Nonsurgical Management of Hyperadrenocorticism in Ferrets

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KEYWORDS

• Ferret • Adrenal disease • Leuprolide acetate • Deslorelin • Melatonin

KEY POINTS

- Medical management of hyperadrenocorticism in ferrets is a suitable alternative to adrenalectomy and in some cases may be preferable.
- Various drugs are available for the symptomatic management of the clinical signs of adrenal disease, with gonadotrophin-releasing hormone agonists being the most widely used.
- Although the drugs used treat just the symptoms and not the abnormal adrenal tissue, they seem to have few adverse effects and many can be used concurrently or in conjunction with surgical resection of the diseased adrenal gland.
- Timely recognition of the less commonly seen but potentially life-threatening clinical signs of urethral blockage secondary to prostatic disease and nonregenerative anemia secondary to hyperestrogenism is vital to the successful management of these conditions.

INTRODUCTION

Hyperadrenocorticism in ferrets, more commonly referred to as adrenal gland disease, is one of the most recognizable conditions in the domestic ferret. The clinical signs of this well-recognized syndrome are a result of hyperandrogenism, in which various sex steroids are overproduced. One case of hypercortisolism and 1 case of hyperaldosteronism in association with hyperandrogenism have been reported, but these variations of adrenal gland disorders may be also under-recognized and under-reported.[1,2]

Clinical signs of hyperadrenocorticism include:

- Progressive and symmetric alopecia. Seen in more than 90% of affected ferrets[3]
- Pruritus
- Vulvar swelling in spayed females

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- Increased aggression or sexual behavior in spayed females and neutered males
- Stranguria in males secondary to urethral obstruction from prostatomegaly
- Anemia or pancytopenia (rare)

Although many of the aforementioned clinical signs are classic for adrenal disease and considered by some clinicians as pathognomonic for hyperadrenocorticism, the following diagnostic tests are recommended in the work-up of the condition:

- Adrenal hormone panel: measures serum levels of estradiol, androstenedione, and 17-hydroxyprogesterone. Available through the University of Tennessee Veterinary Medical Center Endocrinology Service (http://www.vet.utk.edu/diagnostic/endocrinology).[3]
- Abdominal ultrasound: evaluates the adrenal glands for enlargement and architecture abnormalities such as cysts or mineralization.[4] In addition, compression or invasion of the vena cava by the right adrenal gland can be visualized on ultrasonographic examination. Prostatic enlargement may also be noted on ultrasonographic examination in some males.

Surgical resection of the diseased adrenal gland was considered the treatment of choice for many years, but the development of several effective medical therapies has changed the way many practitioners now treat this disease. Although these medical therapies help treat the symptoms of hyperadrenocorticism, they do not eliminate the presence of the adrenocortical neoplasms responsible for the increased androgens. Surgical resection allows for the removal of adrenal neoplasms, but can be associated with typical anesthetic and surgical risks. These surgical risks may outweigh the potential benefits, especially in debilitated or aged ferrets.[5] The right adrenal gland's dorsal position on the caudal vena cava also makes it more difficult to remove than the left adrenal gland. In some cases, surgical resection is still the treatment of choice, especially in those ferrets that have concurrent conditions that benefit from surgical intervention.[5] One such instance is ferrets that also have insulinomas, because removal of insulinomas has been shown to lead to longer disease-free intervals and survival times.[6] Surgical resection of the diseased adrenal gland(s) is also indicated in those ferrets that have only a partial response to medical therapies or have become refractory to long-term use of hormone therapy for relief from their disease. There is also some anecdotal evidence that combined surgical debulking of a diseased adrenal gland with hormone therapy seems to result in longer survival times than either treatment modality alone.[7] Even if both adrenal glands are diseased, complete removal of both is still not recommended because this leads to life-threatening hypoadrenocorticism.

There are several nonsurgical treatment modalities available for addressing the clinical signs associated with the excess sex hormones secreted by adrenocortical tumors in ferrets. Their specific methods of action are diverse and, in some cases, unpublished in ferrets. Following published data in other species, as well as in ferrets, can make many of these agents potentially helpful additions to the medical repertoire available to clinicians treating adrenal disease. Pregnant women should avoid direct contact with many of the drugs discussed in this article.

