Clinical and endocrine responses to treatment with deslorelin acetate implants in ferrets with adrenocortical disease

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Objective—To evaluate the clinical and endocrine responses of ferrets with adrenocortical disease (ACD) to treatment with a slow-release implant of deslorelin acetate.

Animals—15 ferrets with ACD.

Procedure—Ferrets were treated SC with a single slow-release, 3-mg implant of deslorelin acetate. Plasma estradiol, androstenedione, and 17-hydroxyprogesterone concentrations were measured before and after treatment and at relapse of clinical signs; at that time, the adrenal glands were grossly or ultrasonographically measured and affected glands that were surgically removed were examined histologically.

Results—Compared with findings before deslorelin treatment, vulvar swelling, pruritus, sexual behaviors, and aggression were significantly decreased or eliminated within 14 days of implantation; hair regrowth was evident 4 to 6 weeks after treatment. Within 1 month of treatment, plasma hormone concentrations significantly decreased and remained decreased until clinical relapse. Mean time to recurrence of clinical signs was 13.7 ± 3.5 months (range, 8.5 to 20.5 months). In 5 ferrets, large palpable tumors developed within 2 months of clinical relapse; 3 of these ferrets were euthanatized because of adrenal gland tumor metastasis to the liver or tumor necrosis.

Conclusions and Clinical Relevance—In ferrets with ACD, a slow-release deslorelin implant appears promising as a treatment to temporarily eliminate clinical signs and decrease plasma steroid hormone concentrations. Deslorelin may not decrease adrenal tumor growth in some treated ferrets. Deslorelin implants may be useful in the long-term management of hormone-induced sequelae in ferrets with ACD and in treatment of animals that are considered at surgical or anesthetic risk. (*Am J Vet Res* 2005;66:910–914)

Adrenocortical disease (ACD) is a common problem in neutered, middle-aged to old ferrets (*Mustela putorius furo*). The adrenal tissues of these ferrets develop nodular hyperplasia, adenomas, or adenocarcinomas, which produce a variety of steroid hormones, including estradiol, 17-hydroxyprogesterone, and androstenedione. The major clinical signs attributable to these hormones are alopecia in both sexes and a swollen vulva in females. Pruritus, muscle atrophy, hind limb weakness, and sexual activity or aggression are observed less frequently. Males can develop prostatic cysts, prostatitis, and urethral obstruction. As the disease progresses, there is often a decrease in the apparent quality of life. Occasionally, adrenal gland tumors continue to grow, invade tissues locally, and become necrotic; rarely, they rupture causing death. Additional potentially fatal sequelae include metastases and bone marrow suppression associated with chronic exposure to high plasma estrogen concentrations.[1-4,a]

There is speculation that the high prevalence of ACD in pet ferrets is associated with neutering at an early age and may be a result of chronic stimulation of the adrenal gland cortex by pituitary gland gonadotropins (ie, **follicle-stimulating hormone [FSH]** and **luteinizing hormone [LH]**).[1,5,6] Exposure to abnormally long photoperiods associated with indoor housing of pet ferrets is also thought to contribute to the pathogenesis of ACD. Long light cycles of > 8 hours have been shown to stimulate production of **gonadotropin-releasing hormone (GnRH)** and LH and decrease the serum concentration of melatonin, a known antigonadotropic hormone in ferrets.[7] In ferrets, genetic predisposition to adrenal gland tumors and other common endocrine tumors may play a role in the high prevalence of ACD. Ferrets in North America may be highly inbred because of a small founder population; furthermore, large breeding facilities maintain closed colonies, perpetuating an inbred population.[8]

Luteinizing hormone receptors have been detected in normal adrenal gland tissues of humans, mice, and ferrets and in adrenal gland tumors.[6,9-11] Chronic stimulation of the adrenal gland cortex by LH may induce adrenal gland hyperplasia and facilitate tumor induction and growth. Downregulation of GnRH receptors and subsequent suppression of the production and release of the gonadotropin (LH) reduce estrogen production in female and androgen production in male ferrets and eliminate their gender-specific effects.[12,b] In humans, GnRH analogs administered at pharmacologic doses downregulate GnRH receptors at the pituitary gland.[13]

Deslorelin acetate is a synthetic nonapeptide analog of the hypothalamic decapeptide hormone gonadorelin (LH-releasing hormone). Its amino acid sequence varies from that of gonadorelin by having

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D-Trp at position 6 in place of Gly and terminates at position 9 with proethylamide in place of Gly-NH_2. Like gonadorelin, deslorelin stimulates secretion of LH and FSH from the pituitary gland. At high doses, it causes downregulation of GnRH receptors at the pituitary gland, thereby inhibiting production and release of gonadotropins (LH and FSH). Depending on the experimental system used, deslorelin is approximately 30 (range, 10 to 100) times as potent as gonadorelin.

