Topical Review

Medical Management of Pituitary-Dependent Hyperadrenocorticism: Mitotane versus Trilostane

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ABSTRACT

Pituitary-dependent hyperadrenocorticism is a common endocrine disorder in dogs in the United States. Once a diagnosis is established, a decision must be made whether or not to pursue treatment, and if so, which medication to use. Historically, mitotane (Lysodren, o,p’-DDD, Bristol-Myers Squibb, New York) has been the most commonly used treatment for medical management. It is used is complicated and comes with many potential side effects, making many practitioners wary of its use. Recently, trilostane has been proven to be an effective treatment of pituitary-dependent hyperadrenocorticism and is approved for use in other countries. Treatment with trilostane is somewhat simpler and the incidence of side effects seems to be less when compared with mitotane therapy. Either treatment can be a safe and effective method of treatment for pituitary-dependent hyperadrenocorticism when the practitioner and client are well educated regarding their use and an appropriate monitoring protocol is used.

Keywords: pituitary-dependent hyperadrenocorticism, adrenal dependent hyperadrenocorticism, mitotane, trilostane.

Once a diagnosis of pituitary-dependent hyperadrenocorticism (PDH) has been established, a decision must be made as to whether to treat the dog and with what medication to treat with. Though it is rational to treat every patient with a confirmed diagnosis, occasionally clients will be hesitant to initiate therapy, due to the level of commitment involved and risks associated with treatment. The most common medications used to treat PDH are mitotane, an adrenocorticolytic agent, and trilostane, a competitive 3β-hydroxysteroid dehydrogenase (3β-HSD) inhibitor. Other medications that have been used include ketoconazole (Nizoral, Janssen, Titusville, NJ), L-deprenyl (Anipryl, Pfizer, New York), and aminoglutethimide (Cytares, Novartis, East Hanover, NJ). This discussion will be limited to the two most commonly used medications: mitotane and trilostane.

Treatment Considerations

Many of the clinical signs associated with PDH, such as alopecia and panting, do not pose severe physiologic consequences. There are, however, certain parameters that must be assessed and, if found to be abnormal, would indicate that treatment is essential. These parameters include blood pressure (systemic hypertension), urinalysis (recurrent urinary tract infection (UTI), proteinuria), blood glucose (diabetes mellitus), and physical examination (severe muscular weakness, neurologic signs, calcinosis cutis).

In one study, 86% of dogs with uncontrolled hyperadrenocorticism (HAC) were hypertensive. The exact mechanism of the development of systemic hypertension in dogs with hyperadrenocorticism is unknown, but it may be related to the mineralocorticoid-like effect of cortisol which, under normal physiologic conditions, is insignificant, but, in patients with excess, becomes significant. Given the potential for serious consequences associated with uncontrolled hypertension (ie, stroke, retinal detachment), all patients with PDH and hypertension should be treated.

The frequent occurrence of UTI in patients with HAC is well documented; furthermore, many of the dogs will be asymptomatic for urinary tract disease. A recent study documented that 46% of dogs with HAC had UTI on initial presentation with <5% of them having overt signs of lower urinary tract disease (ie, stranguria, pollakiuria).

Any patient with HAC and recurrent UTI should be treated for HAC to prevent more serious, long-term consequences (ie, pyelonephritis).

Proteinuria, as defined as a urine protein:creatinine ratio (UPC) > 1.0, has been documented to occur frequently in dogs with uncontrolled or poorly controlled HAC. It is important in any patient with HAC and proteinuria that UTI and hypertension be investigated, as both are well-documented causes of elevation of UPC. In the absence of these findings, mechanism of protein loss is unclear, although systemic and glomerular hypertension are believed to play a role in the development of glomerulosclerosis. Significant glomerular lesions have been found in dogs with HAC and proteinuria. Although proteinuria may persist after treatment of HAC, its presence indicates a need for treatment in an effort to minimize glomerular damage.

Mitotane Therapy

Mitotane has historically been the drug most commonly used for the medical management of PDH in the United States. Compared with some of the other treatment options, it does require a greater degree of comfort with its use as well as a great deal of client education regarding its effects and toxicity. It is definitely an effective means of managing PDH (Fig. 1).

