Insulinomas: Localization with Selective Intraarterial Injection of Calcium

To facilitate the noninvasive preoperative localization of islet cell tumors less than 15 mm in diameter, the authors examined the use of calcium as an insulin secretagogue in an arterial stimulation venous sampling (ASVS) technique. In four patients with episodic hypoglycemia, calcium gluconate (0.01–0.025 mEq Ca²⁺/kg) was injected directly into branches of the celiac plexus (gastroduodenal, splenic, and hepatic arteries) and the superior mesenteric artery. In all patients, serum levels of insulin rose abruptly in blood samples taken from the right hepatic vein 30 and 60 seconds after the infusion of calcium into the artery supplying the tumor; injection into an artery not supplying the tumor did not result in a similar rise. Accurate localization of the insulinomas was verified at surgery in three patients. In the fourth patient, who did not undergo surgery, arteriographic results were positive for insulinoma at the predicted site. On the basis of these results, the authors believe noninvasive ASVS may replace invasive portal venous sampling as the most effective method for the localization of occult insulinomas.

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The successful resection of insulin-secreting islet cell tumors is greatly facilitated by precise preoperative localization. The noninvasive modalities of ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging often fail to demonstrate insulinomas smaller than 15 mm in diameter (1). Arteriography and portal venous sampling are generally performed when the findings from noninvasive imaging studies are negative or equivocal. In our current experience (1,2) arteriographic findings are positive in only 50–60% of patients. Transhepatic portal venous sampling yields positive results in 75–80% of patients with insulinomas, but it is an invasive procedure that requires considerable expertise to obtain the critical samples from the small veins draining the pancreas.

Arterial stimulation and venous sampling (ASVS) with secretin to stimulate the release of gastrin from islet cell tumors has proved to be a reliable localization study in patients with the Zollinger-Ellison syndrome (3–5). ASVS provides information similar to that provided by portal venous sampling, and, in one series, ASVS results were positive in a higher percentage of patients than were portal venous sampling results (58% vs 42%, respectively) (5). In these patients, arteriography combined with intraarterial injection of secretin demonstrated a sensitivity of 77%, and was the single most effective examination for the localization of gastrin-secreting islet cell tumors (5).

We have attempted to modify this technique with selective intraarterial injection of an insulin secretagogue to locate insulinomas. Calcium was selected as the insulin-releasing stimulant. The results in our first four consecutive patients are presented here.

PATIENTS AND METHODS

Patients

Four consecutive patients with episodic hypoglycemia were studied according to a protocol approved by the National Institute of Diabetes and Digestive and Kidney Diseases. All patients gave informed consent. In each patient the diagnosis of an insulin-secreting beta cell tumor was based on the development of hypoglycemia with inappropriately elevated levels of serum insulin during a prolonged (72-hour) fast. Three patients underwent portal venous sampling followed by surgery. At surgery, insulinomas were resected in all three patients. The fourth patient did not undergo portal venous sampling because of extreme obesity (200 kg). This patient's hypoglycemia is currently controlled by diazoxide, and she is on a weight-reduction diet to reduce her surgical risk.

Blood samples were obtained routinely from both the right and left hepatic veins to avoid any false-negative diagnosis that might be made because of insulin streaming from a tumor of the distal pancreatic body or tail into the left portal vein. However, we found that all increases in insulin levels in this small series occurred simultaneously in both right and left hepatic veins.

Technique

Catheters were positioned in the right and left hepatic veins through bilateral femoral vein punctures. After catheterization of the femoral artery, standard pancreatic arteriography was performed with selective injections of low-osmolar con-

Abbreviation: ASVS = arterial stimulation venous sampling.

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trast material into the gastroduodenal, splenic, proper hepatic, and superior mesenteric arteries. Following each arteriogram, calcium gluconate injection, USP 10% (Lyphomed, Rosemont, Ill) (0.01–0.025 mEq Ca\(^{2+}\)/kg), diluted to a 5-mL bolus was rapidly injected through the proximally positioned catheter in each selectively catheterized artery. Calcium gluconate injection, USP 10% contains 4.65 mEq Ca\(^{2+}\)/mL of drug. The standard dose of 0.025 mEq Ca\(^{2+}\)/kg is recommended for individuals of normal body weight, to be adjusted downward to 0.01 mEq Ca\(^{2+}\)/kg in markedly obese individuals (a common occurrence in hyperinsulinemic patients who snack frequently to avoid hypoglycemic episodes). Five milliliter samples of blood were obtained from the right and left hepatic veins prior to the initial injection and at 0.5, 1, 1.5, 2, and 3 minutes after the calcium injection. Plasma from each sample was frozen and stored at −20°C until assayed for insulin.

