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Treatment of Pituitary Form of Cushing's Syndrome

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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.

Additional Resources

- Quality of Life Survey for Dog Owners With and Without Cushing's disease

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- Symptoms of Cushing's Syndrome
- Cushing's Syndrome: Description
- Laboratory Tests Hinting at Cushing's Syndrome
- Laboratory Tests Confirming Cushing's Syndrome
- Cushing's Syndrome: Classifying the Type
- Pituitary Macroadenoma in Cushing's Syndrome
- Adrenal Tumor Treatment in Cushing's Syndrome

The treatment of pituitary dependent Cushing's disease has been dominated by two medications: Lysodren® (also called Mitotane or o,p'-DDD), and Trilostane (brand name Vetoryl®). 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-dependent Cushing's syndrome. That said, Trilostane has largely captured the market at this point so we will begin with it. Two other medications: ketoconazole and selegiline are also sometimes used but with less reliable results but they may be applicable in specific circumstances. We will review these as well.

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.

While trilostane is substantially newer to the market than Lysodren®, the traditional treatment, several studies have determined trilostane to be as effective as Lysodren® in treating Cushing's syndrome. Furthermore, trilostane is approved to treat pituitary dependent

Cushing's disease (and Lysodren® is not) and there is belief that trilostane has less potential for side effects. For these reasons, trilostane has emerged as the most common treatment for pituitary dependent Cushing's disease.

Trilostane is given once or twice a day with food (as opposed to Lysodren, which is given twice a week). Common side effects are mild lethargy and appetite reduction especially when medication is started and the body adapts to its hormonal changes. More serious Addisonian reactions (see below) have been reported where the adrenal cortex actually dies off and the patient is left with a cortisol deficiency. Most trilostane reactions are minor and can be reversed by discontinuing the trilostane; however, permanent Addisonian reactions, where cortisol suppression is too strong (see below), are possible just as with Lysodren® with an important difference. With Lysodren® reactions depend on the amount being given (higher dose = more chance of reaction) but with trilostane reactions are random and unpredictable (idiosyncratic).

The doses of both Lysodren® and trilostane are adjusted based on results of periodic blood tests (ACTH stimulation tests) typically done at 14 days, 30 days, 90 days and then every 4-6 months depending on results. You might ask why you might consider trilostane given that its monitoring is similar to that of Lysodren while its dosing schedule is less convenient. The answer seems to be that the side effects potential is milder and one is less likely to get into a serious position with trilostane compared to Lysodren®. Trilostane also comes in a formula (a capsule) that is approved for veterinary use, making it more readily available than Lysodren®, which is a human medication and frequently a special order at most human pharmacies. These factors have led to trilostane predominating in the treatment of canine Cushing's disease. Many veterinarians consider trilostane to be their first choice in Cushing's disease treatment.

Lysodren: The Traditional Therapy

For decades, Lysodren® was the only treatment for pituitary dependent Cushing's disease. It is convenient to use and relatively inexpensive, though it does have the potential for serious side effects. One of the disadvantages of Lysodren therapy is the need for regular monitoring blood tests. Too much Lysodren is toxic and too little is not going to control the Cushing's symptoms. Because of the potential for dose-dependent side effects, monitoring tests are especially important from a safety standpoint.

How this Medication Works

Lysodren should be considered to be a chemotherapy drug. 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 responding with excess hormone production because there isn't enough cortex to make excessive hormone amounts. Instead, if everything has gone according to plan, the adrenal cortex will have been eroded away so as to yield normal - rather than excessive - cortisol production. Over several months all the symptoms of Cushing's syndrome resolve and the patient feels active and happy.

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 to the desired thickness 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 to treat pituitary dependent Cushing's disease (though it is worth noting that in Europe it is common to purposely create a cortisol deficiency; see the section below on Addison'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 that 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). Your veterinarian may also send 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 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 half way 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 to 9 days have passed and a clear endpoint has not been observed, the dog should have the ACTH stimulation test at that time anyway

Note: Lysodren therapy should never be used in a dog who does not have a good appetite. A Cushing's dog who does not have a good appetite has an additional problem that 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 (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 are ready for maintenance within the first week of induction but others require more time, especially if they are taking other drugs that alter the metabolism of Lysodren. (Phenobarbital would be the obvious such medication.)

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 symptoms are ignored, 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 creating Addison’s disease is undesirable. That said, in Europe it is common to treat Cushing's disease by purposely creating an Addisonian state because it is much simpler to treat Addison's disease than it is to treat Cushing's. The technique for purposely creating Addison's disease is called medical adrenalectomy. It involves very high doses of Lysodren and is done in a controlled manner. It is not a common procedure in the U.S.

See more information on Addison's disease, which can also be seen in animals and people as a natural occurrence with no help from Lysodren.

Advantages of Trilostane over Lysodren

Trilostane 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. Though not completely free of side effects potential, it is generally felt to be safer.

Disadvantages of Trilostane Compared to Lysodren

- Trilostane is given once or twice daily while Lysodren is given only once or twice a week. More frequent dosing translates to higher expense and less convenience.

- 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.

Ketoconazole and Selegiline: Rarely Used 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: treating fungal disease.

Selegiline (also called L-Deprenyl or Anipryl) acts by increasing dopamine and consequently reducing ACTH production. 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 for Cushing's patients. Side effects are minimal, though there is some expense compared to the other Cushing's medications.

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.

A Note on 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. Unless you live in a unique community where there is a surgeon with extensive experience in this as yet esoteric procedure, I recommend sticking with the medical therapies.

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 for human Cushing's syndrome. Direct further concerns and questions to your veterinarian while you select an option.

Related resources

- Cushing's Syndrome: Classifying the Type - *January 24, 2024*
- Laboratory Tests Hinting at Cushing's Syndrome - *October 7, 2023*
- Pituitary Macroadenoma in Cushing's Syndrome - *October 5, 2023*
- Adrenal Tumor Treatment in Cushing's Syndrome - *August 24, 2023*
- Symptoms of Cushing's Syndrome - *November 16, 2022*
- Laboratory Tests Confirming Cushing's Syndrome - *November 16, 2022*
- Cushing's Syndrome (Hyperadrenocorticism): Description - *September 19, 2017*

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