



PET TALK

Volume 14, Number 03

American College of Veterinary Pharmacists

What is Hyperadrenocorticism (HAC), or Cushing's Disease?

Cushing's disease is caused by prolonged exposure of the body's tissues to high levels of the hormone, *cortisol*. It is called Cushing's disease because it was named after a famous neurosurgeon, Harvey Cushing who first recognized it. It is also sometimes called "*hyperadrenocorticism*" or "*hypercortisolemia*". In the normal dog cortisol is produced by the adrenal glands, (which are located just in front of the kidneys). Cortisol has many effects in the body. Cortisol maintains blood pressure, slows the immune system's inflammatory response, balances the effects of insulin in breaking down sugar for energy, regulates the use of proteins, carbohydrates and fats in the body.

The amount of cortisol produced by the adrenal glands is carefully controlled by hormones produced in the brain (from the pituitary gland). The hormones produced by the pituitary stimulate the adrenal glands. When the adrenal glands receive the signal from the pituitary they respond by producing cortisol. In the normal animal cortisol is produced mainly at times of stress - in Cushing's disease the levels of cortisol in the blood are always too high.

What causes HAC in dogs?

Nearly all cases of Cushing's disease are caused by a tumor in the pituitary gland which is usually benign and causes no effects related to pressure in the brain. A few cases of Cushing's disease are caused by a tumor in the adrenal gland.

The two forms of natural Cushing's disease are:

- **Pituitary-dependant Cushing's disease** A tumor in the pituitary causes excess production of the

hormone adrenocorticotrophic hormone (ACTH) resulting in enlargement of both adrenal glands.

- **Adrenal-dependant Cushing's disease** A tumor of the adrenal gland makes one gland grow bigger and it is therefore able to produce more cortisol.

Sometimes signs of Cushing's disease are caused by steroids given by the veterinarian to treat another disease, such as allergic skin disease.

How will I know if my dog has HAC?

The signs of Cushing's disease are extremely variable and can be subtle in the early stages. It is usually not possible to decide which form of the disease is present by the clinical signs. Cushing's disease affects older pets (over 7 years of age) so these signs are often confused with the effects of aging. Often it will be your veterinarian who examines your pet during its annual or semi-annual examination and points out that changes have occurred since your last visit.

What are the symptoms of HAC?

Steroid hormones affect almost every tissue in the body and the signs of Cushing's disease can be diverse. The most obvious sign of Cushing's disease is increased thirst. If your dog is drinking more (or is asking more often to be let out to urinate) you should always take them to the veterinarian for a check-up. However, not all dogs with Cushing's disease have increased thirst. Increased appetite (and weight gain) is also very common in Cushing's disease but owners

may not recognize this as a sign of illness.

Cushing's disease causes changes to the skin and haircoat. The hair is lost in patches (particularly over the flanks) but there is no scratching. Other symptoms appear in the skin, which becomes fragile and thin. It bruises easily and heals poorly. Purplish pink stretch marks may appear on the abdomen. Female dogs may stop having heat cycles.

Steroid hormones cause muscle wasting and weak muscles may make it difficult for your pet to exercise. You may notice that your dog is panting a lot or they may develop joint problems. In Cushing's disease, fat is deposited in the liver making it swell and this may be visible causing the abdomen to hang down with a pot-bellied appearance.

High levels of steroid hormone in the blood suppress the immune system and healing process; so animals with Cushing's disease may have repeated infections or wounds that do not heal as quickly as expected.

Continued on Page 2

This Newsletter is provided to you by:

Continued from Page 1

In most cases of pituitary-dependent disease the tumor in the brain is tiny and causes no physical effects. However, in a few animals the brain tumor is sufficiently large such that it can cause neurological signs such as depression, blindness or seizures.

Can HAC be treated?