Insulin levels were determined by means of radioimmunoassay. A twofold rise in the serum insulin concentration of a 30- or 60-second hepatic vein sample was considered sufficient to provide localization of an insulin-secreting tumor within the anatomic region perfused by the injected artery. The gastroduodenal artery supplies the superior pancreatic head and neck, the superior mesenteric artery supplies the inferior pancreatic head and uncinate process, the splenic artery supplies the pancreatic body and tail, and the hepatic artery supplies liver metastases.

RESULTS

In all patients the results of ASVS with injection of calcium gluconate provided true-positive localization of insulinomas.

Patient 1.—Pancreatic arteriography and portal venous sampling were negative: Modest elevations in insulin levels in the portal vein samples (Fig 1a) do not help locate the tumor, and there was no increase in insulin in the splenic (pancreatic body and tail) or superior mesenteric (pancreatic head) veins. A more complete sampling of smaller pancreatic veins could not be accomplished because of the patient’s body habitus (weight, 124 kg; height, 170 cm).Calcium (0.015 mEq Ca\(^{2+}\)/kg) injected into the superior mesenteric artery resulted in a fourfold rise in insulin concentrations in a blood sample taken from the right hepatic vein at 30 seconds (Fig 1b). Injections of calcium into the gastroduodenal, splenic, and hepatic arteries failed to stimulate a release of insulin. At surgery, an islet cell tumor, 1.5 cm in diameter, was located with intraoperative ultrasound (US) in the inferior portion of the pancreatic head. Encuclation of the tumor has corrected this patient’s hyperinsulinism.

Patient 2.—Gastroduodenal arteriography demonstrated a densely staining tumor, 1.5 cm in diameter, in the pancreatic head of this 92-kg patient (Fig 2a). The injection of calcium (0.0163 mEq Ca\(^{2+}\)/kg) into the gastroduodenal artery produced a twofold elevation in insulin levels in the right hepatic vein (Fig 2b) in the 0.5- and 1-minute samples. No changes in serum insulin levels were seen in the blood samples from the hepatic vein at 0.5 and 1 minute following injection of calcium into the hepatic, splenic, or superior mesenteric arteries. At 2 minutes there was a gradual increase in insulin levels in the hepatic vein samples following all selective intraarterial calcium injections. Simultaneous blood samples taken from the left hepatic vein showed similar results (Fig 2c). Secretin was compared with insulin as a secretagogue in this patient; however, there was no increase in serum insulin levels in response to the intraarterial injection of secretin (30 IU) into the gastroduodenal and splenic arteries (Fig 2d). Portal venous sampling (Fig 2e) revealed a 15- to 20-fold increase in insulin levels in the inferior pancreaticoduodenal vein as compared with the insulin level in a peripheral vein. There was also a fivefold increase in insulin levels in one sample from the midportion of the splenic vein. At surgery a 1.0 X 1.5-cm islet cell tumor was enucleated from the deep central portion of the pancreatic head. The patient currently has normal insulin levels with no evidence of hypoglycemia on fasting.

Patient 3.—This patient with multiple endocrine neoplasia type I (MEN I) had hypergastrinemia as well as hyperinsulinism. A three-and-one-half-gland parathyroidectomy had been performed 15 years earlier to alleviate parathyroid hyperplasia. The patient had normal serum calcium levels at the time of ASVS. Superior mesenteric arteriography revealed a 3-mm hypervascular tumor in the vicinity of the pancreatic head and second portion of the duodenum (Fig 3a) that was believed to be a gastrinoma because of its size and location. Splenic arteriography revealed a 1.5-cm hypervascular tumor in the distal pancreas and an equivocal area of tumor staining in the midpancreas (Fig
There was no increase in insulin in hepatic vein samples after injection of calcium into the gastroduodenal artery, but a ninefold rise was seen following splenic artery injection (Fig 3c). Portal venous sampling showed a 10-fold increase in insulin levels in the splenic vein and small veins of the distal pancreatic body as compared with the insulin level in a peripheral vein (Fig 3d). At surgery, two tumors (measuring 15 mm and 18 mm) were removed from the pancreatic body and tail, as well as a 4-mm tumor from the wall of the second portion of the duodenum.

