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Treatment of Insulinoma in Dogs, Cats, and Ferrets

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Insulinoma, or functional beta-cell tumor, originates from the islet cells of the endocrine portion of the pancreas. Insulinoma has been described in dogs, cats, ferrets, and other mammalian species. Although insulinoma cells produce a variety of polypeptides, most patients with insulinoma are examined because of clinical signs related to hyperinsulinism.

Insulinoma has been reported in dogs ranging from 3½ to 15 years old but is most common in dogs 8 to 12 years old. Insulinoma is rare in cats; five cats have been reported, ranging in age from 12 to 17 years. Insulinoma is common in domestic ferrets. The median age of ferrets with insulinoma has been reported to be 5 years, and the age range from 2 to 7 years. No sex predilection has been reported in dogs, but male ferrets seem to be affected more commonly than females.

Clinical Signs

Clinical signs in animals with insulinoma are caused by hyperinsulinism, which leads to hypoglycemia. In response to a low blood glucose concentration, catecholamines, glucagon, cortisol, adrenocorticotropic hormone (ACTH), and growth hormone are released. In clinically normal animals, when blood glucose drops, these hormones, in conjunction with a decrease in circulating insulin, help prevent progressive and potentially dangerously low blood glucose concentration. In animals with insulinoma, insulin is secreted even in the face of hypoglycemia and the increase in the counterregulatory hormones listed above. In these patients, the blood glucose is not stabilized but continues to fall.

Dogs with insulinoma may be examined because of clinical signs related to the following: (1) neuroglycopenic symptoms produced by glucose deprivation of the central nervous system, (2) adrenergic symptoms caused by catecholamines such as epinephrine, or (3) a combination of these signs. The most common complaint for dogs with insulinoma is seizures. Other signs include collapse, lethargy, weakness, ataxia, mental dullness, muscle fasciculation, trembling, and nervousness. Similar signs have been reported in cats with insulinoma. Peripheral neuropathy in association with insulinoma and hypoglycemia has been reported rarely in dogs and in a cat.

Ferrets with insulinoma also commonly show signs of weakness and lethargy. As in dogs, these symptoms may be episodic. However, seizures are relatively uncommon in this species. Ptyalism is a clinical sign associated with insulinoma in ferrets that has not been described in dogs. The cause of this sign is not known, but ptyalism in ferrets may indicate nausea.

Diagnosis

A complete history may lead the clinician to suspect that a patient's presenting symptoms are related to hypoglycemia and thus consider insulinoma as a differential diagnosis. A plasma glucose concentration of 40 mg/dl or less supports the conclusion that the signs are caused by hypoglycemia. If administration of glucose relieves symptoms such as weakness, disorientation, seizures, or trembling, the clinician may conclude that these symptoms were caused by hypoglycemia. This response may be seen in animals with hypoglycemia for any reason and is not diagnostic of insulinoma. Other causes of hypoglycemia in mature animals include an extrapancreatic tumor, severe hepatic dysfunction, toxemia of pregnancy, sepsis, insulin overdose, hypoadrenocorticism, starvation, malabsorption, beta-cell hyperplasia, and hunting dog hypoglycemia. Many of these differential diagnoses can be ruled out quickly during the initial history and physical examination. After consideration of these diseases is eliminated, insulinoma should be considered seriously in a mature patient with clinical signs of hypoglycemia.

Hyperinsulinism is best diagnosed by the interpretation of serum insulin and glucose concentrations obtained from the patient at the same time. If the clinician suspects hyperinsulinism at the time of initial examination of an animal with signs associated with hypoglycemia, serum samples for insulin levels can be obtained at that time. If attempts are made to document hyperinsulinism at a later date, samples should be obtained after fasting when the glucose is less than 50 mg/dl (Feldman and Nelson, 2004). Patients suspected of having hyperinsulinism must fast under supervision to allow intervention should signs of hypoglycemia occur. Samples for serum glucose determination should be collected in sodium fluoride. The insulin radioimmunoassay must be validated for the species of interest. Reference ranges vary among laboratories and species.

