Step-by-Step Diagnosis of Hypoadrenocorticism

Courtesy of Professor Ian Ramsey, University of Glasgow
Clinical history

History suggestive of hypoadrenocorticism. E.g. episodic collapse, weight loss, recurrent gastrointestinal signs, lethargy

Sloppy heart rate, thinner or more dehydrated than expected

Routine biochemistry and Electrolytes

Low Na⁺ and/or high K⁺ (important), Na⁺ : K⁺ ratio < 27, low albumin, low glucose and/or increased urea and creatinine

Complete blood cell count (CBC) and blood smear

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

ACTH stimulation test

Hypoadrenocorticism can be ruled out

Post-ACTH cortisol 2 µg/dl or greater*

Post-ACTH cortisol < 2 µg/dl*

Hypoadrenocorticism highly likely

No history of steroid application or administration confirmed through careful medical history

*Veterinarians should use the specific reference ranges of their diagnostic laboratory.
ZYCORTAL® SUSPENSION (desoxycorticosterone pivalate injectable suspension)

For subcutaneous use in dogs only
Mineralocorticoid

CAUTION: Federal law (U.S.A.) restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Desoxycorticosterone pivalate is a mineralocorticoid hormone. Chemically, desoxycorticosterone pivalate is 21-[(2,2-dimethyl-1-oxopropoxy)-pregn-4-ene-3,20-dione.

The structural formula is:

Molecular Formula: C_{29}H_{35}O_{3}

ZYCORTAL Suspension is a white aqueous suspension. Each milliliter contains 25 mg of desoxycorticosterone pivalate, inactive ingredients are 10.5 mg methylcellulose, 0 mg sodium carboxymethylcellulose, 1 mg polysorbate 60, 6 mg sodium chloride, 1 mg chlorocresol and water for injection (to 100%).

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 product.

ZYCORTAL Suspension replaces the mineralocorticoid hormones only. Dogs with combined glucocorticoid and mineralocorticoid deficiency should also be treated with prednisone or prednisolone at an initial dosage of 0.2-0.4 mg/kg/day (0.1-0.2 mg/lb/day).

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ZYCORTAL Suspension is intended for long-term administration at intervals and doses dependent upon individual response. Tailor the dose of ZYCORTAL Suspension and the concurrently administered glucocorticoid replacement therapy to the individual dog based on clinical response and normalization of Na+ and K+ concentrations.

Initial dose of ZYCORTAL Suspension: The initial dose is 2.2 mg/kg (1 mg/lb) body weight, administered by subcutaneous injection.

If the dog is clinically normal and has a Na+/K+ ratio > 32 on Day 25, either adjust the dose of prednisone/prednisolone and/or investigate other causes of the clinical signs.

Prolonging the dosing interval: The dog’s clinical signs have worsened or not resolved, adjust the dose of prednisone/prednisolone and/or investigate other causes of the clinical signs.

Second dose of ZYCORTAL Suspension: At approximately 25 days after the first dose, re-evaluate the dog and repeat the Na+/K+ ratio.

If the dog is clinically normal and has a normal Na+/K+ ratio on Day 25, adjust the dose based on the Day 10 Na+/K+ ratio using the guidelines in Table 1, below.

If the dog is clinically normal and has a Na+/K+ ratio > 32 on Day 25, adjust the dose based on the Day 10 Na+/K+ ratio according to Table 1 or delay the dose (see Prolonging the dosing interval).

If the dog is either clinically normal or has a normal Na+/K+ ratio on Day 25, adjust the dose of prednisone/prednisolone or ZYCORTAL Suspension (see Subsequent doses and long-term management).

Table 1: Day 25: Administering the Second Dose of ZYCORTAL Suspension

If the dog is clinically normal and the Day 25 Na+/K+ ratio is > 32, it is possible to prolong the dosing interval instead of adjusting the dose as described in Table 1. Evaluate the electrolytes every 3-7 days until the Na+/K+ ratio is < 32, and then administer 2.2 mg/kg of ZYCORTAL Suspension.

