**Etiologies**

Pituitary-induced bilateral adrenocortical hyperplasia also known as pituitary-dependent Cushing's disease (PDH) accounts for about 85% of all cases of spontaneous hypercortisolism in the dog. It results from either an adenohypophyseal ACTH-secreting micro- or macroadenoma or from excess pituitary ACTH secretion due to over secretion of corticotrophin releasing factor (CRF) by the hypothalamus. The end result of both processes is hypersecretion of ACTH causing bilateral adrenocortical hyperplasia and subsequent hypercortisolism.

Adrenal tumors consist of either functional adenomas or adenocarcinomas of the adrenal cortex. These comprise 10-15% of all causes of spontaneous Cushing's syndrome in dogs.

Iatrogenic hypercortisolism is by far the most common cause of the "Cushingoid" dog. It is caused by over-treatment with glucocorticoid drugs.

**Normal Canine Adrenal Steroid Production (Chastain and Van Gam: Clinical Endocrinology of Domestic Animals, Lea and Febiger, 1986.**

- Cortisol: 700-800 ug/kg/day = 0.7-0.8 mg/kg/day
- Corticosterone: 300-400 ug/kg/day
- Desoxycortisol: 80-90 ug/kg/day
- Deoxycorticosterone: 5-10 ug/kg/day
- Aldosterone: 5-10 ug/kg/day
- Total adrenal steroid rate = 1.2 mg/kg/day

**Breeds, Age, Sex**

Endogenous Cushing's disease is commonly reported in poodles, dachshunds, and terriers. It can be seen in any breed and mixed breeds as well. The average reported age is 8 years, but can range from very young (3 years) to very old (>12 years). There is no particular sex predilection.

**Clinical Signs**

1. **Polydipsia and polyuria** (PD/PU) are very common complaints. The hypothetical mechanisms include: (1) increased renal free water clearance as a result of increased renal blood flow and (2) inhibition of ADH release and its effect on the renal collecting ducts. A small percentage of dogs (10%) do not show PD and PU.
2. **Polyphagia** is a very common sign. It may be the main complaint along with a tendency toward obesity. The cause is unknown.
3. **Pendulous abdomen** has a high incidence. It results from abdominal muscle weakness, hepatomegaly and intraperitoneal fat deposition and is commonly mistaken for ascites.
4. **Bilateral symmetrical alopecia** typically has truncal distribution and results from atrophy of the pilosebaceous apparatus. There is a variable incidence of skin pathology while a number of dogs do not have any changes whatsoever.

5. **Other skin abnormalities** include hyperpigmentation, comedone formation, thin skin (especially noted in inguinal area), calcinosis cutis (dry or inflammatory forms), tendency toward ecchymosis following venipuncture and superficial bacterial skin infections.

6. **Hepatomegaly** is due to steroid hepatopathy as a result of hepatic glycogen deposition. It does not usually cause significant hepatic dysfunction, however.

7. **Anestrus and testicular atrophy** probably result from inhibition of gonadotropin release.

8. **Muscle dysfunction and weakness - Myotonia** characterized with a stiff gait is a rare complication. Muscle weakness results from the generalized catabolic effects of hypercortisolemia.

9. **Pulmonary calcification** is a rare complication associated with the dystrophic effects of prolonged hypercortisolism. Symptomatic severe respiratory impairment can result.

10. **Systemic hypertension** occurs in dogs with Cushings. Excess cortisol concentrations elevates plasma renin substrate, the circulating protein upon which renin acts to release angiotensin I. Therefore, the hypertension may be partly produced by angiotensin-mediated vasoconstriction.

11. **Central nervous system** signs of stupor, seizures, circling, ataxia, blindness, or Horner's syndrome in a patient with HAC suggests an enlarging pituitary tumor which can be present in as many as 8-13% of dogs with PDH.

**Thromboembolism**

Cushings syndrome is associated with a hypercoagulable state in both dogs and humans. One study (Jacoby RC, et al, Arch Surg, 2001 Sept;136(9):1003-6) showed that levels of procoagulation factors II, V, VII, IX, X, XI, and fibrinogen were significantly increased in dogs with Cushings. In addition, the natural antithrombotic antithrombin was significantly decreased. Sites of involvement can include lungs, brain, bowel as well as others. Providing heparin during surgical procedures should be considered.

**Clinicopathological Laboratory Changes**

The typical abnormalities are provided below:

1. **Hemogram** - Typical findings include mature neutrophilia, eosinopenia, and lymphopenia. Polycythemia (PCV in low 50's) is sometimes present (due to 17-ketosteroid excess). Some dogs lack these hemogram changes.

