Diagnosis, Treatment and Monitoring of Hyperadrenocorticism

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. As with all drugs, side effects may occur. In field studies and post-approval experience, the most common side effects reported were: anorexia, lethargy/depression, vomiting, diarrhea, elevated liver enzymes, elevated potassium with or without elevated sodium, elevated BUN, decreased Na/K ratio, hypoadrenocorticism, weakness, elevated creatinine, shaking, and renal insufficiency. In some cases, death has been reported as an outcome of these adverse events. VETORYL Capsules are not for use in dogs with primary hepatic or renal disease, or in pregnant dogs. Refer to the prescribing information for complete details or visit www.Dechra-US.com.
Confirming the diagnosis of hyperadrenocorticism (HAC)

No test for HAC has 100% diagnostic accuracy. The diagnostic value of all endocrine tests will be significantly enhanced by performing them only when clinical signs consistent with HAC are present in the patient. Three endocrine diagnostic tests are available, all with particular advantages and disadvantages:

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity &amp; Specificity</th>
<th>Additional info</th>
</tr>
</thead>
</table>
| Urinary Cortisol to Creatinine Ratio (UCCR) | • Highest sensitivity of all three tests makes it a great screening test
• Highest confidence in a negative test result
• Lacks specificity
• False positives are relatively common | • To avoid false-positive results, urine samples should be collected at home at least two days after a visit to a veterinary clinic
• Collect first urine sample from patient in the morning
• Specificity and sensitivity can be increased when urine from 2-3 days is pooled and collectively tested and when the test is performed on dogs showing symptoms consistent with HAC |
| Low-Dose Dexamethasone Suppression      | • High sensitivity
• High confidence in a negative test result
• Moderate specificity
• False positives can occur | • Long test (8 hours)
• In some cases may differentiate between PDH and ADH
• Considered the screening test of choice unless iatrogenic HAC is suspected |
| ACTH Stimulation                       | • Highest specificity of all three tests
• Highest confidence in a positive test result
• Lacks sensitivity
• False negatives are relatively common | • Relatively short test (1 hour)
• Test of choice if there is a history of exogenous steroid therapy |

For detailed information on performing and interpreting these tests, please contact Dechra Veterinary Technical Services at (866) 933-2472 or your reference laboratory consult line.

Differentiating between types

It is necessary to differentiate between Pituitary Dependent Hyperadrenocorticism (PDH) and Adrenal Dependent Hyperadrenocorticism (ADH) to provide a more accurate prognosis and enable the full range of possible treatments to be discussed with the dog’s owner.

Discriminatory tests available to differentiate between PDH and ADH include the low- and high-dose dexamethasone suppression tests, ultrasonography, and advanced imaging such as MRI and CT and measurement of endogenous ACTH.

Diagnostic summary

A confident diagnosis requires consistent endocrine confirmatory test results in a dog with clinical signs compatible with hyperadrenocorticism.
Treatment and Monitoring of Hyperadrenocorticism

**DAY 1**
Start VETORYL® Capsules at approximately 1mg/lb (2.2mg/kg) once daily as per prescribing information
Give daily, by mouth, with food, in the morning.

**DAY 10-14**
History, physical examination, serum biochemistry, with electrolytes
Perform ACTH stim test 4-6 hours after morning capsule
Ensure morning capsule was given with food

- **Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well**
  - Stop VETORYL Capsules for approximately 7 days
  - RETURN TO DAY 1 and administer a LOWER DOSE
  - Repeat ACTH Stim test in 10-14 days after restarting lower dose

- **Post-ACTH serum cortisol >1.45 µg/dL (>40 nmol/L) and clinically well**
  - Continue treatment at current dose
  - It is not recommended to increase dose yet, even if cortisol is >9.1 µg/dL

- **≥30 DAYS FROM INITIATION OF TREATMENT**
  History, physical examination, serum biochemistry, with electrolytes
  ACTH stim test 4-6 hours after morning capsule given with food
  Assess degree of clinical improvement

