, insulin-like growth factor binding protein-III (IGFBP-III), and an acid-labile subunit; and a 50-KDa complex (active), which is composed of an IGF and a low-molecular-weight IGFBP.[15] In NICTH, due to an abnormal, high-molecular-weight IGF-II as well as decreased levels of IGFBP-III and acid-labile subunit (ALS), more of the 50-KDa complex is formed, which allows the IGF-II to be more available to target tissues, resulting in hypoglycemia.[2,16,17] High-molecular-weight IGF-II (E-21) was not measured in our patients, but the fact that two of the patients with NICTH responded to the glucagon stimulation test strongly suggests that hypoglycemia was IGF-II–mediated.

Liver metastases are frequently observed in patients with islet-cell and non-islet-cell tumor hypoglycemia. All of our patients presented with liver metastases, but in only two did it result in sufficient destruction of functional hepatic tissue to cause impaired glucose production and hypoglycemia. In fact, liver failure in this setting is a rare cause of tumor hypoglycemia,[1,3] as spared hepatic tissue is often able to compensate with enough glucose output to maintain euglycemia. In our experience, liver failure–induced hypoglycemia was associated with a poor response to

any treatment modality and a grave prognosis; both our patients died within 1 month of developing hypoglycemia (Table 1). These patients can be identified not only by abnormal liver function tests but also by a flat glucose response to the glucagon stimulation test (Fig. 1). They are frequently given glucose infusions with or without concomitant use of steroids.

The best treatment for tumor hypoglycemia is surgical resection of the tumor.[18] However, complete surgical resection is often not possible; in these cases, regional or systemic chemotherapy and radiation therapy are useful in the eradication of hypoglycemia. Measurements to control hypoglycemia while definitive therapy is carried out include glucose infusion, administration of diazoxide, growth hormone, steroids, somatostatin, and glucagon infusion. Growth hormone treatment can be effective in some cases,[16,19] but usually a supraphysiologic dose needs to be given;[16,20] this eventually leads to side effects, such as volume overload and arthralgias, and results in discontinuation of this drug.[6,16] Somatostatin is generally ineffective in the treatment of hypoglycemia.[18,21] In addition to the expected decrease in IGF production, glucagon levels are significantly decreased, which leads to suppression of hepatic glucose production.[18] Glucagon infusion in the treatment of hypoglycemia was first reported by Samaan et al.[6] This patient had a metastatic meningeal sarcoma (Patient 5), responded to the glucagon test, and received a continuous glucagon infusion for 6 months, until control of hypoglycemia by systemic chemotherapy could be achieved.

Glucagon is a major hormone released in response to hypoglycemia;[4] it stimulates hepatic glucose production by the breakdown of glycogen (glycogenolysis) and by induction of gluconeogenesis. Intramuscular injection of glucagon has been used for years in the acute management of diabetic hypoglycemia. Jakob et al. have also shown that intramuscular injection of zinc glucagon enabled a patient to fast for 9 hours without hypoglycemia.[8] Glucagon infusion was administered to five of our patients with a portable pump on an outpatient basis. It proved to be an effective treatment, created minimal side effects (reversible skin rash), and allowed a better quality of life until more definitive treatment abated the hypoglycemia.

CONCLUSIONS

Tumor hypoglycemia is an uncommon but potentially lethal disorder. Since improved antineoplastic therapies have been developed, patients live longer despite the presence of liver involvement, and good glycemic control optimizes their care. We suggest a glucagon stimulation test as a practical approach to diagnosing these patients; it is a fast method that allows the determination of which patients will respond to glucagon, an effective and safe outpatient treatment.