2. **Serum liver enzyme elevation** - is usually characterized with an elevated alkaline phosphatase level (from steroid-induced hepatic isoenzyme induction). ALT, AST, and BSP retention can also be slightly to moderately elevated. Serum bilirubin and albumin levels are always normal in Cushing's.

3. **Glucose** varies from normal to overt diabetic range. Diabetes mellitus occurs in 10
to 20% of dogs with endogenous hypercortisolism.

4. **Plasma lipids** - hypercholesterolemia and hypertriglyceridemia can occur and cause the blood to become lipemic.

5. Serum electrolytes are usually normal. Hypernatremia and hypokalemia are rarely, if ever, seen.

6. **Urinalysis** - often dilute, but kidneys retain ability to concentrate. Bacteriuria due to lower urinary tract infection is common. Glomerulopathy with proteinuria also occurs and may or may not resolve with treatment for Cushings. It is thought to be due several factors including adrenal tumor antigen overload, if present (R. Nelson, UCD), chronic infection, and glomerular hypertension.

7. **Thyroid function** - usually normal despite low T3 and T4 blood levels. The latter is due to ability of cortisol to inhibit thyroid hormone protein binding. A normal TSH response test might be necessary to substantiate euthyroidism.

**Radiographic Abnormalities**

There are several radiographic changes that characterize some dogs with Cushing's syndrome. These include: (1) soft tissue mineralization, that can involve skin, muscles, lungs, and blood vessels, (2) hepatomegaly and pendulous abdomen, and (3) osteoporosis, especially involving the vertebrae.

Approximately one-half of the adrenal adenomas and adenocarcinomas will calcify and subsequently be seen on plain abdominal radiographs. They are visualized cranial and slightly medial to the anterior pole of the kidneys (VD view especially important). An IVP (especially nephrogram phase) can "highlight" the tumor, but selective abdominal arteriography can be more specific. Remember to take thoracic radiographs in suspect neoplasia cases in order to detect pulmonary metastasis. Abdominal ultrasound and abdominal CAT-scan are newer helpful diagnostic procedures. PDH characterizes as bilaterally enlarged adrenal cortices. Contrary to previous descriptions functional adrenocortical tumors often show one enlarged gland with a tumorous bulge while the contralateral adrenal gland can be either of normal or atrophic proportions. Such normal sized contralateral glands can still show atrophy on histopathological examination.

**Adrenal Function Tests**

Today, there is considerable controversy surrounding the optimal endocrinologic tests for diagnosing canine hyperadrenocorticism. The descriptions of these tests are provided:

A. **Urinary steroids** - requires a 24-hour urine collection and is, therefore, not very conducive for the practitioner. It is best to assay for 17-ketogenic steroids (normal: 1.13 to 3.67 mg/24 hours) or 17-hydroxycorticosteroids (average normal: 3.7 mg/m² per 24 hours).

B. **Basal plasma cortisol levels** - One basal value usually not dependable due to the fluctuating and overlapping blood levels that occur in normal and cushingoid dogs.
Normal unstressed dogs range between 1.9 to 2.5 micrograms/dl (by RIA). NOTE: values reported in nanograms/ml can be converted to micrograms/dl by moving the decimal point one place to the left.

C. ACTH stimulation test - assesses the adrenocortical response to exogenous adrenocorticotropic hormone. It will accurately diagnose endogenous hyperadrenocorticism approximately 70-80% of the time, but will not distinguish between pituitary-induced Cushing's and functional adrenocortical tumors. Cortisol and aldosterone are 11-hydroxy corticosteroids, but the sex corticoid (17-ketosteroids) will also respond to the ACTH adrenocortical stimulators.

Some functional adrenal tumors are autonomous and therefore do not hypersecrete cortisol subsequent to ACTH stimulation. The reasons for a tumors poor response include 1) the production of a different hormone such as 17-hydroxyprogesterone, 2) lack of receptors for ACTH, and 3) some aberrant biosynthetic pathway for cortisol synthesis. However, recent findings show that approximately 50% will hypersecrete cortisol similar to pituitary-induced adrenal hyperplasia patients.

