Insulinoma: Anesthetic implications
DEBBIE GLOYSTEIN WATSON, CRNA, BSN
Albuquerque, New Mexico

While insulinomas are rare, they do occur and present an interesting challenge to the anesthetist. Because of the relative scarcity of literature dealing with the anesthetic management of these tumors, this article was written to review the literature and look at the anesthetic implications. The majority of resources recommend a nitrous oxide, oxygen, relaxant technique.

Insulinoma is a rare functioning endocrine tumor of the beta cells of the pancreatic islet of Langerhans. The clinical picture presented is due to episodes of hypoglycemia induced by increased secretion of insulin by the tumor.

Harris in 1924 was the first to suggest the possibility of spontaneous hypoglycemia, and in 1927 Wilder made the first reported preoperative diagnosis of an insulin-secreting tumor. W. J. Mayo operated on Wilder's patient and found a pancreatic tumor with metastasis to the liver. The biopsy showed an islet cell tumor which was confirmed several weeks later by autopsy, and an assay of the liver showed large amounts of insulin in the tumor tissue. In 1929, Graham first successfully removed a benign insulinoma and the patient experienced full recovery.

It is interesting to find that there are few references in the literature to the anesthetic management of patients undergoing operative removal of these tumors. The purpose of this paper, therefore, is to review the literature and acquaint the nurse anesthetist with the preoperative and intraoperative management of this rare disorder.

Incidence and clinical presentation
Insulinomas occur twice as often in women. They are uncommon in persons below the age of 20 years, with half the patients being more than 50 years old.

The diagnosis of hyperinsulinism is validated by the presence of Whipple's triad: (1) a history of repeated attacks of hypoglycemia, (2) serum blood glucose levels less than 50 mg/100 ml during a symptomatic period, and (3) relief of symptoms by glucose administration.

The metabolism of the brain is dependent on adequate supplies of oxygen and glucose in the blood, because the brain cannot store glucose. Insulinomas liberate large quantities of insulin, which in turn cause glucose levels to fall below critical value. When this happens, the symptoms of hypoglycemia are seen. Initially, these symptoms—tremulousness, tachycardia, nervousness, apprehension, restlessness, palpitations, diaphoresis, diplopia, and ataxia—are due to central nervous system stimulation. Patients not uncommonly demonstrate altered mental states ranging from confusion or abnormal behavior to psychosis, convulsions, and irreversible central nervous system (CNS) damage with coma and/or death.

Hypoglycemic symptoms occur most frequently...
in the early morning before breakfast, in the late afternoon, or several hours after a meal. Excessive insulin secretion may be precipitated by the ingestion of alcohol, fasting, or prolonged exercise, but is not physiological in that the excess secretion continues despite the hypoglycemia. The majority of patients will control their symptoms by increasing their food intake, so it is not uncommon for these patients to be obese.

Because of the nature of the presenting symptoms, it is not surprising that a large number of patients will present to neurologists or psychiatrists and that neurologic or psychiatric diagnoses frequently are made initially, serving to delay definitive treatment.

 Patients with positive familial histories of insulinomas should be investigated for other endocrine abnormalities. In cases of familiar multiple endocrine adenomatosis, insulinoma may be associated with other functioning endocrine tumors of the thyroid, parathyroid, adrenals, and pituitary glands. These patients must also be evaluated for functioning tumors such as pheochromocytoma.

Laboratory and radiographic findings

The diagnosis of insulinoma depends on two factors: (1) a glucose level less than 50 mg/100 ml at the time of hypoglycemic symptoms and (2) the presence of hyperinsulinism, a serum insulin concentration greater than 6 microunits/ml. These two factors are demonstrated in all patients diagnosed. With repeated demonstrations, no further diagnostic procedures are necessary.

However, if the symptoms are not frequent enough, provocative testing must be done. The most reliable test is the prolonged withdrawal of food. Usually overnight fasting is sufficient to induce symptoms. If no attack occurs within 12-14 hours, vigorous exercise may be tried. If these test results still remain normal, then a stimulation test may be administered using tolbutamide, glucagon or leucine.

It has been shown that functioning islet cell tumors contain variable amounts of proinsulin in addition to insulin. C-peptide is the protein link between two insulin chains that form the proinsulin molecule. Before insulin is secreted, the C-peptide is cleaved from proinsulin and secreted with the insulin molecules. Recently, an immunoassay test has been developed that measures C-peptide and can be used to distinguish those patients who use exogenous insulin from those who have an insulin secreting tumor of the pancreas. Exogenous insulin has no C-peptide.

The measurement of circulating proinsulin has also proven to be a helpful tool in diagnosing insulinomas. Patients with insulin-secreting tumors demonstrate, almost without exception, elevated serum proinsulin concentrations.