The purpose of the study reported here was to evaluate the clinical and endocrine responses of ferrets with ACD to treatment with a slow-release implant of deslorelin acetate. It was anticipated that this formulation of deslorelin would result in prolonged suppression of the gonadotropins FSH and LH. Adrenal glands were assessed grossly and histologically in an attempt to determine the effect of deslorelin on adrenal gland tissue growth.

Materials and Methods

Fifteen pet ferrets with ACD of varying severity and duration (≥ 2 months) were included in this case series. Informed consent was obtained from all ferret owners. Only ferrets with no known concurrent disease were accepted into the study; the lack of concurrent disease was determined on the basis of history, findings of an initial physical examination and serum biochemical profile, and Hct value. The ferrets were 3 to 7 years old (median age, 5 years) and weighed 0.68 to 1.00 kg. Nine ferrets were female, and 6 were male; all animals had been castrated or spayed before 2 months of age. Five ferrets that had previously undergone left adrenalectomy for the treatment of ACD and had signs of relapse of the disease were included in the case series.

The diagnosis of ACD was confirmed in the ferrets on the basis of clinical findings and results of plasma hormone analyses.[c] Clinical findings included alopecia, pruritus, swollen vulva in females, and increased sexual behaviors and aggression. A subjective assessment of the severity of clinical signs at the start of the investigation (and later in response to deslorelin treatment) was performed by comparing each ferret with a clinically normal ferret. Severity of alopecia was estimated (100% representing full normal pelage and 0% representing whole body alopecia) at every assessment and compared with findings at the initial assessment. Pruritus, vulvar size, sexual behavior, and aggression were evaluated as normal, decreased, no change, or increased from the initial assessment and from the previous assessment. Clinical response to deslorelin was monitored via a physical examination performed monthly. At each examination, clinical evaluations and scoring of the severity of clinical signs in affected animals were performed by the same investigator (RAW) prior to obtaining the results of the plasma hormone assays for that particular time point.

Before treatment, blood was collected for plasma hormone analyses, and examinations were performed after the ferrets were anesthetized with isoflurane; these procedures were performed on the day of SC administration of the deslorelin implant. After administration of the implant, blood was collected for plasma hormone analyses and examinations were performed monthly until relapse of clinical signs was noted. Plasma samples obtained before treatment, at monthly intervals after treatment, and at clinical relapse were analyzed for estradiol, androstenedione, and 17-hydroxyprogesterone concentrations. Plasma hormone concentrations after administration of the implant and at relapse for each animal within the posttreatment and relapse stages were averaged. Examinations included deep abdominal palpation of the adrenal glands in all ferrets. Hematocrit was assessed and serum biochemical analyses were performed for all ferrets before deslorelin treatment and at clinical relapse. Within 2 months of relapse of 1 or more clinical signs (alopecia, pruritus, swollen vulva in females, and increased sexual behaviors and aggression), a celiotomy was performed on 13 of the 15 ferrets to visually examine adrenal glands and surgically remove any adrenal glands that appeared grossly abnormal. Two ferrets did not undergo celiotomy, and measurements of the adrenal glands were made ultrasonographically at the time of clinical relapse.

Each ferret was treated with one 3-mg deslorelin acetate implant[d] that was inserted SC via a single-use syringe, 14-gauge needle at the dorsal aspect of the base of the neck. No suture is needed to close the remaining skin defect after this procedure. Dosages of deslorelin acetate ranged from 3 to 4.41 mg/kg. The implant is manufactured by extruding deslorelin with a matrix from low–melting-point lipids and biological surfactant. The implant is 10 mm long and 2.3 mm in diameter and releases doses of > 1 µg/d for periods of > 1 year. No local or systemic adverse reactions have been observed in implant-treated dogs or cats. Implants can be removed surgically.

