There is a new option for Addison’s Disease
How to recognize Addison’s disease

When presented with an affected dog, Addison’s disease may not be at the top of your rule-out list. Being more aware of this condition and considering it earlier in your diagnostic workup will shorten the length of time it takes to diagnose the disease and deliver appropriate treatment.

Addison’s disease is a potentially life-threatening condition.

Clinical signs associated with the disease are nonspecific, can wax and wane, and dogs can respond to nonspecific therapy (e.g. intravenous fluid therapy). This condition can be easily mistaken for other diseases (e.g. kidney disease, gastroenteritis, neuromuscular disease and metabolic diseases).

The most common signs of Addison’s disease are:

- Inappetence
- Lethargy
- Diarrhea +/- Blood
- Melena (digested blood in stool)
- Weight loss
- Polyuria
- Polydipsia
- Vomiting
- Depression
- Weakness
- Bradycardia
- Hypothermia
- Shivering/muscle stiffness
- Dehydration

If left untreated, Addison’s disease can be acutely life-threatening.

What is Addison’s disease (hypoadrenocorticism)?

Addison’s disease results from loss of corticosteroid production, principally the mineralocorticoid aldosterone and the glucocorticoid cortisol.

The most common type of canine Addison’s disease is primary hypoadrenocorticism, which is nearly always due to an immune-mediated destruction of the adrenal glands. This condition usually results in deficiencies of both mineralocorticoids and glucocorticoids; however, isolated glucocorticoid deficiency has been reported (atypical hypoadrenocorticism).

Secondary hypoadrenocorticism (caused by pituitary dysfunction), results in the deficiency of adrenocorticotropic hormone (ACTH). This is a very rare cause of canine hypoadrenocorticism and tends to result in glucocorticoid deficiency only. These patients will only need glucocorticoid replacement.

Capsule

Zona glomerulosa
Zona fasciculata
Zona reticularis
Adrenal medulla

Adrenal Gland

Medulla
Cortex

(Area enlarged below)

Stress
Hypothalamus

ACTH

CORTISOL

Glucocorticoids
Protein and fat mobilization

Renin-Angiotensin System

Increased blood volume

Gluconeogenesis

Protein and fat mobilization

Adrenal medulla

Zona glomerulosa
Capsule

Adrenal Gland

Medulla
Cortex

(Area enlarged below)

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The most common signs of Addison’s disease are:

<table>
<thead>
<tr>
<th>Almost all cases</th>
<th>Common</th>
<th>Less common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Vomiting</td>
<td>Diarrhea +/- Blood</td>
</tr>
<tr>
<td>Weakness</td>
<td>Dehydration</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Hypothermia</td>
<td></td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Shivering/muscle stiffness</td>
<td></td>
<td>Wirehair/muscle stiffness</td>
</tr>
</tbody>
</table>

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Diagnosis

The gold standard for diagnosing Addison’s disease is the ACTH stimulation test, which assesses the ability of the adrenal gland to produce cortisol.

Although a low basal cortisol value can be useful to rule out Addison’s disease, it is not adequate for a diagnosis.

Affected dogs can present with a gradual onset of clinical signs or an acute life-threatening state (Addisonian crisis). Animals presenting in Addisonian crisis tend to have clinical signs suggestive of hypovolemic shock such as prolonged capillary refill times, weak peripheral pulses, weakness or collapse.

Affected animals may not be tachycardic despite being hypovolemic due to the bradycardic effects of hyperkalemia.

A thorough clinical history in these cases can increase a clinician’s suspicion of this disease and following a detailed physical examination, diagnostic investigations typically include hematology, serum biochemistry (including electrolytes), and potentially radiography, ultrasonography and electrocardiography.

**Diagnostic indices of Addison’s Disease in descending order of frequency:**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Serum biochemistry and Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of stress leukogram in a stressed/difficult animal</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Nonregenerative anemia</td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>Urine specific gravity &gt;1.030</td>
</tr>
<tr>
<td></td>
<td>Hyperchloremia</td>
</tr>
<tr>
<td></td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>

**Step-by-step diagnosis**

*Veterinarians should use the specific reference ranges of their diagnostic laboratory.

**Clinical history**

- No previous relevant medical history
- History suggestive of hypoadrenocorticism e.g. episodic collapse, weight loss, recurrent gastrointestinal signs, lethargy
- Slower heart rate, thinner or more dehydrated than expected
- Low Na+ and/or high K+ (important), Na+ : K+ ratio < 27, low albumin, low glucose and/or increased blood urea nitrogen and creatinine
- Slower heart rate, thinner or more dehydrated than expected

**Physical examination**

- Tachycardia, obesity
- Tachycardia, obesity
- Increased white blood cell count with stress leukogram (neutrophilia, lymphopenia, eosinopenia)
- Increased white blood cell count with stress leukogram (neutrophilia, lymphopenia, eosinopenia)