The typical pituitary-induced Cushing dog will hypersecrete cortisol to levels in excess of 17.0 micrograms/dl following ACTH injection. There are some who respond to levels ranging 8 to 15 μg/dl, however. (A very low to minimal response to ACTH in a cushingoid dog suggests either iatrogenic disease due to prior glucocorticoid treatments or the presence of an adrenal tumor.) The ACTH stimulation test technique is performed as follows:

1. using ACTH gel
   a. collect basal plasma cortisol sample
   b. give ACTH gel IM at dose of 1 unit/lb body weight
   c. after 2 hours collect the post-ACTH plasma cortisol sample

2. using Cortrosyn (cosyntropin, Organon Inc., West Orange, NJ)
   a. collect basal plasma cortisol sample
   b. inject 0.25 mg Cortrosyn IV or IM for dogs > 5.0 kg; give 0.125 mg for dogs < 5.0 kg. An alternative dose is 5 μgm/kg IV.
   c. after 1 hour collect post-ACTH plasma cortisol sample

3. low-dose Cortrosyn
   - can dose Cortrosyn at 5 μg/kg and give this either IM or IV – both routes equally effective.
   - take baseline and 60 minute (postinjection) samples

(from: Behrend E, et al, JAVMA, August 15, 2006)

A recent study shows that 17-hydroxyprogesterone (OHP) along with certain other 17-ketosteroids respond almost the same as cortisol with
the ACTH stimulation test. These other steroids include progesterone, testosterone, and androstenedione. There are some dogs with PDH that will have a minimal cortisol response to ACTH, while simultaneously having an exaggerated 17-ketosteroid response. It is therefore important to measure these other hormones when there is a questionable cortisol response. See Hill KE, et al, JAVA (2005);226:556-561.

Since adrenal tumors can also hypersecrete OHP and other 17-ketostepoid hormones with the ACTH stimulation test, it is important to rule out this diagnosis by using other diagnostic tests such as abdominal ultrasound, CAT scan, and by measuring ACTH plasma levels.

Results of the ACTH stimulation test are positive for hyperadrenal function when the OHP level exceeds 1.32 ng/ml (4 nmol/L) but this value will vary between labs. Our adrenal steroid panel is done at the University of Tennessee.

D. Low-dose dexamethasone suppression test.

1. In the normal dog, dexamethasone will suppress pituitary ACTH secretion by negative feedback inhibition and thereby suppress adrenocortical cortisol secretion. This test is 90-95% reliable for diagnosing endogenous hypercortisolism.

2. Technique (from Peterson). Inject 0.01 mg/kg dexamethasone phosphate IM or IV and collect plasma cortisol sample 8 hours later.

3. Interpretation (from Peterson ME. Hyperadrenocorticism. Vet Clin N Am 14:739, 1984). Suppressed cortisol levels to levels < 1 μg/dl rule out endogenous Cushing's. No suppression indicates Cushing's but does not differentiate adrenal tumors from pituitary-induced adrenal hyperplasia. About 27% of dogs with chronic illnesses (e.g., diabetes mellitus, hepatic and renal disease) fail to "adequately" suppress. In diabetic dogs treated with insulin, the effect of a blood glucose of less than 65 mg/dl may over-ride the suppressive effects of dexamethasone and result in inadequate suppression that may suggest hyperadrenocorticism to the unwary. The stress of the hospital environment uncommonly causes inadequate suppression.

Dogs with spontaneous hyperadrenocorticism are usually resistant to low dose dexamethasone suppression (i.e., they have "inadequate suppression"). The test is approximately 94% accurate in distinguishing normal from spontaneously hyperadrenal dogs. Using a slightly higher dose of dexamethasone (0.015 mg/kg), five patterns of suppression are reported:

a. In 80% of dogs with adrenal-dependent and in 25% of dogs with pituitary-dependent hyperadrenocorticism, there is no suppression.

b. Cortisol decreases by about 50% but is still above 1 μg/dl in 15% of dogs with adrenal-dependent and in 15% of dogs with pituitary-
dependent hyperadrenocorticism (i.e., inadequate suppression).

c. Cortisol decreases by about 50% in 2 to 4 hours but returns to resting values at 8 hours in 5% of adrenal-dependent and in 25% of pituitary-dependent hyperadrenocorticism patients (i.e., inadequate suppression).

d. Cortisol decreases to expected values (i.e., less than 1 μg/dl) at 2 to 6 hours but increases back to resting values at 8 hours in 30% of pituitary-dependent hyperadrenocorticism patients (i.e., inadequate suppression).

e. Cortisol decreased to less than 1 μg/dl in 5% of dogs with early pituitary-dependent hyperadrenocorticism (i.e., normal or adequate suppression). This group usually develops abnormal test results when retested 2 to 4 months later.

