Ferret Insulinoma: Diagnosis and Treatment

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ABSTRACT:
Pancreatic neuroendocrine carcinoma is one of the most commonly diagnosed neoplasms in domestic ferrets (Mustela putorius furo). Typical clinical signs relate to hyperinsulinemia-induced hypoglycemia and can include lethargy, collapse, hindlimb weakness, and, in severe cases, seizures. Tentative diagnosis is made based on history, clinical signs, and blood glucose concentration (<60 mg/dl). Definitive diagnosis is made by histopathologic examination of the pancreatic nodule(s). Therapeutic options include medical and/or surgical management, with surgery being the treatment of choice. Metastasis of insulinoma to other organs is rare in ferrets, but recurrence is likely.

Beta cell tumors of the pancreas originate from specialized neuroendocrine cells that synthesize and secrete peptide hormones. Tumors that develop from these cells are named for the hormone they secrete (e.g., insulinoma), and clinical signs are attributable to the peptide that is produced. Insulinomas are insulin-secreting pancreatic beta cell tumors that are particularly common in ferrets. Based on a recent review of 1,525 neoplasms diagnosed in ferrets over 10 years by the Armed Forces Institute of Pathology (Washington, DC) and a commercial pathology laboratory, insulinoma was the most common neoplasm in ferrets.¹ These findings are similar to others regarding neoplastic diseases in ferrets.²–⁴

CLINICAL SIGNS
Most ferrets with insulinoma begin exhibiting clinical signs around 4 to 5 years of age; however, ferrets as young as 2 years of age have been diagnosed with insulinomas.⁴–⁶ A functional pancreatic islet cell tumor was also reported in a 2-week-old ferret.² There is no reported sex predilection, although males have been overrepresented.⁴–⁶ These functional tumors overproduce insulin, resulting in hypoglycemia, and typical clinical signs can include lethargy, weight loss, stuporous staring, hindlimb weakness, and ataxia (i.e., neuroglycopenic manifestations). Also, signs of possible nausea exhibited by pawing at the mouth and ptyalism, unique to ferrets with insulinoma, can be seen. Some ferrets violently and repeatedly scrape the roof of their mouth, and owners perceive this as ingestion of a foreign body or foul-tasting substance. Ferrets with severe hypoglycemia may be recumbent or having seizures during presentation. In clinically normal mammals, release of glucagon, cortisol, epinephrine, and growth hormone occurs in response to low blood glucose concentration, and these hormones, in conjunction with decreased circulating insulin concentration, prevent development of severe hypoglycemia. We speculate that in ferrets with insulinoma, circulating insulin concentration remains high and blood glucose concentration...
continues to drop, regardless of negative feedback inhibition. As in some dogs, it is theorized that because of the gradual and chronic decline in blood glucose concentration, some ferrets can metabolically adapt to living in a hypoglycemic state and thus show only signs of lethargy. Unlike insulinomas found in cats or dogs, these neoplasms rarely metastasize to other organs, and patients may survive a fairly long time when treated.

**DIAGNOSIS**

Tentative diagnosis for insulinoma is based on history, suggestive clinical signs, and hypoglycemia (<60 mg/dl). In one study, all 57 ferrets with confirmed insulinoma had a blood glucose concentration less than 60 mg/dl. In another report, a mean blood glucose concentration of 44 mg/dl was seen in ferrets with functional islet cell tumors. Insulinomas are characterized clinically by the Whipple triad:

- Episodic hypoglycemia
- Neurologic dysfunction temporally related to hypoglycemia
- Dramatic reversal of neurologic abnormalities by administering glucose or feeding

Although prolonged anorexia or starvation, sepsis, liver disease, and other neoplasms can result in a low blood glucose concentration, insulinoma is most likely in a ferret. In ferrets showing clinical signs during presentation, blood glucose concentration can be quickly assessed with a digital glucometer. If the patient is clinically normal during presentation but shows signs of lethargy at home, blood samples should be collected after a 3- to 4-hour fast. Fasting blood glucose in normal ferrets is 90 to 125 mg/dl. Clinically, handheld glucometers have shown a wide margin of error (up to 20 mg/dl), so a properly handled blood sample should be submitted to a diagnostic laboratory if the blood glucose concentration is lower than 60 mg/dl. Samples should be immediately centrifuged and separated to prevent falsely decreased glucose concentration due to red blood cell metabolism. Because of the size of some patients, sampling should be kept to a minimum to preserve blood vessels and minimize blood loss.

