Hypoadrenocorticism is a relatively uncommon disorder of dogs. In secondary hypoadrenocorticism, a deficiency of adrenocorticotropic hormone (ACTH) results in glucocorticoid insufficiency. Primary hypoadrenocorticism (Addison’s disease) is more common and can give rise to both mineralocorticoid and glucocorticoid deficiency. It is usually attributed to immune-mediated destruction of the adrenal glands. Addison’s disease, either temporary or permanent, is a potential complication of treatment of hyperadrenocorticism with mitotane or trilostane.

In naturally occurring Addison’s disease, most dogs present with evidence of both mineralocorticoid and glucocorticoid deficiency. However, approximately 10 % of cases present with evidence of glucocorticoid deficiency alone (atypical Addisons). These cases may eventually progress to mineralocorticoid deficiency.

Addison’s disease tends to affect young to middle-aged dogs. It is reported to predominantly affect females and Standard poodles, West Highland white terriers, Portuguese water dogs, great Danes, rottweilers and bearded collies are predisposed. The condition is known to be inherited in Portuguese water dogs, standard poodles and bearded collies, although the exact genetic mechanisms are unclear.

Clinical presentation and diagnosis

Dogs typically present with a waxing, waning history of lethargy/depression, weight loss, intermittent gastrointestinal signs, weakness and dehydration that respond, at least initially, to symptomatic therapy. Because of its vague nature, Addison’s disease is rarely suspected initially. The signs typically progressively worsen and eventually most present in an acute addisonian crisis. These dogs exhibit moderate to severe shock as evidenced by extreme weakness or collapse, hypovolaemia, prolonged capillary refill time, weak pulse and inappropriately low heart rate or obvious bradycardia. Other possible signs include polyuria/polydipsia, shaking, vague abdominal pain, melaena which may be severe and occasionally haematemesis. The onset of acute clinical signs may be precipitated by a stressful incident.

None of the above clinical signs are pathognomonic for hypoadrenocorticism but the waxing/waning nature of the illness that is exacerbated by stress and that responds to non-specific therapy often alerts clinicians to the possibility of hypoadrenocorticism. In addition, addisonian dogs often have more severe lethargy/depression, weight loss and dehydration than suggested by the other clinical signs and the length of the clinical history. Many present in an overtly unstable condition requiring intensive medical therapy.
In Addison’s disease, glucocorticoid deficiency contributes to some of the clinical signs such as lethargy, weakness and impaired gastrointestinal function and integrity. Mineralocorticoid deficiency results in sodium loss, dehydration, impaired neuromuscular function and cardiac conduction disturbances. As a consequence animals presenting with atypical (or secondary) hypoadrenocorticism are rarely severely ill but the severity of the signs induced by glucocorticoid deficiency will be exacerbated by the changes associated with mineralocorticoid deficiency. Atypical cases may present with a varying combination of lethargy/depression, vomiting and diarrhoea and inappetance. Occasional dogs present with megaoesophagus and regurgitation as the primary complaint or other neurological signs such as muscle cramping. A few case reports of clinical signs resulting from hypoglycaemia have been described.

Survey radiographs, abdominal ultrasonography and electrocardiography are often performed in dogs with hypoadrenocorticism. Most untreated dogs have one or more radiographic abnormalities including small size of heart, cranial lobar pulmonary artery, caudal vena cava or liver, attributed to hypovolaemia. Megaoesophagus is occasionally described. Atrophy of the adrenal glands can lead to ultrasonographically measurable reduction in the size of the adrenal glands, although this is largely dependent on the use of high quality equipment and operator experience.

Electrocardiographic abnormalities reflect the effect of hyperkalaemia on cardiac function and include spiked T-waves, a shortened Q-T interval, prolongation of the QRS complex, reduction or complete absence of P-waves and bradycardia. In severe cases, ventricular asystole or ventricular fibrillation may be recognised. Although loosely correlated with circulating potassium concentrations, serum measurements are more accurate for assessing severity of hyperkalaemia.

The most common biochemical abnormality (> 90% of cases) is hyperkalaemia and hyponatraemia resulting in a sodium:potassium ratio of less than 1:23. Hypochloraemia is also common. These electrolyte abnormalities are usually accompanied by azotaemia, which can be severe, acidosis and, less commonly, mild hypercalcaemia. Hypoalbuminaemia is frequently seen, and there may be hypocholesterolaemia and mild hypoglycaemia. Mild non-specific increases in the liver enzymes can also occur probably due to circulatory collapse and hypoxic hepatocellular damage. However, these are of no particular diagnostic value. Of more importance is the possibility of Addison’s disease as a potential differential of both hypoglycaemia and hypercalcaemia.

Hyperkalaemia is one of the hallmarks of hypoadrenocorticism and can be one of the most clinically significant abnormalities. Circulating potassium concentrations greater than approximately 7.5-8 mmol/L may be associated with cardiac arrhythmias and further increases can become fatal. Hyperkalaemia can occur in other disorders including renal disease, severe, gastrointestinal disease, in dogs with chylothorax and during pregnancy.
Extremely low sodium:potassium ratios (< 15) are more commonly associated with hypoadrenocorticism than with other disorders. Atypical cases initially have reference range circulating electrolyte concentrations.

