

## **Treatment of PDH Cushing's Disease (Pituitary Dependent Hyperadrenocorticism)**

There are four treatments used in the management of pituitary dependent Cushing's disease in the United States: Trilostane (Vetoryl®), Lysodren® (also called Mitotane or o,p'-DDD), Nizoral® (also called Ketoconazole) and L-Deprenyl (also called Anipryl®, Eldepryl® or Selegiline). These medications are associated with different potential side effects and expense and any of them can possibly produce good results in a confirmed case of pituitary Cushing's disease, depending on the specifics of the case.

### **TRILOSTANE: THE LATEST AND GREATEST**

Trilostane inhibits the enzyme that makes cortisol in the adrenal gland. Adrenal glands that make too much cortisol cause Cushing's Disease. Allergic reaction to Trilostane is rare, but can happen. Stop giving the medication immediately if it makes your pet ill in any way, and call us to let us know. Vomiting and diarrhea can also be seen. If that happens, stop giving the trilostane for 2-3 days, and call us to let us know. If the symptoms stop, we will try giving it twice a week for a week or two, and then slowly increase to the regular daily dose. If vomiting and diarrhea happens again, we may need to lower the dose. Very, very rarely, Trilostane can make the adrenal glands stop working altogether, through a process called acute adrenal necrosis. Should this happen, your dog will need to take daily medication to treat Addison's Disease or the rest of his or her life. The exceedingly rare, Addison's disease can be life threatening if untreated. Symptoms might include vomiting, diarrhea (especially with blood), weakness and pale gums.

We will dispense a prescription of Prednisone at a very low dose to give if it becomes apparent that the Trilostane dose is too high, or if there are signs of Addison's Disease. It is just to be kept on hand for emergency, and not to be given on a regular basis to a dog with Cushing's Disease.

If all goes well, we will want you to come for a recheck in 3-4 weeks, to check cortisol levels and electrolytes to make sure dose does not need to be adjusted. It's best to take the blood about 2 hours after giving the Trilostane in the morning. We start out with a low dose, and sometimes need to increase dose to reach the ideal dose for your dog. Once the proper dose is reached, we will want to check bloodwork at least twice a year. Over time (months to years), dose may need to be gradually decreased, based on blood tests.

### **LYSODREN: THE TRADITIONAL THERAPY**

Lysodren (generically known as "mitotane" and chemically known as "o,p'-DDD") has been the only treatment for pituitary dependent Cushing's disease until relatively recently. It is convenient to use and relatively inexpensive, though it does have the potential for very serious side effects if given too much or too often. Because this medication has been in use for canine Cushing's disease for decades, many veterinarians have experience with its use and with the monitoring tests needed to prevent side effect difficulties. While this drug can have significant side effects if used excessively, keep in mind that Cushing's Disease can be fatal if left untreated.

#### **How Lysodren Works**

Lysodren should be considered to be a drug of chemotherapy. The definition of chemotherapy is: using chemicals (drugs) to treat medical conditions. Lysodren actually erodes the layers of the adrenal gland that produce corticosteroid hormones, which are overactive with Cushing's Disease. The pituitary tumor continues to secrete excess stimulation, but the adrenal gland is no longer capable of excess hormone production in response. Problems can result if too much of the adrenal cortex is eroded. Short term Lysodren reactions are common (something like 30% of dogs will have one at some point), necessitating the use of a prednisone "antidote" pill which the veterinarian supplies. In the event of such short term reactions, Lysodren is discontinued until the adrenal gland can re-grow and therapy is resumed, possibly at a lower dose. Rarely, excess adrenal erosion is permanent and the dog must be treated for cortisone

deficiency for the rest of its life. The potential for this kind of reaction has been the driving force behind the search for better medications for the treatment of pituitary dependent Cushing's disease.

### **How Lysodren is Used**

There are two phases to the treatment of Cushing's disease with Lysodren: an induction phase to gain control of the disease and a lower dose maintenance phase which ideally lasts for the animal's entire life.

*Induction.* During induction (usually 5-10 days), the pet owner receives a prescription for Lysodren plus a bottle of prednisone tablets to be used as "antidotes" should any Lysodren reactions erupt. Be sure you understand which pill is which. Lysodren is given twice a day with meals during this period so that the plump, excessively stimulated adrenal gland can be gradually shaved down to the desired size. It is very important that Lysodren be given with food or it will not be absorbed into your dog's body. A test called an ACTH stimulation test (one of the same tests which may have been used to diagnose Cushing's disease originally) is used to confirm that the induction endpoint has been reached. An ACTH stimulation test is generally scheduled for after the induction period is complete. However, it is important that you recognize the signs of endpoint should they occur sooner.

