

Melatonin treatment of hyperadrenocorticism

By Michael Janke

There are several options for the treatment of adrenal disease in ferrets. Most will agree that surgery is the best option; however, surgery is not possible in all cases. The ferret may be a high surgical or anesthetic risk, or the owner simply may not have the funds needed. Fortunately, there are several non-surgical options and this article will discuss one of those options - the use of melatonin for both the treatment of adrenal disease and the possibility of using it as a preventative measure. Lupron Depot is another option, and while it works wonderfully (in this author's experience) it may be cost prohibitive in some cases. The use of Lupron Depot is discussed in detail in several places on this website (<http://www.miamiferret.org/fhc>).

HOW MELATONIN WORKS

Melatonin is a natural hormone that is released by the pineal gland (a tiny structure located at the base of the brain) in response to darkness. Conversely, the release of melatonin is inhibited by light. According to Dr. Jerry Murray, "Melatonin directly and indirectly activates the breeding season (spring/summer) during the 'long day' photoperiods, and it terminates the breeding season (fall/winter) during the 'short day' photoperiods. In the fall/winter there is more melatonin released during the dark time, and less released in the spring/summer. In addition to the breeding season, the increased melatonin causes the winter fur to come in and the winter weight gain. Likewise the low levels cause the summer fur to come in and the summer weight loss."

It is likely that the abnormal lighting to which we subject our ferrets may be at least partially responsible for the high incidence of adrenal disease. Their in-home environment is naturally light during daylight hours and we add many hours of artificial light on top of that during the evening hours. This constant lighting causes a natural reduction of the ferret's production of melatonin and adds to the stimulation (LH) to the adrenal glands.

So how does melatonin combat the effects of adrenal disease? Once again from Dr. Murray: "Melatonin inhibits GnRH release, which decreases LH and FSH and stops the stimulation to the adrenal glands [Adrenal glands have LH receptors] which decreases the amount of adrenal sex hormones being produced."

The overproduction of sex hormones is what causes the typical symptoms we see with adrenal disease in ferrets. Hair loss, vulva swelling in females, prostate swelling in males and sexual or aggressive behavior; any one or

more of these symptoms may be present. If this constant stimulation can be stopped, the results can often be dramatic. Hair grows, the vulva or prostate swelling resolves, and except in some cases of carcinoma, the adrenal glands may get no larger and in some cases may actually reduce in size.

TREATMENT PROTOCOL

A suggested dosage is 1 milligram of melatonin given around 7-9 hours after sunrise. This timing would mimic the body's natural release of melatonin during the short days of fall and winter. In cases where there is no response to this level of melatonin, up to 3 milligrams may be given daily. In mink, doses as high as 78.2 mg produced no adverse side effects in adults, and doses as high as 124 mg/kg produced no side effects in kits. The only side effects seen in ferrets have been sleepiness for the first 3-5 days when beginning this treatment and weight gain. Some ferrets will even get fat pads on the sides of their necks.

In the study conducted by the University of Wisconsin, 10 ferrets with confirmed adrenocortical disease were given 0.5 mg of melatonin (liquid) daily and were monitored over the course of a year. Nine of the ten ferrets had moderate to dramatic improvement in clinical signs including hair growth, reduction of vulva swelling, or reduction of prostatic size. There was no significant change in the size of the adrenal glands. This can be interpreted to mean that although the size of the gland was not reduced, they also did not get any larger during the one year study.

The most difficult part of this treatment protocol is compliance with the timing of giving melatonin 7-9 hours after sunrise. For many, this means the dosage would be due while still at work. A more convenient method that Dr. Murray uses is the male mink melatonin implant. This implant is roughly the size of a grain of rice that is injected subcutaneously (under the skin) over the shoulder blade area. The implant slowly releases melatonin over a 3-4 month period and eliminates the need to give melatonin daily.

HOW CAN MELATONIN PREVENT ADRENAL DISEASE?

Any endocrine tissue which is constantly stimulated over a long period of time becomes hyperplastic, and the more cell cycles and stimulation, the greater the chance for neoplasia. This is particularly true with organs that secrete hormones, such as the adrenal glands.

Although there have been no controlled studies to prove this theory, by giving melatonin before a ferret develops adrenal disease, we may be able to prevent the constant stimulation of the adrenal glands. This may prevent the glands from becoming hyperplastic and eventually, neoplastic.

WHERE DO I GET MELATONIN?