Note: Remember that the ACTH stimulation test is the preferred screening test for iatrogenic hyperadrenocorticism.

4. This is the most accurate screening test for diagnosing endogenous hypercortisolism. (The 1-2 hour ACTH Stimulation test might be more convenient for the client, however.)

E. Hi-dose dexamethasone suppression test

1. Autonomous cortisol secreting adrenal tumors are independent of the ACTH inhibition caused by high doses of dexamethasone. On the other hand, dogs with pituitary-dependent hyperadrenocorticism ideally will show suppressed cortisol secretion subsequent to hi-dose dexamethasone-induced ACTH inhibition thereby differentiating the pituitary-induced form from functional adrenal tumors.

2. Technique (from Peterson ME: Hyperadrenocorticism. Vet Clin N Am 14:741, 1984): Collect basal plasma cortisol samples. Give dexamethasone phosphate (dose range, 0.1-1 mg/kg b.w.) IM or IV. Collect 8 hour post injection sample.

3. Interpretation: When using 0.1 mg/kg dexamethasone (high dose), "adequate suppression" is defined as the serum cortisol decreasing to less than 50% of the resting value. In many dogs with pituitary-dependent hyperadrenocorticism, adequate suppression occurs, whereas dogs with adrenal-dependent disease do not have adequate suppression. Hence, if adequate suppression occurs, pituitary-dependent hyperadrenocorticism is diagnosed, but inadequate suppression is inconclusive because 25-50% of pituitary-dependent patients have this finding.

When using 1.0 mg/kg (megadose), careful patient selection is required. Adequate suppression is defined as serum cortisol decreasing to less than 1.5 μg/dl, which is diagnostic of pituitary-dependent
hyperadrenocorticism. Four patterns of plasma cortisol responses are seen:

1. In 80% of dogs with pituitary-dependent hyperadrenocorticism but in no dogs with adrenal-dependent disease there is adequate suppression.

2. In 5% of dogs with pituitary-dependent but in no dogs with adrenal-dependent disease, there is adequate suppression at 2 to 4 hours but inadequate suppression by 8 hours.

3 and 4. In 15% of dogs with pituitary-dependent disease, there is inadequate suppression. These dogs oftentimes go on to develop large pituitary chromophobe tumors.

Additional testing is indicated to differentiate pituitary-dependent from adrenal-dependent disease when inadequate suppression occur in the high dose dexamethasone suppression tests because 15% to 25% of pituitary-dependent cases do not "adequately" suppress. Abdominal radiographs and abdominal ultrasound will help detect an adrenal mass; the majority of adrenal tumors are calcified, but calcification does not indicate malignancy. If a mass is found, exploratory surgery is indicated; large adrenal masses are usually adenocarcinomas. In the absence of a mass, several choices are available. Measurement of endogenous plasma ACTH concentrations will assist in separating pituitary from adrenal-dependent disease. If ACTH measurement is not available, exploratory laparotomy and adrenal biopsy can be done.

F. Technique for the combined ACTH stimulation and hi-dose dexamethasone suppression test for the out-patient.

1. Collect basal cortisol sample
2. Inject dexamethasone phosphate (0.1 mg/kg b.w.) IV
3. After two hours, collect post-dexamethasone suppression plasma cortisol sample. Then give Cortrosyn (0.25 mg) IV or IM or ACTH gel (1 unit/lb IM).
4. After 1-2 hours (depending on whether you use Cortrosyn or ACTH gel respectively) collect the post-ACTH stimulation plasma cortisol sample.

G. Plasma ACTH levels (by RIA) - useful for differentiating pituitary dependent Cushing's from functional adrenal tumors. Levels less than 20 pg/ml suggest adrenocortical neoplasia. Levels exceeding 40 pg/ml suggest pituitary-dependent Cushing's. Intermediate levels (between 20-40 pg/ml) are non-diagnostic.

H. Urine cortisol:creatinine ratio

1. Urine cortisol measured by RIA
2. Urine creatinine measured by Jaffe reaction
3. Values expressed in μmol/L and all ratio values expressed as 10⁻⁶

4. Interpretation:
   a. Test results > 10 x 10⁻⁶ suggests Cushings
   b. Test results < 10 x 10⁻⁶ rules out Cushings

5. Some overlap exists between Cushings and other polydipsia-polyuria syndromes

6. This test is simple and inexpensive to run. Because of overlap, confirmation of Cushings in a dog with a positive c:c should be made with an additional test; i.e. ACTH stimulation, lo-dose dexamethasone suppression.

