

# Cushing's Syndrome (Hyperadrenocorticism) in Dogs

(Excessive Levels of Steroids in the Body)

## Basics

### OVERVIEW

- “Spontaneous” hyperadrenocorticism (HAC) or Cushing's syndrome is a disorder caused by excessive production of steroids by the adrenal glands; “spontaneous” denotes lack of apparent cause
- Spontaneous hyperadrenocorticism is a hormonal disorder; it can involve problems in the pituitary gland (the “master gland” of the body), in which case the pituitary gland “directs” the adrenal glands to produce excessive amounts of steroids—this type is known as “pituitary-dependent hyperadrenocorticism” or PDH, or it can involve problems in the adrenal gland itself (benign tumors or cancer), in which the adrenal glands produce excessive amounts of steroids on “their own” and not under the control of the pituitary gland
- “Iatrogenic” hyperadrenocorticism or Cushing's syndrome results from the use of medications containing steroids; the medications can be given by mouth or by injection, or can be applied topically to the skin, ears, or eyes; the signs of iatrogenic Cushing's syndrome usually are related to the dose of steroids and length of treatment, but some dogs are very sensitive to steroids and may show signs with normal doses of steroids or relatively short length of treatment; “iatrogenic” refers to changes induced by the medication itself, the changes generally are unfavorable
- In both types of hyperadrenocorticism, clinical signs are due to deleterious effects of elevated circulating steroid concentrations on multiple organ systems



### SIGNALMENT/DESCRIPTION OF PET

#### Species

- Dogs

#### Breed Predispositions

- Poodles, dachshunds, Boston terriers, German shepherd dogs, and beagles reportedly are more likely to develop hyperadrenocorticism as compared to other breeds

#### Predominant Sex

- No increased likelihood for either sex has been identified for pituitary-dependent hyperadrenocorticism in dogs; possible increased likelihood that female dogs will have adrenal tumors that produce excessive steroids

### **Mean Age and Range**

- Hyperadrenocorticism is generally a disorder of middle-aged to old dogs; pituitary-dependent hyperadrenocorticism very rarely can be seen in dogs as young as 1 year of age

## **SIGNS/OBSERVED CHANGES IN THE PET**

- Severity varies greatly, depending on duration and severity of steroid excess
- In some cases, the physical presence of cancer in the pituitary gland (leading to pituitary-dependent hyperadrenocorticism [PDH]) or the adrenal gland itself contributes to signs
- Excessive urination (known as “polyuria”) and increased thirst (known as “polydipsia”); increased appetite (known as “polyphagia”); sagging abdomen due to weakened abdominal muscles (known as “pendulous abdomen”); increased panting; enlarged liver (known as “hepatomegaly”); hair loss; darkening of the skin (known as “hyperpigmentation”); thin skin; muscle weakness; obesity; sluggishness (lethargy); loss of muscle mass (known as “muscle atrophy”); “blackheads” (known as “comedones”) on the skin; bruising; loss of size or tissue of the testicles (known as “testicular atrophy”); lack of heat cycles in female dogs (known as “anestrus”); calcium deposits in the skin (known as “calcinosis cutis”); facial nerve paralysis

## **CAUSES**

- Pituitary-dependent hyperadrenocorticism—benign tumor (known as a “pituitary adenoma”) most common; cancer (known as a “pituitary adenocarcinoma”) rare
- Adrenal gland itself (not under control of pituitary gland)—benign tumor (known as “adrenal adenoma”) or cancer (known as “adrenal carcinoma”)
- Iatrogenic hyperadrenocorticism—due to administration of steroid-containing medications

## **RISK FACTORS**

- Poodles, dachshunds, Boston terriers, German shepherd dogs, and beagles more likely to develop hyperadrenocorticism as compared to other breeds
- No specific risk factor none for spontaneous hyperadrenocorticism
- Presence of any condition that leads to treatment with steroid-containing medications is a risk factor for iatrogenic hyperadrenocorticism

## **Treatment**

### **HEALTH CARE**

- Dictated by the severity of clinical signs, the pet's overall condition, and any complicating factors (such as diabetes mellitus [“sugar diabetes”], blood clots to the lungs [known as “pulmonary thromboembolism”])
- If doing medical therapy, will be life-long

### **ACTIVITY**

- No alteration of activity necessary

### **DIET**

- Usually no need to alter diet; use appropriate diet if dog also has diabetes mellitus (sugar diabetes)

### **SURGERY**

- Surgical removal of the pituitary gland (known as “hypophysectomy”)—described in veterinary literature, but generally not available in the United States
- Surgical removal of both adrenal glands (known as “bilateral adrenalectomy”) not used for treatment of pituitary-dependent hyperadrenocorticism in dogs
- Surgery is the treatment of choice in dogs with adrenal adenomas (benign tumors of the adrenal gland) and small carcinomas (cancer of the adrenal gland), unless the pet is a poor surgical risk; appropriate personnel and facilities are required as this is a technically demanding surgery and intensive postoperative management is required

- Depending on status of the pet, medical control of hyperadrenocorticism may be desirable prior to surgery, if possible

## Medications

- Medications presented in this section are intended to provide general information about possible treatment. The treatment for a particular condition may evolve as medical advances are made; therefore, the medications should not be considered as all inclusive