If the patient is hypoglycemic based on in-house testing, a blood sample can also be submitted to determine absolute insulin concentration. When blood glucose concentration is low, insulin secretion is normally inhibited; thus a presumptive diagnosis of insulinoma is made when serum insulin concentration is elevated in the presence of hypoglycemia. Reported serum insulin concentrations in normal ferrets are 5 to 35 µU/ml and 4.6 to 43.3 µU/ml. Ferrets with insulinomas have had insulin concentrations of 108 to 1,738 µU/ml. However, a normal insulin concentration with hypoglycemia does not necessarily rule out insulinoma, and an elevated insulin concentration without hypoglycemia is not diagnostic of insulinoma. In one study, plasma insulin concentrations were high in 40 of 48 ferrets with confirmed insulinoma that were tested. Because a ferret with insulinoma can have a normal or even low insulin concentration, insulin concentration testing is controversial and many clinicians do not use it. The lack of reliability of insulin concentration testing also makes the insulin:glucose and amended insulin:glucose ratios difficult to interpret, and these tests can have a high incidence of false-positive results. It is important to note that insulin concentration, like glucose concentration, can be affected by delayed centrifugation of blood samples.

Provocative tests involving administering glucagon, glucose, calcium, and leucine have been used in other species, but their use has not been reported in ferrets. These tests have not been shown to be any more diagnostic than absolute insulin concentration because islet cell tumors vary in their response and testing may result in prolonged hypoglycemia. In addition, a report of a dog with confirmed insulinoma suggested that a single low
measurement of fructosamine may indicate persistent hypoglycemia and may be helpful, in conjunction with an insulin measurement, in diagnosing insulin-secreting tumors. Fructosamine concentration has not been studied in ferrets but may prove to be clinically useful.

Blood samples should also be submitted for a complete blood count and biochemistry profile to identify underlying conditions and for preanesthetic evaluation if surgical treatment may be indicated. Complete blood count findings are usually normal, although leukocytosis, neutrophilia, and monocytosis have been seen. Other than hypoglycemia, abnormalities in the biochemical profile can include elevated alanine aminotransferase and alkaline phosphatase concentrations, which are typically nonspecific findings.

Insulinomas are typically small and may even be microscopic. Therefore, diagnostic imaging such as radiography and ultrasonography is usually unrewarding; however, if insulinomas are large (Figure 1) or have metastasized to adjacent liver or lymph nodes, changes may be seen during ultrasonographic examination. In one report, pancreatic nodules were identified in 5 of 23 ferrets that had abdominal ultrasonography. Metastasis of insulinoma to the lungs has not been reported.

Definitive diagnosis of insulinoma is made by histologic examination of pancreatic biopsy specimens. These masses are typically well circumscribed and consist of a monomorphic population of polygonal to cuboidal epithelial cells arranged in pseudorosettes and nests on a fine fibrovascular stroma (Figure 2). This histologic pattern is typically called neuroendocrine carcinoma.

**TREATMENT**

Therapeutic options for treating insulinoma in ferrets include medical or surgical management or, sometimes, both. The choice of therapy depends on severity of the disease, clinical signs, preexisting disease, and owner preferences and finances.

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**The biologic behavior of insulinoma in ferrets is different than that in other species.**
Medical Management

Medical therapy is aimed at controlling clinical signs of hypoglycemia and resulting altered metabolism. It does not affect or stop progression of the pancreatic tumor. Glucocorticoids such as prednisone are typically the initial drugs of choice, especially in ferrets with mild to moderate clinical signs. Prednisone acts by increasing both hepatic gluconeogenesis and peripheral blood glucose concentration by inhibiting glucose uptake by peripheral tissues. Also, glucocorticoids inhibit insulin binding to insulin receptors and consequently inhibit the postreceptor effects of insulin. Published doses for prednisone in ferrets are 0.5 to 2 mg/kg PO q12h. In our experience, most ferrets require 1 mg/kg PO q12h to control clinical signs. An oral suspension, Pediapred (Celltech Pharmaceuticals, Inc, Rochester, NY), is commercially available as a 1-mg/ml syrup and is most commonly used. Prednisone can also be compounded (sugar-free) for higher concentrations. Prednisone formulations containing alcohol should be avoided to prevent sedative effects that can be confused with clinical signs. It is important to note that the actions of prednisone become progressively less effective over time and at increasing doses; therefore, prednisone therapy should be reserved for post- and nonsurgical candidates. Side effects of long-term steroid use are rare in ferrets.

