Melatonin

By Jerry Murray, DVM

Adrenal gland disease ranks as one of the most common problems seen in pet ferrets. It's the top ferret problem seen in my practice. Most ferret owners are all too familiar with the clinical signs of adrenal gland disease such as hair loss, itchy skin, an increase in the musky body odor, an enlarged prostate in males, and a swollen vulva in females. Surgery remains the recommended treatment for otherwise healthy adrenal ferrets. Medical treatment may be required in geriatric ferrets, those with concurrent illnesses that would make anesthesia and surgery too risky, cases where the owner declines surgery due to cost, and cases where the entire adrenal gland cannot be removed surgically. Melatonin is the newest medical treatment option for adrenal gland disease.

Drugs To Avoid

Mitotane, such as Lysodren, is the primary medicine used to treat adrenal gland problems in dogs. However adrenal gland problems in dogs (Cushing's syndrome) are quite different than adrenal gland disease in ferrets. Dogs with adrenal problems overproduce cortisol. Ferrets overproduce the sex hormones and androgens. In dogs ACTH is stimulating the adrenal glands. In ferrets LH stimulates the adrenal glands. Lysodren will destroy the cortisol-producing cells in the adrenal glands. This product does not work well in ferrets, and it can cause serious low blood-glucose problems in ferrets with concurrent insulinomas.

Ketoconazole, such as Nizoral, is another medicine used in adrenal dogs. It is an enzyme blocker that lowers cortisol and androgens. This product does not work well in ferrets.

Trilostane, such as Vetoryl, is a new medicine that is used in adrenal dogs. Unfortunately this product increases 17-hydroxyprogesterone levels in dogs. This is one of the common hormones that is elevated in ferrets with adrenal gland disease. It will likely raise this hormone in ferrets, too, and make the adrenal problem even worse. Preliminary work with Vetoryl in the Netherlands has shown this to be the case.

Tamoxifen, such as Nolvadex, is a common anti-estrogen used in human medicine. This product works by blocking estrogen receptors. Unfortunately a study in ferrets showed Nolvadex to have estrogenlike effects in ferrets, which would make estrogen-induced anemia, thrombocytopenia and mammary gland hyperplasia even worse.

What Is Melatonin?

Melatonin is the main hormone that the pineal gland produces. In an intact (unneutered) ferret, melatonin is directly and indirectly involved in activating (in the spring/summer) and in terminating (in the fall/winter) the ferret's natural breeding season. As daylight increases in the spring, lower levels of melatonin are produced. The low levels of melatonin start the breeding season, cause the ferret to shed and put on its summer coat, and lose weight. As the daylight decreases in the fall, higher levels of melatonin are released during the nighttime hours. The high levels of melatonin end the breeding season, cause the ferret to put on its winter coat and its extra winter weight.

How Does It Work?

To understand how melatonin works in adrenal ferrets, let's review what causes adrenal gland disease. Two major factors cause the adrenal glands to go wild and overproduce the sex hormones and androgens. The main factor is neonatal spaying and neutering. Most ferret breeders spay or neuter the kits at 4 to 6 weeks of age. Without ovaries or testicles, the adrenal glands begin to behave like the ovaries or testicles. The adrenal glands then respond to the same hormone, luteinizing hormone (LH), that stimulates the ovaries and testicles to produce the sex hormones and androgens. Spaying and neutering also raises the LH level. [The exact cause of adrenal gland disease is still under debate. Some studies seem to confirm that neonatal spay/neuter might be a cause, but others do not. -- Editors.]

The second factor is long day photoperiods. Photoperiod refers to the amount of light exposure during a 24-hour period. Under natural light conditions, long day photoperiods during the spring and early summer start the breeding season. It would also raise the LH

level and stimulate the adrenal glands in altered ferrets. Unfortunately most pet ferrets live indoors under long day photoperiods due to artificial lights, which stimulates the adrenal glands year-round.
Chronic overstimulation of the adrenal glands will eventually cause them to become hyperplastic or neoplastic (cancerous). It is believed that melatonin will lower the LH levels, just like it does when it ends the breeding season. This stops the stimulation of the adrenal glands. Melatonin will also help your ferret grow a thick winter coat, and increase its appetite so it can gain its winter weight.

Forms of Melatonin

Melatonin comes in three basic forms: tablets, liquid suspension and injectable implants. However, the tablets and liquid version are not FDA approved. They are classified as nutritional supplements and are not monitored by any government agency. All three forms are inexpensive.

