**Preventing Ferret Insulinomas and Adrenal Tumors**

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**Introduction**

Endocrine neoplasia in ferrets is extremely common; the author first recognized these disease conditions in the 1980’s, at which time islet cell tumors (insulinomas) were seen at approx. ten times the frequency of adrenal neoplasia. In my practice, the incidence of insulinomas has remained fairly constant over the years, whereas adrenal tumors showed a marked increase in incidence in the 1990’s. This was the era where a few ‘mega breeders’ took over the market, and small scale breeder operations ceased to provide the majority of pet ferrets sold in the U.S. Historic changes in disease incidence provide clues as to possible factors contributing to endocrine neoplasia in pet ferrets; this in turn can help us develop protocols to reduce disease risk.

**Insulinomas**

These are tiny, discrete neoplasms in the pancreas which secrete excessive amounts of insulin. This in turn leads to progressive hypoglycemia, causing gradual lethargy, dulled mentation, stupor, sialosis, ataxia, and in severe cases, coma or seizures. Patients respond rapidly to oral or injected glucose. Medications such as diazoxide or prednisolone can alleviate signs, but unless surgically removed, the neoplasms grow and signs worsen, eventually resulting in death. Surgery in the author’s hands is effective in nearly all cases, but historically some patients have developed new islet neoplasms over time, causing a reoccurrence of clinical signs six to 18 months post operatively. Prevention of these tumors would be ideal, but this requires an understanding of the underlying causes or factors which may be stimulating development of islet tumors.

Insulinomas are extremely common in ferrets. Biopsies have shown that discrete islet tumors are often accompanied by diffuse islet hyperplasia in the pancreas. This seems contrary to what should occur: islet tumors produce excessive insulin, which in theory should cause the non-neoplastic islets to cease production and possibly atrophy. Therefore, concurrent islet hyperplasia should not be seen, unless some factor is stimulating all the islets to enlarge and become more active. In essence this is what appears to occur; islet cell pathology begins as hyperplasia, then progresses to neoplasia, either adenomas or adenocarcinomas. This is supported by the multifocal tumor distribution often seen in both lobes of the pancreas; metastatic lesions would not spread in this pattern. Instead, these are multiple independent neoplasms developing concurrently; the question is, why?

Obviously there is a species predisposition in ferrets, as islet cell neoplasia is rare in most other species. Authors have hypothesized that presence of a M.E.N. (multiple endocrine neoplasia) gene may increase incidence of islet and adrenal tumors in ferrets. This author, and others, have hypothesized carbohydrate overload as a risk factor in development of islet hyperplasia. For decades, traditional dry pet diets were all high in carbohydrates, due to addition of starch as a texturing agent to produce cohesive kibbles when baked. Excessive carbohydrate intake may stimulate pancreatic islets to produce high insulin output, to process the incoming sugars. For obligate carnivores adapted to ingest a low-carb diet, this may place an unnatural burden on the islet cells, causing eventual hyperplasia which progresses to neoplasia.

This theory can be tested via feeding a high protein/low carbohydrate diet to patients exhibiting insulin overload and hypoglycemia. While such a diet might best be used to prevent islet hyperplasia before it becomes advanced, one might also be able to see improvement in hypoglycemic animals. The improvement would not be due to elimination of an insulinoma, but rather reduction in any concurrent islet hyperplasia which could contribute to the total insulin load.

Example case: 6 year old male neutered ferret “Buddy”; diagnosed with insulinoma 1 year prior, owners declined surgery, has been on increasing doses of diazoxide and prednisolone since. Signs slowly progressing; currently on 1 mg/kg pred PO BID + 25 mg diazoxide PO BID (nearing maximum dosing protocol for both drugs). Despite meds, Buddy’s glucose is low enough that he barely functions, and he goes into a coma-like state at least once daily, requiring oral glucose administration and force feeding to revive him. I had the owners switch Buddy to a low carb high protein kibble (Purina D-M feline); over the next 4 months, the owners reported a gradual steady improvement in Buddy’s energy level; comatose spells were reduced to one every 3 weeks. Medications could not be reduced without Buddy becoming symptomatic, but on current doses, he was much more controlled. Explanation: islet hyperplasia was reduced, improving overall insulin output, but islet tumor(s) remained, necessitating ongoing medication. If such an improvement can be seen in an advanced insulinoma patient via simple dietary management, how much might diet do to prevent the disease before it occurs?