DRUGS USED TO PROVIDE GENERALIZED SYMPTOMATIC TREATMENT

Gonadotropin-releasing Hormone Agonists

When administered at sufficiently high levels for a prolonged period, gonadotropin-releasing hormone (GnRH) agonists desensitize GnRH receptors at the pituitary to downregulate the release of the gonadotropins follicle-stimulating hormone (FSH)

and luteinizing hormone (LH). This suppressed release of LH and FSH leads to the decreased production of estradiol, androstenedione, and 17-hydroxyprogesterone. Multiple clinical studies have investigated the use of 2 GnRH agonists, leuprolide acetate and deslorelin acetate.

Leuprolide acetate

Until recently, this was the most widely used and studied GnRH agonist.[7–10] This hormone is labeled for the treatment of prostate and testicular cancer in men, uterine fibroids and endometriosis in women, and precocious puberty in children. Various formulations exist; however, all must be diluted to a suitable concentration for the extra-label use in ferrets. There is anecdotal evidence that the diluted form is active after being in the freezer for up to a year,[11] but no studies have been performed to investigate the stability of the frozen drug.[12] In the author's experience, 100 μg of the 30-day formulation (LupronDepot, Abbott Laboratories) given intramuscularly every 4 to 6 weeks seems to adequately control the clinical signs in most ferrets early in the course of the disease. However, over time, many ferrets require a higher dose of 200 μg, and in some instances ferrets have become completely refractory to the leuprolide acetate. It has been suggested that leuprolide acetate could be used annually for chemical breeding to elicit an LH surge and therefore prevent the stimulation of the adrenal gland production of androgens.[10] Because ferrets are seasonal breeders, the leuprolide acetate needs to be administered when they typically would have been bred; thus, one study[10] recommends 200 μg of leuprolide acetate (LupronDepot, Abbott Laboratories) in January for males and 100 μg in mid-February to mid-March for the females. Other treatment protocols have also been described (**Table 1**).

Clinical signs of vulvar swelling, pruritus, dysuria, and aggression are typically diminished within a few days to weeks. Regrowth of the hair coat takes a little longer, usually between 4 and 8 weeks. Owners sometimes mistake the initial regrowth of hair in dark-furred ferrets as bruising. If only 1 dose (100 μg) of leuprolide is administered, the time to recurrence of clinical signs averages around 3 months (range 1.5–8 months).[8] There are also 3-month and 4-month formulations available, but anecdotally they do not seem to have the expected duration of action.[7]

There are conflicting reports on whether or not the adrenal gland size is affected when leuprolide acetate is administered and owners should be advised that the drug is not curative for adrenal neoplasia. In 1 author's experience (SC), adrenal tumors measuring as large as 12 cm in diameter have been observed in ferrets that have been managed long term (>2 years) with leuprolide acetate (**Fig. 1**). It is thought that some tumors may become autonomous and nonresponsive to the effect of the leuprolide acetate, especially after prolonged therapy. Reported adverse effects include irritation at the injection site, lethargy, and dyspnea.[12]

Deslorelin acetate

Deslorelin acetate is a synthetic analogue of gonadorelin. It stimulates LH and FSH secretion, which desensitizes the pituitary by downregulating GnRH receptors, which in turn effectively stops the release of gonadotropins. Deslorelin implants have been used as contraceptives in intact male and female ferrets and have been shown to be an effective alternative to surgical castration.[19,20] In the past it was only available in Australia and in Europe, but deslorelin acetate implants (Suprelorin F, Virbac Animal Health) are now commercially available in the United States for use in ferrets.

Wagner and colleagues[13] showed improved clinical signs within 2 weeks of receiving a single 3-mg implant. Ferrets receiving the implant had decreased levels of estradiol, 17-hydroxyprogesterone, and androstenedione concentrations, which remained

Table 1
Medical therapies available for the treatment of adrenal disease in ferrets

