Effects of melatonin administration on the clinical course of adrenocortical disease in domestic ferrets

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Objective—To evaluate the effect of oral administration of melatonin on clinical signs, tumor size, and serum steroid hormone concentrations in ferrets with adrenocortical disease.

Design—Noncontrolled clinical trial.

Animals—10 adult ferrets with clinical signs of adrenocortical disease (confirmed via serum hormone concentration assessments).

Procedures—Melatonin (0.5 mg) was administered orally to ferrets once daily for 1 year. At 4-month intervals, a complete physical examination; abdominal ultrasonographic examination (including adrenal gland measurement); CBC, serum biochemical analyses; and assessment of serum estradiol, androstenedione, and 17α-hydroxyprogesterone concentrations were performed. Serum prolactin and dehydroepiandrosterone sulfate concentrations were evaluated at the first, second, and last examinations, and serum cortisol concentration was evaluated at the first and last examinations.

Results—Daily oral administration of melatonin greatly affected clinical signs of adrenocortical disease in ferrets; changes included hair regrowth, decreased pruritus, increased activity level and appetite, and decreased vulva or prostate size. Mean width of the abnormally large adrenal glands was significantly increased after the 12-month treatment period. Recurrence of clinical signs was detected in 6 ferrets at the 8-month evaluation. Compared with pretreatment values, serum 17α-hydroxyprogesterone and prolactin concentrations were significantly increased and decreased after 12 months, respectively.

Conclusions and Clinical Relevance—Results suggest that melatonin is a useful, easily administered, palliative treatment to decrease clinical signs associated with adrenocortical disease in ferrets, and positive effects of daily treatment were evident for at least an 8-month period. Oral administration of melatonin did not decrease adrenal gland tumor growth in treated ferrets. (J Am Vet Med Assoc 2006;229:1743–1748)

Abbreviations

ACD Adrenocortical disease
GnRH Gonadotropin-releasing hormone
LH Luteinizing hormone
FSH Follicle-stimulating hormone
DHEAS Dehydroepiandrosterone sulfate
17-OHP 17α-hydroxyprogesterone
UW-VMTH University of Wisconsin Veterinary Medical Teaching Hospital

Adrenocortical disease is a common disorder of domestic ferrets (Mustela putorius furo). In ferrets, the disease may be associated with a variety of pathologic changes in adrenal glands including hyperplasia, adenoma, and adenocarcinoma. Adrenocortical adenocarcinoma is one of the most common neoplastic diseases of ferrets in the United States. This disease is typically identified in neutered male and female ferrets that are 3 to 5 years old. The pathogenesis of this disease is not well understood, but ACD in ferrets clearly differs from hyperadrenocorticisms in dogs and is not influenced by ACTH.

A correlation between early neutering and age of onset of this disease has been determined. It has been hypothesized that neutering causes the loss of negative gonadal feedback on endogenous hypothalamic GnRH. Without the feedback of gonadal hormones, there would be no signal to decrease release of GnRH, leading to stimulation of adrenal gland cortices by LH and FSH. Findings of a GnRH-challenge study in ferrets support the importance of LH in the pathogenesis of ACD in ferrets. Long light cycles (> 8 hours) stimulate GnRH and LH synthesis and decrease circulating melatonin concentration, a known antagonodotropic hormone in ferrets. This has lead to the speculation that housing ferrets indoors is a practice associated with abnormally long photoperiods that contribute to the pathogenesis of ACD.

The most consistent clinical sign of ACD in ferrets is bilateral hair loss, which may be severe. Affected ferrets may also have signs of pruritus, thinning of skin, swollen vulva, and lethargy. Male ferrets can develop prostatic hypertrophy and urethral obstruction. Diagnosis of adrenocortical disease in ferrets is made on the basis of clinical signs, ultrasonographic evidence of an abnormally large adrenal gland (both glands may be affected), and high serum concentrations of 1 or more of the steroid reproductive hormones. Values for adrenal gland size in clinically normal ferrets as determined via ultrasonographic examination have been established. In ferrets with...
ACD, circulating concentrations of at least 1 of the serum androgens (androstenedione, DHEAS, or estradiol) and 17-OHP are high. Reference ranges for these hormones have been established for ferrets.\textsuperscript{11,12}