Pharmacology

Mitotane works by causing necrosis or atrophy of the adrenal cortex with the zona reticularis (the part that secretes cortisol) being more sensitive than the zona glomerulosa (the part that secretes aldosterone). It also interferes with steroid biosynthesis by an unknown mechanism.

Mitotane generally has poor systemic availability. This can be improved by administration with food, since it is fat-soluble. It is distributed throughout the body but is stored mostly in adipose. It must be...
activated in the liver by the cytochrome P450 system and is believed to be metabolized in the liver and excreted in the bile and urine.5

Side Effects

Side effects associated with mitotane should be divided into two categories: those associated with administration of the drug itself or those associated with the effects of the drug. The most common side effects are gastrointestinal upset, manifested as nausea, vomiting, and diarrhea, which usually occur within a short period of time after administration. After a brief discontinuation of the medication, therapy can be re instituted but with further division of the dose (ie, if a patient was initially receiving 250 mg orally, once daily with food, the dose can be changed to 125 mg orally twice daily with food). Given that the typical size of a patient with PDH is <20 kg in body weight, this will frequently necessitate reformulation by a compounding pharmacist.

Adverse reactions associated with the effect of mitotane unfortunately manifest similarly, with vomiting, diarrhea, anorexia, weakness, and ataxia being the most common. They are all signs of glucocorticoid deficiency. Dogs with severe glucocorticoid deficiency may present in acute Addisonian crisis (ie, shock, electrolyte disturbances, hypoglycemia). The only true way to discern between the two categories of reaction would be to perform an ACTH stimulation test. A patient with glucocorticoid deficiency would have an absence of increased cortisol associated with ACTH administration, whereas a dog reacting just to the medication would show an increase in cortisol in response to ACTH administration. A patient with glucocorticoid deficiency should be treated with prednisone as a glucocorticoid supplement until it is established whether the deficiency is reversible.

Dosage

Treatment with mitotane occurs in two phases. First there is a loading phase, during which there is a rapid destruction of adrenal tissue. The typical loading dose is 25 to 50 mg/kg per day. After the loading phase is completed, the patient is switched to a maintenance dosage, which typically is whatever the loading dose was divided throughout the week rather than daily (ie, if a patient was receiving 125 mg PO three times per day for a loading dose, the maintenance dose would be 125 mg PO three times a week).

Loading Phase

It is during the loading phase that a patient is most likely to suffer serious side effects from the medication. This is due to the higher dosage being used during this period. The duration of the loading phase can be quite variable from patient to patient with a range of 5 to 65 days being reported.6 The biggest mistake made during the loading phase is to merely select a period of time to administer mitotane and send the clients away with their prescription to return in that time period for the ACTH stimulation test. It is essential that the owners understand what clinical signs to look for to indicate adequate loading (Appendix 1). If the owners know that they should return earlier if they note the slightest change in appetite, the likelihood of an Addisonian crisis will be minimized.

During the loading period, regardless of clinical response, it is advisable to reassess adrenal function with an ACTH stimulation test within 10 to 14 days of initiation of mitotane treatment to get some idea of cortisol response in a patient without clinical response. If the test does not indicate adequate suppression, monitoring should continue weekly until adequate suppression is achieved or at any time the owner notes a clinical response.

Ideally, at the end of the loading period, the baseline cortisol should be within the normal range (1 to 4 μg/dl or 25 to 125 nmol/L) and the poststimulation cortisol should show little or no increase from normal (4 μg/dl or 25 nmol/L). Typically, this will correlate to clinical response.8 For dogs that seem to have good clinical control but test slightly above ideal cortisol range, it may be reasonable to go ahead and switch them to a maintenance protocol as long as the poststimulation cortisol indicates limited adrenal responsiveness.