Treatment

Adrenalectomy is the treatment of choice for focal nonmetastatic adrenocortical carcinoma with a 50:50 incidence of adenomas and adenocarcinomas. Perioperative mortality is reported to range from 9 to 60% with infection, thromboemboli, and wound dehiscence being common complications. The average survival period for those that survive surgery is 141 weeks.

Adrenocortical Adenomas and Adenocarcinomas: If surgical removal of the abnormal gland is elected, the contralateral adrenal will be atrophic due to prior inhibition of ACTH secretion. During surgery and for 2 days post-operatively, large doses of prednisolone are necessary (1 mg/kg per day) followed by a tapering dose over the subsequent 3-4 weeks (use alternate-day steroids during the 3rd and 4th weeks). A repeat ACTH stimulation test should be done 4-6 weeks postoperatively in order to assess the function of the remaining adrenal gland (discontinue steroids 2-3 days prior to test).

Mitotane (Op'-DDD) is indicated if gross metastatic disease is evident prior to surgery, if the tumor is unresectable or if the owner refuses surgery. Initially, mitotane is given daily. Maintenance therapy is begun if and when serum cortisol levels have decreased to undetectable to low values.

Treatment is initiated at a dosage of 50 to 75 mg/kg/day in divided doses for 10 to 14 days and prednisone, 0.2 mg/kg/day, is given concurrently. The effectiveness of this initial treatment period is evaluated with a ACTH stimulation test. Prednisone supplementation must be withheld on the morning of the test. If the basal and post-ACTH cortisol concentrations decrease but remain within or above the normal resting range, daily mitotane should be continued (50 to 75 mg/kg/day) and ACTH stimulation testing repeated at seven to 14 day intervals until cortisol concentrations fall to below the normal resting range (< 1.0 μg/dl or < 30 nmol/L). If the serum cortisol response to ACTH remains greatly elevated or unchanged from pretreatment test results, the daily dosage of mitotane should be increased to 100 mg/kg/day and ACTH stimulation testing continued at 7 to 14 day intervals. If cortisol concentrations remain greatly elevated, the dose should be increased by 50 mg/kg/day increments (at 7 to 14 days, if necessary) until ACTH stimulation testing reveals that the serum cortisol concentrations have decreased to at least some extent or until intolerance to the drug develops, which is not uncommon at dosages exceeding 100 mg/kg/day. If these incremental
increases in drug dosage have partially lowered cortisol concentrations, but not to undetectable to low levels, daily mitotane is continued at the previous week's dosage and ACTH stimulation testing continued at 7 to 14 day intervals until circulating cortisol values fall below normal resting range (< 1.0 μg/dl or < 30 nmol/L. If direct drug toxicity develops (not a result of low serum cortisol concentration) daily therapy is continued at the highest tolerated dose until cortisol levels have fallen. Maintenance mitotane therapy is begun once serum cortisol levels falls to undetectable to low values.

An initial maintenance dose of 100 to 200 mg/kg/week, in divided doses, together with daily maintenance prednisone (0.2 mg/kg/day) should be given. An ACTH stimulation test should be repeated one to two months after initiation of maintenance therapy to ensure that serum cortisol concentrations remain suppressed to desired levels. If basal and post-ACTH serum cortisol concentrations remain at undetectable to low values at the time of follow-up evaluations, the previous maintenance dosage is continued. If, however, cortisol concentrations have risen into the normal resting range (1-4 μg/dl or 25-125 nmol/L) the weekly maintenance dose is increased by 50 per cent. If cortisol concentrations rise above normal resting range, daily mitotane is re instituted (50-100 mg/kg/day) until cortisol concentrations fall to low or undetectable values; the weekly maintenance dose is then increased by 50 per cent. Weekly doses of 300 to 400 mg/kg or greater may eventually be necessary. These adjustments in dosage should be assessed by repeat ACTH stimulation testing in one month to ensure an adequate response to the new maintenance dose. Subsequent dosage adjustments are based on periodic ACTH stimulation tests at three to six month intervals, as well as the dog's tolerance of the medication itself (M. Peterson, Animal Medical Center). The mean survival time of 32 dogs with adrenal tumor treated with O,p'-DDD was 65 weeks, ranging from 20 days to 5.1 years (Kintzer and Peterson, 1994).

**Pituitary-dependent Cushing's Disease** can be treated surgically or medically. Bilateral adrenalectomy or hypophysectomy are technically difficult and require life-long hormonal supplementation.

