Excel CPD Webinar

Pass the salt-diagnosis and management of Addison’s Disease

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THE ADRENAL GLANDS

Normal adrenocortical function:
The adrenal glands consist of a cortex which synthesises and secretes steroid hormones and a medulla which synthesises and secretes amines.

**The adrenal cortex**
The adrenal cortex is divided into the following zones:
- Zona glomerulosa (outer) making mineralocorticoids e.g. aldosterone
- Zona fasciculata (middle) and Zona reticularis (inner) making glucocorticoids and sex hormones

All steroid hormones come from cholesterol, via pregnenolone and the final hormone made depends on the presence of certain enzymes. For example, 17-alpha hydroxylase is not present in the zona glomerulosa therefore these cells cannot make glucocorticoids and sex hormones. Steroids are lipophilic and therefore are transported in the blood in association with proteins such as transcortin.
Hypoadrenocorticism (Addison’s Disease)

Hypoadrenocorticism is caused by a deficiency in mineralocorticoid and/or glucocorticoid production. It can be either primary (due to immune destruction of >90% of the adrenal cortices - “Addison’s Disease”) or secondary (due to lack of ACTH with normal mineralocorticoid levels) – usually iatrogenic.

Signalment
The disease usually affects young / middle aged dogs with a median age of 4-6 years. 70% of cases are female. Breeds with an increased risk of hypoadrenocorticism include:
- Standard poodles*
- Bearded collies~
- Portuguese water dog*
- Leonberger#
- Great Dane#
- Rottweiler#
- WHWT#
- Soft coated wheaten terrier#

*Autosomal recessive mode of inheritance
#Genetic predisposition suspected
~Highly heritable but exact mode not determined

Clinical signs
The chronic waxing waning form of the disease with vague non-specific signs is the most common and can be difficult to recognise. However patients may also present in an acute Addisonian “crisis” with marked hypovolaemia and azotaemia.

- Chronic presentation
The chronic form of the disease is usually worsened by stress e.g. going into kennels. Signs can include anorexia, vomiting, lethargy, depression, weakness, shivering, weight loss, PUPD, abdominal pain. Hypoadrenocorticism must be considered as a differential in any animal with waxing/waning signs – especially intermittent GI disease/ bleeding. Animals can often appear normal between bouts, especially after intravenous fluid or glucocorticoids treatment.

Physical findings MAY BE UNREMARKABLE but can include depression, weakness, dehydration, bradycardia and weak pulses. ECG changes are common and owners might report intermittent signs of GI haemorrhage.
Acute presentation

This is a genuine medical emergency which can be fatal if not recognised and treated. Clinical signs are usually caused by hypovolaemic shock, but with the paradox of relative bradycardia in some cases. The patient is usually collapsed or extremely weak and hypothermic with recent history of V+/D+. Abdominal pain is often a feature and the disease can resemble pancreatitis clinically. Cardiac abnormalities may be present when potassium exceeds 7-8 mmol/l.

Blood parameter changes are a reflection of the lack of aldosterone and lack of cortisol and hypovolaemia. Lack of aldosterone leads to renal loss of water, sodium and chloride, retention of potassium and hydrogen ions and pre-renal failure. Glucocorticoid deficiency leads to decreased stress tolerance, appetite loss, impaired gluconeogenesis and normocytic normochromic anaemia.

Clinical pathology

Biochemistry:
- Hyponatraemia
- Hyperkalaemia
- Hypochloraemia
- Azotaemia
- Hypercalcaemia (~30%)
- Mild hypoglycaemia
- Hypoalbuminaemia
- Mild increases in ALT possible
- Metabolic acidosis

Note serum sodium and potassium can be normal. The use of the sodium:potassium ratio is sometimes recommended, when normal varies between 27:1 and 40:1. Values in hypoadrenocorticism are often less than 27 and sometimes less than 20.

10% OF CASES DO NOT HAVE CLASSICAL ELECTROLYTE CHANGES- some of these cases have primary hypoadrenocorticism and develop mineralocorticoid deficiency in weeks to months.