A high insulin concentration in any animal with concurrent hypoglycemia is consistent with hyperinsulinism. If a hypoglycemic patient has an insulin concentration within the reference range, the animal again should fast and the test should be repeated when two consecutive serum glucose readings of 50 mg/dl or less are obtained.

If the patient is consistently hypoglycemic, an insulin level within the normal range is considered inappropriate, and the patient likely has hyperinsulinism.

A basic medical workup (complete blood count, serum chemistry profile, and urinalysis) generally reveals no abnormalities, and thoracic radiography only rarely reveals abnormalities related to insulinoma. When possible, abdominal ultrasound should be performed in dogs and cats with suspected insulinoma. It can be difficult to detect small pancreatic nodules via ultrasound, but it may be helpful in identifying abdominal metastases. In all species, abdominal ultrasonography may help rule out other neoplasms as a cause of hypoglycemia. In dogs, computed tomography (CT) can identify accurately pancreatic nodules, and this procedure may be helpful in surgical planning.

Although hyperinsulinism can be confirmed by clinical pathologic testing, histologic examination is required for a definitive diagnosis of insulinoma. Exploratory celiotomy is recommended in all patients with hyperinsulinism if the owner wishes to pursue treatment of a pet with insulinoma.

Therapy

Emergency Treatment

All patients with serious neurologic signs referable to hypoglycemia should be treated immediately by intravenous administration of a 50% dextrose solution. Clinicians give 1 to 5 ml slowly over 10 minutes. If the animal responds clinically, continuous intravenous administration of fluids with a 5% dextrose solution should be considered. Some clinicians prefer to dilute the initial dose in 5% dextrose or sterile water to create a 20% to 25% solution before injection and thereby reduce the osmolality of the infused solution.

Regardless of the glucose concentration chosen to be administered in an emergency, the goal of glucose administration is not to establish a normal serum glucose level but to eliminate clinical signs related to hypoglycemia.

When glucose is administered intravenously in patients with insulinoma, the tumor may be stimulated to release massive amounts of insulin, leading to severe hypoglycemia. This may result in a vicious cycle of the patient receiving larger volumes and more frequent dosing of intravenous dextrose even as clinical signs become more severe. In dogs with insulinoma, intravenous glucagon may be considered if the low serum glucose and associated clinical signs are not reversed with infusions of dextrose. Glucagon stimulates hepatic gluconeogenesis and glycogenolysis. According to package directions 1 mg of lyophilized glucagon USP should be reconstituted according to package directions and mixed with 1 L of 0.9% saline solution. This resulting 1 µg/ml solution is given at 5 to 10 ng/kg/min. The dosage is adjusted as needed to maintain the serum glucose at a concentration of 50 to 100 mg/dl. When the dog is able to eat and maintain its own blood sugar and/or other surgical or medical therapy is used to treat the insulinoma, the glucagon infusion may be tapered slowly over 1 to 2 days as the serum glucose and clinical signs are monitored (Fischer et al, 2000).

Owners who witness a hypoglycemic seizure may be instructed to rub a sugar solution (corn syrup) on their pets' gums. Most animals respond rapidly. Owners should be warned not to place their hands directly into the mouth of an animal having a seizure and not to pour a sugar solution into the mouth of an unconscious pet.

If the animal responds to intravenous or oral glucose administration, it then should be fed a small, high-protein meal and kept as quiet as possible. Owners who notice a pet is becoming weak may prevent a hypoglycemic seizure by feeding.

Prolonged hypoglycemia can cause focal laminar and pseudolaminar necrosis of the cerebral cortex, which can result in an acquired seizure disorder. Anticonvulsants may be required long term for some animals recovering from hypoglycemic seizures.

In an emergency situation, if seizures persist despite the correction of hypoglycemia, cerebral hypoxia and edema may be responsible. Glucocorticoids, mannitol, or both, should be administered. Diazepam and phenobarbital may be required to control the seizures. The clinician also should consider the possibility that a condition other than hypoglycemia may be the cause of the seizures.

Uptake of glucose by cells is accompanied by the intracellular transport of potassium. The serum potassium concentration should be monitored in patients receiving dextrose infusions and supplemented in most cases (e.g., 16 mEq KCl/L of fluid). This is particularly important for animals unable to eat.