Medical therapy with drugs such as cyproheptadine and bromocriptine have been tried in the dog with minimal success. These work centrally to inhibit CRF secretion by the hypothalamus.

O,p'-DDD (mitotane), commercially known as Lysodren and marketed by Bristol, is my medical treatment of choice. At the prescribed dose, it hopefully causes selective destruction of the zona fasciculata and zona reticularis while simultaneously sparing most of the function of the zona glomerulosa (thereby preserving the mineralocorticoid secreting capacity). O,p'-DDD is initially administered in a loading dose. The general treatment protocol is as follows:

1. **Loading** - give Lysodren at a dose of 50 mg/kg orally once daily for first 7 days. Prednisolone (0.3 mg/kg per day) is also administered during this period in order to counter toxic side effects.
2. **Maintenance** - beginning approximately 3 to 7 days after completion of the loading doses, give Lysodren at dose of 25 mg/kg every 3 days thereafter.
3. **Re-assessment** - An ACTH stimulation test should be repeated 1-3 weeks after the loading period. No medication should be given for 48 hrs prior to the test. If the test result is still abnormally elevated (usually accompanied by persistent Cushing's
signs) the loading regimen should be re instituted for approximately one additional week. The treatment goals include cessation of Cushing’s signs and a post-ACTH stimulation serum cortisol level ranging between 3-6 μg/dl. A level of 10 μg/dl or more calls for re-loading with O,p'-DDD.

Complete remission occurs in most dogs with the above protocol. Usually polyuria, polydipsia, and polyphagia abate within the first few weeks. Hair regrowth may begin within the first several weeks or require several months (one of my patients required 18 months). Many treated Cushing's dogs eventually "break away" from therapeutic control at some time during the first year necessitating re-loading followed by an increased (25 to 50%) maintenance dose. Rarely, some dogs acquire high tolerance for Lysodren and require 2-3 X the original maintenance dose. This is particularly prevalent in dogs receiving phenobarbital where induction of the hepatic microenzyme system increases the metabolism of Lysodren thereby allowing for drug resistance.

Treatment failure should be expected after 14 to 21 days without response. Reasons for this include an undiagnosed tumor, poor drug potency, an incorrect diagnosis, the rare dog with pituitary-dependent hyperadrenocorticism and epilepsy that requires 30 to 60 days of O,p'-DDD therapy and concurrent anticonvulsant therapy.

All controlled dogs should be retested with the ACTH stimulation test every 4-6 months in order to assess the adequacy of treatment. As stated above, those with post ACTH cortisol values between 3-6 μg/dl are adequately controlled. Values > 10 μg/dl will soon require a re-load with Lysodren. Simply increasing the maintenance dose has not proved to be successful in my experience, thus justifying the need for re-load. Patients with serum cortisol levels < 1 μg/dl should be closely observed; they might be candidates for dosage reduction or temporary discontinuation. Prednisone treatment is necessary if signs of hypocortisolemia occur.

The following principles apply to the use of O,p'-DDD for the aged (> 12 years) dog:

1. Use lower doses for dogs 12 years of age and older.
2. Use similar loading protocol, but adjust the Lysodren dose to 25-35 mg/kg/day.
3. Use similar maintenance protocol, but dose at 12-16 mg/kg every 3 days.

**O,p'-DDD in the Diabetic Dog**

The guidelines include:

1. Loading dose of Lysodren is 25-35 mg/kg per day along with simultaneous prednisolone (0.3 mg/kg/day) for 7 days.
2. Maintenance dose is 12-16 mg/kg every 3 days.
3. Anticipate increased insulin sensitivity and tendency toward hypoglycemia after the 2nd day of the loading regimen. This occurs from the decreased gluconeogenesis and peripheral insulin resistance associated with lowered plasma cortisol levels. The insulin dose should therefore be empirically decreased by approximately 50% following the 3rd day of Lysodren loading. The insulin dose must subsequently be titrated on an as-needed basis. Weakness can occur from either hypoglycemia or
hypocortisolemia. Weakness associated with moderate glycosuria suggests hypocortisolemia and necessitates prednisolone supplementation. In the absence of glycosuria, the dog should receive carbohydrates and prednisolone.

4. Recurrent hypocortisolemia is evidenced by subsequent increased insulin requirements and a return of Cushing's signs. Note that recurrent PD, PU, and polyphagia in the presence of minimal (trace to +1) glycosuria suggest hypocortisolemia.