Drug	Dosing	Onset and Duration of Effect	Comments	Refs.
Leuprolide acetate (LupronDepot), Abbott laboratories, Abbott Park, IL	1 mo Depot: • 100 μg/ferret <1 kg or 200 μg/ferret >1 kg IM q 4–6 wk • 100–250 μg/kg IM q 4 wk	Improvement noted within a few days to 2 wk, hair growth can take 4–8 wk. Last 1.5 to 8 mo (mean 3.7 mo)	q 4 wk until clinical resolution, then q 4–8 wk PRN, lifelong	7–9,11
	3 mo Depot: • 1 mg IM q60–75 d IM 4 mo Depot • 2 mg/ferret IM q70–80 d	Both the 3-mo and 4-mo formulations have longer durations of effect, but both seem to be effective for less than 3 mo	May be useful for annual December/February suppression	10
Deslorelin acetate (Suprelorin, Virbac Animal Health, Carros, France)	3 mg or 4.7 mg implant Subcutaneous implant	Improvement of clinical signs within 1–2 wk. Lasts 8.5–20.5 mo (mean 13.7 mo)	—	13,14
Melatonin (Ferretonin, Melatek, Middleton, WI)	0.5–1 mg/animal PO q 24 h	Improvement within 4 mo, but recurrence of clinical signs at 8 mo in 6 of 10 ferrets	To be given 8 h after sunrise. Timing of medication may affect effectiveness	9,15
	5.4 mg subcutaneous implant	Last 6–12 mo	Lethargy noted in the first 3–5 d after implantation	16
Anastrozole (Arimidex, AstraZeneca Pharmaceuticals)	0.1 mg/kg PO q 24 h	—	Inhibits the synthesis of estrogen by inhibiting aromatase, the enzyme involved in estrogen and estradiol production	17
Finasteride (Proscar, Merck)	5 mg/kg PO q 24 h	—	Treatment of prostatic enlargement	9
Flutamide (Eulexin, Schering)	5–10 mg/kg PO q 12–24 h	—	Androgen inhibitor; No studies in ferrets, dose based on study on rats	18
Bicalutamide (Casodex, AstraZeneca Pharmaceuticals)	5 mg/kg q 24 h. Use until clinical signs resolve, then 7 d on, 7 d off	—	Blocks androgen receptors. Testosterone inhibitor	9,17

Abbreviations: IM, intramuscularly; PO, by mouth; PRN, as needed; q, every.

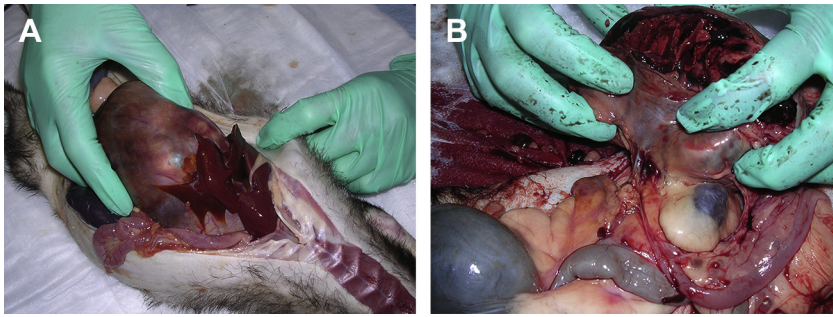

Fig. 1. (*A*) Adrenal mass measuring 12 cm in length in a ferret whose clinical symptoms were managed with leuprolide acetate for more than 2 years. (*B*) Mass opened up. Note the attachment to the vena cava.

decreased until clinical relapse 8.5 to 20.5 months later (mean 13.7 months).[13] Ferrets that previously underwent a left adrenalectomy before implantation had a longer time to relapse than ferrets that did not.[13] Similar results have been noted in the authors' clinic, with most ferrets showing either complete or partial response to the hormone implant within 1 month of implantation; however, a few have had a delayed response. A few of the ferrets that previously showed only a partial response to leuprolide acetate had complete resolution of clinical signs after receiving a deslorelin implant. The duration of effect has ranged from 3 to 17 months for most of the ferrets. One ferret received a second implant when clinical signs recurred 16 months after the first implant.

Minor local swelling and soreness at the implantation site that lasts for 1 to 2 weeks is listed as a possible adverse reaction (Deslorelin drug insert) and 1 ferret in our clinic became temporarily lame in the forelimbs because of swelling around the implant. Weight gain, lethargy, and failure to respond to therapy were also reported side effects in ferrets (Deslorelin drug insert). Lennox and colleagues[5] found that relapse times for ferrets treated medically with deslorelin (mean 16.5 months) was longer than those of ferrets that had surgical resection (mean 13.6 months). Although this hormone has been shown to be effective in controlling the clinical signs of adrenocortical disease, like leuprolide acetate, there is equivocal evidence on whether or not it deters tumor growth or metastasis.[13,14] However, based on the findings found in Lennox and colleagues'[5] study comparing the implant with surgical treatment, deslorelin should be considered a first-line treatment of ferrets with hyperadrenocorticism, especially for those ferrets who are poor surgical candidates.[5]