The preferred treatment for ACD in ferrets is surgical removal of the affected gland.\textsuperscript{13} Complications with surgical treatment include recurrence of the tumor because of incomplete excision or hyperplasia; neoplasia may also develop in the remaining adrenal gland. In 1 study\textsuperscript{14} in ferrets, the recurrence rate of ACD after unilateral adrenalectomy was 17%, with clinical signs recurring within 3 to 14 months after surgery. Metastatic disease in association with ACD is rare. Medical management of ferrets with ACD and drugs that are currently available for treatment of hyperadrenocorticism in humans, dogs, and cats (ie, mitotane, ketoconazole, or streptozocin) is generally unsuccessful and may be accompanied by adverse effects. Leuprolide acetate,\textsuperscript{15} a long-acting synthetic GnRH analog, administered via IM injection can relieve clinical signs of ACD in ferrets for 2 to 8 months.\textsuperscript{16} Exogenous administration of GnRH analog causes a surgelike release of FSH and LH after a single injection of leuprolide acetate, but long-term treatment downregulates GnRH receptor expression in the anterior portion of the pituitary gland, decreasing release of FSH and LH and potentially reducing adrenal gland stimulation by these hormones.\textsuperscript{17,18} One leuprolide treatment regimen includes IM injections every 1 to 4 months, depending on the formulation. Subcutaneous placement of a slow-release implant of deslorelin acetate, another synthetic GnRH analog, may temporarily eliminate clinical signs and decrease plasma steroid hormone concentrations but may not decrease adrenal tumor growth.\textsuperscript{19}

Exogenous melatonin has been given to farmed mink to stimulate molt and subsequent winter coat growth and has been used in studies\textsuperscript{20-22} of seasonal pelage cycles in ferrets. Endogenous melatonin is an indoleamine, the principal hormone of the vertebrate pineal gland, and the circulating concentration sustains a remarkable circadian rhythm. Biosynthesis of melatonin involves the hydroxylation and decarboxylation of tryptophan to form serotonin. The synthesis of melatonin from serotonin is catalyzed by 2 enzymes that are largely confined to the pineal gland. Melatonin synthesis is controlled by the light-dark cycle and increases during the dark phase of each day. Melatonin enters the bloodstream through passive diffusion. Its exact mechanism of action is poorly understood but is thought to involve regulation of GnRH and possibly prolactin secretion through melatonin-specific receptors in the pituitary gland. Mink are a species that display renewed reproductive activity during fall and winter (short days); in those animals, circulating melatonin concentration increases in fall with the onset of winter coat growth and circulating prolactin concentration increases in spring with the onset of spring molt.\textsuperscript{23,24} In mink, administration of exogenous melatonin during the summer months (long days) initiates molt and subsequent growth of a thick winter coat and decreases circulating prolactin concentration.\textsuperscript{25,26} Results of a recent study\textsuperscript{27} suggest that the effects of melatonin on hair growth in mink involve regulation of prolactin; prolactin receptors have been identified in the adrenal glands and skin of mink.

Ferrets are a species that has renewed reproductive activity during spring and summer (long days). Administration of exogenous melatonin in the form of 8-mg continuous-release implants results in coat growth earlier in winter and estrus earlier in spring, compared with findings in untreated ferrets.\textsuperscript{28} Two recent reports\textsuperscript{29,30} of the use of 5.4-mg constant-release melatonin implants in ferrets with presumed ACD state that there is a decrease in severity of clinical signs during the 3 to 4 months after initiation of treatment. The purpose of the study reported here was to evaluate the effect of oral administration of melatonin on clinical signs, tumor size, and serum steroid hormone concentrations in ferrets with ACD. We hypothesized that consistent oral administration of melatonin will reduce ACD-associated clinical signs in ferrets. To our knowledge, this study is the first long-term investigation of the clinical and endocrine responses of ferrets with ACD to treatment with melatonin.

**Materials and Methods**

Ferrets from a ferret rescue facility were assessed for inclusion in the study on the basis of certain criteria as follows: the ferret had ≥1 clinical sign consistent with adrenocortical disease (eg, hair loss, pruritus, or swollen vulva or enlarged prostate); was neutered; and had at least 1 abnormal (width > 3.3 mm) adrenal gland, as determined ultrasonographically, and the owner of the rescue facility had elected not to pursue surgical treatment for that ferret. The diagnosis of ACD was confirmed when serum concentrations of one or more of the adrenal hormones tested were high. Among 16 ferrets initially evaluated, 10 adult ferrets (6 males and 4 females) met the inclusion criteria.