Surgery

Surgery is the treatment of choice for the initial long-term management of animals with insulinoma. Exploratory celiotomy is useful in confirming the diagnosis, staging the patient, and removing the neoplastic tissue. All identifiable pancreatic nodules should be removed, and metastatic lesions should be resected whenever possible. When possible, pancreatic masses should be removed by partial pancreatectomy. Survival time for dogs undergoing partial pancreatectomy is longer than that for those undergoing nodulectomy. Partial pancreatectomy can be performed by the suture-fracture technique, the dissection-ligation technique, or through the use of an electrothermal bipolar vessel-sealing device (LigaSure V). The bipolar vessel-sealing device (BVSD) denatures collagen and elastin within vessel walls and thus safely seals tissue and vessels while causing less tissue damage than is seen with the higher temperatures used in traditional cautery. Using the BVSD to perform partial pancreatectomy in dogs results in shorter surgical times and a decreased incidence of postoperative pancreatitis when compared with dogs undergoing the suture fractionation technique. The BVSD is likely more effective in sealing pancreatic ducts during partial pancreatectomy and thus minimized the leakage of pancreatic juices in to the remaining tissue that could cause local or generalized pancreatitis (Wouters et al, 2011). Whether metastatic lesions are visible, biopsy of the liver and mesenteric lymph nodes is recommended for staging.

Localizing a pancreatic nodule can be difficult, especially in dogs. In ferrets, nodules are less challenging to

find. In cats with insulinoma, all those reported have had a pancreatic nodule identified. The entire pancreas should be palpated carefully and the liver and mesenteric lymph nodes visualized. Intravenous infusion of methylene blue has been suggested as a means of enhancing the visibility of insulinomas, but this procedure has not been evaluated in a large study, and methylene blue can cause serious Heinz body hemolytic anemia. It is not recommended routinely but can be given intraoperatively if no nodule can be identified. The surgeon must allow 30 minutes for tumor staining to occur. Intraoperative ultrasonography is safe, but the accuracy of this technique depends on the experience of the ultrasonographer. If no mass has been imaged preoperatively and equipment is available, it is prudent to plan for intraoperative ultrasound.

When a nodule cannot be identified intraoperatively, biopsy specimens should be taken from the pancreas, liver, and mesenteric lymph nodes. In dogs, insulinoma develops within the right and left pancreatic lobes with equal frequency, and occult nodules are most common in the body of the pancreas. Thus random removal of pancreatic tissue offers no advantage.

Nodules were identified during surgery in the five cats with insulinoma that have been described. One of these cats had a relapse in clinical signs 6 days after surgery, suggesting that occult nodules were present. A second cat, which had a large tumor, died during the immediate postoperative period. In each of the other three cats, a single nodule was identified and removed.

In ferrets, multiple pancreatic nodules are more common than solitary nodules. Occult insulinoma appears to be rare in ferrets. Full abdominal exploratory celiotomy is recommended in all species but is especially important in ferrets. Nonpancreatic neoplasia has been identified frequently in ferrets undergoing celiotomy for insulinoma. Adrenal tumors are seen most commonly.

The serum glucose concentration should be stabilized before induction of anesthesia and surgery. Although it is not necessary for the serum glucose to be in the normal range, ideally the measured levels should be stable and the patient should have experienced one or more days without seizures before surgery. Frequent feedings, continuous intravenous infusion of dextrose solution (5% dextrose or higher), or both, are the best ways to accomplish this. If these methods are unsuccessful, more aggressive medical management (see section on medical management) should be considered. In dogs, as mentioned above, a constant rate infusion of glucagon can be considered to stabilize refractory patients.

Monitoring the serum glucose concentration throughout and after surgery is important. Surgical manipulation of insulinoma can enhance the release of insulin from the tumor(s). Anesthesia masks the signs of neuroglycopenia; thus the only way of preventing serious hypoglycemia is to monitor the patient carefully and administer dextrose as needed. While the surgeon is manipulating the pancreas and any metastatic lesions, the serum glucose concentration should be evaluated every 10 to 20 minutes. Because the patient may require several different concentrations of dextrose-containing solutions throughout the surgery and postoperative period, such solutions should be prepared in small quantities and supplies should be close at hand.