Three medications may be used to treat the pituitary form of the disease:

- The traditional therapy has been the drug, **mitotane** (Lysodren). Mitotane is toxic to the part of the adrenal gland that produces cortisol. It destroys the adrenal gland so that is unable to produce so much hormone. Mitotane can also kill cells in adrenal tumors. Remember that most cases of Cushing's disease are caused by a small tumor in the brain and so mitotane does not usually address the underlying cause of the disease. When treatment is started the drug is given once daily for around 7-10 days. This causes rapid destruction of the adrenal gland. Once levels of hormone have dropped, mitotane is given as a weekly maintenance dose, just enough to kill off any new cells that have grown that week. Routine blood tests are taken three or four times a year to ensure that treatment does not need to be altered. Mitotane may need to be compounded by a pharmacist for your dog. It is important to tell the pharmacist if you have been giving liquid or pills of mitotane because sudden changes from pills to liquid and vice versa can make your dog very sick.
- **Selegilene** (Anipryl) is approved by the FDA for the treatment of pituitary dependent Cushing's disease in the dog. Unlike mitotane, the drug works at the level of the pituitary to decrease ACTH levels and does not have a direct effect on the adrenal gland. Anipryl is given once a day, has very few side-effects, requires no additional blood tests to monitor treatment and works in about 50% of cases. It may take 1-2 months of daily

treatment to control the signs so it usually is reserved for dogs with mild or moderate signs of Cushing's disease. It cannot be used in dogs with an adrenal tumor. Anipryl is currently not commercially available, so your veterinarian may ask your pharmacist to compound it.

- A new treatment for Cushing's disease is **trilostane** (Vetoryl). This is a drug that inhibits the adrenal glands' ability to produce cortisol. Unlike mitotane it does not destroy adrenal tissue. It is important to realize that this drug does not do anything to treat the tumor (pituitary or adrenal) causing the disease but it can be used to control the signs of cortisol excess in dogs with both pituitary and adrenal dependent Cushing's syndrome. The drug is given as a tablet once (or sometimes twice) daily and it must be given regularly or hormone levels will rapidly rise again. As is the case with mitotane, routine blood tests are taken three or four times a year to ensure that treatment does not need to be altered. Trilostane can cause women to miscarry if pregnant, so it should not be handled by women who are pregnant or are intending to become pregnant.

In a few cases, surgical removal of an adrenal tumor is possible. This surgery is difficult and should be performed by a specialist in veterinary surgery. In addition to the risks of surgery itself, it is very important that animals are closely monitored immediately after surgery and they may need to spend time in an intensive care facility. Your veterinarian may want to start medical treatment before surgery to help decrease the side-effects of high cortisol levels during anesthesia and surgery.

If your dog has signs associated with a mass in the brain it will need additional treatment; as the drugs available will not affect the size of this tumor. Radiotherapy is available at some specialty hospitals and this can help shrink the tumor and eventually decrease the levels of ACTH and cortisol in the blood. Unfortunately, because of its location, surgical removal of the tumor

in the brain is usually not possible in Cushing's disease.

What are the risks of treatment?

Very few side-effects are reported with the use of selegilene. There are few reported side-effects from trilostane - provided that careful monitoring is performed. Mitotane is a more potent drug and can have significant side-effects if not used correctly. An overdose of mitotane can completely destroy the adrenal gland and result in a deficiency of the stress hormones. Close monitoring of dogs receiving treatment with mitotane or trilostane is very important, particularly in the early stages.

Should I treat my dog if it gets HAC?

Most dogs with Cushing's disease are middle-aged or elderly and owners sometimes ask if it is worth treating them. Once an animal with Cushing's disease is stabilized on treatment they will usually live a normal life (simply taking their tablets on a regular basis). The outcome for dogs with pituitary-dependent Cushing's disease with treatment is very good and most of them live long into old age. Some signs will disappear quickly and others more gradually. Appetite and water consumption usually return to normal in a few weeks; whereas full return of the fur may take several months. Many dogs go on to live a normal lifespan. Without treatment the complications can be significant and will seriously affect the quality of your pet's life.

This article was submitted by:

*Gigi Davidson, BSPH, RPh, DICVP
Director of Clinical Pharmacy Services
North Carolina State University
College of Veterinary Medicine*