Steroid hormone concentrations of estradiol, androstenedione, and 17-hydroxyprogesterone were determined in plasma samples. Plasma hormone concentrations were measured via commercially available radioimmunoassays validated for use in ferrets.[c] Plasma hormone concentrations before deslorelin treatment were compared with reference ranges as follows: estradiol, 30 to 180 pmol/L; androstenedione, 1 to 15 nmol/L; and 17-hydroxyprogesterone, 0.05 to 0.8 nmol/L.[1,2,a] These values of plasma hormone concentrations before deslorelin treatment were used in conjunction with clinical signs to confirm a diagnosis of ACD.

Statistical methods—Plasma hormone concentrations were measured in samples obtained before and after deslorelin treatment and at clinical relapse. During the posttreatment and relapse stages, blood samples were obtained from each ferret monthly and results of plasma hormone assays for each animal were averaged; these mean values were used in a repeated-measures analysis[e] to compare plasma hormone values before treatment, after treatment, and at relapse of clinical signs. The model consisted of stage (before treatment, after treatment, and at clinical relapse) with ferret being considered as the experimental unit. Differences in individual least squares means for plasma hormone concentrations were evaluated by use of the least significant difference assessment. Results were log transformed prior to statistical analysis, and data are presented as geometric means ± SEM. This transformation was necessary to meet the assumption of normality. In addition, the means (before treatment, after treatment, and at relapse) were tested against the upper reference limit by use of a *t* test. A *t* test was used to compare the difference in time to clinical relapse between ferrets that had both adrenal glands and those that had previously had the left adrenal gland removed. A value of $P < 0.05$ was considered significant.

Results

Clinical findings—Prior to treatment, all 15 ferrets had clinical signs consistent with ACD. The most common findings were bilateral, symmetric, truncal alopecia in males and females, and vulvar swelling of at least 2 months' duration in females. No ferrets had palpably enlarged adrenal glands at the time of administration of the deslorelin implant. No adverse effects from deslorelin implants were noted during the study.

Before and after deslorelin treatment, values of Hct and serum biochemical variables were within reference intervals for all ferrets, except 2 that had concurrent disease that was diagnosed after implantation. Lymphoma was diagnosed in 1 ferret, and its serum alkaline phosphatase activity was high; insulinoma was diagnosed in the other ferret, and its blood glucose concentration was low. These abnormalities were thought to be associated with the concurrent disease in each ferret. In the first 14 days after administration of the deslorelin implant, most owners reported that the treated ferrets were more alert and had increased activity levels, compared with their behavior before treatment. Five of 15 ferrets had varying degrees of pruritus before treatment; the severity of pruritus was greatly decreased in all 5 animals by 3 weeks after treatment. Sexual behaviors or aggression observed in 5 ferrets before treatment was greatly decreased or eliminated by 3 weeks after treatment. Eight of the 9 female ferrets had a swollen vulva before treatment; by 10 to 14 days after treatment, vulvar turgidity was decreased, and by 6 weeks after treatment, all 8 ferrets had a normal appearing vulva. By 6 weeks after treatment, most ferrets had regrowth of hair. Thirteen of 15 ferrets initially had 40% to 60% pelage; by 8 weeks after treatment, these ferrets had 90% to 100% coat cover. The remaining 2 ferrets initially had 40% and 50% pelage; by 12 weeks after treatment, these ferrets had 70% to 80% pelage, which was maintained throughout the study period. Three ferrets had thin, incomplete regrowth of the hair on the tail.

Three ferrets required additional evaluation and treatment for concurrent diseases during the study period. Shortly after deslorelin implantation, prostatitis was diagnosed in 1 ferret (determined on the basis of clinical signs and results of urinalysis). This ferret was treated orally with trimethoprim sulfamethoxazole[f] (30 mg/kg, q 12 h, for 21 days). Insulinoma was suspected in 1 ferret on the basis of repeated low blood glucose concentrations and clinical signs consistent with the disease. This ferret was treated orally with prednisone[g] (0.5 mg/kg, q 12 h) for the last 3 months of the study period before surgical removal of the insulinoma. Another ferret developed peripheral lymph node enlargement during the study period; histologic evaluation of a popliteal lymph node biopsy specimen confirmed a diagnosis of lymphoma. This ferret was treated orally with prednisone[f] (0.5 to 1.0 mg/kg, q 12 h), producing a moderate reduction in lymph node size. The concurrent diseases in all 3 ferrets were managed successfully during the study period.