According to the results of immunoperoxidase staining, the duodenal nodule was positive for chromogranin, gastrin, and somatostatin; weakly positive for insulin; and negative for glucagon. The tumor in the pancreatic tail was positive for insulin, chromogranin, and gastrin; weakly positive for somatostatin; and negative for glucagon. The tumor in the pancreatic body was not studied immunocytochemically.

Postoperatively the patient had normal fasting serum glucose and insulin levels. Serum gastric levels were reduced compared with preoperative levels but remained elevated (250–400 pg/dL [2.5–4.0 ng/L]). Thus, he appears cured of hypoglycemia but not of Zollinger-Ellison syndrome.

Patient 4.—Superior mesenteric arteriography demonstrated a 2-cm hypervascular tumor in the uncinate process of the pancreatic head (Fig 4a). The splenic and hepatic arteries could not be catheterized. The examination was compromised by the patient’s weight (200 kg) that impaired fluoroscopic visualization and limited catheter manipulation. There was a sevenfold rise in insulin concentrations from the hepatic vein in the 0.5-minute sample following injection of calcium (0.012 mEq Ca²⁺/kg) into the superior mesenteric artery (Fig 4b). Portal venous sampling was not attempted in this patient because of her obesity. Her hypoglycemia is currently well controlled with diazoxide therapy, and she is on a weight-reduction program in an attempt to lessen the risks of surgery.

**DISCUSSION**

For many years pancreatic arteriography has been the localization procedure of choice for patients with insulin-secreting beta cell tumors of the pancreas. Our own experience (6) prior to 1980 demonstrated that the results of arteriography were correct in 85% of patients, a finding similar to that of other large series (7). During the past 10 years we have encountered a higher prevalence (>50%) of occult insulinomas (1,2), that is, insulinomas with negative imaging studies (arteriography, US, CT, MR imaging). A similar experience has been reported from the Mayo Clinic (8). For the localization of small (<2-cm) occult insulinomas, we have come to rely heavily on portal venous sampling and intraoperative US. However, the skills and experience needed to perform these two studies are not widely available. It is for these reasons that we sought to develop a localization test based on selective intraarterial injection of an insulin secretagogue.

The choice of an agent to stimulate insulin release from a pancreatic beta cell tumor is more controversial than is the use of secretin for gastrinomas. Secretin is widely accepted as the most effective stimulant of gastrin release and is the obvious choice for
performing a diagnostic intravenous test (9) or an intraarterial localization examination (3–5) in patients with Zollinger-Ellison syndrome. Various intravenous provocative agents have been used in the past to aid in the differential diagnosis of functional hypoglycemia from insulinoma. The number of proposed agents suggests that no single one is universally accepted. Tolbutamide (10), glucagon (11), and leucine (12) are each associated with a significant number of both false-positive and false-negative results. On occasion the administration of tolbamamide has caused precipitous drops in plasma glucose levels and has resulted in severe hypoglycemia. In addition, no precedent exists for intraarterial injection of any of these agents.

The use of intravenous calcium to stimulate the release of insulin from islet cell tumors was first described by Gaeke et al (13). Its effectiveness has been confirmed by others (14). A recent publication by Brun et al (15) demonstrated a rise in peripheral insulin levels following the rapid intravenous infusion of calcium (0.01 mEq/kg) in 1 minute in 11 patients with beta cell tumors, with only a minimal response in 16 healthy control subjects. These clear-cut differential results in distinguishing healthy subjects from patients with insulinoma, as well as the physiologic nature of calcium gluconate (16), led us to select it as the intraarterial stimulant.