Melatonin is both inexpensive and readily available in the U.S. One can find melatonin at health food stores, the local drugstore or supermarkets and even at Wal-Mart. It comes in both a pill and a liquid form but one must pay close attention to the actual amount of melatonin contained within the particular form, particularly liquid. Because melatonin that is available in these stores is treated as a supplement (and not a drug) it is not controlled by the FDA. This means that the actual quantity and quality of melatonin in the product is not regulated or guaranteed. Price is not always an indication of quality either, but one may do better to buy a known brand name. Melatonin may not be available over the counter in countries other than the United States (i.e. Canada).

A form of melatonin that has been found to work much better than oral melatonin is an implant that was created for the mink and fox fur industry. This implant provides a steady level of melatonin over a three to four month period, eliminating the need to dose your ferret at a specific time daily with an oral product. Neo-Dynamics, LLC originally supplied these implants to veterinarians for use in ferrets. This company no longer serves this segment and the implants are now marketed and sold exclusively through several distributors:

For Veterinarians:

- Professional Veterinary Products 800-228-0077
- AAHA's MARKETlink 888-722-2242

For Shelters:

- Contact Sharon Bearden, sharon@supportourshelters.org
- Melatek direct 877-635-2835

Ferretonin comes prepackaged in a single dose, sterilized syringe (implant device) with needle. It contains the same amount of melatonin (5.4 mg) as the male mink melatonin implant. Contact your veterinarian for pricing information. If you need bulk quantities, they may be purchased as aseptic individual implant packages. Contact Melatek for more information. Please note that they will only sell this product to a veterinarian.

WHY IS THE ORAL DOSAGE DIFFERENT THAN THE IMPLANT?

Several have asked why ferrets have to receive 1 mg of melatonin orally every day, but if given as an implant, 5.4 mg will last three to four months. The short answer is that when given orally, it is quickly metabolized by the body, whereas when given as an implant, a constant, steady level of melatonin is provided over a long period of time.

WHAT IF MELATONIN DOES NOT WORK FOR MY FERRET?

There may be instances where neither melatonin nor Lupron will produce the expected or desired results. This would be the case if the adrenal gland is affected in a way that causes it to secrete sex hormones independent of any outside influence (some carcinomas). In these cases, the only option is surgical removal of the affected gland. There also may be cases where melatonin alone does not work, but Lupron will. One can use both products (melatonin and Lupron) at the same time.

DRAWBACKS OF USING THE MELATONIN IMPLANT

Dr. Cathy Johnson-Delaney found during a study of the melatonin implant's effects on hormone levels that when a 560g female was given the melatonin implant, she became so lethargic within two weeks of implantation that she had to be roused daily to eat. No medical or physical cause for this change in her behavior was found and her activity level gradually increased to normal levels after three months. This appears to indicate that the level of melatonin being released by the implant was too high for this ferret. One may want to consider this possible effect in small (less than 600g) ferrets.

Previously, the melatonin implant came in one dosage level (5.4 mg). Melatek's website indicates they now have an implant available with a smaller dosage size if needed for a very small ferret.

Cost is another possible drawback in the use of the melatonin implant. In its current form, that is, one implant along with an implant syringe, the cost may approach that of Lupron Depot for those vets that treat a large number of ferrets with Lupron.

For more information on melatonin usage

1) Diagnostic Laboratory Insight with Regard to Adrenal Disease by Jack Oliver (U of Tenn), Proc 20th ACVIM 2002, p541-543.

2) Melatonin use in ferret adrenal gland disease by J. Paul-Murphy (U of Wisconsin) Proc N. Am. Vet Conf. Vol 15, 2001 pg 897.

3) Melatonin therapy for canine alopecia. Kirk's CVT 13 by Manon Paradis (U de Montreal) p546-549. She also describes the mink melatonin implant.

4) Diagnosis and Treatment of Adrenal Tumors in Ferrets by James Johnson (Texas A&M) Annual Exotic Pets Conf. 2001 p3-6.

5) Studies on the duration of the breeding season and photorefractoriness in female ferrets pinealectomized or treated with melatonin. by Penelope Thorpe + J. Herbert (U of Cambridge) Journal of Endocrinology 1976, 70, p 255-262.

6) Effect of oral melatonin administration on sex hormone, prolactin, and thyroid hormone concentrations in adult dogs. by Patricia Ashley et al (U of Tenn) JAVMA Vol 215 No 8, 10/15/99, p 1111-1115.

7) Induction of winter fur growth in mink with melatonin. by J. Rose, J. Anim Sci, 1984 Vol 58 p 57-61.

8) The role of luteinizing hormone in the pathogenesis of hyperadrenocorticism in neutered ferrets. By N.J. Schoemaker, et al. (Utrecht University), Molecular and Cellular Endocrinology, 2002, vol 197, p 117-125.

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