Given recent issues associated with the availability and cost of Cor tsyn, one could also consider using urine cortisol to creatinine ratios (UCCR) to monitor the loading phase of mitotane treatment. Unfortunately, UCCR can overpredict good control (ie, can be normal in dogs whose ACTH stimulation test would indicate need for dosage increase) and will not always recognize overdose (ie, will be normal in a dog whose ACTH stimulation test is <1 μg/dl after ACTH administration).8

Some endocrinologists advocate the administration of glucocorticoids during the loading period to minimize the incidence of adverse events during this time. Prednisone or prednisolone at a dose of 0.15 to 0.25 mg/kg/d may be used. A disadvantage of concurrent administration of steroids is that it might mask the change in clinical signs the client is looking for to determine clinical effect (ie, change in appetite). If glucocorticoids are included in the loading protocol, ACTH stimulation tests should be monitored at 10 to 14 days and then every 3 to 5 days until the results are satisfactory. It is also important that the dog not receive prednisone within 24 hours of the ACTH stimulation test as prednisone will impact the cortisol assay (ie, the cortisol results may be higher than expected).

Whether they are included in the treatment protocol or not, prednisone or prednisolone should be dispensed to the owner at the time of initiation of treatment as they need to be handy in the event of a
potential hypoadrenal crisis with limited access to veterinary care. I typically recommend that clients administer 0.3 to 1.0 mg/kg/d if the dog starts to vomit profusely, have diarrhea, or stops eating during this period. Though it is clearly superior to obtain an ACTH stimulation test before glucocorticoid supplementation to determine if the dog truly has hypoadrenocorticism, the potential consequences of not administering lifesaving steroids can be dire. Once the crisis is over, adrenal function should be reassessed.

Maintenance Protocols

Once the ACTH stimulation test and clinical signs indicate good control, the patient should be switched to a maintenance protocol. Typically, this represents taking the daily divided dose and dividing it throughout the week. Once on the maintenance protocol, an ACTH stimulation test should be reevaluated 1 month after the dosage change. The goal is for the ACTH stimulation test to be similar to that after the loading phase (ie, baseline within normal range and minimal stimulation of cortisol secretion in the poststimulated sample).

As long as the clinical signs seem well controlled, if the poststimulation cortisol is not ideal, one could consider reloading or simply adjusting up the maintenance dose slightly and reevaluating another ACTH stimulation test in 1 month.

While on the maintenance protocol, an ACTH stimulation test, biochemical profile, and urinalysis and urine culture should be performed on these dogs every 3 to 6 months. Changes in the ALP and ACTH stimulation test may predict an impending relapse. The urinalysis and culture may also serve as markers of control as the presence of proteinuria or UTI may indicate relapse as well.

Relapse

It is not uncommon for dogs being treated with mitotane to relapse (ie, redevelop overt clinical signs of HAC), with as many as 50% of dogs requiring a second loading period within the first year of treatment. When a dog displays clinical signs of relapse, an ACTH stimulation test should be performed to confirm the HAC is out of control. It is also important to rule out other potential causes of polyuria/polydypsia (PU/PD) (ie, diabetes mellitus, pyelonephritis, renal failure, hypercalcemia); therefore, a biochemical profile, urinalysis, and urine culture should be performed simultaneously.

Once relapse is confirmed, another loading period should be initiated (50 mg/kg/d of mitotane). One should be aware of the duration of the previous loading period but the duration may change. Once the ideal ACTH stimulation test has been established, the maintenance dosage should be increased by 30 to 50%. Another ACTH stimulation test should be performed 30 days after the new maintenance dosage is established.

Nonselective Adrenocorticotolysis

It is also possible to attempt to completely obliterate adrenal glucocorticoid secretion in an effort to simplify treatment. Using this protocol, mineralocorticoid secretion will also be suppressed so patients will end up requiring their supplement as well. This would be protocol to consider in a dog with both Cushing's disease and diabetes mellitus, as minimizing relapses of HAC will improve diabetic regulation.

When attempting medical adrenocorticolysis, mitotane should be administered at 50 to 75 mg/kg/d for 25 days. The dose should be divided throughout the day and administered with food. On the third day, hormone supplementation is initiated. In the study reported, cortisone was used at a dosage of 2 mg/kg/d, fludrocortisones at a dosage of 0.0125 mg/kg/d, and sodium chloride supplemented at 1 g/kg/d. All mitotane doses were divided into at least two administrations. The owners were also given injectable glucocorticoid and mineralocorticoid preparations to have on hand, should they miss more than two doses of the oral supplements. The owners were instructed to communicate with their doctor at least once a week with clinical updates.