After surgery, the glucose concentration should be monitored every 30 to 60 minutes for the first 3 to 4 hours, and then every 2 to 4 hours until the glucose concentration has stabilized and the appropriate concentration of dextrose solution has been selected. The patient may have hyperglycemia after surgery, and intravenous fluids without dextrose may be appropriate.

In dogs, the most common postoperative complication is pancreatitis. Documented or suspected pancreatitis has been reported in cats and ferrets as well postoperatively. During surgery, the pancreas should be handled gently, and the surgeon should pay special attention to preserving the blood supply to the pancreas when performing a partial pancreatectomy. Use of an electrothermal BVSD (LigaSure V) may reduce the risk of pancreatitis in dogs undergoing partial pancreatectomy. Intravenous administration of fluids (e.g., lactated Ringer's solution with 5% dextrose) before, during, and after surgery helps to ensure adequate pancreatic circulation. Dogs should be treated as if they have pancreatitis after pancreatic surgery and held off food and water for 36 to 48 hours after the procedure, or longer if clinical signs of pancreatitis are apparent. Small amounts of water and bland food may be started on the second or third day after surgery.

Postoperative pancreatitis and postoperative hyperglycemia appear to be uncommon complications in ferrets. Ferrets may be fed 24 hours after surgery. The prevalence of postoperative complications in cats undergoing surgery for insulinoma is not known, in part because pancreatitis is difficult to diagnose in cats due to variable clinical signs (see Chapter 138). The conservative postoperative management described earlier also is recommended for cats.

In some animals, the high concentration of circulating insulin secreted by the tumor suppresses the function of normal beta cells, leading to hyperglycemia once the insulin-producing tumor is removed. As function of the beta cells returns, postsurgical hyperglycemia is resolved. If treatment with insulin is required after resection of an insulinoma, the clinician and the owner should be aware that endogenous insulin eventually may be produced either by the normal beta cells or by recurrent tumor cells. The owner should monitor glucose in the urine several times per week, and serum glucose should be checked at least monthly to avoid an iatrogenic hypoglycemic crisis.

When a patient that has previously undergone surgery for insulinoma begins to show signs of hypoglycemia, a second surgery may be attempted or medical management instituted. If all visible tumor can be resected again, animals may remain symptom free for a number of additional months. It appears that ferrets whose first symptom-free interval was several months are most likely to benefit from a second surgery.

Medical Management

Chemotherapy

Specific antineoplastic therapy can be considered in animals in which all of the tumor cannot be resected and in animals that have undergone previous surgery and again are showing signs of hypoglycemia. Just more than

half of dogs with insulinoma have metastases at the time of diagnosis, so it is reasonable to discuss the possibility of follow-up chemotherapy with owners before surgery. Chemotherapy should be given only to patients with a confirmed histologic diagnosis of insulinoma.

Streptozotocin (Zanosar) is a chemotherapeutic drug that selectively destroys pancreatic beta cells. When given alone, this drug causes severe, acute renal failure in dogs. The drug can be administered safely if given with aggressive saline diuresis. Normal saline should be given at 18 to 20 ml/kg/hr for 7 to 8 hours. Streptozotocin is administered in saline solution over the fourth and fifth hours at a dosage of 500 mg/m^2 intravenously. In the published reports of dogs treated with this drug, butorphanol was administered at the end of the 7-hour period. In addition to butorphanol, the authors currently recommend that dogs receiving streptozotocin receive maropitant citrate (Cerenia) orally or subcutaneously at the beginning of the saline infusion and continue it daily for 3 to 4 days after chemotherapy. Care should be taken to ensure that the dog does not become dehydrated in the days after therapy. Intravenous fluid support is recommended strongly if the dog is vomiting or is not drinking adequately in the days after streptozotocin.

