Cushing's Disease (Hyperadrenocorticism): Treatment

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Treatment of Pituitary Cushing's

Pituitary-dependent Cushing's syndrome does not always require treatment. The ultimate goal of therapy is to improve the patient's life quality and to fortify the patient's bond with his owner, so if the Cushing's patient is not having problems with symptoms, treatment may not be indicated. In deciding whether or not to treat Cushing's syndrome, consider symptoms that this particular individual patient is dealing with. For example, if the patient is drinking excessively but is not urinating in the house, this may not be a problem. If the patient has recurrent bladder or skin infections, high blood pressure, urinary protein loss, or is so hungry as to be raiding the kitchen regularly, then treatment is needed.

There are two medications commonly used to manage pituitary dependent Cushing's disease: Lysodren (also called Mitotane or o,p'-DDD), and Trilostane (brand name Vetoryl®). These medications are associated with different expense and potential side effects, and both can be expected to produce good results in a confirmed case of pituitary-dependent Cushing's. Two other medications: Ketoconazole and Selegiline, are also sometimes used but with less reliable results.

Lysodren: The Traditional Therapy

Lysodren (generically known as mitotane) was 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 (~30% incidence), 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.

How This Medication is Used

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

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 an antidote 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 important that lysodren be given with food or it will not be absorbed into your dog's body. A test called an ACTH stimulation or stim 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 approach gaining popularity involves reducing the dog's food intake by 30% the day before induction begins to ensure the dog is very hungry for induction. The food is restricted in this way throughout the induction period. The endpoint of induction is determined by a subtle reduction in the patient's appetite (looking up halfway through eating the bowl of food, not running to the bowl as quickly as usual, not finishing the meal etc.) Should any of these signs be observed, this would indicate that the endpoint of induction has been reached and it is time for the ACTH stimulation test. Induction proceeds until endpoint has been reached but if 8-9 days have passed and a clear endpoint has not been observed, the dog should have the ACTH stim test anyway.

Note: Lysodren therapy should never be used in a dog that does not have a good appetite.

A Cushing's dog that does not have a good appetite has an additional problem

which must be diagnosed before pursuing therapy for Cushing's syndrome.

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

- Diarrhea or vomiting
- Appetite loss
  (may be as subtle as less enthusiasm towards eating, 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 vet know. It may be time for an early ACTH stim test or possibly even for an prednisone pill. It is a good idea to maintain daily phone contact with your vet after the third day or so of induction, when 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 metabolism of Lysodren.

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 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/Addisonian Crisis?

Addison's disease, also called hypoadrenocorticism, is the opposite of Cushing's disease; Addison's disease results from a deficiency of cortisone. If Lysodren® erodes away too much of the adrenal gland or if there is an idiosyncratic trilostane response, an Addisonian reaction occurs that can be temporary or permanent. The symptoms mentioned above (vomiting, diarrhea, listlessness, appetite loss) may be seen and if untreated, the patient can go into shock and die. If you suspect an Addisonian reaction is occurring, a dose of prednisone (which has hopefully been provided to keep on hand in case of emergency) should reverse the reaction within 30 minutes, or a couple of hours at most. If no response to prednisone is seen, the dog has some other illness. If the dog is back to normal after the prednisone dose, then contact the veterinarian for further instructions. The prednisone will likely have to be continued for a couple of weeks.

Addison's disease can be permanent after a drug reaction. 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 on its own. Medications to treat Addison's disease can be expensive, especially for larger dogs, and it is generally felt that inducing Addison's disease is undesirable.

It should be noted that there are some specialists who feel that treating Addison's disease is much simpler than treating 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 in the U.S. and if "medical adrenalectomy" is performed, it is done in a controlled way.

Addison's disease, can also happen as a natural occurrence with no help from Lysodren.

Trilostane

Trilostane 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 as effective as Lysodren in treating Cushing's syndrome.

