6 Treatment: Pituitary Cushing's Syndrome

By Wendy C. Brooks DVM, DABVP

There are three treatments commonly used in the management of pituitary dependent Cushing's disease: Lysodren (also called Mitotane or o,p'-DDD), Nizoral (also called ketoconazole), and Anipryl (also called L-Deprenyl, Eldepryl or Selegiline). These medications are associated with different side effects potential and expense and any of them can be expected to produce good results in a confirmed case of pituitary Cushing's disease.

Related Articles
* Cushing's Disease (Hyperadrenocorticism)
1 Symptoms of Cushing's Syndrome
2 What Exactly is Cushing's Disease
3 Testing: Laboratory Hints Suggesting Cushing's Syndrome
4 Testing: Confirming Cushing's Syndrome
5 Classifying Cushing's Syndrome: Pituitary vs Adrenal
6 Treatment: Pituitary Cushing's Syndrome
7 Pituitary Macroadenoma: an FAQ
8 Adrenal Tumor Treatment

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. Because this medication has been in use for canine Cushing's disease for decades, most veterinarians have extensive experience with its use and with the monitoring tests needed to prevent side effect difficulties. One of the disadvantages of lysodren therapy is the need for regular monitoring blood tests.

How This Medication Works

Lysodren should be considered to be a drug of chemotherapy. It actually erodes the layers of the adrenal gland that produce corticosteroid hormones. The pituitary tumor continues to secrete excess stimulation but the adrenal gland is no longer capable of excess hormone production in response. Problems result when 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 that the veterinarian supplies. In 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. Sometimes excess adrenal erosion is permanent and the dog must be treated for cortisone deficiency. This is more serious and 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 This Medication 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, the pet owner receives a prescription for lysodren (usually obtained through a local human pharmacy) 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 rapidly 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 (the same test 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 the 8^{th} or 9^{th} day of induction however, it is important that you recognize the signs of endpoint should they occur sooner.

You should call your veterinarian if any of the following signs of induction endpoint are observed:

- Diarrhea 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 (it may be helpful for you to measure water consumption during the induction period)
- Lethargy or listlessness

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.

If none of the above signs are noted, then the ACTH Stimulation test proceeds as scheduled on the 8th or 9th day of 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. Most dogs have reached maintenance by the 16 th day of induction but others require more time, especially if they are taking concurrent drugs that alter the metabolisim of lysodren. (Phenobarbital would be the obvious such medication.)

Maintenance
After achieving maintenance, another ACTH stimulation test is recommended afterabout 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 can be expected after 4 to 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.
- If appetite loss, vomiting, diarrhea or listlessness occur at any time during maintenance, a lysodren reaction should be suspected. The veterinarian should be notified; it may be time for one of the prednisone antidote pills. A lysodren reaction generally reverses within 30 minutes on an antidote pill.

What is Addison's Disease?

Addison's disease, also called hypoadrenocorticism, is the opposite of Cushing's disease; Addison's results from a deficiency of cortisone. If lysodren erodes away too much of the adrenal gland, Addison's disease can be a permanent result. If this occurs, hormone supplementation becomes needed indefinitely to prevent life threatening shock as the body becomes unable to adapt to any sort of stress. Medications to treat Addison's disease can be very expensive, especially for larger dogs, and it is generally felt that the induction of Addison's disease is undesirable.

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 and 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 a treatable condition.

See more information on Addison's disease, which can also occur in animals (and people) as a natural occurance with no help from lysodren.

Ketoconazole: Another Approach

The potential for the induction of Addison's disease as well as the need for periodic expensive monitoring tests have provided impetus for the development of a Lysodren alternative. Ketoconazole was actually developed for a totally different purpose.

Prior to the introduction of Ketoconazole in the 1980s, systemic fungal infections could only be treated with a medication called Amphotericin B. Amphotericin B could only be given by intravenous infusion and was associated with an unacceptably high rate of kidney failure. Ketoconazole was

developed as an alternative to Amphotericin B. Ketoconazole can be given orally and is not associated with severe side effects either in the kidneys or other body systems. Hospitalization and monitoring expenses could be eliminated. This was an amazing breakthrough in the treatment of patients with fungal infections but soon a problem was noted: 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 problem was eliminated from males being treated for fungal disease.

But 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 most certainly were and are of definite relevance. Ketoconazole was investigated as an adrenal suppressor and by 1990, ketoconazole was becoming widely used in the treatment of Cushing's disease in dogs. Typically, a low dose is used for a week and if no adverse symptoms result in that time, the higher maintaining dose is used.

Advantages of Ketoconazole over Lysodren
Because of the nature of the adrenal interference produced by Ketoconazole, it is not possible to induce Addison's disease. Because Addison's disease is not of concern, monitoring tests are not necessary when Ketoconazole is used to treat Cushing's disease. An ACTH stimulation test is often recommended after the first month or so of ketoconazole therapy simply to determine if the medication is working.

Ketoconazole lists vomiting and diarrhea as potential side effects as does Lysodren but with ketoconazole, no "antidote" pills are needed. Ketoconazole is simply discontinued until the side effects resolve. The dose is modified and re-started.

Advantages of Lysodren over Ketoconazole Ketoconazole is given twice a day indefinitely whereas Lysodren is given once or twice a week, a much more convenient scheduling.

Ketoconazole is enormously expensive even when compared to the cost of all the monitoring tests associated with Lysodren.

Because few people can afford to treat with Ketoconazole, most veterinarians do not have a lot of experience using this drug. Most veterinarians have extensive experience with Lysodren.

Approximately one dog in five will not respond to Ketoconazole. This is thought to be a problem with absorption of the drug from the intestinal tract.