**STOP VETORYL TREATMENT**
Confirm whether clinical signs are due to hypoadrenocorticism with ACTH stim test and analysis of serum electrolytes (in particular Na+ and K+)
Treat symptomatically as required, e.g.
- dexamethasone to treat hypocortisolemia
- IV 0.9% NaCl to resolve hyperkalemia

- **Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well**
  - Stop VETORYL Capsules for 7 days depending on the severity of the clinical signs and then RETURN TO DAY 1 AT LOWER DOSE

- **Post-ACTH serum cortisol 1.45-5.4 µg/dL (40-150 nmol/L)**
  - Continue treatment at current dose
  - Continue monitoring history, physical examination, electrolytes and ACTH stim test every 90 days.
  - If dose is altered always recheck ACTH stim again 10-14 days later

- **Post-ACTH serum cortisol 5.41-9.1 µg/dL (150-250 nmol/L)**
  - Continue on current dose but monitor clinical signs carefully for recurrence

- **Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L)**
  - Continue current dose and recheck in 1-3 months OR RETURN TO DAY 1 and increase morning dose

**SIGNIFICANT IMPROVEMENT**

- **Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well**
  - Stop VETORYL Capsules
  - RETURN TO DAY 1 AT LOWER DOSE

- **Post-ACTH serum cortisol 1.45-5.4 µg/dL (40-150 nmol/L)**
  - Continue treatment at current dose

- **Post-ACTH serum cortisol 5.41-9.1 µg/dL (150-250 nmol/L)**
  - Continue current dose and recheck in 3 months OR RETURN TO DAY 1 and increase morning dose

- **Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L)**
  - Continue current dose and recheck in 1-3 months OR RETURN TO DAY 1 and increase morning dose

**CLINICAL SIGNS NOT FULLY CONTROLLED**

- **If clinical signs are not controlled for a full 24 hour period, twice daily dosing may be indicated or a dosage increase**
  - If Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L), total daily dose can be slowly increased and split into two doses.

- **Post-ACTH serum cortisol >5.4 µg/dL (>150 nmol/L)**
  - Increase dose
  - RETURN TO DAY 1

- **To change to twice daily dosing, use combinations of capsule sizes to split the current daily dose into two doses.**

**Rule out concurrent illness**

If you have questions at any point during patient management, contact Dechra Veterinary Technical Services at (866) 933-2472

- **If you have questions at any point during patient management, contact Dechra Veterinary Technical Services at (866) 933-2472**

**If clinical signs are not controlled for a full 24 hour period, twice daily dosing may be indicated or a dosage increase**

- **Increase dose**
  - RETURN TO DAY 1

**To change to twice daily dosing, use combinations of capsule sizes to split the current daily dose into two doses.**

- **If Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L), total daily dose can be slowly increased and split into two doses.**

- **Continue monitoring as per approved label recommendations**
  - Perform ACTH stim test 4-6 hours post morning capsule
Two dogs developed hyperadrenocorticism during the study. These two dogs had clinical signs consistent with hyperadrenocorticism (hypertension, polyuria/polydipsia, and partial loss of weight) present before treatment. One dog responded to treatment and had improvement in blood pressure and partial resolution of weight loss, but one dog did not respond. The dog that did not respond had an adrenal mass and was euthanized. The other dog died of congestive heart failure and was euthanized.

Additional adverse reactions were observed in 93 dogs. The most common of these included diarrhea (21 dogs), lethargy (20 dogs), inappetence/anorexia (17 dogs), vomiting (26 dogs), mucoid/serous (31 dogs), listlessness, weakness, exercise intolerance, depression, and weight loss (25 dogs). In addition to the two dogs with adrenal neoplasia, two dogs developed renal failure and one dog had pancreatitis. One dog with hyperadrenocorticism, an additional four dogs were removed from the study as a result of possible trilostane-related adverse reactions, including collar, collapse, lethargy, renal failure, and weight loss.

Complete blood counts conducted pre- and post-treatment revealed a statistically significant (p < 0.001) reduction in red cell variables (HCT, HEG, and RBC), but the mean values remained within the normal range. Additionally, approximately 10% of the dogs had a white cell count lower than normal due to the absence of concurrent canine leukemia. These changes were considered as clinically normal at the time of the elevated BUN.