You should stop giving Lysodren at the induction dose and call your veterinarian if any of the following signs of induction endpoint are observed:

- Diarrhea (especially with blood) or vomiting
- Appetite loss (this may be as subtle as less enthusiasm towards eating when the food is served, not running for the bowl etc.)
- Decrease in water consumption to below what was normal before the dog had Cushing's Disease (it may be helpful for you to measure water consumption during the induction period)
- Lethargy, listlessness or weakness

If any of these signs occur, let your veterinarian know. It may be time for an early ACTH Stimulation test or possibly even for an antidote pill. It is a good idea to maintain daily telephone contact with your vet after the third day or so of induction as it is at this point that a dog becomes at risk for reaching an early induction endpoint. A Lysodren reaction generally reverses within 30 minutes on an antidote pill. If problems persist longer, call your veterinarian.

If none of the above signs are noted, then the ACTH Stimulation test proceeds as scheduled after induction. If this test indicates that sufficient adrenal erosion has taken place, then the Lysodren dose is given once or twice a week instead of twice a day and the dog has successfully entered maintenance. If the test indicates that more adrenal erosion is needed, induction continues. Many dogs have reached maintenance by the end of the first induction period, but others require more time, especially if they are taking concurrent drugs that alter the metabolism of Lysodren (phenobarbital would be the obvious such medication). Some dogs take weeks to months to reach induction.

*Maintenance.* After achieving maintenance, another ACTH stimulation test is recommended after about a month and then twice a year or so thereafter. Approximately 50% of dogs will experience a relapse at some point and require a second round of induction. Full reversal of clinical signs associated with Cushing's disease usually occurs after 4-6 months of Lysodren therapy. Usually the first sign to show improvement is the excess water consumption. The last sign to show change will be hair re-growth. Occasionally (but rarely), all of the clinical signs are never well controlled.

While Trilostane is the latest and greatest treatment for most simple cases of pituitary hyperadrenocorticism, Lysodren is still the treatment of choice for adrenal tumors and dogs with both Cushing's Disease and insulin dependent diabetes mellitus.

## **What is Addison's Disease?**

Addison's disease, also called hypoadrenocorticism, is the opposite of Cushing's disease; it is the disease resulting from a deficiency of cortisone. If Lysodren erodes away too much of the adrenal gland, Addison's disease can be the result, but it rarely is permanent. If this occurs, hormone (prednisone and sometimes others) supplementation becomes needed indefinitely to prevent life threatening shock as the body becomes unable to adapt to any sort of stress.

It should be noted that there are some specialists who feel that the treatment of Addison's disease is much simpler than the treatment of Cushing's disease. They use Lysodren at high doses on purpose with the goal of inducing Addison's disease and administering long term treatment accordingly. This is not a common method of treating Cushing's disease, as a small percentage of dogs will not survive this protocol. Those who do survive can do very well. Our hospital chooses the more traditional therapy goals of not treating Cushing's disease in this extreme way. Still, should this complication arise, one should be aware that it is an easily treatable condition.

## **KETOCONAZOLE: ANOTHER APPROACH**

Ketoconazole was actually developed for a totally different purpose—to treat fungal infections. As ketoconazole was used for this purpose, it was noted that some of the male patients on this medication developed breast tissue and a more feminized physical appearance. Ketoconazole was interfering with the metabolism of sex steroid hormones. Soon newer generations of anti-fungal products were developed (such as itraconazole and fluconazole) and this side effect was eliminated.

This steroid interference did not go unnoticed by the veterinary profession. Since most pets have been spayed or neutered, the sex steroids were generally not of concern, but adrenal steroids were and are of definite relevance. Ketoconazole was investigated as an adrenal suppressor and by 1990, ketoconazole was becoming an alternative in the treatment of Cushing's disease in dogs who had mild signs of disease, or who could not tolerate Lysodren. However, ketoconazole often is not effective in dogs who have very high cortisol levels, or advanced disease. Approximately one dog in five will not respond to Ketoconazole at all. This is thought to be a problem with absorption of the drug from the intestinal tract.

Monitoring tests (liver enzymes) are required once or twice a year when a dog is being treated with ketoconazole, because ketoconazole can sometimes cause liver toxicity. Vomiting and diarrhea are potential side effects with ketoconazole as with Lysodren, but no "antidote" pills are available for ketoconazole. The drug is simply discontinued until the side effects resolve. The dose is modified and restarted, or another drug is chosen.

## **L-DEPRENYL**

So the search for a better Lysodren alternative continued. L-deprenyl represents a completely different approach. Rather than trying to interfere with the adrenal gland's over-production of steroid hormones, L-deprenyl addresses the pituitary tumor directly. Studies with L-deprenyl began when it was found that this medication might be helpful in treating humans with Parkinson's disease. Research in dogs, however, uncovered some surprising results involving ACTH release from the pituitary gland.