Physical examination findings and historical data (when available) were obtained for each ferret in the study. Ferret 1 was a 6-year-old neutered male with unknown history that had been at the rescue facility for 1 year. Initial physical examination findings included severe, generalized alopecia; dry skin; large adrenal glands (width of left gland on ultrasonographic examination, 7.2 mm; width of right gland, 3.8 mm; upper reference limit of left gland, 3.3 mm; upper reference limit of right gland, 3.0 mm); and a palpably large prostate (width, 19 mm; the prostate cannot be easily palpated on a healthy male ferret). Ferret 2 was a 5-year-old neutered male that had been kept at the rescue facility for 2 years. The left adrenal gland was surgically removed when the ferret was 3 years old; histologic evaluation revealed the presence of an adrenal gland adenoma. Initial physical examination findings included alopecia at the tail base, large right adrenal gland (width, 3.4 mm), and a palpably large prostate (width on ultrasonographic examination, 7.8 mm). Ferret 3 was a 4-year-old neutered male with unknown history that had been kept at the rescue facility for 1 year. Initial physical examination findings included severe generalized alopecia, mild pruritus, and a large left adrenal gland (width, 7.8 mm). Ferret 4 was a 3-year-old neutered male with unknown history that had been recently acquired by the rescue facility. Initial physical examination findings included severe dorsal alopecia and large adrenal glands (width of left gland, 4 mm; width of right gland, 3.8 mm). Ferret 5 was also a 3-year-old neutered male with unknown history that had been recently acquired by the rescue facility. Initial physical examination findings included bilateral thinning of hair, alopecia at the tail base, and large adrenal glands (width of left gland, 4.1 mm).
mm; width of right gland, 3.4 mm). Ferret 6 was a 5-year-old spayed female previously owned by an individual for 2 years before arriving at the rescue facility. Initial physical examination findings included thin hair on the dorsal aspect of the head, swollen vulva, and large adrenal glands (width of left gland, 6.3 mm; width of right gland, 4 mm). Ferret 7 was a 7-year-old spayed female. At 4 years of age, the left adrenal gland was surgically removed and a biopsy specimen was collected from the right adrenal gland; histologic findings were indicative of bilateral adrenal gland hyperplasia. Initial physical examination findings included thin hair along the dorsum, swollen vulva, and a large right adrenal gland (width, 4.2 mm). Ferret 8 was a 7-year-old spayed female with unknown history that had been kept at the rescue facility for 1 year. Initial physical examination findings included generalized alopecia, atrophy of lumbar muscles and muscles of the hind limbs, swollen vulva, and a large left adrenal gland (width, 6.9 mm). Ferret 9 was a 2-year-old spayed female with unknown history that had been kept at the rescue facility for 10 days. Initial physical examination findings included rough coat, thinning hair on the tail, apparently normal vulva, and a large left adrenal gland (width, 5 mm). Ferret 10 was a 6-year-old neutered male with unknown history that had been kept at the rescue facility for 6 months. Initial physical examination findings included generalized hair loss and a large right adrenal gland (width, 6 mm). Ferret 10 died prior to the 3-month recheck examination; therefore, no analyzable data were collected from this ferret.

All ferrets received 0.5 mg of melatonin orally daily. A suspension of 1.0 mg of melatonin/mL was prepared by dissolving 2.5 mg of commercially available melatonin tablets in sterile water and adding syrup vehicle to the desired concentration. Suspensions were prepared and dispensed by the UW-VMTH Pharmacy at 6-month intervals. This study was approved by the University of Wisconsin School of Veterinary Medicine Animal Care and Use Committee. The rescue facility owner was aware that administration of melatonin to ferrets is an extralabel treatment and gave full consent; the owner is believed to have reliably administered the medication at the rescue facility and recorded all treatments in the ferrets’ records.

At the initiation of the study in early spring and every 4 months for a period of 1 year, each ferret underwent a complete physical examination, which included measurement of body weight and detailed assessments of the pelage, skin, and vulva, if applicable. At each examination, a report for the ferret was obtained from the owner, including a subjective evaluation of activity, appetite, and degree of pruritus. Isoflurane was administered by mask to anesthetize the ferret for abdominal ultrasonography. Blood was collected from the cranial vena cava and placed into serum separator tubes and tubes containing EDTA. Blood smears were prepared from samples with EDTA, and a CBC was performed within 24 hours of blood sample collection by use of an automated analyzer at the UW-VMTH Clinical Pathology Laboratory. Manual differential WBC counts (100 to 200 cells) were performed on blood smears stained with Wright’s stain. Tubes containing separated serum were centrifuged immediately, and analytes were measured by use of an automated chemical analyzer within 24 hours of collection. Remaining serum was frozen at −70°C. The first blood sample was taken 1 day before treatment was initiated.