Melatonin

The function of melatonin and its method of action within the brain have not yet been fully elucidated. The mechanism by which melatonin affects LH and FSH secretion is unknown,[21] but it has been shown to inhibit prolactin secretion via the pars tuberalis of the pituitary gland of sheep.[22] In ferrets, the pars tuberalis is the only location within the brain in which melatonin receptors have been detected.[23] Ferrets are known to be long-day breeders, because GnRH is released in response to increasing photoperiods.[24] The release of GnRH is seen as an increase in sexual activity in reproductive ferrets as the amount of daylight increases.[24] It is thought that as photoperiods decrease, circulating levels of melatonin, an antigonadotropic hormone, increase. The increase in melatonin is thought to suppress the release of GnRH, which in turn inhibits the release of LH and FSH.[16] In female ferrets, melatonin secretion occurs during dark hours as early as 10 weeks of age.[25] Melatonin

is also involved with the neuroendocrine stimulation of hair growth in periods of decreased daylight, and, conversely, shedding occurs in the spring as levels of melatonin decrease as photoperiods lengthen.[26] Melatonin administration and its effects caused by changes in prolactin secretion have been more extensively studied in the mink because of its effect on fur quality and reproduction,[27] but there have been several published articles in the last decade involving the effect of melatonin supplementation in ferrets.

In one study,[15] melatonin (0.5 mg) was administered orally once per day for 1 year with monitoring of overall health, adrenal size, complete blood count (CBC), and serum chemistry analysis every 4 months. During the course of treatment, the investigators noted a temporary reduction of clinical signs including varying degrees of hair regrowth, decreases in vulvar or prostate size, increased vigor, as well as decreased androgen level. No deleterious responses to the melatonin treatment were noted in any of the animals. However, recurrence of clinical signs and increased androgen levels were noted at the 8-month recheck in more than half of the ferrets in the study. Treatment also did not stop enlargement of the affected adrenal gland despite temporary alleviation of clinical sings.[15]

Recommended oral dosing ranges from 0.5 to 2 mg per ferret once daily.[7,10,15] Some references recommend administering melatonin 7 to 9 hours after sunrise.[7] A concern with melatonin is that, as with other nutraceuticals, there are no regulations for quality control for this over-the-counter supplement. A 5.4-mg melatonin implant (Ferretonin, Melatek, LLC) with good anecdotal results[16] is commercially available, but no studies evaluating the long-term efficacy have been published at this time. The only adverse effect in ferrets was lethargy for the first 3 to 5 days after implantation.[16]

MEDICAL MANAGEMENT OF SPECIFIC CONDITIONS CAUSED BY ADRENAL DISEASE

Although the typically seen clinical signs of alopecia and vulvar swelling tend to be purely cosmetic issues, 2 life-threatening conditions can occur in ferrets with hyperadrenocorticism. Prostatic enlargement and cysts can result in partial or complete urinary blockage. Prolonged hyperestrogenemia can cause a life-threatening nonregenerative anemia or pancytopenia. The clinical signs and the medical management of these two specific conditions associated with hyperadrenocorticism are discussed in the following section.

Prostatic Disease

Prostatic cysts, prostatitis, and prostatic abscesses can result in prostatomegaly, which leads to urethral obstruction in middle-aged and older castrated male ferrets.[28] Increased sex hormones are thought to result in the proliferation of prostatic tissue and the development of squamous metaplasia of prostatic ducts, which lead to fluid-filled cysts containing keratin and proteinaceous debris.[28]

Clinical signs of urinary obstruction from prostatic disease include:

- Pollakiuria
- Stranguria
- Anuria
- Hematuria
- Tenesmus
- Rectal prolapse (from constant straining)
- Red prepuce (from excessive licking)
- Lethargy, weakness, and anorexia

Diagnosis

An enlarged prostate dorsal to the bladder may be noted on abdominal palpation. The bladder is usually distended and painful and is often difficult to express. A mass lesion caudodorsal to the urinary bladder may be noted on survey radiographs and in some cases may be larger than the bladder. Ultrasonography is especially useful in characterizing prostatomegaly, allowing differentiation between prostatic cysts and prostatic abscesses. Ultrasound-guided fine-needle aspiration of the prostatic cysts should be performed under sedation for cytology and bacterial culture. An inflammatory leukogram may or may not be present and postrenal azotemia, hyperkalemia, hyperphosphatemia, and metabolic acidosis may be noted on serum biochemistries.[28]