Diazoxide can be used alone or added to the treatment regimen when prednisone alone is not effective. Diazoxide also exhibits hyperglycemic activity by directly inhibiting pancreatic insulin secretion. This action may be a result of the drug’s ability to decrease intracellular release of ionized calcium, thereby preventing insulin release from insulin granules. Diazoxide does not apparently affect insulin synthesis or possess antineoplastic activity. Diazoxide also increases blood glucose concentrations by stimulating the β-adrenergic system, thereby stimulating epinephrine release and inhibiting glucose uptake by cells. In one study, diazoxide therapy controlled hypoglycemia in 70% of dogs with insulinomas. The major disadvantage of this medication is the expense, which may make it cost prohibitive. The client cost for a 1-oz bottle is around $120, with the cost of a 1-month supply at around $28. Doses for diazoxide in ferrets are 5 to 30 mg/kg PO q12h, starting at the low end of the dose. Proglycem (Baker Norton Pharmaceuticals, Inc, Miami, FL) is available as an oral suspension at a concentration of 50 mg/ml. The dose of prednisone can sometimes be reduced when using diazoxide. Because prednisone increases total blood volume and is suspected to lead to congestive heart failure in cats with underlying heart disease, clinicians may choose to treat ferrets with heart disease using diazoxide instead of prednisone. Also, glucocorticoids such as prednisone have some mineralocorticoid activity, and resultant sodium retention rarely exacerbates pulmonary edema in dogs. When diazoxide is used to treat insulinoma in dogs, the most common adverse reactions include anorexia, vomiting, and/or diarrhea. Administering the drug with meals or temporarily reducing the dose may alleviate gastrointestinal side effects.

Somatostatin (Sandostatin, Novartis Corporation, New York, NY) use is reserved for a small number of clinical cases with equivocal results. Octreotide, a synthetic long-acting analog of somatostatin, acts by inhibiting the synthesis and secretion of insulin (as well as glucagon, secretin, gastrin, and motilin) from normal and neoplastic beta cells in the pancreas. The response is variable (it is presumably dependent on whether the tumor cells have receptors for somatostatin). Octreotide is often used to manage insulinoma in dogs, with alleviation of hypoglycemia in up to 50% of patients seen in one hospital. In dogs, the drug is well tolerated and easy to administer (subcutaneously), and adverse reactions have not been seen. Clinical trials have not evaluated use of this drug in ferrets. The dose for ferrets is reportedly 1 to 2 µg/kg SC bid to tid.

Streptozocin (Zanosar, Pharmacia & Upjohn Co, Kalamazoo, MI) has been used in treating pancreatic endocrine tumors in humans and dogs. In one study, results suggested that streptozocin can be administered safely to dogs when combined with a protocol for diure-

Clients often misinterpret the early phase of this disease as the normal aging process.


Ferret Insulinoma

Ferret Insulinoma is one of the most common tumors in domestic ferrets, and clinical signs relate to hypoglycemia.

There are no reports of use of this chemotherapeutic agent in ferrets, and because of potential nephrotoxicity, its use is not recommended.

Doxorubicin (Adriamycin, Pharmacia, Inc, Kalamazoo, MI) is also reportedly effective in humans with insulinoma. It is thought to be safe and well tolerated by ferrets. A dose of 1 mg/kg IV q21d has been reported. We have not used this drug in treating ferret insulinoma.