Trilostane is given once or twice a day with food. Common side effects are mild lethargy and appetite reduction especially when medication is started and the body adapts to its hormonal changes. Addisonian reactions (see below) have been reported in which the adrenal cortex dies off. Most reactions are minor and can be reversed with discontinuation of trilostane; however, permanent Addisonian reactions are possible, just as with Lysodren. While these permanent reactions are generally dose-dependent with Lysodren, they are idiosyncratic with trilostane, meaning that they can occur unpredictably and at any dose. For this reason, monitoring blood tests are just as important with trilostane as they are with Lysodren. In two studies, the risk of a permanent or life-threatening Addisonian reaction was 2-3% with trilostane and 2-5% with Lysodren.

As with Lysodren, the 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 monitoring is similar to that of Lysodren while its dosing schedule is less convenient. Initially it was believed that because trilostane uses an enzyme inhibitor with reversible effects, trilostane would not have the potential to cause a life-threatening Addisonian reaction. This is no longer felt to be true but at least there is an alternative effective medication for pets that do not tolerate Lysodren or who have had difficulty achieving regulation with Lysodren.

Advantages of Trilostane over Lysodren

- Trilostane does not erode the adrenal cortex. It acts as an enzyme inhibitor and the inhibition it causes is fully reversible. It is unclear why Addisonian reaction is still possible with this medication. In theory it should be safer.

Disadvantages of Trilostane Compared to Lysodren

- Because initial references to trilostane suggested it was safer than Lysodren, it is possible for a pet owner to have a false sense of security and ignore important signs of drug reaction.
- Some dogs do better with once daily administration, and for other dogs the medication simply does not last long enough to allow for once daily dosing. Monitoring tests will help determine what regimen is best for a given patient. Timing of the monitoring blood tests relative to the administration of the medication is much stricter with trilostane than with Lysodren.
- Lysodren costs substantially less since it is given less frequently.
- Trilostane is given once or twice daily while Lysodren is given only once or twice a week.

Ketoconazole and Selegiline: Rarely seen Alternatives Nowadays

At this time, meaningful treatment with medication involves a choice between trilostane and Lysodren but in the years before trilostane was available in the U.S., alternatives for dogs intolerant of Lysodren® were in great demand. Ketoconazole, an antifungal medication, was found to have steroid-suppressing side effects that could be exploited to treat Cushing's syndrome. Unlike the other drugs, ketoconazole did not pose a risk for Addisonian reaction. Unfortunately, sustained responses were hard to come by and since more effective alternatives have emerged, ketoconazole is now relegated to its original function of treating fungal disease. Typically, a low dose is used for a week and if no adverse symptoms result in that time, the higher maintenance 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 stim test is usually recommended after the first month of 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.

Selegiline (also called L-Deprenyl or Anipryl) acts by increasing dopamine and consequently reducing ACTH production. Rather than trying to interfere with the adrenal gland's overproduction of steroid hormones, L-Deprenyl addresses the pituitary tumor directly. The problem is that this type of ACTH regulation does not work well when a pituitary tumor is involved as tumors tend not to respond to regulation like normal tissues do. Selegiline breaks down into amphetamines (strong stimulants) that may be therapeutic in other ways to Cushing's patients. Side effects are minimal (approximately 5% of patients in a study experienced nausea, restlessness, or reduced hearing). There is some expense compared to the other medications used for Cushing's syndrome.

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. 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.

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. L-Deprenyl is the only medication approved by the FDA for Cushing's in the dog. For frail dogs with only mild symptoms, L-Deprenyl may be a good choice.

Advantages of Lysodren Over L-Deprenyl

L-Deprenyl is substantially more expensive than Lysodren. Response to L-Deprenyl is not reliable. 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.

Surgery

Since pituitary-dependent Cushing's syndrome is caused by a pituitary tumor, the question arises about removing the tumor surgically. This treatment has received more attention, recently but the location of the pituitary (at the base of the brain) makes surgery problematic. Surgery is not at this time a common treatment in the U.S. and special facilities are required for this surgery; therefore, surgery is generally not recommended.

Summary

Choosing a therapy for pituitary Cushing's syndrome should take into account effectiveness, cost, monitoring schedule, dosing schedule, and side effects potential. In the future, surgical options are likely to come forward as they have in the treatment of human Cushing's syndrome. Direct further concerns and questions to your veterinarian while you select an option.