Treatment

Urethral catheterization with a specially designed 3.0-French, 11-cm, open-ended silicone catheter (Slippery Sam, Smiths Medical PM) allows relief of urethral obstruction, although a 3.5-French red rubber catheter or tom cat catheter are suitable alternatives.[29] General anesthesia is highly recommended, because all but the most ill ferrets do not tolerate the placement of a urinary catheter. The opening to the penis is exposed from the prepuce by placing gentle, cranially directed pressure at the base of the os penis. Stretch gauze can be hooked at the curved end of the os penis to keep the penis exposed. The opening to the urethra can be difficult to visualize because it often lays flat just lateral to the tip of the penis. A 24-gauge or 22-gauge intravenous catheter with the stylet removed or a stiff piece of suture can sometimes be used as a guide to locate the opening (**Fig. 2**). Once placed, the catheter can be secured with suture through the suture holes in the silicone hub of the Slippery Sam catheter or butterfly tape tabs secured around the red rubber catheter, which is then sutured to the skin by the prepuce.[28,29] A closed line should be attached to the catheter to monitor urine production. Urine output should be, at a minimum, 1 to 2 mL/kg/h.[28]

The following antiandrogens have, anecdotally, been used to treat prostatic enlargement with and without concurrent use of a GnRH agonist. There are no controlled studies to confirm whether these drugs have any additional benefit compared with administering them with or instead of the administration of a GnRH agonist.

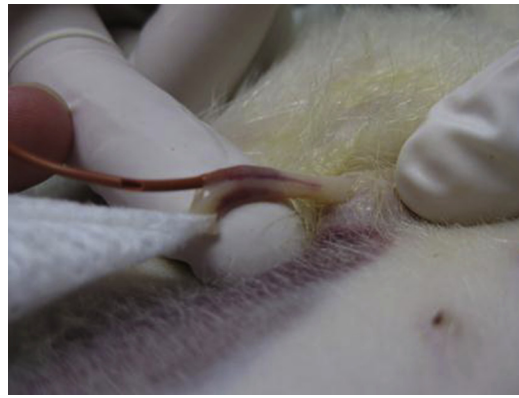

Fig. 2. Urinary catheterization of a male ferret with a 3.5-French red rubber catheter. Note the lateral position of the urethral opening.

Androgen receptor blockers: flutamide and bicalutamide

Flutamide is a nonsteroidal antiandrogen drug used for the treatment of prostate cancer in men by inhibiting the formation of the 3S nuclear protein-androgen receptor as well as decreasing whole-tissue uptake and retention of testosterone.[30] It is metabolized by the Cytochrome P450 1A2 (CYP1A2) enzyme in the liver into its active metabolite 2-hydroxyflutamide. This metabolite has been associated with hepatic dysfunction in humans through an unknown mechanism. Clinical signs include increased serum alanine aminotransferase (ALT), aspartate aminotransferase, and bilirubin as well as hepatic necrosis and cholestasis.[31]

In laboratory animal studies, the ability and mechanism by which flutamide causes liver damage has been investigated. In knockout mice containing a mitochondrial defect that increases sensitivity to oxidative stress, exposure to flutamide caused increased reactive oxygen species leading to hepatic necrosis and hepatocellular apoptosis. This finding suggests that reactive oxygen species may play an important role in hepatotoxicity reported in people treated with flutamide.[32] In rats, flutamide has been found to act as a liver tumor promoter when given after exposure to the known carcinogen N-diethylnitrosamine.[33] In vitro, flutamide has been shown to cause free radical lipid peroxidation and hemolysis when exposed to ultraviolet A light.[34]

Flutamide is used for the treatment of prostatic cancer in conjunction with an LH-releasing hormone agonist in men. One 250-mg capsule is taken orally every 8 hours to limit uptake of testosterone by prostatic cancer cells.[35,36] According to the drug insert, serum ALT levels should be monitored before beginning treatment, every month for 4 months after initiation, and then routinely after. Serum chemistry analysis before beginning treatment, and then every 2 weeks for 8 weeks, followed by routine analysis is recommended. Treatment should be stopped if serum transaminase values exceed 4 times the normal range and/or clinical signs of hepatic insufficiency (including anorexia, nausea, vomiting, fatigue, jaundice, and/or abdominal pain) are noted.[35] Side effects in men include gynecomastia, changes in body mass and fat distribution, normochromic normocytic anemia, changes in hair growth, fatigue, dermatitis, vitiligo, pseudoporphyria, lupus, photoallergic reactions, diarrhea, pulmonary toxicities, alcohol intolerance, and rash.[34,37]

There are no published experimental data for the use of flutamide in ferrets. In rats, 5 to 10 mg/kg orally every 24 hours has been found to be hormonally suppressive.[18] Monitoring for side effects listed earlier, as well as strict monitoring of liver values with serial serum chemistry analysis as in people, is safest to avoid hepatic disease in treated ferrets.