There are three parts to the pituitary gland: the anterior (front) part, the intermediate (middle) part and the posterior (back) part. Abnormalities of either the front part, the middle part, or both can result in Cushing's disease (the back part is not involved). L-deprenyl inhibits the enzymes involved in degradation of a neurotransmitter called dopamine, so it lasts much longer in the middle part of the pituitary. When there is more dopamine in the middle part of the pituitary, then it releases less of the hormone (ACTH) that is excessive in pituitary hyperadrenocorticism. Too much ACTH causes the adrenal glands to be overactive and results in Cushing's Disease. Unfortunately, only about 20-25% of dogs with pituitary hyperadrenocorticism have it because there is an abnormality in the middle part of the pituitary, so a

maximum of 25% of dogs with pituitary Cushing's disease will be helped at all by L-deprenyl. 80-85% of dogs with Cushing's Disease have a pituitary tumor rather than an adrenal tumor causing their problem. So in total, only about 15-20% of dogs with Cushing's Disease will respond to L-Deprenyl. With L-Deprenyl, there are no tests to monitor therapy—you have to go by clinical signs in the patient.

The usual protocol if no response has been seen after two months of therapy is to double the dose and continue for one more month before determining the patient to be a "non-responder" and selecting another medication. L-Deprenyl is the safest option for treatment of Pituitary Cushing's Disease, but it is effective only for a minority of dogs. Other names for L-Deprenyl include Anipryl, Eldepryl and selegiline.

### **ADVANTAGES OF TRILOSTANE**

- There are fewer side effects with Trilostane as compared to Lysodren
- Some dogs with adrenal tumors or concurrent diabetes will not respond to Trilostane therapy
- Adrenal necrosis is a rare side effect, but must be treated immediately in order to prevent death

### **ADVANTAGES OF LYSODREN**

- Lysodren is less expensive than the other medications.
- Lysodren is given once or twice a week long term, and the other two medications must be given every day (sometimes twice daily).
- Most dogs with pituitary Cushing's disease will respond to Lysodren, but L-Deprenyl only works for about 25% of dogs, and ketoconazole works for about 50% of dogs.
- There is no risk of liver damage as there is with ketoconazole.

### **ADVANTAGES OF KETOCONAZOLE**

- There is no risk of Addison's disease as with Lysodren.
- Because Addison's disease is not of concern, periodic ACTH stimulation tests (which can be expensive) are not necessary as with Lysodren and Trilostane.

### **ADVANTAGES OF L-DEPRENYL**

- While L-Deprenyl is substantially more expensive than Lysodren, the blood tests needed to monitor therapy with the other two drugs in order to use it safely are not needed with L-Deprenyl, so total costs can be less for L-Deprenyl in the beginning, and there are fewer visits to the vet.
- Addison's disease is not a concern as it is with Lysodren.
- Liver damage is not a concern as with ketoconazole.

### **WHEN WHAT WAS THOUGHT TO BE PDH TURNS OUT TO BE ADH**

As has already probably been discussed with you, there are 2 different types of Cushing's Disease.

1. *Pituitary Dependent Hyperadrenocorticism (PDH)*. PDH is caused by an overactive pituitary gland in the brain, which sends messages by the hormone ACTH to cause the adrenal glands to make too much cortisol and other hormones. This causes the signs of Cushing's Disease, including increased thirst, increased appetite, increased urination, weight gain, hair loss, other skin problems, etc. 80-85% of dogs with Cushing's Disease have PDH. The overactive pituitary gland is usually a benign pituitary tumor which never gets very big and never causes problems of its own. Rarely, the benign tumor will grow big enough to cause neurologic problems, including depression, reluctance to eat and drink, and weakness in the legs. When this happens, it is called "Pituitary Macroadenoma." Extremely rarely, the pituitary tumor can be malignant. Most of

the time, the pituitary tumor stays much smaller than 1 centimeter, and often less than 3 millimeters.

2. *Adrenal Dependent Hyperadrenocorticism (ADH)*. ADH is caused by an adrenal tumor which makes too much cortisol and other adrenal hormones, causing the same symptoms as PDH. About half of these tumors are benign, and about half are malignant. Theoretically, removal of the benign adrenal tumor can be curative. However, adrenal surgery is dangerous, and ¼ to 1/3 of dogs who have adrenal surgery do not survive. As well, the only way to tell for sure if an adrenal tumor is malignant or not is to look for signs of tumor spread on ultrasound of the belly and surgery, and then send the removed tumor for biopsy. Even biopsy is not 100% accurate at distinguishing malignant from benign adrenal tumors.

There can be hints on the hormonal blood tests which suggest that your dog could have an adrenal tumor. However, looking at the adrenal gland with ultrasound, CT scan, MRI or surgery is often the final word on whether we think your dog has an adrenal tumor. Occasionally, a small adrenal tumor is not seen on the initial imaging used to determine if your dog has PDH or ADH. That tumor may grow and be found later. Dogs with ADH tend to need much higher doses of Lysodren to control their Cushing's Disease. If your dog is initially thought to have PDH, and high doses of Lysodren are needed to control the symptoms, we may recommend repeating ultrasound of the belly to look again for an adrenal tumor that may have become bigger.

*References:*

Wendy Blount, DVM – PracticalVetMed  
Wendy Brooks, DVM – VeterinaryPartner.com