All 15 ferrets had relapse of clinical signs after deslorelin treatment. The mean ± SD time to recurrence of clinical signs was 13.7 ± 3.5 months (range, 8.5 to 20.5 months). In the 5 ferrets that had previously undergone left adrenalectomy, the mean time to clinical relapse was 16.3 ± 2.8 months. In the remaining 10 ferrets from which an adrenal gland had not been removed, the mean time to clinical relapse was 12.4 ± 3.1 months. This difference in time to clinical relapse between adrenalectomized and nonadrenalectomized ferrets was significant ($P < 0.05$).

In 5 of 15 ferrets, large (> 2 cm) periadrenal abdominal masses were detected by deep abdominal palpation within 2 months of clinical relapse. Via exploratory celiotomy, these masses were identified as enlarged adrenal glands and confirmed histologically as adrenal gland tumors. Three of these 5 ferrets were euthanatized during surgery because of nonresectable necrotic tumors (2 ferrets) or metastases to the liver (1 ferret).

After relapse of clinical signs, grossly abnormal adrenal glands were surgically removed and evaluated histologically. Twenty-five adrenal glands were examined either grossly during laparotomy (23 adrenal glands in 13 ferrets) or ultrasonographically (2 adrenal glands in 2 animals); 18 glands were surgically removed and examined histologically. Having undergone adrenalectomy previously, 5 ferrets had no left adrenal gland. Two of these ferrets did not undergo surgery, and the right adrenal glands were examined via ultrasonography; the glands were considered normal in size and shape. The 3 remaining ferrets had the right adrenal gland and tumor removed or had a subtotal adrenalectomy. During surgery, 7 adrenal glands were considered to be of normal size and shape and were left in situ. Of the 18 glands examined histologically, hyperplasia was diagnosed in 1, adenoma in 7, and adenocarcinoma in 10.

Plasma hormone assay results—Before deslorelin treatment, findings of plasma hormone analyses supported a diagnosis of ACD in all ferrets. At least 1 of the 3 hormones assessed was greater than the upper reference limit in all ferrets; 7 ferrets had 2 and 3 ferrets had 3 plasma hormone concentrations that were greater than the upper reference limit. Prior to treatment, 7 of 15 ferrets had plasma estradiol concentrations greater than the upper reference limit, 12 of 15 ferrets had plasma androstenedione concentrations greater than the upper reference limit, and 9 of 15 ferrets had plasma 17-hydroxyprogesterone concentrations greater than the upper reference limit. After implantation, plasma estradiol concentrations remained within reference range for all animals until 8.5 months after treatment, at which time concentrations began to increase in some ferrets. Compared with values before treatment, mean plasma 17-hydroxyprogesterone concentrations decreased significantly after treatment in all but 1 ferret in which the concentration exceeded the upper reference limit throughout the study period. A similar pattern of change was detected in plasma androstenedione concentrations in that the mean concentration was significantly decreased after treatment, compared with pretreatment values. However, in some ferrets, the values remained near or slightly above the upper reference limit for most of the study period.

Geometric mean ± SEM plasma hormone concentrations before and after treatment and after relapse of clinical signs were calculated. Before treatment, after treatment, and after clinical relapse, mean plasma estradiol concentrations in the ferrets were 141 ± 0.435 pmol/L, 110 ± 0.435 pmol/L, and 160 ± 0.462 pmol/L, respectively. After treatment, the concentration was significantly ($P < 0.05$) lower than either the value before treatment or the value at relapse. Following

treatment with deslorelin, the plasma estradiol concentration was significantly ($P < 0.05$) decreased to below the upper reference limit of 180 pmol/L.

Before treatment, after treatment, and after clinical relapse, mean plasma 17-hydroxyprogesterone concentrations in the ferrets were 1.87 ± 1.083 nmol/L, 0.34 ± 1.148 nmol/L, and 1.74 ± 1.083 nmol/L, respectively. The concentrations after treatment and after clinical relapse were significantly ($P < 0.05$) lower than the value before treatment. Following treatment with deslorelin, the plasma 17-hydroxyprogesterone concentration was significantly ($P < 0.05$) decreased to below the upper reference limit of 0.8 nmol/L.

Before treatment, after treatment, and after clinical relapse, mean plasma androstenedione concentrations in the ferrets were 30.11 ± 0.812 nmol/L, 9.13 ± 0.812 nmol/L, and 15.22 ± 0.861 nmol/L, respectively. After treatment, the concentration was significantly ($P < 0.05$) lower than either the value before treatment or the value at relapse. Following treatment with deslorelin, the androstenedione concentration was significantly ($P < 0.05$) decreased to below the upper reference limit of 15 nmol/L.