Tablets are available over-the-counter in most drug stores, health stores and supermarkets. They normally come in either a 1-milligram or a 3-milligram size. The suggested dose is 1 to 3 milligrams once a day. These will need to be used daily.

Liquid versions are also available over-the-counter in most drug stores, health stores and supermarkets. The concentration varies from a quarter of a milligram all the way up to 21Ú2 milligrams per milliliter. Read the label to see how many milligrams per milliliter are in it. The suggested dose is 1 to 3 milligrams once a day. These will need to be used daily.

Implants are now available for use in ferrets. They are called ferretonin and are injected under the skin over the shoulder blades. They are a constant-release product that will last for three to four months. This is the easiest way to give melatonin to your ferret and may work even better than daily oral melatonin.

Melatonin Research In Ferrets

Many studies with ferrets and melatonin exist. Several studies were done in the 1930s using artificial light to induce estrus (heat) cycles. During the 1950s the neuropathways of light-induced estrus were studied. During the 1960s, '70s and '80s, the hormones and neuropathways involved in reproduction and endocrinology in ferrets were studied. All of this preliminary work proved that melatonin was the hormone that responded to changes in the light cycle, and directly and indirectly controlled the seasonal breeding season, seasonal coat changes and seasonal weight changes.

Recently melatonin has been studied as a treatment option for adrenal gland disease. Researchers at the college of veterinary medicine at the University of Wisconsin gave 10 adrenal ferrets just 0.5 milligram of melatonin in a liquid suspension orally once a day. These ferrets were rechecked every four months for one full year. In addition to the clinical signs, hormone levels and ultrasound measurements of the adrenal glands were done.

Nine of the 10 ferrets experienced improvement in their clinical signs, including hair growth, reduction in vulva swelling and reduction in the size of the prostate. No change occurred in the size of the adrenal glands. Hormone levels decreased after four months of treatment, but increased at eight and twelve months.

Likewise, good clinical results with melatonin tablets have also been seen at Texas A&M's College of Veterinary Medicine and at my practice. The suggested dose for oral melatonin is 1 to 3 milligrams once a day, ideally given at seven to nine hours after sunrise. This simulates the fall/winter photoperiod. The main problem with the liquid and tablets was the difficulty ferret owners had in giving it every day, especially at seven to nine hours after sunrise. Thus the search continued for an easier way to give melatonin.

Melatonin also comes in injectable implants approved by the FDA for use in mink. Numerous studies were done in mink and even one study in ferrets in order to get the FDA to approve the implants. In a safety study, 8- to 10-week-old mink kits were

treated with 80 to 124 milligrams per kilogram. No signs of toxicity were noted in the bloodwork, gross pathology or histopathology of the organs. This very high dose did not lower the blood-glucose level either. Adult minks treated with 100 milligrams of melatonin also exhibited a complete lack of toxicity when tested. However, the treated mink did gain more weight when compared to the control group.

Other Treatment Options

Several human medicines are currently used to treat adrenal gland disease and to treat the secondary prostate enlargement and estrogen-induced anemia, thrombocytopenia and mammary gland hyperplasia. These medicines work well, but they are expensive.

Leuprolide acetate, such as Lupron depot, is an injectable product that stops LH production, which stops the stimulation to the adrenal glands. Lupron comes in three different versions -- once a month, once every three months and once every four months. The recommended dose is 100 to 500 micrograms per kilogram on a monthly basis.

Finasteride, such as Propecia or Proscar, is a tablet that can be used to treat an enlarged prostate in male adrenal ferrets. This product is an enzyme inhibitor that stops the formation of DHT. DHT is the main hormone that causes the prostate to enlarge. After the DHT level is reduced, the prostate will shrink with time. The suggested dose is 1 milligram once a day for the first 30 days. After the first 30 days, the dose can usually be reduced to just one tenth of a milligram once a day.

Bicalutamide, such as Casodex, is another tablet that can be used to treat an enlarged prostate in male adrenal ferrets. This product blocks the androgen (DHT) receptors on the prostate. After the receptors are blocked, the prostate will shrink with time; however, this product does not actually reduce the DHT levels. The suggested dose is 5 milligrams once a day.

Anastrozole, such as Arimidex, is a tablet that can be used to treat estrogen-induced anemia, thrombocytopenia and mammary gland hyperplasia. This product is an enzyme inhibitor that stops the formation of estrogen. After the estrogen level is lowered, the bone marrow can start making red blood cells and platelets again. The suggested dose is one tenth of a milligram per kilogram once a day.