In addition to receiving medications, ferrets should eat a high-protein meat-based diet, and owners should avoid leaving their ferrets without food for prolonged periods. Ferrets should not eat high-carbohydrate diets or consume too many sugary treats. Supplements such as Nutri-Cal (EVSCO Pharmaceuticals) should be avoided unless treating a patient for a hypoglycemic episode. Some ferrets require assistance feedings for the long term or until they are eating readily on their own. Hill’s Prescription Diet Canine/Feline a/d (Hill’s Pet Nutrition) or Eukanuba Maximum Calorie (Iams Company) formulas are often used for assistance feeding ferrets in the hospital and can be used in anorectic ferrets at home. Homemade gruels containing various ingredients have been described; however, ingredients with high sugar content such as karo syrup and Nutri-Cal should be avoided. In addition, chicken baby food is reportedly an adequate temporary food replacement in anorectic ferrets. Brewer’s yeast, a good source of chromium, can be added to the diet because chromium has reportedly helped stabilize blood glucose and insulin concentration in humans. Supplementation of vitamins C and E have also been shown to aid in glucose regulation. Medical management can control clinical signs for 6 months to 1½ years, and many ferrets may have or develop concurrent disease, supporting the use of medical therapy in these cases.

Emergency Treatment of Hypoglycemia

Owners should be able to recognize the clinical signs of hypoglycemia and how to treat mild to moderate hypoglycemic episodes at home. Products such as corn syrup or honey should be kept on hand for emergencies. Owners should apply these liquid sugar products to the gingiva cautiously so that they are not bitten. To avoid aspiration, owners should be instructed not to pour liquids into the mouth of an unconscious pet. Once the ferret improves, it should be fed and evaluated by a veterinarian.

Ferrets that are having seizures and do not respond to oral sugar solutions require immediate emergency care and hospitalization. Ferrets should be administered a slow bolus of 50% dextrose intravenously after blood glucose evaluation at a dose of 1 to 2 ml/kg until a favorable response is seen. Additional dextrose may be given if the ferret does not respond to the initial bolus. In an emergency, the goal of therapy is to resolve clinical signs and seizures. Shock therapy may be indicated, requiring dextrose supplementation in intravenous flu-
treated with surgery redeveloped hypoglycemia within a median of 10.6 months, and 26 of 50 remained hypoglycemic, requiring medical therapy. Overall median survival time of ferrets treated with medical and/or surgical management was 17 months (range: 14 days to $3^{\frac{1}{3}}$ years). Those treated with medical management alone were euthanized 6 to 9 months after diagnosis. Overall, there was no significant difference in median survival times between ferrets that remained euglycemic after surgery, those that had persistent hypoglycemia, and those that redeveloped hypoglycemia after surgery. Reported complications in this study group included suspected pancreatitis in one ferret and iatrogenic diabetes mellitus in another. These authors have concluded that, based on these results, it is unclear whether surgery or medical management is most beneficial and that further studies are needed.

In contrast, Ehrhart et al reported that hypoglycemia in 16 of 17 ferrets treated with surgery resolved within 24 hours. Although 12 of these ferrets had multiple nodules in the pancreas, the existence of single versus multiple neoplastic pancreatic nodules and other concurrent neoplasia did not affect survival times or disease-free intervals. The authors also reported that ferrets with malignant carcinoma did not differ significantly from those with benign adenomas when comparing survival times and disease-free intervals. In addition, ferrets with a longer duration of clinical signs before a diagnosis was made had significantly shorter survival times. Median survival time of all 20 ferrets was 483 days (mean: 563 days; range: 1 to 1,100 days). Although tumor recurrence and associated hypoglycemia is likely to recur in ferrets undergoing surgery, resection usually results in increased disease-free intervals and survival times compared with medical therapy alone, and many ferrets survive well beyond redevelopment of clinical signs.

Ferrets should be fasted for 3 to 6 hours before surgery, and intravenous dextrose should be administered to prevent severe hypoglycemia before and during the procedure. It is recommended to check blood glucose concentration before, during, and after the surgical procedure as well. Prophylactic therapy for stress-induced Helicobacter mustelae gastritis may be indicated in these surgical cases.