L-Deprenyl (Brand name: Anipryl):

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.

Previously in this web site, we reviewed the feed back loop involving the regulation of adrenal secretion by the pituitary gland. In fact, only part of the pituitary gland (the anterior pituitary) is involved in the feedback loop presented. There are two other parts to the pituitary gland: the intermediate part and the posterior part. The posterior part is involved in the regulation of unrelated hormones and does not concern us but the intermediate part is definitely able to secrete ACTH and is not subject to the same feedback loop as the anterior pituitary is.

So how might we influence ACTH secretion of the intermediate pituitary gland? Research using L-Deprenyl showed us that ACTH secretion in this area of the pituitary is governed by the neurotransmitter: dopamine. When dopamine levels are high, ACTH secretion shuts down.

Pituitary tumors are not very responsive to normal regulatory mechanisms in the body, but most pituitary tumors in dogs with Cushing's disease are not located in the intermediate pituitary area. This means the intermediate area is still able to respond normally to dopamine regulation.

So how do we raise dopamine levels in the pituitary gland? L-Deprenyl inhibits the enzymes involved in degradation of dopamine. This means that the dopamine present lasts much longer. It also stimulates the production of other neurotransmitters that serve to stimulate dopamine production. It

is also able to synergize with dopamine as dopamine binds to the intermediate pituitary gland. More dopamine, means less ACTH release overall, which means less steroid production by the adrenal glands.

SIDE EFFECTS HAVE AN ESPECIALLY LOW INCIDENCE WITH L-DEPRENYL USE

(APPROXIMATELY 5% EXPERIENCED MINOR NAUSEA, RESTLESSNESS, OR REDUCED HEARING CAPACITY)

Does it really work? The metabolic breakdown products of L-Deprenyl are amphetamine and methamphetamine (strong stimulants that also suppress hunger). When dogs with Cushing's disease become more active and their excessive appetites become more normal, is it because their Cushing's disease is controlled or because of the stimulant by-products of L-Deprenyl? No one knows and because of the way L-Deprenyl works in the pituitary, the usual monitoring tests to evaluate Cushing's treatment progress are not helpful. In independent studies, about one dog in 5 was felt to improve on L-Deprenyl. In studies funded by the manufacturer, about one dog in five did not improve on L-Deprenyl.

Advantages of L-Deprenyl Over Lysodren
Because of the unique mechanism of this medication, Addison's disease is not a concern and thus no monitoring tests are required with the use of L-Deprenyl. L-Deprenyl is the only medication approved by the FDA for the treatment of Cushing's disease in the dog.For frail dogs with only light Cushing's symptoms, L-Deprenyl may be an excellent choice.

Advantages of Lysodren Over L-Deprenyl
L-Deprenyl is substantially more expensive than Lysodren. Response to L-Deprenyl is not reliable or may be partial or may take some time. 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. With Lysodren, response is rapid and documentable with testing.

Trilostane

Trilostane, sold in the U.K. under the name Vetoryl, is an inhibitor of an enzyme called 3-beta-hydroxysteroid dehydrogenase. This enzyme is involved in the production of several steroids including cortisol. Inhibiting this enzyme inhibits the production of cortisol. Several studies have determined this medication to be effective in the treatment of pituitary-dependent Cushing's disease.

Trilostane is given once or twice a day with food. Common (a reported 63% incidence) side effects are similar to those of Lysodren: vomiting, diarrhea, and lethargy. These reactions usually resolve with discontinuing medication 3 to 5 days and restarting at an every other day frequency. Addisonian reactions have been reported.

Trilostane is not available in the U.S. and must be obtained from another country with special permission from the FDA. As with Lysodren, dose is modified according the results of periodic ACTH stimulation tests (at 10-14 days, 30 days, 90 days, and then every 6 months). One might ask why one might consider trilostane given that its side effects are similar to those of Lysodren, its monitoring is similar to that of Lysodren, but its availability is problematic. In fact, the general feeling is that trilostane is effective but severe reactions are less common than with Lysodren.

Advantages of Trilostane over Lysodren

- Less potential for Addisonian or other serious reaction.
- Trilostane does not erode the adrenal cortex. Its action is as an enzyme inhibitor and the inhibition it causes is fully reversible.

Disadvantages of Trilostane Compared to Lysodren

- To obtain trilostane, a letter to the FDA from the veterinarian is needed. After a couple of weeks the approval letter from the FDA is obtained and product may be purchased from another country but only a 90 days supply maximum is obtainable. The periodic refills needed may be subject to shipping delays.

- Approximate annual cost of trilostane for a 20 lb dog is approximately $1900. Lysodren costs substantially less.
- Trilostane is given once or twice daily while Lysodren is given only once or twice a week.
- There is currently very little experience with trilostane in the U.S. veterinary community. Your veterinarian may require periodic consultation with other experts throughout therapy.
- Some work from Europe suggests Trilostane should not be used in dogs with pre-existing heart disease.

Trilostane may be a reliable alternative for dogs that do not tolerate Lysodren. If this is a treatment you are interested in, discuss trilostane with your veterinarian.

It is our policy not to give dosing information over the Internet.

Date Published: 1/1/2001
Date Reviewed/Revised: 3/31/2008

This article is also available to your clients on our veterinary client site, Veterinary Partner at http://www.VeterinaryPartner.com/Content.plx?P=A&A=637. If you'd like to send the article to a client just open the article (click the above link) and click 'Email article'.

800.700.4636 | VINGRAM@vin.com | 530.756.4881 | Fax: 530.756.6035
777 W. Covell Blvd, Davis, CA 95616