If the dog’s appetite decreased significantly, the owners were instructed to discontinue the mitotane and to resume it only after the appetite returned to normal. Dosage adjustments occurred if these events were recurrent with either a dosage decrease or an increased division of dose (ie, if a dog was receiving the mitotane twice daily, it was changed to a smaller dose three times daily). After the 25-day period of mitotane administration, glucocorticoid and mineralocorticoid supplementation must be continued throughout the rest of the dog’s lifetime.

In a study evaluating this protocol, 19/129 dogs had their protocols discontinued before 25 days. Complete remission of HAC occurred in only 11/129 dogs (10%) using this aggressive protocol. Fifty dogs (39%) experienced relapse of HAC using this protocol and 15 dogs (12%) died during the study. Although this protocol is very aggressive, it may still be the best choice for patients with concurrent diabetes mellitus. Aggressive treatment of the HAC will then allow the clinician to regulate the diabetes mellitus.

Trilostane Therapy

Trilostane has recently been proven to be a safe and effective method of treating PDH in dogs. Trilostane is not currently approved by the FDA in the United States. In countries in which it is available, it has virtually replaced mitotane as the first line of treatment. This is due to a relative ease of usage and low incidence of side effects. When and if it is approved in the United States, cost may be a determining factor for clients as it is considerably more expensive than mitotane (Fig. 2).

**Fig. 2.** Algorithm for the use of trilostane for the treatment of PDH.
Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Protocol(s)</th>
<th>Final/Dose</th>
<th>Monitoring</th>
<th>Target Poststimulated Cortisol</th>
<th>Dose Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vet Dec 2002</td>
<td>11.4 mg/kg if dose 1 3.2 mg/kg if dose 2</td>
<td>10d, 30d, 90d, 2 weeks post dose change</td>
<td>Not reported</td>
<td>&lt;290 nmol/L</td>
<td>Not reported</td>
</tr>
<tr>
<td>AWR 2002</td>
<td>6.1 mg/kg (4.1-6.5 mg/kg)</td>
<td>1.3-4.6-7-12-16-24 weeks</td>
<td>Not reported</td>
<td>&gt;15 nmol/L excessive</td>
<td>27.6-69 nmol/L</td>
</tr>
<tr>
<td>AWR 2003</td>
<td>17 mg/kg (5-50 mg/kg)</td>
<td>10d, 30d, 90d, 2 weeks post dose change</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>JBA 2004</td>
<td>5-20 kg 60 mg SID 20 kg 120 mg SID</td>
<td>6 months</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>AWR 2005</td>
<td>&gt;31 kg (60 mg SID) to 60 mg BID</td>
<td>7.5 mg/kg/day (26.1-18.4 mg/kg)</td>
<td>JBA @ 6 months</td>
<td>15.8 mg/kg/day (26.1-18.4 mg/kg)</td>
<td>JBA @ 6 months</td>
</tr>
<tr>
<td>AVJ 2003</td>
<td>30-60 mg per day</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Pharmacology

As mentioned earlier, trilostane is an orally acting steroid analog, which acts as an inhibitor of the enzyme 3β-HSD. This enzyme normally causes the conversion of pregnenolone to progesterone. This results in inhibition of conversion of progesterone to cortisol, aldosterone, and androstenodione. 3β-HSD exists as different isoenzymes in the zona fasciculata and zona glomerulosa, which may result in different effects on cortisol versus aldosterone secretion.

Trilostane is poorly water soluble. It is recommended that trilostane always be administered with food to enhance absorption. It is metabolized in the liver and excreted in bile and urine. Its duration of action is less than 20 hours.10

Side Effects

Lethargy and inappetence may be noted during the first few days of therapy secondary to steroid withdrawal. Vomiting, anorexia, shakiness, and diarrhea may also be seen. Typically, these signs should be reversible within 24 to 48 hours of drug withdrawal (see Protocols). Patients should be examined and have an ACTH stimulation test performed to assure above signs are not associated with hypoadrenocorticism. Rarely, acute death, without the development of clinical signs of hypoadrenocorticism, has occurred.