For each ferret, ultrasonographic images of the abdomen were obtained by use of an ultrasonography machine with a 7.5-MHz linear transducer. After processing, images of the output signal were collected via computer-assisted direct digitization. Adrenal gland measurements were made from the static video images by use of built-in calipers.

Serum concentrations of estradiol, 17-OHP, androstenedione, DHEAS, and cortisol were measured within a week of each blood collection via radioimmunoassays validated for ferrets. Serum concentrations of estradiol, 17-OHP, and androstenedione were evaluated after each blood collection; serum DHEAS concentration was not measured at the 9-month evaluation because of a change in laboratory policy regarding the definition of components of an adrenal gland assessment panel in ferrets. Serum cortisol concentration was measured at the first and last blood collections. Serum prolactin concentration was assessed via a protein radioimmunoassay validated for ferrets; serum prolactin concentrations were parallel to the standard prolactin curve via linear regression with a parallel line biological assay. Prolactin assays were completed for all ferrets for which there was sufficient serum available after completion of all other tests. Assays were run in 2 batches; the first batch included the pretreatment and 4-month serum samples, and the last batch included the 8- and 12-month serum samples.

Ferrets that died during the study underwent a complete necropsy. Necropsies were completed by the UW-VMTH Pathology Service.

The statistical model for each response was a repeated-measures ANOVA with an autoregressive correlation structure over months within each ferret. Plots of the residuals versus fitted values and residuals versus normal quantiles were generated to evaluate the adherence of the data to the ANOVA assumptions of homogeneous variance and normality, respectively. For 3 of the responses (serum progesterone, DHEAS, and androstenedione concentrations), a log transformation of the response was required to improve the adherence to the assumptions. For each response, if the overall ANOVA F test indicated differences between the evaluation time points, Tukey-adjusted pairwise tests were subsequently performed to determine exactly which time points differed. A value of P < 0.05 was considered significant.

Results

Clinical signs—All ferrets had some degree of hair loss at the onset of the study, varying from total alopecia to patchy, thinning hair. All but 1 ferret (ferret 4) had marked hair improvement within the first 4 months of treatment; however, 6 of the 9 remaining ferrets had renewed hair loss at the 8-month examination. Three ferrets (ferrets 1, 5, and 6) developed and maintained a normal coat throughout the study period. Three of 4 females had a swollen vulva prior to melatonin treatment. In 2 females (ferrets 7 and 8), the swollen vulva resolved within the first 4 months of treatment but recurred between 8 to 12 months after the start of treatment. Of the 5 males, 2 (ferrets 1 and 2) had a markedly large prostate (determined via palpation and ultrasonographic examination; ultrasonographically, the glands were 19 and 7.8 mm in width) prior to melatonin treatment. Both ferrets had a marked decrease in prostate size after 4 months of treatment (decreased to 5.1 and 4.0 mm in width, respectively) and had minimal subsequent changes in width at the 8- or 12-month examinations.

The primary caregiver reported marked increased activity and improved appetite in all ferrets within the first 4 months of treatment and maintenance of good activity and appetite throughout the study period. One ferret (ferret 1) was reported to have pruritus at the beginning of the study, but pruritus-associated behaviors resolved within the first 3 months of treatment. The primary caregiver provided no other reports of pruritus in any of the study animals throughout the remainder of the study period.
Clinicopathologic analyses—One ferret (ferret 2) in the study was consistently hypoglycemic at each blood collection and was suspected of having a coexistent insulinoma. There were no other abnormal findings in CBC and serum biochemical results for any of the 9 other ferrets.

Serum hormone concentrations—Serum steroid hormone concentrations were assessed according to the schedule described previously (Table 1). Before treatment, results of hormone analyses supported a diagnosis of ACD in all ferrets; all ferrets had at least 1 serum hormone concentration that was greater than the upper reference limit. Mean serum cortisol concentrations did not change significantly during the study period. Serum concentrations of DHEAS and androstenedione decreased in 7 of 9 ferrets after 4 months of treatment; subsequently, concentrations increased progressively in all ferrets through the end of the study. These changes in mean serum concentrations of DHEAS and androstenedione were not significant.