Epoetin alfa, such as Epogen or Procrit, is an injectable product that can be used with Arimidex to treat estrogen-induced anemia. After the estrogen level has been reduced by Arimidex and/or Lupron, Epogen can be used to stimulate the bone marrow to produce red blood cells again. The suggested dose is 100 to 200 units per kilogram three times a week to start with, then taper off as the packed cell volume normalizes.

This prompted James Johnson, DVM, MS, DACZM, from Texas A&M's College of Veterinary Medicine and me to try the male mink melatonin implants in adrenal ferrets in the spring of 2002. In our initial pilot study, 70 adrenal ferrets were implanted, and their clinical signs were monitored. This initial group was composed of 38 males and 32 females. Swollen vulvas returned to normal in one to two weeks. Thick "winter coats" grew in six to eight weeks. Several owners said this was their ferret's "best coat ever." Itchy skin usually resolved in one to three weeks. Most of the ferrets became more active, had an increase in appetite and gained weight.

One of these original ferrets was my pet ferret, Barney. Barney had his left adrenal gland previously removed. He had been on Lupron depot for roughly two and a half years. Despite this treatment, he was still itchy and had a thin hair coat on his tail. The scratching stopped shortly after the implant was administered. His appetite increased, which also helped in the treatment of his insulinoma. His hair coat improved and his tail filled in too. Only one ferret in this initial group of 70 did not respond well to the mink melatonin implants. She had a large right adrenal gland carcinoma. She also had another serious cancer, lymphoma.

I have used more than 200 melatonin implants. I have used these after surgery to regrow the hair coat faster, and to increase the appetite and put weight back on. It is safe to use in combination with other adrenal medicines such as leuprolide acetate (Lupron depot), finasteride (Propecia or Proscar) and anastrozole (Arimidex). It is even safe to use with ferrets that have insulinomas in addition to adrenal gland disease. The only side effect seen is lethargy for the first three to five days, and increased weight gain. Several ferrets have even developed large fat pads on the sides of their neck.

Melatonin implants may also be helpful to actually prevent adrenal gland disease. This is an exciting possibility. My two young males will be monitored over their entire life span to see if they develop adrenal gland disease. Likewise, several

owners have started to use the implants in their young ferrets to see if the implants will prevent adrenal gland disease. Surprisingly, ferrets as young as 15 weeks of age respond to changes in the photoperiod, so melatonin may need to be started when the ferret is very young to work as a preventive.

The manufacturer of the mink melatonin implants is now making implants for use in pet ferrets. These are called ferretonin. The ferretonin implant contains the same amount of melatonin as the male mink implant, and they come in a ready-to-use, sterilized implanter. It is administered by simply injecting the implant under the skin over the shoulder blades. Most ferrets can be distracted with their favorite treat while the injection is done. The implants will last for three to four months. Most pet ferret owners will likely have a veterinarian perform the implant.

Melatonin Research In People

Melatonin has also been studied for use in humans with breast cancer, prostate cancer and other cancers. Melatonin has repeatedly been shown to prevent the growth of human breast cancer cells. Studies have shown that melatonin has some direct anti-estrogen properties. Breast cancer cells thrive on a fat called linoleic acid, and melatonin can interfere with linoleic acid uptake by the cancer cells. In addition there are also melatonin receptors on the cancer cells. These receptors can prevent the growth of the cancer cells. Melatonin can also inhibit other estrogen pathways inside the cancer cell. These four actions prevent the breast cancer cells from growing. Therefore melatonin may help ferrets with secondary mammary gland hyperplasia or neoplasia.

Melatonin has also been shown to prevent the growth of human prostate cancer cells because there are melatonin receptors on the human prostate. In a mice study when melatonin was given for 10 days before inoculation of human prostate cancer cells, half of the mice did not develop a tumor. Melatonin caused a significantly smaller tumor in the half that did form a tumor when compared to the control group.

Melatonin has also been shown to reduce the growth of benign prostate cells. It is likely that melatonin works in this same way in ferrets too. Remember a reduction in the size of the ferret's prostate was documented in the University of Wisconsin study with oral melatonin.

Your Ferret

As a new treatment option for ferrets with adrenal gland disease, melatonin is both safe and inexpensive. It can be used by itself, or it can be safely combined with other adrenal medications such as Lupron depot, Propecia and Arimidex. It may even be useful in preventing adrenal gland disease. In addition, melatonin is also a potent antioxidant, so talk to your ferret's veterinarian about using this hormone.

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