Kaplan and Lee demonstrated in previous studies that the infusion of calcium also aids in the diagnosis of insulin-secreting tumors. Preoperatively, the infusion of calcium resulted in an increase in serum insulin and a decrease in circulating glucose concentrations. After successful resection of these tumors, the infusion of calcium no longer resulted in changes in serum insulin or glucose levels.

Selective angiography is the method of choice for tumor localization. In 60% of the cases, localization may be accomplished by celiac angiography. A technique has recently been developed in which a catheter is placed transhepatically through a long needle into the portal vein. Blood samples are taken from various small pancreatic veins and hormone determinations are performed on the samples. The location of an area of elevated serum insulin levels has correlated well with the presence of an insulinoma. Once the diagnosis has been established, other functioning endocrine tumors should be sought.

Treatment

Most insulinomas are small, benign adenomas. They may be found in any portion of the pancreas. Occasionally, the tumors are malignant (10%) and may metastasize to the liver. In these instances, solitary tumors may be surgically removable. If widespread metastasis is present, palliative treatment only is initiated. Diazoxide is used because it specifically blocks the release of insulin from the pancreas. A cytotoxic drug, streptozotocin, has specific activity against the beta cells in the pancreas and has been used with some success.

Surgical excision is the only curative procedure for benign insulinomas. About two-thirds of these tumors can be localized during surgery.

Implications for anesthesia

Preoperative preparation. Preoperative preparation of the patient must involve the complete operative team. The preoperative assessment should document all neurologic damage which has occurred as a result of previous hypoglycemic episodes. Special attention should be focused on cerebral function and the peripheral nervous system.

It is also helpful to determine at what glucose level symptoms will occur. With this information, glucose levels can be kept well above symptomatic
CNS levels. The patient should be aware of the risks of hypoglycemia during surgery and the possibility of neurologic damage. Obese patients should be aware of the possibility of postoperative ventilation. An intravenous line should be started on the patient’s admission to the hospital, and drugs inhibiting the release of insulin should be discontinued.

The decision as to the selection of intravenous fluids to be infused prior to surgery is controversial and is dependent on the technique of anesthetic management chosen. This will be discussed more fully later in this article. The most recent study reviewed, however, suggested starting an intravenous glucose infusion (D5W) to maintain plasma glucose in a range of 100-150 mg/dl. It has been demonstrated that some patients will become symptomatic from hypoglycemia after a short fast of two to four hours. Frequent serum glucose determinations are imperative in the management of these patients, particularly those with histories of labile serum sugars. Sufficient recommends that serum glucose be checked every one to two hours and that therapy be adjusted accordingly.

The patient should be on NPO status after midnight the night before surgery. Premedication given should alleviate anxiety, yet allow the patient to remain alert so that he can report his own state accurately before induction of anesthesia.

Intraoperative management. The administration of anesthesia for the removal of these tumors can be very difficult, due to the challenge of trying to maintain a normal blood glucose level. The main concern intraoperatively is the prevention of hypoglycemia which could damage the CNS. Profound hypoglycemia can occur during tumor manipulation, with hyperglycemia following tumor removal. Roizen recommends that these tumors be operated on only at facilities that have a mechanical pancreas as well as specialists in endocrine disorders.

The signs of severe intraoperative hypoglycemia may be masked by anesthesia or by surgical stimulation. For this reason, it is essential to have some method available for rapid blood glucose level determination. This can be achieved in several ways.

The use of Dextrostix® is a rapid means of determining blood glucose levels, but it may be inaccurate in the high and low blood sugar ranges. The Ames Eyetone® is a small spectrophotometer that can accurately measure the color of the Dextrostix® from 50-400 mg/100 ml of blood in 60 seconds. This device can be kept in the operating room and is relatively simple to operate.

The development of an artificial beta cell called Biostator® allows for control of blood glucose through its ability to continuously analyze blood glucose, and through its computerized control system that infuses glucose or insulin in sufficient quantities to maintain a pre-set constant blood glucose level. If it is not possible to have a rapid glucose analyzer, then arrangements must be made with the institution’s laboratory in advance to allow priorities in the determinations of blood glucose levels. The importance of rapid laboratory results must be stressed.

It is recommended that a blood glucose level be checked prior to induction of anesthesia and every 15-30 minutes from then on through the recovery room period. It is important to follow glucose levels through the recovery room period for two reasons: (1) there is a risk of rebound hyperglycemia following tumor resection and (2) multiple adenomas may exist which could result in early postoperative hypoglycemia that was not discovered during the operative procedure. Due to the required frequency of blood sampling, an arterial line is essential. This also allows for rapid analysis of the respiratory status and perfusion pressure.

Signs of hypoglycemia under anesthesia are initially those of sympathetic stimulation evidenced by sweating, tachycardia, hypertension, and/or dilated pupils. Later, the symptoms are due to failure of cerebral metabolism as evidenced by slowing of the EEG, seizures and coma or by arterial hypotension causing cyanosis, sweating and tachycardia.