Other causes of a low Na:K ratio (<27) (from Nielsen L et al. Low ratios of sodium to potassium in the serum of 238 dogs. The Veterinary Record 2008;162:431-435):
- Renal disease: CRF, ARF, NDI
- Cardiorespiratory: CH, endocardiosis, bronchopneumonia
- Gastrointestinal: Chronic hepatopathy, IBD, anal furunculosis, pancreatitis
- Endocrine: DKA
- Other: Other neoplasia, lymphoma, idiopathic epilepsy, inflammatory brain disease
Haematology:
- Lymphocytosis
- **Eosinophilia**
- (Neutropaenia)
- Anaemia (usually the result of GI haemorrhage)

Urinalysis
NOTE: With dehydration and azotaemia, a high USG might be expected but this does not always happen as chronic sodium wasting (washout) can reduce urine concentrating ability. Some Addisonian dogs have urine SG in the isosthenuric range (1.007-1.012)

**ECG** changes are mostly the result of the level of hyperkalaemia, but some animals with very high potassium have none of these changes:
- \(>5.5\) mmol/l: T wave peaking and Q-T shortening
- \(>6.5\) mmol/l: Increased QRS duration
- \(>7.0\) mmol/l: P wave decreased, P-R interval prolonged
- \(>8.5\) mmol/l: P waves absent and severe bradycardia

Radiographic changes usually relate to the hypovolaemia e.g. micocardia, decreased pulmonary vessel size, reduced caudal vena cava size, microhepatica. Occasionally oesophageal dilation can be seen due to muscle weakness.

**Diagnosis of Hypoadrenocorticism**
This should be based on history and physical exam along with diagnostic tests.

- **ACTH stimulation** is the most useful test and can also be used to diagnose atypical hypoadrenocorticism (no electrolyte changes). A dog with hypoadrenocorticism will show no or minimal response to ACTH stimulation (pre and post ACTH cortisol usually <20nmol/l).

Note: Prolonged or excessive inflammatory cytokine activity can suppress pituitary and adrenal function in humans as possibly also in dogs. In a recent study, dogs with severe sepsis had a marked suppression of the response of the adrenal cortex to exogenously administered ACTH.
- Aldosterone pre and post ACTH. This can be used to distinguish primary and secondary causes of hypoadrenocorticism. A dog with secondary hypoadrenocorticism will have a raised post ACTH Aldosterone, but a dog with primary disease will have no response. This test is also useful in a dog that is on treatment for hypoadrenocorticism (florineff only) if the diagnosis needs to be confirmed.

- Endogenous ACTH will be high in primary disease and low if secondary or iatrogenic disease.

**Treatment of the acute crisis**

1. **Restore intravascular volume**
2. **Reversal of hyperkalaemia**
3. **Reversal of hyponatraemia**
4. **Provision of glucocorticoids and mineralocorticoids**

**1. Restore intravascular volume**
This is achieved using aggressive intravenous fluid therapy and should be started at 80-90ml/kg/hr. 0.9% NaCl or lactated Ringer’s (Hartmann’s) solutions are suitable choices. Some clinicians may argue that Hartmann’s is not appropriate in the addisonian patient, as it contains potassium. The amount of potassium however is far outweighed by the provision of a large volume of fluid and the associated diuresis and kaluresis. I therefore believe that the use of Hartmann’s solution in the hyperkalaemic patient is more of a theoretical, than practical concern. Hartmann’s also has the added advantage of being an alkalising solution, which may be beneficial in the acidotic addisonian patient.

**2. Reversal of hyperkalaemia**
Hyperkalaemia is life-threatening due to negative effects on myocardial cells. There are several treatments that can be used in the hyperkalaemic animal:

- **Intravenous fluid therapy** is very effective in reversing hyperkalaemia, since restoring renal perfusion will usually result in a dramatic decrease in $K^+$. This may be all that is required in the majority of patients. If however hyperkalaemia is having effects on the cardiovascular system i.e. arrhythmias, evidence of poor cardiac output, other treatments can be used to decrease potassium:

  - **Calcium gluconate** (10% solution, 0.5-1.0 ml/kg). Calcium does not directly lower the potassium but is cardioprotective. Calcium counteracts the effects of hyperkalaemia on the cardiac conduction system by re establishing the normal resting membrane potential of -90 MV. Calcium
should be administered slowly over 10-20 minutes with electrocardiographic or heart rate monitoring as calcium itself can be cardiotoxic.