In recent years some good high protein/low carb kibbles have been created, where starch was not added during processing. Examples include Pretty Pets Natural Gold ferret food, Purina D-M feline, or Hills M/D feline. Pretty Pets is harder to find, but may have the best formula. To reduce insulinoma risk, I recommend a gradual switch to one or more of these diets (ferrets may imprint on a food if not fed more than one brand). Minimize sweet treats, such as ‘yogies’, raisins, or FerretVite (basically, relabeled Nutrical). Other ferret foods have emerged recently which claim high protein/low carb profiles, but many have formulations which are less than ideal. In general, be cautious when recommending diets which advertise as ‘grain free’, but load up on less desirable carb sources such as fruits and peas. Pea-containing diets have been implicated in causing cysteine uroliths in ferrets, which can cause potentially fatal urethral obstructions. Fruits are simple-sugar sources, in theory not ideal for carnivores prone to insulinomas. Complex starch sources are preferable; look for diets which use *small* amounts of a single grain (such as rice), or potato, or sweet potato.

**Adrenal tumors**

The situation with adrenal tumors is different; there are no known dietary associations, and as mentioned previously, the incidence has changed dramatically in the U.S. over time. Light cycle influences have been suggested as a potential risk factor (lack of seasonal cycle in day length causing pituitary-adrenal disturbances). Historical perspective suggests that this is a minor influence at best: ferrets in the 1980’s had far fewer adrenal tumors, usually seen only in old age; yet ferret housing and lighting situations haven’t changed significantly from the 1980’s to the present.

The main change which seems to correlate chronologically with the increased tumor incidence in the U.S. is the emergence of a few large scale breeder operations in North America which currently dominate the pet ferret industry in the United States. These few breeders nearly all of the pet ferrets seen today; the loss of genetic diversity in this situation is extreme. One explanation for the increased adrenal disease incidence is that the breeder stock used by these facilities happened to carry a genetic predisposition (such as the M.E.N.-1 gene).

If this is the case, it is unfortunately a situation that cannot easily be remedied. But another explanation may exist for the high incidence of disease in U.S. ferrets. The large scale breeders brought another change to the pet ferret industry: early spays & neuters. Prior to the ferret-mill breeders, domestic ferrets were sold intact, and the owners took the pet to a veterinarian to be spayed/neutered (and often descented) around 5-6 months old. Using that protocol, we saw only occasional adrenal problems in ferrets. The large breeders adopted a policy of neutering and descenting all ferrets prior to sale; this increased their marketability, and gave the breeders a monopoly: no one else could buy and breed their sterilized ferrets. To accomplish this goal, breeders had to neuter the ferrets very young, as early as 3 weeks in some cases. The lack of gonadal hormones during early development has been hypothesized to lead to hyperplasia of the sex-hormone secreting regions within the adrenals, as these glands attempt to secrete more hormone. The cortical hyperplasia may eventually lead to neoplasia. Histopathology confirms a spectrum of pathology from hyperplasia to adenoma to adenocarcinoma, often with all three changes evident within one adrenal gland.

If the high disease incidence is due at least in part to changes at the breeder level (genetic factors, early husbandry influences), what is a pet owner to do? We can’t alter the pet’s genetics, nor reverse a gonadectomy. I advise prospective ferret owners to look for a small local breeder source, if they can find one, and buy an intact animal when possible. Delay neutering of these pets until they reach approx. 6 months old.

With ferrets that were neutered young, we can greatly reduce disease risk by using medication to suppress adrenal gland activity, and minimize hyperplasia & neoplasia in the glands. Luprolide (Lupron) works reasonably well, but is relatively short in duration (1-4 months, depending on dosing form), and costly. Deslorelin 4.7 mg implants are superior, being as effective (or more effective) as Lupron, and lasting at least one year per implant. Cost is similar to 1 to 2 months’ worth of Lupron. Peptec Animal Health in Australia developed this drug for canine birth control; recently Virbac acquired the product, and marketed it for ferrets in the U.S. under the name “Suprelorin-F”. Ironically, with increased availability came a significant cost hike to U.S. vets, but the implant still is far more convenient and inexpensive than Lupron. The product appears quite safe, even when used at 9.6 mg doses. One could justify using the implants over the entire life of the animal, but the drug is most strongly indicated as the ferret becomes older and more at risk for adrenal disease. I currently recommend implants for all ferrets 3 years old and older.