Bicalutamide, like flutamide, is a nonsteroidal testosterone antagonist. However, bicalutamide has been shown experimentally to have a 2-fold to 4-fold greater affinity for wild-type rat and human androgen receptors than 2-hydroxyflutamide.[38] In mature intact rats, this increased affinity results in a 5-fold increase in potency with regard to reduction of ventral prostate and seminal vesicular gland weight between bicalutamide and flutamide treatments. In dogs, bicalutamide was 50 times more potent than flutamide at producing prostate atrophy.[18] Bicalutamide not only blocks androgen receptors in accessory sex organs but also at central androgen receptors, which results in increased LH secretion and an associated increase in serum testosterone caused by loss of negative feedback inhibition. The increase in testosterone combined with the inhibition of uptake by secondary sex organs leads to increased aromatization and therefore an increase in circulating estrogens and the most commonly reported side effect of gynecomastia and breast pain in treated men.[38] Like flutamide, hepatotoxicity can occur with bicalutamide treatment and judicious

monitoring of serum aminotransferases is recommended.[39,40] Other side effects similar to those of flutamide are possible but seem to be less severe.[38]

For the treatment of prostate cancer in men, one 50-mg tablet is taken orally every 24 hours in combination with an LH-releasing hormone agonist according to the manufacturer's insert.

In immature rats receiving exogenous testosterone (200 μg/kg), 10 mg/kg bicalutamide daily inhibited accessory sex organ growth, but the effect was seen with as low as 0.25 mg/kg. No adverse clinical effects were reported. Adult male beagles receiving 0.05 mg/kg, 0.1 mg/kg, and 0.25 mg/kg orally every 24 hours for 6 weeks showed dose-dependent histologic atrophy of the prostate versus controls. Atrophy of the epididymides was also seen at 0.25 mg/kg. No adverse clinical effects were reported.[18]

In ferrets, 5 mg/kg orally every 24 hours has been used clinically,[9] but no controlled toxicologic or pharmacologic studies have been published at this time. The potential for increased circulating testosterone and estrogen could lead to exacerbation of the clinical signs associated with adrenal disease if bicalutamide is used without a concurrent GnRH agonist.

5-Alpha-reductase inhibitor: finasteride

Finasteride (Proscar/Propecia, Merck) is an antiandrogen used in men for the treatment of benign prostatic hyperplasia, prostate cancer, and male pattern baldness. Blockage of the enzyme 5-alpha-reductase by finasteride prevents the synthesis of dihydrotestosterone (DHT) from testosterone. Prolonged exposure to DHT and testosterone by prostatic cells commonly leads to benign prostatic hyperplasia (BPH) in most middle-aged and older intact dogs.[41] Ferrets exposed to increased androgens because of adrenal overproduction similarly can experience periurethral cysts of the prostatic region leading to urethral compression and potentially obstruction.[3] At present, there is no published experimental use of 5-alpha-reducatase inhibitors in ferrets. A double-blind controlled study in 2001 was performed involving 9 client-owned intact male dogs with spontaneous BPH. Animals were treated with one 5-mg capsule (0.1–0.5 mg/kg based on weight) of finasteride orally every 24 hours for 16 weeks. By the completion of treatment there was a significant decrease in mean prostatic diameter, prostatic volume, and serum DHT.[42]

Use of finasteride has been published anecdotally in the literature as being safe at 5 mg/kg orally every 24 hours as in the aforementioned study,[9] but its efficacy is unknown at this dose. Anecdotal use at 5 mg/kg orally once daily for life seems to be effective in treating BPH; however, it takes 6 weeks for maximal effect, so a GnRH agonist such as leuprolide acetate may be necessary to bridge that time, especially if the ferret is presenting for urethral obstruction (Nicole Wyre, personal communication, July 2013).