One unexpected, rare reported side effect is adrenal necrosis. In the published report, the dog initially presented 21 days after therapy was instituted with signs of inappetence, depression, and diarrhea. The dog was diagnosed with hypoadrenocorticism and responded to intravenous fluid therapy and mineralocorticoid and glucocorticoid supplementation. Trilostane therapy was discontinued. Clinical signs persisted and an abdominal exploratory surgery confirmed necrosis of the adrenal gland.11

Treatment Protocols and Monitoring

Though there have been many studies documenting the safety and effectiveness of trilostane, there is a lack of consistent dosing protocol and treatment monitoring (Table 1). Part of this is related to the currently available capsule sizes (30, 60 and 120 mg capsules) limiting precise dosing. Even within the studies listed, capsules were formulated into different doses to fit desired dosage.

Once a dose has been selected, owners should be instructed to administer the medication in the morning with food (Appendix 2). In contrast to mitotane, the dogs should come back at the timeframe determined by the selected protocol to have an ACTH stimulation test performed. It is critical that the test be performed 4 to 6 hours after the pill is administered to ensure maximal effect (ie, if you wait too long, the drug effect may be tapering off and the poststimulation cortisol will be higher). It is important to realize that, due to its mechanism of action (enzyme inhibition) and half life, the effect of trilostane will likely wear off throughout the day, as evidenced by absence of correlation of urine cortisol creatinine ratios collected 24 hours post pill to ACTH stimulation tests performed 4 to 6 hours post pill.14 Morning administration enables testing during typical clinic hours. A physical examination, CBC, biochemical profile, and urinalysis should be performed at each recheck as well.

It is critical to interview the owner carefully at each recheck regarding clinical signs as changes in water consumption or appetite may help guide your treatment decisions. Unlike mitotane therapy, the exact goal for poststimulated cortisol is not clearly defined (Table 1) and, therefore, whatever goal is set must be correlated to clinical signs. For example, if a dog’s poststimulation cortisol falls outside of the target range but the owner reports a significant decrease in water consumption and treatment monitoring (Table 1). Part of this is related to the currently available capsule sizes (30, 60 and 120 mg capsules) limiting precise dosing. Even within the studies listed, capsules were formulated into different doses to fit desired dosage.

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Despite the known drop-off in drug effect when administered once daily, for many dogs, once daily administration does seem adequate to control clinical signs of Cushing’s disease. Recently, a study investi-
gated the advantages of twice-daily trilostane administration. They found that twice-daily administration was well tolerated and that total daily doses were lower for dogs receiving twice daily administration. A study comparing the two dosing protocols directly has not been done.17 However, it is generally recommended that a patient with poor clinical response to once-daily administration be switched to twice-daily administration.

Once an ideal dose is established, the dogs should be monitored with a physical examination, CBC, biochemical profile, urinalysis and urine culture, and ACTH stimulation test every 3 months. Dosage changes are not uncommon and may occur either as an increase or as a decrease in dose.

**Expected Outcomes and Comparisons**

As far as expected outcome, results of response rates for trilostane are quite similar to mitotane therapy with 70 to 86% of dogs having resolution of their PU/PD within the first week of treatment.1.12,17 As expected outcomes and comparisons with mitotane versus mitotane is abdominal ultrasound findings.

Another important difference to highlight between dogs treated with trilostane versus mitotane is hair, coat, and body composition changes seem to lag behind changes in water consumption, attitude, and appetite.12 This is likely due to the fact that the former clinical signs are signs of chronic glucocorticoid excess, whereas the latter are signs of the effects of cortisol itself.

Interestingly, one study found that half of the dogs treated with once-daily trilostane with elevated pretreatment serum ALP showed no significant decrease in this parameter during treatment. It was presumed that this was due to the short duration of action of the medication.13 In the study investigating twice daily administration, there was a significant decrease in mean serum ALP at the 6-month reevaluation but there were still several dogs whose serum ALP fell outside the normal range.