**O,p'-DDD Toxicity**

O,p'-DDD toxicity can cause hypocortisolemia, but the drug can be directly toxic itself. The toxic signs usually occur within the first 2-3 weeks of Lysodren treatment, but can occur at any time. The most common signs include anorexia, depression and weakness. Vomiting and diarrhea can also occur. The owners should be informed of these potential side effects and be advised to stop Lysodren, give prednisolone (½-1.0 mg/lb) orally immediately, and call their veterinarian for further advice. Should the dog not recover within a few hours or if vomiting precludes oral prednisolone treatment, the dog must then receive prompt parenteral prednisolone treatment.

A repeat ACTH stimulation test and serum sodium and potassium levels should be done (stop prednisolone 24-36 hours prior to serum cortisol assessment). If the cortisol levels are less than 1 µg/dl, the Lysodren should be temporarily discontinued until repeated testing shows serum cortisol levels at 2.0-5.0 µg/dl after ACTH injection. If the signs of hypocortisolemia persist the dog should be given daily prednisolone treatment (0.3 mg/kg per day) thereafter. This latter situation may persist indefinitely or perhaps be interrupted in the future by recurrent hypercortisolism requiring repeated Lysodren loading and maintenance at the lower dose schedule (see Rx of the aged dog). If hyponatremia and/or hyperkalemia occur, fludrocortisone (Florinef) or DOCP and prednisone should be administered.

In my experience, whenever I had a dog that lost both aldosterone and cortisol production capability from O,p-DDD toxicity, it became Addisonian forever. If the hyponatremia occurs before the hyperkalemia take heed that the crisis is not too far off and that treatment should commence in order to avoid a full blown crisis. Taking these dogs off treatment for Addisons is ill advised.

On the other hand, when O,p'-DDD causes only hypocortisolism while maintaining normal serum electrolytes, the dog should only receive prednisone along with close follow-up. If the electrolytes become abnormal, then treat them as Addisons forever. If sodium and potassium levels remain normal, there is a possibility that the ongoing ACTH hypersecretion will eventually cause recurrent hyperadrenocorticism over the ensuing 1-2 years.

There are more rare complications of O,p'-DDD toxicity. These include:

1. Addison's disease - a small percentage of dogs might acquire destruction of the entire adrenal cortex thereby requiring long-term mineralocorticoid (Florinef, Squibb or DOCP, Ciba) treatment.

2. Rapidly expanding pituitary tumor - known as Nelson's syndrome. This has occurred in approximately 5-7% of all pituitary-dependent Cushing's dogs treated.
by the author. It was once thought to occur from cessation of negative feedback inhibition caused by lowered plasma cortisol levels that subsequently allows increased trophic factor release from the hypothalamus which in turn causes a microadenoma to enlarge to macroscopic clinical proportions. However, it is now thought that the tumor will grow by itself without trophic factor stimulation. This complication can occur between 1 week and several months following the commencement of Lysodren treatment. The most common signs include dementia, circling, and weakness. At necropsy, most of the tumors are chromophobe adenomas and show considerable invasion into the hypothalamus and thalamus.


**Ketoconazole Treatment (Nizoral; Janssen)**

This drug is an imidazole derivative that has antifungal properties. It also has the ability to interfere with gonadal and steroid synthesis in vitro and in vivo. It has been shown to effectively suppress serum cortisol concentrations and the adrenocortical response to ACTH, as well as serum levels of testosterone, progesterone and estrogen in the dog.

This drug provides a viable means of treating canine Cushing's disease due to its low incidence of toxicity, reversible inhibition of adrenal steroidogenesis and negligible effects on mineralocorticoid production. The indications for treatment include:

1. Palliative medical treatment for dogs with nonresectable malignant adrenal tumors.
2. Initial therapy prior to adrenalectomy.
3. Treatment option for pet owners refusing surgery.
4. Use as test therapy for dogs with equivocal diagnosis.
5. Primary therapy for dogs that are intolerant to O,p'-DDD.