REFERENCES

1. Marks LJ, Steinke J, Podolsky S, Egdahl RH. Hypoglycemia associated with neoplasia. *Ann N Y Acad Sci* 1973;147–60.
2. Zapf J. Role of insulin-like growth factor II and IGF binding proteins in extrapancreatic tumor hypoglycemia. *Horm Res* 1994;42:20–6.
3. Younus S, Soterakis J, Sossi AJ, Chawla SK, LoPresti PA. Hypoglycemia secondary to metastases to the liver: a case report and review of the literature. *Gastroenterology* 1977;72:334–7.
4. Service FJ. Medical progress: hypoglycemic disorders. *N Engl J Med* 1995;332:1144–52.
5. Marks V, Alberti KGMM. Selected tests of carbohydrate metabolism. *Clin Endocrinol Metab* 1976; 5:805–21.
6. Samaan NA, Pham FK, Sellin RV, Fernandez JF, Benjamin RS. Successful treatment of hypoglycemia using glucagon in a patient with an extrapancreatic tumor. *Ann Intern Med* 1990;113:404–6.
7. Silbert CK, Rossini AA, Ghazvinian S, Widrich WC, Marks LJ, Sawin CT. Tumor hypoglycemia: deficient splanchnic glucose output and deficient glucagon secretion. *Diabetes* 1976;25:202–6.
8. Jakob A, Meyer UA, Flury R, Ziegler WH, Labhart A, Froesch ER. The pathogenesis of tumour hypoglycemia: blocks of hepatic glucose release and of adipose tissue lipolysis. *Diabetologia* 1967; 3:506–14.
9. Marks V. Hypoglycemia. 2. Other causes. *Clin Endocrinol Metab* 1976;5:769–83.
10. Kumar D, Mehtalia SD, Miller LV. Diagnostic use of glucagon-induced insulin response: studies in patients with insulinoma or other hypoglycemic conditions. *Ann Intern Med* 1974;80:697–701.
11. Nadler WH, Wolfer JA. Hepatogenic hypoglycemia associated with primary liver cell carcinoma. *Arch Intern Med* 1929:700–10.
12. Doege KW. Fibro-sarcoma of the mediastinum. *Ann Surg* 1930;92:955–60.
13. Megyesi K, Kahn CR, Roth J, Gorden P. Hypoglycemia in association with extrapancreatic tumors: demonstration of elevated plasma NSILA-s by a new radioreceptor assay. *J Clin Endocrinol Metab* 1974;38:931–4.
14. Daughaday WH, Trivedi B. Measurements of derivatives of pro-insulin-like growth factor II in by a radioimunoassay directed against the E-domain in normal subjects and patients with non-islet cell tumor hypoglycemia. *J Clin Endocrinol Metab* 1992;75:110–5.
15. LeRoith D, Clemmons D, Nissley P, Rechler MM. Insulin-like growth factors in health and disease. *Ann Intern Med* 1992;116:854–62.
16. Baxter RC, Holman SR, Corbould A, Stranks S, Ho PJ, Braund W. Regulation of the insulin-like growth factors and their binding proteins by glucocorticoid and growth hormone in nonislet cell tumor hypoglycemia. *J Clin Endocrinol Metab* 1995;80:2700–8.
17. Zapf J. IGFs: function and clinical importance & role of insulin-like growth factor (IGF) II and IGF binding proteins in extrapancreatic tumour hypoglycemia. *J Intern Med* 1993; 234:543–52.

18. Chung J, Henry RR. Mechanisms of tumor-induced hypoglycemia with intra-abdominal hemangiopericytoma. *J Clin Endocrinol Metab* 1996;81:919–25.
19. Katz LEL, Liu F, Baker B, Baker B, Agus MSD, Nuun SE, et al. The effect of growth hormone treatment on the insulin-like growth factor axis in a child with nonislet cell tumor hypoglycemia. *J Clin Endocrinol Metab* 1996;81:1141–6.
20. Wing JR, Panz VR, Joffe BI, Kalk WJ, Seftel HC, Zapf J, et al. Hypoglycemia in hepatocellular carcinoma: failure of short-term growth hormone administration to reduce enhanced glucose requirements. *Metabolism* 1991;40: 508–12.
21. Gama R, Marks V, Wright J, Teale JD. Octreotide exacerbated fasting hypoglycemia in a patient with a proinsulinoma: the glucostatic importance of pancreatic glucagon. *Clin Endocrinol* 1995;43:117–20.