All four patients tolerated intraarterial injections of these small doses of calcium gluconate without effect. The patients usually noted a warm sensation in the abdomen at the time of injection, but the sensation disappeared rapidly. Serum glucose and calcium levels were monitored during the study in three patients and the levels remained stable. Hypoglycemic symptoms did not develop in any patient. The potential for profound hypoglycemia due to massive insulin release exists, but it can be readily controlled with intravenous glucose. In addition, insulin discharges stimulated by these doses of intraarterial calcium were short-lived, reaching their maximum at 30–60 seconds and usually declining by the time of the 2- and 3-minute samples. Patient 2 noted increased salivation immediately following the injection of calcium into the gastroduodenal artery, perhaps reflecting the release of a salivary secretagogue from the duodenal mucosa. The effect was short-lived. In this patient, as anticipated, intraarterial secretin failed to stimulate release of insulin (17).

Calcium should be administered cautiously to patients with sarcoidosis, renal disease, or cardiac disease, particularly those patients receiving cardiac glycosides. The inotropic effects of cardiac glycosides and calcium are synergistic; therefore, dysrhythmias may occur if both drugs are given together. A total dose of 0.1 mEq/kg calcium (0.025 mEq Ca2+/kg X 4) could be given in our protocol over a 1-hour period since a minimum of 15 minutes always separated the arterial calcium injections. In the study by Brun et al (15) a similar total dose (0.1 mEq Ca2+/kg) was given over 1 minute as an intravenous bolus and produced an abrupt rise in plasma calcium from a baseline of 9.0 mg/dL ± 0.1 (2.24 mmol/L ± 0.02) to a peak of 10.5 mg/dL ± 0.1 (2.61 mmol/L ± 0.02) in the control group.

For unexplained reasons, the patients with insulinoma showed a larger calcium increase (average, 2.5 mg/dL ± 0.2 [0.62 mmol/L ± .05]) than the controls. Because of their body weight, we gave patients 2, 3, and 4 a smaller total dose (0.015 mEq Ca2+/kg X 4, or 0.06 mEq Ca2+/kg over 1 hour), but we still observed diagnostic elevations in serum insulin levels in the hepatic vein when the artery supplying the insulinoma was injected. It seems unlikely that this dose schedule would raise calcium levels. No evidence of such a rise was seen in the three patients whose peripheral calcium levels were monitored. However, in patients with heart disease who are receiving glycosides, a cardiologist should be consulted before intraarterial calcium is administered.

Drugs such as diazoxide or calcium-channel blockers may attenuate the responsiveness of islet cell tu-
Figure 4. Patient 4. (a) Superior mesenteric arteriogram shows a hypervascular tumor, 2.5 cm in diameter (arrows), supplied by an enlarged inferior pancreaticoduodenal artery branch. Its location and blood supply suggest that the tumor is in the uncinate process of the head of the pancreas. (b) Graph illustrates a 10-fold increase in insulin concentration in blood samples taken from the hepatic vein after injection of calcium into the superior mesenteric artery. (Insulin levels are reported in micounit per milliliter; conversion for SI unit picomole per liter is 7.175.)

mors to calcium stimulation. Patient 4 was receiving diazoxide for a few days prior to ASVS and showed a positive response to calcium gluconate stimulation. Nonetheless, we recommend that all such drugs be discontinued prior to testing.

In the present study, three insulinomas (found in patients 2, 3, and 4) were relatively large (>1.5 cm) and were demonstrable by selective arteriography. However, more than 50% of insulinomas currently seen in patients at the National Institutes of Health are arteriographically occult (1,2). In patient 1 the calcium ASVS localized a tumor that had not been demonstrated on the simultaneously performed arteriogram. We had similar results from secretin ASVS for gastrinomas (5,6). Because arterial anatomy (18) is less variable than venous anatomy, localization by means of intraarterial injection may prove more reliable than portal vein sampling, especially if only large portal tributaries are sampled. Patient 2 had a fivefold increase in insulin concentration in blood samples from the splenic vein. This could have been incorrectly interpreted as indicating the presence of an insulinoma if the selective sample from the inferior pancreaticoduodenal arcade, showing a much larger increase, had not been obtained.

The stimulation of hormone release from an endocrine tumor by the intraarterial injection of a secretagogue combines a physiologically based procedure (venous sampling) with an imaging procedure (angiography) and adds only a few minutes to the time necessary to perform the standard angiographic study. Our much larger experience with secretin ASVS in patients with Zollinger-Ellison syndrome suggests that the ASVS technique is superior to portal venous sampling for the localization of gastrinomas. Further experience with calcium ASVS will be necessary to establish its value in locating occult insulinomas.

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References