**Routine biochemistry and electrolytes**

- Normal Na+ and K+
- Normal Na+ and K+

**Complete blood count (CBC) and blood smear**

- Anemia and low white blood cell count with relative lymphocytosis, eosinophilia and neutropenia, lack of stress leukogram
- Anemia and low white blood cell count with relative lymphocytosis, eosinophilia and neutropenia, lack of stress leukogram

**ACTH stimulation test**

- Post-ACTH cortisol 2 µg/dl or greater*
- Post-ACTH cortisol 2 µg/dl or greater*
- Post-ACTH cortisol < 2 µg/dl*
- Post-ACTH cortisol < 2 µg/dl*

**Hypoadrenocorticism can be ruled out**

**Hypoadrenocorticism highly likely**

*Veterinarians should use the specific reference ranges of their diagnostic laboratory.

Courtesy of Professor Ian Ramsey, University of Glasgow

Addison’s disease resembles many other illnesses so it can be challenging to recognize. It is often referred to as ‘the great pretender’. Fortunately, once Addison’s disease is suspected, confirming the diagnosis is as simple as running an ACTH stimulation test.
Treatment

Once Addison’s disease has been confirmed and the patient is hydrated (i.e., no continued evidence of vomiting, diarrhea, weakness, depression or dehydration); replacement therapy can begin. Long-term replacement therapy consists of glucocorticoid replacement at physiological doses (very low) and mineralocorticoid replacement.

The recommended therapy for glucocorticoid replacement is oral prednisone/prednisolone at 0.2-0.4 mg/kg/day (0.1-0.2 mg/lb/day).

For mineralocorticoid replacement, the treatment of choice is desoxycorticosterone pivalate (DOCP).

What is DOCP?

Desoxycorticosterone is a corticosteroid with primarily mineralocorticoid activity, similar to aldosterone.

ZYCORTAL Suspension contains desoxycorticosterone pivalate which is a mineralocorticoid hormone indicated for use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison’s disease). ZYCORTAL Suspension was formulated and approved specifically for subcutaneous use.

ZYCORTAL Suspension contains desoxycorticosterone pivalate (DOCP), which is a pure mineralocorticoid hormone that regulates electrolytes and water balance, which are impaired in cases of mineralocorticoid deficiency in Addison’s disease. DOCP has limited glucocorticoid activity, allowing the independent dose titration of mineralocorticoid without the risk of inducing marked side effects from glucocorticoid oversupplementation e.g. polyuria, polydipsia, polyphagia and muscle atrophy.

Initial Dose

2.2 mg/kg body weight administered by subcutaneous injection.

ZYCORTAL Suspension allows you to tailor the dose of mineralocorticoid replacement and the concurrently administered glucocorticoid replacement therapy to the individual dog based on clinical response and normalization of Na⁺ and K⁺ concentrations.

Please see the Monitoring and Dose Adjustment Algorithm on page 8 and the ZYCORTAL Suspension package insert on page 11 for complete details.

Seeing the same dog with the same issues? There could be a different conclusion.
Efficacy

A double-blinded, multi-site, 180-day field study evaluated the effectiveness of ZYCOR TAL Suspension compared to an existing FDA-approved desoxycorticosterone pivalate active control. Non-inferiority was achieved compared to the existing FDA-approved control product containing DOCP.1

A dog was considered a treatment success if it remained clinically normal or had improved clinical signs compared to baseline and the Na⁺ and K⁺ concentrations were within the reference range of the analyzer, or the Na⁺/K⁺ ratio was between 27-32.

The mean final dose for ZYCOR TAL Suspension was 1.9 ± 0.27 mg/kg (range 1.2-2.5 mg/kg) and the mean final dose interval was 38.5 ± 12.5 days (range 20-99 days).1

As with all drugs, side effects may occur. In field studies the most common side effects reported were polyuria, polydipsia, depression/lethargy, inappropriate urination, alopecia, decreased appetite/anorexia, panting, vomiting, diarrhea, shaking/trembling, polyphagia, urinary tract infection, urinary tract incontinence and restlessness. ZYCOR TAL Suspension should be used with caution in dogs with congestive heart disease, edema, severe renal disease or primary hepatic failure. Dogs presenting in Addisonian crisis must be rehydrated with appropriate intravenous therapy before starting treatment with ZYCOR TAL Suspension. Refer to the prescribing information for complete details or visit www.dechra-us.com/zycortal.

ZYCOR TAL Suspension is efficacious, well tolerated and allows tailored dosing for each dog with Addison’s disease.

The mean final dose for ZYCOR TAL Suspension was 1.9 ± 0.27 mg/kg (range 1.2-2.5 mg/kg) and the mean final dose interval was 38.5 ± 12.5 days (range 20-99 days) with the majority of dogs having a dosing interval between 20 and 46 days.1

Non-inferiority was achieved compared to an FDA-approved control DOCP product.1

Subsequent doses and long-term management:

Once the dog is optimally controlled, keep the same dosing regimen. In case of abnormal clinical condition or abnormal electrolytes at subsequent visits, continue to titrate the dose in similar increments as described above. Prior to a stressful situation, consider temporarily increasing the dose of prednisone/prednisolone.