As with all chemotherapy agents owners should sign an informed consent form before treatment with streptozotocin is initiated. It should be used in dogs with known metastatic disease or those with clinical signs of hypoglycemia. Ideally, a baseline abdominal ultrasound or CT scan should be performed before any chemotherapy for insulinoma is initiated. This allows an assessment of tumor size during the course of treatment. Such imaging should be repeated at 8- to 12-week intervals. Streptozotocin may be repeated every 3 weeks. Treatment is discontinued in cases of tumor progression, resistant or recurrent hypoglycemia, or drug toxicity. Giving streptozotocin every 3 weeks in all dogs with insulinoma may be impractical. In dogs that tolerate the drug, two to four treatments are recommended initially. Ideally, streptozotocin should be administered at least once after hypoglycemia resolves. The intertreatment interval then can be increased to 4 to 6 weeks or streptozotocin may be used as needed. Streptozotocin may induce diabetes in some individuals, but the chemotherapy drug may be given along with appropriate insulin therapy if gross disease is still present. No reports have described the use of streptozotocin in cats or ferrets with insulinoma. Further study of this agent is needed in all species.

Doxorubicin has been reported effective in a few human patients with insulinoma. This drug is used commonly in veterinary oncology, but its efficacy against insulinoma is unknown. It generally is well tolerated by dogs, cats, and ferrets and thus could be considered for use as a single agent or in combination with other drugs for the treatment of insulinoma. The accepted dosage for doxorubicin in dogs is 30 mg/m^2 given intravenously every 3 weeks. For cats 25 mg/m^2 or 1 mg/kg is recommended every 3 weeks. In ferrets, 1 mg/kg given intravenously every 3 weeks is recommended. At this time, doxorubicin is the only drug discussed here known to be safe in cats and ferrets and thus would be reasonable to consider for further study in client-owned animals.

Combination protocols of streptozotocin with doxorubicin are used in the treatment of human patients with insulinoma. Given the aggressive nature of the disease in veterinary patients, such protocols merit further investigation in animals.

Symptomatic Therapy

Symptomatic therapy is recommended for animals showing signs of hypoglycemia and that previously have undergone surgery and for those whose owners have declined surgery.

Animals with insulinoma should be fed a diet high in protein, fat, and complex carbohydrates. Simple sugars, often contained in semimoist pet foods, should be avoided. Dogs should be fed small meals three to four times daily. Cats may be fed free choice if they do not become obese. Ferrets may be fed free choice. Exercise should be controlled and owners should attempt to limit excitement in these pets.

Glucocorticoids are recommended when frequent feedings are no longer successful in controlling clinical signs. These drugs inhibit glucose uptake in the peripheral tissues and stimulate glycogenolysis. Prednisone (or prednisolone) is started at 0.25 mg/kg q24h PO. The dosage may be increased gradually as needed to control clinical signs or may be decreased if the disease is well controlled at the initial dosage. The clinician should be aware that dosages of 1.1 mg/kg or higher given twice daily are considered immunosuppressive.

Diazoxide (Proglycem) is a nondiuretic benzothiadiazide that decreases insulin secretion, promotes gluconeogenesis and glycogenolysis, and inhibits the cellular uptake of glucose. Diazoxide can be difficult to obtain in the United States; however, reputable compounding pharmacies often can supply this drug. The recommended starting dosage is 5 mg/kg q12h PO. As with prednisone, the dosage may be increased as needed to control clinical signs. The maximal recommended dosage is 30 mg/kg q12h PO.

The most common side effects of diazoxide are anorexia, vomiting, and diarrhea. These signs may be avoided or lessened by giving the medication with food. Ferrets find the diazoxide suspension distasteful, but because only small volumes are required, owners usually are able to administer it. Other potential side effects of diazoxide are hyperglycemia, bone marrow suppression, and sodium retention. Because of the potential for sodium and fluid retention, this drug should be used with caution in patients with heart disease. Diazoxide is metabolized by the liver. Patients with hepatic dysfunction may exhibit side effects at lower dosages than do normal animals.

Thiazide diuretics enhance the effects of diazoxide. Hydrochlorothiazide given at a dosage of 1.0 to 4.0 mg/kg q24h PO can be used in combination with diazoxide in patients that have not responded to diazoxide alone or that have progression of their clinical signs despite other treatments. The combination of diazoxide and hydrochlorothiazide likely may offer only modest improvement of glucose control in patients with insulinoma.