### MITOTANE

- Mitotane (also known as o,p'-DDD or Lysodren®) is one of two main drugs used for medical management of pituitary-dependent hyperadrenocorticism in dogs; mitotane may be the drug of choice for medical management of adrenal tumors since it may destroy tumor cells as well as control steroid secretion
- Inadequate levels of aldosterone (another hormone produced by the adrenal gland; involved in sodium and potassium regulation in the body) are possible secondary to mitotane therapy; if occurs, likely the pet will have permanent complete adrenal-gland insufficiency; treatment for inadequate or too low levels of steroids produced by the adrenal glands (known as “hypoadrenocorticism” or “Addison's disease”) should be initiated

### L-DEPRENYL

- *l*-Deprenyl (also known as selegiline hydrochloride or Anipryl®) Federal Food and Drug Administration (FDA)-approved for treatment of pituitary-dependent hyperadrenocorticism; it decreases secretion of the pituitary hormone (known as ACTH) that directs the adrenal gland to produce steroids, thus decreasing serum steroid concentrations; not recommended for treatment of PDH in dogs with concurrent illnesses, such as diabetes mellitus; not used for adrenal hyperadrenocorticism
- Effectiveness of the drug in treating PDH is questionable; one study found 20% effectiveness and another found it to be ineffective
- Adverse effects (such as lack of appetite [anorexia], sluggishness [lethargy], vomiting and diarrhea) are uncommon and usually mild; disadvantages include the need for lifelong daily administration and medication expense

### KETOCONAZOLE

- Ketoconazole inhibits enzymes responsible for steroid production; indicated for dogs unable to tolerate mitotane at doses necessary to control hyperadrenocorticism; may be useful for control of clinical signs in dogs with adrenal tumors; effective in approximately 50% or fewer cases; adverse effects include lack of appetite (anorexia), vomiting, diarrhea, sluggishness (lethargy), decreased number of platelets in the blood (platelets are small cellular structures found in the blood that help control bleeding; the condition characterized by decreased number of platelets is known as “thrombocytopenia”) and liver disease

### TRILOSTANE

- Trilostane (Vetoryl®) is approved for use in Europe and the United States; efficacy for treatment of pituitary-dependent hyperadrenocorticism is high, comparable to mitotane; survival of dogs with PDH is the same for dogs treated with mitotane or trilostane
- Trilostane can suppress aldosterone (another hormone produced by the adrenal gland; involved in sodium and potassium regulation in the body) secretion, causing a sudden change in sodium and potassium regulation (known as an “Addisonian crisis”), which requires immediate medical treatment; fortunately, the low levels of aldosterone generally resolve within 48–72 hours of discontinuation of drug administration, but low levels of weeks' to months' duration or even permanently have been reported
- Can be used to treat adrenal tumors and will control clinical signs, at least temporarily, but is not the drug of choice; for adrenal tumors, mitotane is the drug of choice, as it is truly chemotherapeutic and may kill tumor cells

### OTHER TREATMENT—RADIATION THERAPY

- Radiation therapy is required for dogs with large, benign pituitary tumors (known as “pituitary macroadenomas”)
- Decreases in secretion of the pituitary hormone (known as ACTH) that directs the adrenal gland to produce

steroids, thus decreasing serum steroid concentrations levels, may take several months; meanwhile, control signs of hyperadrenocorticism with previously described drugs

## Follow-Up Care

### PATIENT MONITORING

- Response to therapy—signs resolve several days to months after control achieved
- Periodic bloodwork (such as complete blood count [CBC] and serum biochemistry profile as well as specific tests for adrenal gland function [known as ACTH stimulation])—schedule and type of testing varies according to the medication being used

### POSSIBLE COMPLICATIONS

- High blood pressure (known as “hypertension”)
- Presence of protein in the urine (known as “proteinuria”)
- Recurrent infections
- Stones in the urinary tract (known as “urinary calculi”) frequently composed of calcium oxalate
- Diabetes mellitus (also known as “sugar diabetes”)
- Blood clots in the lungs (known as “pulmonary thromboembolism”)
- Nervous system signs secondary to the presence of a large tumor in the pituitary gland (pituitary macroadenoma)

### EXPECTED COURSE AND PROGNOSIS

- Untreated hyperadrenocorticism—generally a progressive disorder, with a poor prognosis
- Treated pituitary-dependent hyperadrenocorticism—usually a good prognosis; median survival time for a dog with PDH treated with mitotane or trilostane is approximately 2 years; at least 10% survive 4 years; dogs living longer than 6 months tend to die of causes unrelated to HAC
- Dogs with large, benign pituitary tumors (macroadenomas) and nervous system signs—poor-to-grave prognosis; dogs with macroadenomas with no or mild nervous system signs—fair-to-good prognosis with radiation and medical therapy
- Dogs with benign adrenal-gland tumors (adrenal adenomas)—usually a good-to-excellent prognosis; dogs with small adrenal-gland cancers (carcinomas) that have not metastasized have a fair-to-good prognosis, prognosis good to excellent with surgical removal
- Dogs with large adrenal-gland cancers (carcinomas) and/or with widespread spread (metastasis)—generally a poor-to-fair prognosis, but impressive responses to high doses of mitotane are seen occasionally

## Key Points

- If using medical therapy, lifelong therapy required
- If adverse reaction to mitotane or trilostane occurs—discontinue drug, give prednisone, and have veterinarian reevaluate next day; if no response to prednisone is noted within a few hours of administration, veterinarian should evaluate immediately
- Regular administration of medications with appropriate follow-up required for effective management