** Use Day 25 electrolytes, if Day 10 electrolytes are normal
Switching dogs from fludrocortisone

Data from the ZYCORTAL Suspension clinical study has shown there is no significant difference in the efficacy of ZYCORTAL Suspension when given to newly diagnosed patients who started treatment with fludrocortisone Suspension compared to existing patients which started treatment with fludrocortisone and then switched to ZYCORTAL Suspension (p > 0.05). 2

In the clinical study, 31 dogs were enrolled who were receiving fludrocortisone prior to the administration of ZYCORTAL Suspension. Twelve of these dogs received fludrocortisone for > 30 days; nineteen were treated for < 7 days. When transitioning to ZYCORTAL Suspension, the majority of dogs (17/31) received the last dose of fludrocortisone on the same day of ZYCORTAL Suspension administration (Day 0). A "wash-out" or transition period was not required between the last administration of fludrocortisone and the first administration of ZYCORTAL Suspension. 2

Treatment of Addisonian crisis (Acute Hypoadrenocorticism)

Acute and severe cases of Addison’s disease represent a life-threatening emergency. Aggressive fluid therapy with isotonic crystalloids (0.9% NaCl, Lactated Ringer’s or Hartmann’s Solution) is critical to reversing the hypovolemic, hypotensive shock these dogs commonly experience. Fluid therapy will also temporarily address the life-threatening electrolyte imbalances. In stable, non-shocky patients, diagnostic samples (CBC, biochemistry, urinalysis and baseline cortisol) can be collected before starting therapy. In shocky, critically affected patients, priority should be given to stabilizing the patient. Diagnostic samples can be collected once the patient is stable. Diagnostic samples can then be used for baseline electrolyte concentrations and for the initial ACTH stimulation test confirm the presence of hypoadrenocorticism and the patient is hydrated.

1 - For suspension use in dogs only
2 - Microencapsulated

CAUTION: Not for human use. Not for veterinary use in pregnant or lactating animals. Not for use in rabbits.

DESCRIPTION: Desoxycorticosterone pivalate is a mineralocorticoid hormone. Dexamethasone pivalate is a glucocorticoid hormone. The structural formulas are:

Molecular Formulas: 

ZYCORTAL® Suspension is a white aqueous suspension. Each milliliter contains 25 mg of desoxycorticosterone pivalate, 10.5 mg methylcellulose, 3 mg sodium carboxymethylcellulose, 1 mg polysorbate 20, 8 mg sodium chloride, 1 mg sorbitan monolaurate and water for injection (USP).

INDICATION: For use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison’s disease).

DOSAGE AND ADMINISTRATION: Prior to each use, thoroughly shake the vial to resuspend the medication. The dose of ZYCORTAL Suspension should be adjusted based on the physician’s judgment to achieve the therapeutic effect and the minimum dose necessary to maintain a normal sodium/potassium ratio (Na+/K+ ratio) of at least 32.

For dogs which are clinically normal and have a Day 25 Na+/K+ ratio > 32, it is possible to prolong the dosing interval instead of administering the Day 25 dose. Prolonging the dosing interval:

- Increase the dosing interval for Day 25 (or the next dose): if the Day 25 Na+/K+ ratio is > 34, decrease the dose to: 2.0 mg/kg.
- If the Day 25 Na+/K+ ratio is 26-30, increase the Na+/K+ ratio to a normal level before increasing the dosing interval.
- If the Day 25 Na+/K+ ratio is: 20-25: increase the dosing interval by 2.0 mg/kg.
- If the Day 25 Na+/K+ ratio is: 15-19: increase the dosing interval by 5.0 mg/kg.
- If the Day 25 Na+/K+ ratio is: < 15: increase the dosing interval by 10.0 mg/kg.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

HOW SUPPLIED:

ZYCORTAL Suspension is available in a concentration of 25 mg/mL of desoxycorticosterone pivalate in a 3 mL vial. Each vial contains 75 mg desoxycorticosterone pivalate (25 mg/mL).

Storage:

Store at 25°C (77°F) and protect from light. Use the vial within 24 hours of opening, or as directed by your veterinarian.

ZYCORTAL Suspension is contraindicated in dogs with concurrent hyperaldosteronism or adrenal tumors.

ADVERSE REACTIONS: One dog with acute illness with a Blau stunt nodule developed anterior lobe failure 11 days after the first administration of ZYCORTAL Suspension and was removed from the study.

In addition to the adverse reactions reported during the field study and post-approval adverse drug experience reporting for desoxycorticosterone pivalate suspension suspension included reports of anaphylaxis and anaphylactoid reactions. If anaphylaxis or anaphylactoid reactions are suspected, immediate medical attention should be sought.

The full Prescribing Information is available at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

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References


2. Data on file

Further reading


www.dechra-us.com

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