In a long-term follow-up study of dogs in the US effectiveness study, the adverse reactions were similar to the short-term study. Vomiting, diarrhea and general gastrointestinal signs were most commonly observed. Lethargy, inappetence/anorexia, renal failure, or cardiac failure were reported. Hypoadrenocortical crisis, urinary tract infections or genitourinary disease, and neurological signs were reported. Included in the US follow-up study were 14 deaths, of which three were possibly related to trilostane. Eleven dogs were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown cause. One dog died of congestive heart failure and one of myositis ossificans, a non-neoplastic connective tissue formation. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.

In a long-term follow-up of dogs included in the UK studies, the following adverse reactions were seen: vomiting, diarrhea, dose/loose stools, and abdominal pain. The medications included in the list are categorized under: nausea, renal disturbances, vomiting, diarrhea, and colonic/rectal inflammatory syndrome and diarrhea. Three dogs were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown cause. One dog died of congestive heart failure and another of myositis ossificans, a non-neoplastic connective tissue formation. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.

Three dogs developed hyperadrenocorticism due to an adrenal tumor or due to concurrent pituitary and adrenal tumors. Evaluation of these cases failed to demonstrate a difference in clinical, endocrine, or biochemical response when compared to cases of pituitary-dependent hyperadrenocorticism.

HUMAN WARNINGS:

- Owners should be advised of the importance of follow-up visits to evaluate the dog's response to treatment. Owners should be advised to discontinue therapy if signs of potential drug toxicity are observed. Owners should be advised to discontinue therapy if the dog becomes ill and/or inactive or shows signs of hypoadrenocorticism or hypoadrenal crisis. Owners should be advised to discontinue therapy if the dog becomes ill and/or inactive or shows signs of hypoadrenocorticism or hypoadrenal crisis.

In this study, there were a total of 10 pigs diagnosed with hyperadrenocorticism due to an adrenal tumor or due to concurrent pituitary and adrenal tumors. Evaluation of these cases failed to demonstrate a difference in clinical, endocrine, or biochemical response when compared to cases of pituitary-dependent hyperadrenocorticism.

Two dogs were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown cause. One dog died of congestive heart failure and one of myositis ossificans, a non-neoplastic connective tissue formation. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.

HUMAN WARNINGS:

- Owners should be advised of the importance of follow-up visits to evaluate the dog's response to treatment. Owners should be advised to discontinue therapy if signs of potential drug toxicity are observed. Owners should be advised to discontinue therapy if the dog becomes ill and/or inactive or shows signs of hypoadrenocorticism or hypoadrenal crisis.

In this study, there were a total of 10 pigs diagnosed with hyperadrenocorticism due to an adrenal tumor or due to concurrent pituitary and adrenal tumors. Evaluation of these cases failed to demonstrate a difference in clinical, endocrine, or biochemical response when compared to cases of pituitary-dependent hyperadrenocorticism.

Two dogs were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown cause. One dog died of congestive heart failure and one of myositis ossificans, a non-neoplastic connective tissue formation. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.

In this study, there were a total of 10 pigs diagnosed with hyperadrenocorticism due to an adrenal tumor or due to concurrent pituitary and adrenal tumors. Evaluation of these cases failed to demonstrate a difference in clinical, endocrine, or biochemical response when compared to cases of pituitary-dependent hyperadrenocorticism.

Two dogs were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown cause. One dog died of congestive heart failure and one of myositis ossificans, a non-neoplastic connective tissue formation. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.

In this study, there were a total of 10 pigs diagnosed with hyperadrenocorticism due to an adrenal tumor or due to concurrent pituitary and adrenal tumors. Evaluation of these cases failed to demonstrate a difference in clinical, endocrine, or biochemical response when compared to cases of pituitary-dependent hyperadrenocorticism.

Two dogs were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown cause. One dog died of congestive heart failure and one of myositis ossificans, a non-neoplastic connective tissue formation. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.