At surgery, pancreatic nodules can be either visualized or palpated during abdominal exploration. Most visible insulinomas easily shell out because of their encapsulation by using blunt dissection with mosquito hemostats. During visual inspection of the pancreas, nodules are usually pinpoint sized to approximately 5 mm in diameter, although they can become larger. Ferrets can have multiple nodules in any region of the pancreas, and ferrets with obvious diffuse pancreatic disease would likely benefit more from partial pancreatectomy than nodulectomy alone. Surgeons should explore the abdomen for other abnormalities and perform biopsies as indicated; also, diseased adrenal glands can be removed at this time. The surgical procedure has been thoroughly described in veterinary texts. Distal metastasis of insulinomas is uncommon in ferrets, but local recurrence is likely. When treating ferrets with insulinoma, client communication is essential to prevent owners from developing high expectations or expecting a cure.

After surgery, blood glucose should be monitored twice daily while the ferret is hospitalized. Complications relating to pancreatic surgery are rare in ferrets. Some ferrets develop transient hyperglycemia that resolves within weeks and does not require treatment. Other ferrets remain hypoglycemic, and medical therapy must be continued or initiated. Blood glucose concentration should be checked 1 to 2 weeks after surgery and then every 2 to 3 months based on clinical signs. Many ferrets treated surgically require medical management within 4 to 6 months after surgery. In many cases, the value of surgery is in reducing tumor burden, determining whether metastasis has occurred, and confirming the diagnosis.

CONCLUSION

Insulinoma is common in domestic ferrets. Clinical signs are associated with hyperinsulinism-induced hypoglycemia and include lethargy, ataxia, pawing at the

Surgical removal of insulinoma is the recommended therapy and allows for definitive diagnosis. Medical management also plays an important role in controlling clinical signs.
mouth, and, sometimes, seizures. Tentative diagnosis is made based on clinical signs and documented hypoglycemia, and absolute insulin concentration may help. Definitive diagnosis is based on histopathologic examination of pancreatic biopsy specimens obtained at surgery. Treatment recommendations may include medical therapy and/or surgical management. Prognosis for complete resolution is guarded because most ferrets redevelop clinical signs within a year.

REFERENCES


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1. Insulinoma should be suspected in a ferret with a glucose measurement of less than ____ mg/dl.
   a. 60
d. 100
   b. 70
   c. 82

2. Which of the following is the drug of choice for managing ferret insulinoma?
   a. Depo-medrol
d. vincristine
   b. cyclophosphamide
   c. prednisone

3. Definitive diagnosis of insulinoma is made by
   a. determining the insulin:glucose ratio.
d. abdominal ultrasonography.
b. a finding of persistent hypoglycemia.
c. histopathologic examination.

4. Which clinical sign is not typical in a ferret with insulinoma?
   a. lethargy
c. pawing at mouth
d. diarrhea
5. The main mechanism of action of diazoxide is
   a. inhibition of insulin release.
   b. increased uptake of glucose from the gastrointestinal tract.
   c. decreased cellular metabolism of glucose.
   d. islet cell necrosis.

6. The average age at which ferrets typically start showing clinical signs of insulinoma is _______ years.
   a. 1 to 2  c. 4 to 5
   b. 2 to 3  d. 6 to 7

7. With which treatment option for insulinoma have ferrets had the longest survival times?
   a. prednisone therapy
   b. pancreatic nodulectomy
   c. prednisone and diazoxide therapy
   d. nodulectomy and partial pancreatectomy

8. Insulinomas in ferrets _______ compared with those in dogs.
   a. have low metastatic rates
   b. readily metastasize to the spleen
c. typically metastasize to the lungs late in the disease course
d. are always benign

9. Why is ultrasonography usually not useful in diagnosing insulinoma in ferrets?
   a. The ferret pancreas is hard to visualize.
   b. Pancreatic nodules can be easily confused with lymph nodes around the pancreas.
   c. Most insulinomas are too small to be seen.
   d. Ultrasonographic probes are not sensitive enough for ferrets.

10. Which statement regarding treatment of ferret insulinoma is correct?
    a. Most ferrets with insulinoma live less than 3 months with medical therapy.
    b. Ferrets treated with diazoxide survived longer than those treated with prednisone.
    c. The dose of prednisone can sometimes be lowered when adding diazoxide.
    d. Ferrets treated with surgery alone died sooner than those treated with medical therapy alone.