Hyperestrogenism-induced Anemia

Prolonged hyperestrogenemia can lead to bone marrow suppression, resulting in a nonregenerative anemia, thrombocytopenia, and leukopenia that can occur in both males and females. Compared with other clinical signs observed in ferrets with adrenal disease, the clinical signs of hyperestrogenism are uncommonly seen. It seems to only affect ferrets that have had long-standing, untreated adrenal disease and the progression of anemia seems to be slower and less severe than in intact female ferrets with protracted estrus (>4 weeks) or spayed ferrets with remnant ovarian tissue.[28] However, in the author's experience, several ferrets have presented with petechia

and an anemia less than 25% requiring emergency supportive care and blood transfusions. Owners should be advised that these ferrets have a poor prognosis, especially if their anemia is severe.

Clinical signs for hyperestrogenemia may include:

- Generalized weakness and lethargy
- Vulvar swelling with or without discharge
- Pale mucous membranes
- Petechial and/or ecchymotic hemorrhage
- Melena
- Systolic murmur

Diagnosis

Clinicians who do not routinely work with ferrets could miss a mild to moderate anemia if they are not aware that the normal hematocrit of ferrets (46%–61%) is higher than in other species.[43] On a CBC, a nonregenerative anemia (<25%), nucleated red blood cells, neutropenia, and thrombocytopenia (<50,000/μL) are typically noted. A reticulocyte count should be performed to confirm a nonregenerative anemia and a bone marrow aspirate is recommended to evaluate the bone marrow.

Treatment

Ferrets that are clinical for their anemia should receive a blood transfusion, especially if their packed cell volumes decrease to less than 25%. Multiple blood transfusions may be necessary until the bone marrow can regenerate once the estrogen levels are reduced. Because there are no known blood types in ferrets, transfusions from multiple donors seem to be well tolerated and the risk of transfusion reactions is lower than in other species.[44]

When collecting blood from a donor, sedation is highly recommended for safe venipuncture from the anterior vena cava or jugular. The ferret can also be anesthetized with isoflurane; however, this can cause a significant reduction in packed cell volume (PCV) caused by splenic sequestration of red blood cells.[45] Before venipuncture, the neck of the donor should be shaved and sterilely prepped. A 23-gauge butterfly catheter attached to a syringe prefilled with acid-citrate-dextrose (ACD) anticoagulant (1 part ACD to 9 parts blood) is used for blood collection. To collect blood from the anterior vena cava, the ferret is placed in dorsal recumbency with the head and neck extended and the forelimbs pulled caudally. The needle is inserted into the thoracic cavity just cranial to the first rib and directed toward the opposite rear limb at a 30° to 45° angle to the body. To access the jugular, the ferret is placed in sternal recumbency with the neck extended up and the forelimbs extended over the edge of the table. Pressure is applied to the thoracic inlet for better visualization and palpation of the jugular vein, which is located more laterally than in the dog or cat.[46] Approximately 1% of the donor's body weight can be collected safely and large healthy males are preferred because they are able to donate larger volumes of blood. Subcutaneous fluids and an injection of iron dextran (10 mg/kg intramuscularly [IM]) can be administered to the donor ferret during recovery to compensate for the acute blood loss.

When administering the blood transfusion to the anemic ferret, a small in-line filter (18 μm, Hemo-Nate blood filter, Utah Medical Products) should be used to prevent administration of blood clots.[47,48] A 22-gauge or larger intravenous catheter should be used to administer the collected blood to prevent cell lysis; alternatively an intraosseous catheter can be used if an intravenous catheter cannot be placed.[46] During the transfusion, the recipient should be closely monitored for

spikes in temperature, tachycardia, tachypnea, pruritus, and vomiting because these may be signs of a transfusion reaction. If noted, administration of the blood is immediately stopped and diphenhydramine (0.5–2 mg/kg IM, intravenously [IV], or by mouth), dexamethasone sodium phosphate (1–8 mg/kg IM, IV), and/or epinephrine (0.02 mg/kg subcutaneously, IM IV, intratracheal [IT]) can be administered.[47,49] Once the signs have abated, the transfusion can be resumed at a slower rate. Oxyglobin (OPK Biotech, Cambridge, MA) is a purified, polymerized bovine hemoglobin glutamer that can be administered to a ferret in an acute anemic crisis if a donor cannot be located.[48] Doses of 2 mL/kg over 10 to 20 minutes can be administered for ferrets in hypovolemic shock.[48] Oxyglobin was withdrawn from the market in 2010 and is currently not available in the United States, but production resumed in early 2013 and it is now available in Europe (http://www.oxyglobin.com. Accessed July 25th, 2013).