Although serum concentration of 17-OHP decreased in 7 of 9 ferrets after 4 months of treatment (Figure 1), mean concentration of 17-OHP was not significantly different from the pretreatment value. Mean concentrations of 17-OHP at 8 and 12 months were significantly (P < 0.02 and < 0.001, respectively) increased, compared with the 4-month value (Table 1). Mean serum concentration of 17-OHP after 12 months of treatment was significantly (P = 0.003) greater than the pretreatment value.

After 4 months of treatment, serum estradiol concentration had decreased in all ferrets (Figure 2); mean estradiol concentration was significantly (P = 0.002) less than the pretreatment value (Table 1). Mean serum estradiol concentrations at 8 and 12 months were significantly (P = 0.004 and < 0.001, respectively) greater than the 4-month value but were not significantly different from the pretreatment concentration.

Mean serum prolactin concentrations steadily decreased during the treatment period in all but 1 ferret (ferret 9). Before initiation of treatment, mean serum prolactin concentration was 1.2 ± 0.1 ng/mL (assessed in only 5 ferrets for which sufficient sample volumes were available). After 4 months of treatment, mean serum prolactin concentration was 1.1 ± 0.2 ng/mL. After 8 months of treatment, mean serum prolactin concentration was 0.3 ± 0.6 ng/mL (data available for 7 ferrets). Compared with both the pretreatment and 4-month concentrations, the mean serum prolactin concentration at the 12-month examination was significantly (P = 0.004 and 0.02, respectively) greater than the pretreatment. The changes in prolactin concentration after 12 months were significantly different from 4-month value for this variable.

Figure 1—Serum 17-OHP concentrations in 9 ferrets (designated 1 through 9) with ACD before (pretreatment) and during treatment (initiated in spring) with melatonin (0.5 mg) once daily for 12 months. All ferrets had increased serum 17-OHP concentrations after 8 and 12 months of treatment, compared with pretreatment. Mean serum 17-OHP concentration at the 12-month examination was significantly (P < 0.05) greater than the pretreatment value.

Figure 2—Serum estradiol concentrations in 9 ferrets with ACD before (pretreatment) and during treatment (initiated in spring) with melatonin (0.5 mg) once daily for 12 months. All ferrets had increased serum estradiol concentration after 8 and 12 months of treatment, compared with pretreatment values. Mean serum estradiol concentration at the 8-month examination was significantly (P < 0.05) greater than the pretreatment value. See Figure 1 for key.
lower. There was no significant difference between the pretreatment serum prolactin concentration and the 4-month value.

Adrenal gland measurements—Abdominal ultrasonography was performed for all ferrets in the study at each examination to assess the widths of the left and right adrenal glands (Table 2). However, there were several ultrasonographic examinations in which one or both adrenal glands could not be visualized; therefore, the sample size for calculation of mean adrenal gland width varied among examinations. The reference values for adrenal gland width in ferrets were defined as 2.8 ± 0.5 mm for the left adrenal gland and 2.6 ± 0.4 mm for the right adrenal gland. Most of the adrenal glands increased in width over time, including the adrenal glands that may have been within reference range prior to treatment. The width of the abnormally large adrenal gland prior to treatment was compared with its width at the last measurement, which was either after 12 months of treatment or the last measurement obtained prior to death. There was a significant increase in width of the initially large adrenal gland in all ferrets; the mean percentage increase in width of the large adrenal gland was 47% (range, 4% to 131%).

Necropsy—Ferret 10 died after only 3 months of melatonin treatment. This ferret had acute gastrointestinal hemorrhage of unknown etiology. Histologically, adrenocortical carcinoma was identified in the left adrenal gland and the right adrenal gland was considered normal. There was also evidence of myocardial fibrosis, lymphocytic myocarditis, and mild interstitial lymphoplasmacytic nephritis.

Ferret 3 died after 10 months of melatonin treatment. The cause of death was renal disease including intratubular oxalate crystals consistent with a history of possible toxic plant ingestion. There was postmortem evidence of cardiac disease and acute mild hemorrhagic enteritis. This ferret had adrenocortical carcinoma of the left adrenal gland and adrenocortical adenoma of the right adrenal gland.

Ferret 7 also died after 10 months of melatonin treatment. The cause of death was acute hemorrhage of hepatocellular carcinoma that resulted in hemoperitoneum. Two years prior to the study, the left adrenal gland had been surgically removed and a biopsy procedure performed on the right adrenal gland. Histopathologic findings for the left adrenal gland were not available; however, the right adrenal gland was affected with adrenocortical carcinoma and fibrous adhesions to the liver.