Another important difference to highlight between dogs treated with trilostane versus mitotane is abdominal ultrasound findings. Typically we expect a patient with well-controlled PDH from mitotane therapy to have a measurable decrease in adrenal gland size.14 In contrast, patients treated with trilostane will have enlargement of their adrenal glands during treatment. At 6 months into treatment, 84% of dogs were found to have an increase in the size of the right adrenal gland length and caudal pole thickness with the median width increasing from 7 to 10 mm.15 In some dogs, there may also be a change in ecogenicity of the adrenal gland with increased difference between the inner and outer layers; heterogeneity of the echogenicity has also been reported. These changes will typically be evident within 6 weeks of initiation of therapy.

A recent retrospective study directly compared mitotane therapy to trilostane therapy. Though there were a larger number of dogs treated with trilostane in this study, median survival time between the two was quite similar (708 (33-1399) days for mitotane and 662 (8-1971) days for trilostane). They found that the only factor that impacted survival was age at initiation of treatment (ie, older dogs lived a shorter period of time). These numbers are fairly similar to previously reported median survival times.

**Conclusions**

Trilostane and mitotane are both effective therapies for the treatment of dogs with PDH. Although there are differences in treatment protocols, side effects, and treatment monitoring, once familiar with either drug, any practitioner should feel comfortable treating PDH. With both drugs, an educated client, as well as monitoring of history, physical examination, biochemical, hematologic, endocrinologic, and urine parameters are essential to successful treatment.

**References**


**Appendix 1**

**Client Instructional Handout for Mitotane Therapy**

**Hyperadrenocorticism: Diagnosis and Treatment—Mitotane**

**Introduction.** Your dog has been diagnosed with pituitary-dependant hyperadrenocorticism (Cushing’s disease). This disease is typically caused by a small, benign growth of the brain that results in over-secretion of the hormone cortisol. Typical clinical signs of Cushing’s disease include excessive drinking and urination, increased appetite, panting, potbellied appearance, and hair loss. In addition, dogs with Cushing’s disease are more susceptible to infection, can develop hypertension, and are more prone to the development of diabetes mellitus.

**Treatment.** The treatment we have chosen is a medication called mitotane (also known as Lysodren and o,p'-DDD). This medicine causes destruction of the adrenal glands (the ones that secrete the excessive amount of cortisol) leading to a decrease in cortisol secre- tion. Treatment occurs in two phases:

1. Loading phase—the mitotane is administered daily to cause abrupt cessation of cortisol secretion.

2. Maintenance phase—to keep cortisol secretion suppressed.

**Monitoring.** We will need to perform ACTH stimulation tests intermittently to assess whether the therapy is effective. This test takes an hour so be prepared for the visits to take at least 1 hour.

**Complications.** The biggest risk of therapy is that it will wipe out too much of the adrenal gland function. This is a problem because the
body needs cortisol to respond to stress. Also, the secretion of a second hormone, aldosterone, can be affected, leading to electrolyte disturbances. Clinical signs that this has happened include vomiting, diarrhea, loss of appetite, and weakness. The drug itself can cause loss of appetite and vomiting.

Instructions.
1. Your dog should get ______ mg of mitotane ______ times a day. Typically the loading period takes between 5 and 10 days. Signs to look for that the medication is working include the following:
   a. Decreased appetite
   b. Decreased water consumption
   c. Vomiting
   d. Diarrhea

   *****If these signs develop, contact your doctor immediately for instructions.

   *****If you are unable to get in touch with your doctor and you are concerned that your dog is having a reaction or overdose—discontinue mitotane therapy.

   *****If your dog is vomiting or not eating, administer ______ mg prednisone ______ times a day until you can contact your doctor.

2. Once the loading phase is completed, your dog will be switched to ______ mg mitotane given ______ times a week. We will then want to repeat an ACTH stimulation test in 1 month and then every 1 to 3 months thereafter, depending on how things are going.

3. Always make sure you have prednisone in the house. If at any point in the therapy you are concerned that your dog may be sick from the mitotane therapy and you cannot get in touch with your doctor, it is better to give the prednisone (_______ mg of prednisone).

4. It is very common for dogs to need to be reloaded throughout therapy, sometimes every few months. If you think that your dog is drinking excessively again, an appointment should be made for a repeat ACTH stimulation test.