Discussion

Treatment of ferrets with ACD with a slow-release formulation of deslorelin resulted in significant decreases in plasma estradiol, androstenedione, and 17-hydroxyprogesterone concentrations and eliminated or greatly decreased the clinical signs associated with this disease. There were no deslorelin-related adverse effects in ferrets during the study period. Hematocrit values and serum biochemical variables were within reference intervals before and after deslorelin treatment, except for the low blood glucose concentration detected in the ferret with insulinoma and high alkaline phosphatase activity detected in the ferret with lymphosarcoma. Decreases in plasma hormone concentrations were temporary, and clinical signs began to recur at 8.5 months after treatment. The duration of clinical effect ranged from 8.5 to 20.5 months (mean, 13.7 ± 3.5 months). Similar variability in duration of activity of deslorelin implants and other GnRH agonists has been reported in dogs, cats, and cattle.[14-16] The reason for this variability is unknown but may be related to dose and individual sensitivity to the GnRH analog. In the present case series, age, sex, and weight (dose) had no apparent effect on duration of activity. However, the duration of clinical effect in ferrets that had previously undergone adrenalectomy (left gland) was almost 4 months longer than that of ferrets with both adrenal glands. This may be a reflection of the smaller total adrenal gland mass involved in hormone production in animals with only 1 adrenal gland.

On inclusion of ferrets in the study, no attempt was made to differentiate nodular hyperplasia from adenoma or carcinoma of the adrenal gland. Results of 2 previous histologic studies[3,4] of adrenal gland tissue in ferrets with ACD indicated that the prevalence of pathologic changes varied from 26% to 56% for nodular hyperplasia, 64% to 16% for adenoma, and 10% to 26% for carcinoma. In another study[8] in ferrets, the prevalence of adrenocortical carcinoma was twice that of adrenocortical adenoma. In the present case series, hyperplasia, adenoma, and adenocarcinoma were diagnosed in 1 (6%), 7 (39%), and 10 (55%) of 18 glands examined histologically, respectively. The higher prevalence of adenocarcinoma observed in the present investigation might be a function of the limited number of animals evaluated. Assuming that pathologic changes in adrenal glands progress from hyperplasia to adenoma to adenocarcinoma, the increased prevalence of adenocarcinoma in the ferrets of the present case series may simply be a function of longer survival times and, hence, development of more advanced pathologic changes before surgical removal of the glands. Another possibility is that deslorelin treatment somehow increased the prevalence of adenocarcinoma in ferrets. This latter possibility seems unlikely because in an earlier study,[12] the use of leuprolide acetate (a slow-release GnRH analog of similar structure as deslorelin) resulted in a similar clinical response with no evidence of enhanced tumorigenesis. In addition, widespread clinical use of slow-release formulations of deslorelin and other GnRH analogs for chronic indications in human and veterinary practice do not suggest these compounds are tumorigenic.[13-16] Nonetheless, all ferrets had a similar clinical response to deslorelin treatment, regardless of individual adrenal gland abnormalities.

In 5 of 15 deslorelin-treated ferrets, large palpable tumors developed within 2 months of clinical relapse. This suggests that deslorelin may not control tumor growth or if it does, that the effect is lost after some time in some ferrets. Tumors that are initially hormone dependent can progress over time to a hormone-resistant state and may grow regardless of the removal of stimulatory hormones.[17] In such instances, downregulation of GnRH receptors will not prevent further tumor growth. The effectiveness of deslorelin in ferrets with specific types of adrenal gland disease and its effect on tumor growth need to be further evaluated.

Our data indicate that a slow-release formulation of deslorelin can be used to temporarily decrease plasma steroid hormone concentrations and eliminate or decrease the clinical signs of ACD in ferrets. Chronic suppression of gonadotropin production and release has not yet been thoroughly investigated in ferrets, and the long-term effects on adrenal gland hyperplasia or tumor growth are unknown. Presently, surgical removal of the adrenal tumor is the only curative treatment, but slow-release depot formulations of deslorelin appear promising as a safe and minimally invasive short-term alternative to adrenalectomy.[2-4,12] Deslorelin may be especially helpful in the treatment of old or medically compromised ferrets with ACD that may not be able to undergo anesthesia and surgery and in ferrets with ACD that have previously undergone unilateral adrenalectomy.

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