Discussion

Treatment of ferrets with ACD via oral administration of melatonin (0.5 mg/d) resulted in temporary reduction of clinical signs, including hair regrowth, decreased prostate size, and increased vigor. On the basis of findings of physical examinations and clinicopathologic analyses at 4-month intervals, there was no deleterious response to melatonin treatment during the study. All ferrets tolerated administration of the oral formulation well.

Oral administration of melatonin has been used successfully in the treatment of dogs with recurrent flank alopecia and decreases circulating reproductive hormone concentrations in both male and female dogs. In dogs, melatonin likely has a negative influence on secretion of endogenous GnRH, thereby decreasing secretion of LH and FSH and ultimately decreasing circulating concentrations of the sex hormones. This theory is supported in the present study by the significant decrease in serum estradiol concentration after ferrets received the first 4 months of treatment, compared with the pretreatment value. Thereafter, serum estradiol concentration increased significantly from the 4-month value. Furthermore, serum 17-OHP concentration was significantly increased from the pretreatment value after 12 months of treatment, whereas there was no significant change in serum concentrations of androstenedione and DHEAS throughout the study. These data suggest that as ACD progressed in the study ferrets, the daily treatment with melatonin at the study dose was insufficient to maintain the negative influence on GnRH secretion or that the target receptor for melatonin became refractory to the exogenous treatment over time. The increases in serum concentrations of estradiol and 17-OHP were coincident with a return of clinical signs, including hair loss, in several study ferrets.

The exact mechanism of hair growth stimulation after oral treatment with melatonin remains speculative in mink, dogs with recurrent flank alopecia, and the ferrets in the present study. It has been suggested that melatonin may have a direct effect on prolactin secretion and therefore affect hair growth; this is supported by findings of a study in dogs, which indicated that early growth of winter fur was initiated when prolactin secretion was inhibited. However, in that study, serum prolactin concentration was unaffected by oral administration of melatonin. Another theory is that melatonin may directly effect hair follicles; hair shaft growth is longer in follicles that are cultured in vitro with melatonin than it is in those that are cultured without melatonin. In the present study, the serum prolactin concentrations in ferrets with ACD were low, compared with previously published values in normal ferrets, this difference is interesting

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Numbers in parentheses represent number of adrenal glands included in the mean. *Includes abnormally large and apparently normal adrenal glands.

Table 2—Mean ± SD adrenal gland width* (mm) in ferrets with ACD before and during treatment (initiated in spring) with melatonin (0.5 mg) once daily for 12 months.
and merits further investigation. Paradoxically, the progressive decrease in serum prolactin concentration throughout the 12-month study period (evident in all but 1 ferret) was not associated with continued hair growth in all ferrets. Further investigation into the relationship between melatonin and prolactin in ferrets is warranted.

The measurable decrease in prostate width in 2 of the ferrets after initiation of melatonin treatment was not surprising. In humans and rats, melatonin reduces the number and size of prostatic epithelial cells. At the 12-month examination, the width of the abnormally large adrenal gland (determined ultrasonographically) had significantly increased from the pretreatment value in all ferrets. There is a large amount of variation inherent in ultrasonographic measurements, even among measurements in the same animal obtained at different times; such inherent variation may have contributed to the large SD and low P value obtained when mean adrenal gland widths before and at the end of the study were compared.

In the 3 ferrets that died during the study, clinical signs had improved with melatonin treatment; adrenocortical carcinoma was diagnosed in 2 of those 3 ferrets. None of the histopathologic findings in the 3 ferrets were identified as adverse effects associated with long-term use of melatonin, which are generally restricted to inhibition of reproductive function, delay of puberty, and influence on circadian status of fetus or neonate if the recipient is pregnant or lactating. Recently, one of our group has established a direct correlation between duration of clinical disease and development of adrenocortical carcinoma. Further investigation into the relationships among adrenal gland size, stage of neoplastic change, circulating steroid hormone concentrations, and severity of clinical signs might provide useful prognostic and diagnostic information.

In the present study, oral administration of melatonin did not stop the progression of ACD in ferrets and did not inhibit the continued growth of the affected adrenal glands. Nevertheless, melatonin treatment did improve hair growth, reduce prostate or vulva size, and increase the level of activity of ferrets with ACD for at least 8 months.

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