The final dosage ranges from 5-25 mg/kg BID. It is best to begin with 5 mg/kg BID for 7 days, then 10 mg/kg BID for 7 days, and then maintain on 15 mg/kg BID. Discontinue the ketoconazole if adverse signs of vomiting, anorexia, depression, diarrhea, or weakness occur. Glucocorticoid treatment might be necessary to counteract the hypocortisolemia. It is recommended to assess the patient's response to the ACTH stimulation test approximately every 4 months. A recent study in JVIM, December

**l-Deprenyl (Anipryl - Novartis)** is a drug belonging to the monoamine oxidase inhibitor group that is used to treat canine cognitive dysfunction. In healthy dogs, ACTH secretion from the pars distalis is stimulated by corticotropin releasing hormone (CRH) from the hypothalamus, while secretion of ACTH from the pars intermedia is under negative control by dopamine. Experimentally induced chronic dopamine inhibition unmasks CRH-stimulated release of ACTH, and it has been hypothesized that dopamine depletion may play a role in pituitary dependent Cushings disease (PDH). Dopamine is metabolized by monoamine oxidases (MAO), and l-deprenyl is a specific inhibitor of MAO-B. Therefore, administration of l-deprenyl to dogs with
PDH may ameliorate dopamine depletion, and in turn promote normalization of pituitary ACTH regulation and secretion. This may lead to normalization of cortisol secretion and resolution of the clinical signs and laboratory abnormalities associated with hyperadrenocorticism.

The recommended dose of l-deprenyl is 2 mg/kg orally every 24 hours. Clinical response is assessed by remission of signs as well as an improved lo-dose dexamethasone response test. One of the advantages of l-deprenyl is the absence of drug induced adrenocorticoctyolysis as seen with the use of O,p-DDD. Expense, variable response rate, and the need for daily treatment might be limiting factors to its use in dogs. It is important to note that the true clinical efficacy of l-deprenyl has yet to be established. Drug efficacy trials are currently underway (1997). Until these results are known, the recommendations for using this drug to treat canine PDH can only be given with reservations. I have not recommended nor have used this drug to treat Cushing’s in the dog because of all of the treatment failures I have witnessed over the years.

**Trilostane** - A synthetic orally active steroid analog: 4 alpha,5-EpOxy-17 beta-hydroxy-3-oxo-5 alpha-androstane-2 alpha-carbonitrile. Currently licensed for veterinary use and sold as Vetoryl. It acts as a competitive inhibitor of the 3 β hydroxysteroid dehydrogenase enzyme system that converts pregnenolone to progesterone in the adrenal gland and other tissues. The blockade of this enzyme system results in a decrease in the synthesis of cortisol, aldosterone, and 4-androstenedione. Trilostane also decreases additional enzymes in the steroid casecaden, namely 11 beta-hydroxylase and possibly 11 beta-hydroxysteroid dehydrogenase. These various enzyme inhibitory actions can lead to increases in 17 alpha-OH-pregnenolone and dehydroepiandrostenedione. Unlike O,p-DDD it is not a cytotoxic agent but it will interfere with cortisol and aldosterone synthesis. Therefore all clinicians must be aware that potentially fatal episodes of hypoadrenocorticism can still occur with Trilostane. Available in 30 mg and 60 mg capsules.

**Dosing**: The earlier literature used a dose of 5-10 mg/kg/day but subsequent use and more recent literature recommend a starting dose of approximately 2.0 mg/kg bid and titrate to effect over the following weeks (Vaughn MA, et al, JAVMA 2008, 232 (9): 1321-1328). Another paper by Alenza in J Am Anim Hosp. Assoc 2006;42:269-276 reports on the efficacy of an average dose of 3.1 mg/kg q12h initially and an average maintenance dose of 3.2 mg/kg q12h on a daily basis. Feldman, et.al at UC-Davis stresses that the starting dose in the dog should be 2.0 mg/kg/day divided. Some lethargy and decreased appetite can occur during the first few days of treatment. Hypoadrenalism can occur as a side effect calling for adequate monitoring and any necessary medical emergency measures. My review of the papers describing trilostane and comparing it to O,p’-DDD cause me to find little advantage to using trilostane based on ease of administration, anticipated effects, and the fact that adrenocortical insufficiency is still a potential complication with both drugs.

Monitoring is done using the ACTH stimulation test at days 10 to 14, 30 days and 90 days after starting. Periodic serum chemistry profiles should be done as well in order to assess serum electrolyte status. When trilostane is given twice daily, the acceptable post-ACTH stimulation test results should range from 5 to 10 μg/dl.

An abstract by Sieber-Ruckstuhl in the 2005 ACVIM Proceedings hypothesizes that there can be an incomplete inhibition of the beta-hydroxysteroid dehydrogenase enzyme with an
additional inhibition of the 21-hydrolase or the 11-beta-hydroxylase. This might explain the typical increased steroid intermediate concentrations, as determined on the patient’s steroid profile, when trilostane is used to treat PDH.