5. In addition to the serial ACTH stimulation tests, your doctor may perform frequent urine tests (ie, urinalysis and urine culture and sensitivity) as dogs with Cushing’s disease are prone to urinary tract infection without signs of one. Also, biochemical profiles will be performed intermittently to assess the effect of the disease and its treatment on your dog’s kidneys and liver.

The treatment of Cushing’s disease can be quite complicated and frustrating. It requires frequent visits and blood work with changes in drug doses and intervals. However, with commitment and communication, we can work together to give your dog a good quality-of-life.

Appendix 2

Client Instructional Handout for Trilostane Therapy

Hyperadrenocorticism: Diagnosis and Treatment—Trilostane

Introduction. Your dog has been diagnosed with pituitary-dependent hyperadrenocorticism (PDH/Cushing’s disease). This disease is typically caused by a small, benign growth of the brain that results in over-secretion of the hormone cortisol. Typical clinical signs of Cushing’s disease include excessive drinking and urination, increased appetite, panting, potbellied appearance, and hair loss. In addition, dogs with Cushing’s disease are more susceptible to infection, can develop hypertension, and are more prone to the development of diabetes mellitus.

Treatment. The treatment we have chosen is a medication called trilostane. This medication is not officially licensed in the United States and has been obtained by provisional approval from the FDA. Trilostane has been proven to be an effective treatment for PDH and is used quite widely in countries where it is approved.

This medication works by blocking an enzyme that is necessary to make cortisol, therefore decreasing its production. As part of its effect, it may also block other hormones normally made by the adrenal gland (aldosterone).

Complications. The biggest risk of therapy is that it will wipe out too much of the adrenal gland function. This is a problem because the body needs cortisol to respond to stress. Also, the secretion of a second hormone, aldosterone, can be affected, leading to electrolyte disturbances. Clinical signs that this has happened include vomiting, diarrhea, loss of appetite, and weakness. The drug itself can cause loss of appetite and vomiting.

Instructions.
1. Your dog should get ______ mg of trilostane ______ times a day. If given once daily, this medication must always be given in the morning, with food. If given twice daily, then it should be given 12 hours apart, also with food.

2. We will need to see him/her back in ______ days to perform follow-up testing. We will need to perform ACTH stimulation tests at this visit to assess whether the therapy is effective. This test takes an hour so be prepared for the visits to take at least 1 hour. Other laboratory tests will be performed simultaneously.

3. Signs to look for to indicate that your dog is having a problem with the medication include the following:
   a. Decreased appetite
   b. Vomiting
   c. Diarrhea
   d. Lethargy
   e. Trembling

   *****If these signs develop, contact your doctor immediately for instructions.

   *****If you are unable to get in touch with your doctor and you are concerned that your dog is having a reaction or overdose—discontinue trilostane therapy.

   *****If your dog is vomiting or not eating, discontinue the trilostane and administer ______ mg prednisone ______ times a day until you can contact your doctor.

4. Always make sure you have prednisone in the house. If at any point in the therapy you are concerned that your dog may be sick from the trilostane therapy and you cannot get in touch with your doctor, first, discontinue the trilostane, and, if there is no immediate improvement, it is better to give the prednisone (_______ mg of prednisone).

5. It is not uncommon for dogs to need dose adjustment throughout therapy. If you think that your dog is drinking excessively again or seems sluggish, an appointment should be made for a repeat ACTH stimulation test. The dose change may involve either an increase or a decrease in dosage.

6. In addition to the serial ACTH stimulation tests, your doctor may perform frequent urine tests (ie, urinalysis and urine culture and sensitivity) as dogs with Cushing’s disease are prone to urinary tract infection without signs of one. Also, biochemical profiles will be performed intermittently to assess the effect of the disease and its treatment on your dog’s kidneys and liver. Once a proper dose is established, we will want to see your dog back every 3 to 6 months.

The treatment of Cushing’s disease can be quite complicated and frustrating. It requires frequent visits and blood work with changes in drug doses and intervals. However, with commitment and communication, we can work together to give your dog a good quality-of-life.

Doctor’s Name _______________________________________
Phone Number _______________________________________
Emergency Contact ________________________________