Subsequent doses and long-term management: For subsequent doses, use the following guidelines if the dog is not clinically normal and/or has abnormal Na+ or K+ concentrations.

Clinical signs of polyuria/polydipsia: Decrease the prednisone/prednisolone dose first. If the polyuria/polydipsia persists, then decrease the dose of ZYCORTAL Suspension without changing the dosing interval.

Hyperkalemia, hypernatremia or Na+/K+ ratio < 27: Decrease the ZYCORTAL Suspension dosing interval by 2-3 days.

Hyperkalemia or hypernatremia: Decrease the ZYCORTAL Suspension dose.

Prolonging the dosing interval: If the dog’s clinical signs worsen or do not resolve, adjust the dose of prednisone/prednisolone and/or investigate other causes of the clinical signs.

Table 2: Percentage of Dogs with Adverse Reactions in the Field Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZYCORTAL Suspension (n = 113 dogs)</th>
<th>Active Control (n = 39 dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria</td>
<td>15.0% (17)</td>
<td>12.8% (5)</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>13.3% (15)</td>
<td>15.4% (6)</td>
</tr>
<tr>
<td>Depression/lethargy</td>
<td>9.7% (11)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Inappropriate urination</td>
<td>8.9% (10)</td>
<td>10.3% (4)</td>
</tr>
<tr>
<td>Raiaza</td>
<td>5.3% (6)</td>
<td>5.1% (2)</td>
</tr>
<tr>
<td>Decreased appetite/anorexia</td>
<td>4.4% (5)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Panting</td>
<td>3.5% (4)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.5% (4)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.3% (8)</td>
<td>7.9% (3)</td>
</tr>
<tr>
<td>Shaking/trembling</td>
<td>2.7% (3)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Polyphagia</td>
<td>1.8% (2)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.8% (2)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>0.9% (1)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0.9% (1)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Uricina facial edema</td>
<td>0.9% (1)</td>
<td>5.1% (2)</td>
</tr>
</tbody>
</table>

The effectiveness of ZYCORTAL Suspension may be reduced if potassium-sparing diuretics, such as spironolactone, are administered concurrently.

ADVERSE REACTIONS: One hundred fifty-two dogs were included in the field safety analysis. Adverse reactions are summarized in Table 2.

POLYURIA/POLYDIPSIA: For dogs with polyuria/polydipsia, the maximal concentration (C_{max}) was 13.2 ± 5 ng/mL, and time to maximum concentration (T_{max}) was 15-24 hours.

The mean final dose for ZYCORTAL 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 45 days.

ANIMAL SAFETY: In a laboratory study, ZYCORTAL Suspension was administered via subcutaneous injection to 32 Beagle dogs (four groups of 8 dogs each) at doses of 0, 1, 2 and 3 mg/kg in a randomized, blinded, cross-over study; the plasma half-life (mean ± standard deviation) is approximately 17 ± 7 days, with a maximum concentration (C_{max}) of 13.2 ± 5 mg/mL, and time to maximum concentration (T_{max}) of 10 ± 3 hours.

EFFECTIVENESS: A double-blind, multi-site, 180-day field study evaluated the effectiveness of ZYCORTAL Suspension compared to an FDA-approved desoxycorticosterone pivalate active control. One hundred fifty-two (152) dogs of various breeds, 0.5-12.4 years of age and weighing 0.95-61.2 kg were enrolled. One hundred thirteen (113) dogs were treated with ZYCORTAL Suspension and 39 dogs were treated with the active control. Both groups were administered an initial dose of 2.2 mg/kg. Subsequent doses administered and/or frequency of administration were adjusted according to the clinical needs of the dog.

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HUMAN WARNINGS: Not for human use. Keep this and all drugs out of the reach of children. Consult a physician in case of accidental human exposure.

PRECAUTIONS: Any dog presenting with severe hyponatremia, dehydration, pre-ezrenal azotemia and inadequate tissue perfusion ("Addisonian crisis") must be rehydrated with intravenous fluid (saline) therapy before starting treatment with ZYCORTAL Suspension.