Treatment of Adrenal Cushing's

We begin here assuming an adrenal tumor has been confirmed with either blood testing, imaging, or both. Two questions must be answered next:

1. Is the tumor benign or malignant?
2. Should you choose surgical treatment or medical management?

Benign vs. Malignant

While only approximately 15% of canine Cushing's syndrome patients have adrenal tumors, half of that 15% will have benign tumors and half will have malignant tumors. The choice of therapy may depend on which type.

If imaging has not yet been done, this is the time to do so. Chest radiographs will be important as malignant adrenal tumors tend to spread to the chest. If such spread is seen, the tumor can be assumed to be malignant. Absence of tumor spread does not mean the tumor is benign. Ultrasound of the stomach, if this has not already been done (or even CT scanning, MRI imaging, or nuclear medicine scanning), will be needed to determine the size of the tumor, and to check for invasion of local abdominal tissues, especially in the liver.

Between evaluation of the chest and the abdomen, it may be possible to non-invasively determine if the tumor is malignant. The absence of tumor spread does not mean that the tumor is benign. If there is obvious spread to other organs, medical management is the only meaningful hope for the patient. It may be necessary to consult with an oncologist for the most current medication plan.

What if Imaging Fails to Confirm that the Tumor is Malignant?

As mentioned, it is not possible to say that the tumor is benign simply because tumor spread has not been detected. Still, no evidence of spread is about as close to determining that the tumor is benign as we can get without actually obtaining tissue samples. If the adrenal tumor is benign, there is an excellent chance for complete recovery if the tumor is surgically removed. The smaller the tumor, the easier the surgery, though the surgery involves delicate tissue in a difficult area.

What if Imaging Indicates the Tumor is Malignant?

If there is obvious tumor spread, surgery may be too risky. The decision to proceed with medical therapy will depend on how debilitated the patient is, and the degree of tumor spread versus the severity of the clinical signs of Cushing's disease. Relief, but not cure, of the clinical signs may be achieved by removing part of the tumor. Medical management with high doses of Lysodren would be a fair alternative.

What you Should Know about Surgery

- Removal of the adrenal gland is a relatively difficult surgery and is probably best left to board certified surgeons who perform this surgery with some regularity. (The adrenal gland is located between the aorta, which is the body's largest artery; the renal artery and vein, which are the sole blood supply to the kidney; and the phrenicoabdominal artery. This vascular area is half-jokingly referred to by surgeons as the Bermuda triangle. Surgery here is not for the inexperienced.) Removal of an adrenal tumor is generally considered to be one of the most difficult surgeries in all of veterinary practice.
- Risk of bleeding is higher for larger tumors, especially if they are malignant and have invaded local structures. It is quite possible that the full extent of invasion will not be apparent prior to surgery.

- Animals with Cushing's syndrome have poor healing ability and tend to have high blood pressure. Several months of medical therapy (i.e. Lysodren, Anipryl, or ketoconazole) prior to surgery may be a good means to strengthen the patient, especially if the tumor is believed to be benign. If the tumor is believed to be malignant, there may not be time for such stabilization.
- The dog's natural cortisone mechanisms will have been suppressed by the tumors. Several months of prednisone will likely be required at home. Some patients require Florinef as an additional supplement. ACTH stimulation tests are used to monitor the need for medication.
- Adrenal tissue is notoriously difficult for pathologists to grade as benign or malignant. It is possible that a tumor initially graded as benign will later turn out to be malignant.
- In a statistical survey of 63 dogs undergoing surgery for adrenal tumors:
    - + 6% (4) had inoperable tumors and were euthanized on the surgery table.
    - + 29% (18) died either in surgery or shortly thereafter due to complications.
- Average life span for dogs undergoing surgery is 36 months (this includes averaging in those who died shortly after surgery).

Medical Therapy for the Adrenal Tumor

Lysodren is a chemotherapy drug that can erode the cortisol-producing layers of the adrenal gland. This ability has made Lysodren the traditional medication for the treatment of pituitary Cushing's disease, and it turns out the adrenal tumors will respond to higher doses as well. The higher doses needed to control adrenal tumors tend to produce more Lysodren reactions than are seen in the treatment of pituitary tumors. The average survival time for this type of therapy is 16 months.