- **Sodium bicarbonate.** Sodium bicarbonate combines with hydrogen ions in ECF. This creates a gradient for additional hydrogen ions to move out of cells, into ECF. As hydrogen ions move out of cells, potassium ions move into the cells.

  The following formula can be used to determine the amount of bicarbonate to administer:

  \[ \text{Body weight (kg)} \times 0.3 \times \text{base deficit} = \text{bicarbonate dose in mEq} \]

  One half of the calculated replacement is administered intravenously over 30 minutes, and the remainder provided with intravenous fluids over 2-3 hours if required.

- **Glucose** (50% solution, 1.0ml/kg) with or without regular insulin (0.25u/kg). As glucose moves into cells under the influence of insulin, potassium “tags” along into the cells. Glucose can be administered without insulin, depending upon endogenous insulin release from the pancreas or regular insulin can be administered with glucose. Regular insulin (crystalline) is very soluble and readily available. Do not administer insulin without administrating glucose or hypoglycaemia will result.
3. Reversal of hyponatraemia

The provision of intravenous fluid therapy is usually all that is required to reverse hyponatraemia. Some care should be taken to ensure that sodium does not rise too rapidly as this can lead to central nervous system signs. This rarely happens in clinical practice however. Mineralocorticoid therapy will also help to correct hyponatraemia.

4. Provision of glucocorticoids and mineralocorticoids

Glucocorticoid deficiency is best corrected by the intravenous administration of a rapid-acting glucocorticoid. Mineralocorticoid supplementation is not strictly necessary during the acute crisis, although some of the drugs do also have mineralocorticoid activity (e.g. hydrocortisone).

A variety of glucocorticoids are available for use in the crisis situation:

- Dexamethasone as a single dose of approximately 0.2mg/kg intravenously
- Hydrocortisone (sodium phosphate) 2mg/kg intravenously
- Methylprednisolone sodium 1-2mg/kg intravenously
- Prednisolone 0.5mg/kg orally

Dexamethasone has the advantage of no cross-reactivity with the measurement of cortisol during an ACTH stimulation test, and so can be used before or during this test. The other corticosteroids cross react with the laboratories assay of cortisol and so should not be administered until after an ACTH stimulation test has been performed.

Maintenance therapy

Mineralocorticoids

- Once stable, mineralocorticoid replacement therapy should be commenced whilst continuing to monitor electrolytes / urine / BUN / creatinine. Fludrocortisone 0.02 mg/kg/day (SID or divided BID) is a good starting dose but this might need gradually increasing over the first 6-18 months of therapy.

  The major problems with this drug are the development of glucocorticoid side effects. Resistance has also been noted in some animals.

- DOCP (Percorten-V) is an alternative mineralocorticoids supplement, which is given as in injection. It released mineralocorticoid slowly over approximately 25 days. The dose is 2.2mg/kg given im or sc. Subsequent adjustments are based on serum electrolytes, which are initially measured every 12 and 25 days after each of the first two or three DOCP injections. Note this preparation contains NO glucocorticoid activity so prednisolone must be supplemented. This preparation is difficult to get hold of however.

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Glucocorticoids
Prednisolone is initially provided at a dose of 0.2mg/kg BID. Over the ensuing 1-2 months the dose should gradually be reduced to the lowest amount given once a day that still prevents signs of hypocortisolaemia. Approximately 50% of patients receiving florineff require long term prednisolone. Steroids may need to be given at times of stress / illness (kennelling, fireworks etc) and the owner should be provided with a small supply of prednisolone for emergency use (dose no more than 0.1 – 0.5 mg/kg).

Salt
Small quantities of salt can be given on food to help correct hypochloraemia and hyponatraemia. Alternatively slow release salt tablets can be obtained from chemists and make a good salt supplement in the Addisonian patient.

Once stable, treatment lifelong treatment is required. Monitor electrolytes weekly initially then every 3-4 months. Over time, Florinef requirements often gradually increase, either due to weight gain of the patient (glucocorticoid side-effects) or due to continued destruction of the remaining adrenal cortices.