Somatostatin is a polypeptide hormone that inhibits the secretion of insulin, glucagon, gastrin, secretin, and motilin. Octreotide acetate (Sandostatin) is a long-acting somatostatin analog that can be used in the management of patients with insulinoma.

Reports on the use of octreotide acetate in veterinary patients are limited. Of the eight reported dogs with insulinoma that were refractory to other forms of treatment, six dogs exhibited improvement in their clinical signs. In three of these dogs, a decrease in serum insulin concentration was documented. One dog acquired diabetes mellitus, but no other important side effects were observed. To the authors' knowledge, no reports have been published on the use of octreotide acetate in ferrets or cats with insulinoma. The authors have used octreotide acetate to treat one ferret that was refractory to other forms of treatment, and clinical signs improved, although other clinicians have reported patients that have not responded. The recommended dosage is 1 to 2 μg/kg q8-12h SC. This drug is relatively expensive but may be practical for use in ferrets because of their small size.

Currently, there is no way of predicting which patients will respond to octreotide acetate. Metastatic lesions may express fewer somatostatin receptors than the primary mass, so octreotide may be less effective in patients with advanced disease. This agent does appear safe and can be administered by owners at home; thus it should be considered for the treatment of animals with insulinoma refractory to or unable to tolerate traditional medical or surgical therapy.

Prognosis

The short-term prognosis for dogs with insulinoma is good, although most will die of this disease. Clinicians should discuss the difference between survival and symptom-free interval with owners. Although survival time is somewhat dependent on the stage of the disease and the success of surgery, it also depends on clients' willingness to follow up with symptomatic therapy once signs of hypoglycemia return. The median survival time for dogs with insulinoma that undergo surgery is approximately 1 year. In one study, dogs that had complete resection of all visible disease via partial pancreatectomy had a mean survival time of 17.9 months (range, 3 to 51 months). The stage of disease is an important prognostic factor. Only 20% of dogs with metastatic disease live longer than 1 year. Stage of disease is also prognostic for symptom-free interval. Dogs with tumors confined to the pancreas have a reported median symptom-free interval of 14 months, whereas dogs with more advanced disease have a median symptom-free time interval of 1 month. The prognosis for survival in dogs treated medically is not known. In one study in which dogs with unresectable metastatic disease were treated with diazoxide, the mean survival time was approximately 8 months. Even in dogs in which all disease cannot be removed, cytoreduction may reduce the frequency and severity of hypoglycemic episodes.

The prognosis for cats with insulinoma cannot be determined accurately. Two of the five cats described that underwent surgery died in the perioperative period. One cat remained free of clinical signs for 7 months after surgery, and one had recurrence of clinical signs 10 months postoperatively. The cat that was symptom free for 10 months postoperatively survived an additional 8 months while being treated with prednisone. Intermittent seizures persisted during this time. The longest surviving cat reported in the literature lived 32 months after surgery. In this individual, the tumor was excised easily and did not have an aggressive histologic appearance.

As with dogs, it appears that surgery or a combination of surgical and medical treatment benefits most ferrets with insulinoma. The reported median postoperative survival time of ferrets with insulinoma is 15.8 to 17 months. Survival times for ferrets undergoing partial pancreatectomy are superior to those for ferrets undergoing nodulectomy. The reported median symptom-free interval after surgery is 8 to 11 months. Ferrets that do not undergo surgery or that have a relapse of their clinical signs after surgery may survive several months with medical treatment, but their clinical signs rarely resolve completely. One study reported the mean survival for ferrets treated medically only was approximately 6 months.

In dogs, the Ki67 index (a marker of cellular proliferation) has been shown to have prognostic significance. Dogs with a positive Ki67 index experienced shorter symptom-free intervals and survival times than dog whose tumors had a negative Ki67 index. The role of immunohistochemistry in predicting outcome for dogs, cats, and ferrets with insulinoma likely will continue to be evaluated as a tool for clinicians.

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