In the author's clinical experience, administration of leuprolide acetate has not proved effective in the management of ferrets with pancytopenia caused by hyperestrogenism. This ineffectiveness may be caused by a delay in the bone marrow's ability to generate new blood cells once the estrogen levels had subsided. It is unknown whether the leuprolide acetate was able to suppress estrogen levels in these ferrets because blood was not collected to measure hormone levels because these ferrets were usually severely anemic.

Aromatase inhibitor: anastrozole

Anastrozole (Arimidex, AstraZeneca Pharmaceuticals LP) is a nonsteroidal inhibitor of the enzyme aromatase, the enzyme responsible for the synthesis of estrogens from androgens. It is labeled for the treatment of breast cancer for postmenopausal women.

A study in 1996[50] compared the effectiveness and safety of anastrozole with other aromatase inhibitors (primarily fadrazole) in vitro and in vivo. It was shown to have significant activity in vitro in human placental aromatase and had maximal activity at 0.1 mg/kg orally in rats by suppression of ovulation and in monkeys by lowering plasma estradiol. In a concurrent part of the study, rats and monkeys were given increased doses of anastrozole to evaluate for adverse effects. No evidence of effect on the synthesis of adrenocorticoids, mineralocorticoids, or primary hormonal effects of anastrozole was detected in any of the test animals. However, there was a significant increase in circulating testosterone in test monkeys (averaging up to 150% of pretreatment values at 7 days after treatment at 0.1 mg/kg).[50]

Anastrozole is currently used as an adjuvant treatment of breast cancer under the brand name Arimidex at a dose of one 1-mg tablet orally every 24 hours (Arimidex drug label). There are currently no published studies in ferrets. It has been trialed in ferrets at 0.1 mg/kg every 24 hours and may be useful for treating ferrets with increased estradiol levels.[17] However, treatment can exacerbate clinical signs related to increased androstenedione levels.[9]

Tamoxifen, another chemotherapeutic medication used for breast cancer in people, blocks estradiol receptors, but seems to have a high incidence of adverse side effects with minimal efficacy.[9] Its use is not recommended in ferrets.[9]

Treatment of Ferret Adrenal Disease Versus Cushing Disease

Because of the pathophysiologic differences, agents used for the treatment of Cushing disease are not recommended for the treatment of adrenal disease in ferrets. These commonly used drugs reduce the production of sex hormones, but result in deleterious effects in treated ferrets because of their method of action.

Mitotane

Mitotane (o,p'-DDD [1,1-(o,p'-dichlorodiphenyl)-2,2-dichoroethane]) is commonly used for the treatment of Cushing disease because it causes inhibition of the adrenal cortex with and without cell destruction.[51] In dogs, this destruction generally involves only the zona fasciculata and reticularis but can also affect the glomerulosa.[52] Use in the ferret has rarely been successful at reducing clinical signs.[53] Destruction of the zona fasciculata causes a decrease in cortisol production that, although ideal for cushinoid patients, is detrimental to treated ferrets, especially those with concurrent insulinoma.[9]

Trilostane

Trilostane is a competitive inhibitor of the enzyme 3b-hydroxysteroid dehydrogenase/isomerase. Deactivating this enzyme prevents side chain cleavage from cholesterol and the synthesis of all adrenocortical products (corticosteroids, mineralocorticoids, and sex hormones).[52] As with mitotane, the loss of corticosteroid and mineralocorticoid production in ferrets can lead to serious complications.

Ketoconazole

Ketoconazole inhibits several cytochrome P-450 enzyme pathways[52] and therefore inhibits the synthesis of corticosteroids, mineralocorticoids, and sex hormones by blocking various intermediate reactions. It shares the same negative effects as mitotane and trilostane.

SUMMARY

Medical management of hyperadrenocorticism in ferrets is a suitable alternative to adrenalectomy and in some cases may be preferable. Various drugs are available for the symptomatic management of the clinical signs of adrenal disease, with GnRH agonists being the most widely used. Although the drugs used treat just the symptoms and not the abnormal adrenal tissue, they seem to have few adverse effects and many can be used concurrently or in conjunction with surgical resection of the diseased adrenal gland. Timely recognition of the less commonly seen, but potentially life-threatening, clinical signs of urethral blockage secondary to prostatic disease and nonregenerative anemia secondary to hyperestrogenism is vital to the successful management of these conditions.

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