Any of these signs can be demonstrated while the patient is under anesthesia by hypovolemia, surgical stimuli and the like. The only certain sign of hypoglycemia is a low blood glucose level, which further emphasizes the importance of numerous rapidly analyzed blood samples.

The selection of an anesthetic technique will vary with individual patient requirements. It must be remembered that general anesthesia may affect glucose concentrations by inducing a state of glucose intolerance, increasing hepatic glycogenolysis, increasing sympathetic activity, and causing changes in renal function and plasma levels of corticosteroids which may alter carbohydrate metabolism.

Thiopental should be used cautiously for the induction of anesthesia because its hypotensive action could intensify the normal signs displayed should the patient become profoundly hypoglycemic at the same time. Ketamine is contraindicated because it increases oxygen consumption by the

December 1987/Vol. 55/No. 6 541
brain and in turn increases the cerebral metabolism of glucose.5

The majority of the sources reviewed recommended using a nitrous oxide, oxygen, relaxant technique for this procedure. This technique combines adequate relaxation with light anesthesia and allows for immediate recovery of consciousness at the end of the procedure. One source pointed out that this technique often requires a high concentration of nitrous oxide, the effects of which must be considered in patients undergoing prolonged retroperitoneal dissection.5

The volatile anesthetic agents all tend to cause hyperglycemia, with the exception of halothane, which results in an increased sensitivity to insulin.5,6,11-13 For this reason, their use has been relatively discouraged.14 It is thought to be unwise to use agents that have actions that may produce complications intraoperatively and postoperatively.15 Hypocarbia should be avoided intraoperatively because of the decrease in cerebral blood flow and in glucose delivery.

Recent research has suggested that if an inhalation agent is selected, enflurane may be the anesthetic of choice for these tumors.5,11 Enflurane significantly decreases the cerebral metabolic rate as reflected by the CMRO2 (consumption of oxygen by the brain). In theory, a decrease in oxygen consumption would reflect a decrease in cerebral metabolism of glucose.5 Animal studies have also demonstrated a greater inhibition of insulin release with enflurane, although the effects of this agent on active insulin-producing tumors is not known.5,11

As previously mentioned, the maintenance of adequate glucose levels intraoperatively is the main anesthetic concern. This can be done in several ways. Classically, an IV of 5% dextrose is begun the night before surgery and continued throughout the procedure to eliminate any intraoperative hypoglycemia.

Another method is to keep the patient slightly hypoglycemic throughout the procedure in order to allow for rapid assessment of the adequacy of pancreatic resections. If the entire tumor is removed one would expect to see a rapid rise in glucose levels; thus a rise in these levels after tumor removal is suggestive of adequate resection.16 It should be noted that Tutt and associates demonstrated that one quarter of the patients they studied failed to show a hyperglycemic rebound until approximately 90 minutes had elapsed after tumor excision. It was their opinion that intraoperative glucose monitoring cannot be relied upon to document removal of all hyperfunctioning tissue.19

Using this method, an IV solution containing dextrose is started the night before surgery and glucose levels are checked every one to two hours thereafter, with intermittent infusion of dextrose given to maintain glucose levels at about 50 mg or at whatever levels were shown preoperatively to cause CNS symptoms.5

Intraoperatively, monitoring should include ECG, arterial line, central venous pressure (CVP) monitoring with at least one other large bore IV, Foley catheter, temperature probe and a method to rapidly determine glucose levels.

It is important to keep in mind that if blood transfusions are required intraoperatively, the plasma levels obtained may be invalid. This is because blood contains CPD, an anticoagulant preservative. When transfused, the dextrose in CPD may cause an abrupt increase in plasma glucose levels. If this were to occur at the approximate time the tumor were removed, it could simulate a hyperglycemic rebound.10

Postoperative considerations. After surgical removal of the tumor, blood sugars may become high enough to require short-term insulin therapy. Usually this is due to the fact that the anti-insulin hormones like glucagon, growth hormones and glucocorticosteroids persist at higher levels for several days following tumor removal.10 Unless as much as 90% of the pancreas has been removed, this hyperglycemia is usually transient. Hypoglycemia following surgery should alert one to the possibility that the tumor was not found or that multiple other insulinomas are still present.5

Summary
While the incidence of insulinoma is rare, a basic understanding of the tumor and its effect can facilitate safe intraoperative care of patients with this condition.

REFERENCES


**AUTHOR**

Debbie Gloystein Watson, CRNA, BSN, graduated from the University of Nebraska Medical Center with a BSN degree. She received her anesthesia education at the University of Texas Health Science Center at Houston and is currently completing her MSN degree. She is employed as a staff nurse anesthetist by Lovelace Medical Center in Albuquerque, New Mexico.