Haematological abnormalities include lymphocytosis and eosinophilia. Even without obvious abnormalities, maintenance of reference range eosinophil and lymphocyte numbers should alert the clinician to the possibility of hypoadrenocorticism as they are unusual in a severely ill animal (in which lymphopenia and eosinopenia are both more typical findings). Hypoadrenocorticism is frequently associated with mild normocytic normochromic anaemia, presumably as a consequence of chronic hypocortisolaemia. If gastrointestinal haemorrhage has occurred then a corresponding regenerative anaemia may be present.

Confirmation of the diagnosis of hypoadrenocorticism has traditionally required the demonstration of a minimal cortisol response to exogenous ACTH administration. A number of protocols for the ACTH stimulation test have been recommended but intravenous administration of synthetic ACTH (tetracosactrin) appears to be most widely used. Cortisol determinations are usually performed immediately prior to and between 30 minutes and two hours afterwards (usually one hour). The main potential complicating factor in interpretation of test results is iatrogenic adrenal suppression, usually due to prior glucocorticoid/progestagen therapy. This can usually be ruled out based on the patient history, the clinical presentation and additional test results. A further complicating factor is diagnosing Addison’s disease by depicting hypocortisolaemia while ignoring the role of aldosterone. As a consequence in most dogs impaired aldosterone production is not truly demonstrated and difficulties arise in accurately differentiating secondary hypoadrenocorticism from primary atypical cases or primary cases where previous treatment has masked the electrolyte abnormalities. Although ACTH plays only a minor role in regulating aldosterone secretion in the healthy dog, aldosterone measurement before and after administration of a pharmacological dose can be helpful diagnostically. Resting circulating aldosterone concentrations are reduced in primary hypoadrenocorticism and typically show little or no increase in concentrations following ACTH administration. Measurement of aldosterone concentrations may also be valuable if glucocorticoids, other than dexamethasone, have already been used. Endogenous ACTH measurement may also help differentiate primary from secondary disease providing glucocorticoid therapy has not yet been instituted. Endogenous ACTH is highly labile and strict sample handling precautions must be observed to prevent in vitro degradation following sample collection. Measurement of the cortisol-to-ACTH and the aldosterone-to-renin ratios may also be helpful and obviates the need to perform a dynamic adrenal function test.

Most glucocorticoid preparations cross-react with the widely used commercial cortisol assays and cause artefactually increased cortisol results. The exception to this is dexamethasone, which therefore can be used as emergency treatment in an acute hypoadrenocorticotoid crisis whilst the ACTH stimulation test is being performed.
Acute and chronic treatment

Addison’s disease is usually a true medical emergency, and rapid identification and treatment is required. Treatment of acute hypoadrenocorticism is primarily directed at
- Restoring circulating blood volume
- Correcting electrolyte and acid-base abnormalities
- Glucocorticoid supplementation.

The emergency treatment is summarised in Table 1.

Rapid blood volume replacement with intravenous fluid therapy is the single most important component of treatment. Judicious use of fluids is required in severely hyponatraemic animals in order to avoid neurological complications. Fluid therapy can be withdrawn when the dog is eating well, rehydrated, urine production has returned to normal, and the electrolyte abnormalities and azotemia are corrected.

Considerable improvement of the electrolyte abnormalities usually occurs once fluid therapy has been instituted without the need for specific mineralocorticoid replacement. However, administration of glucocorticoids with mineralocorticoid activity certainly decreases the need for treatment of hyperkalaemia by other methods and leads to a more rapid recovery of the animal than when glucocorticoids alone are used. The drug of choice is hydrocortisone sodium succinate/phosphate.

The clinical response to emergency therapy in a dog presenting in an acute hypoadrenal crisis is usually dramatic and long-term oral therapy with mineralocorticoid and glucocorticoid supplementation should be started as soon as tolerated.

Mineralocorticoid therapy using oral fludrocortisone acetate should be started at 0.015 mg/kg/day. Monitoring of electrolytes should be performed weekly initially and the dosage adjusted accordingly. Most dogs can be successfully treated on once daily therapy but some will require twice daily treatment to maintain electrolyte concentrations within the reference ranges. Fludrocortisone possesses a small degree of glucocorticoid activity and therefore also assists in weaning affected dogs off prednisolone therapy. The dosage of fludrocortisone increases with time for reasons that are yet unclear.

An alternative method of providing mineralocorticoid replacement is the use of desoxycorticosterone pivalate (DOCP). This preparation is administered at a dose of approximately 2 mg/kg by intramuscular injection and provides mineralocorticoid activity for an average of 25 days. As with oral supplementation, monitoring is based on blood electrolyte measurements. This preparation is not commercially available worldwide.

Oral glucocorticoid therapy should also start as soon as the patient has been stabilised and is not vomiting. Prednisolone is an appropriate drug to use, being widely available and inexpensive. Initial therapy at 0.5 mg/kg once daily should be used, but this can usually be reduced fairly quickly. Adjustments in the dose should be based on clinical response and the presence of side
effects to the drug. In many dogs the prednisolone therapy can eventually be stopped altogether except at times of stress such as the development of other illness, kennelling etc. However, in others a low maintenance dose, often approximately 0.2 mg/kg/day will be permanently required. Oral glucocorticoid therapy is the sole drug used to treat secondary and atypical cases. However, care should be taken with atypical cases as mineralocorticoid supplementation may be required with time.

References


### Intravenous fluids

<table>
<thead>
<tr>
<th>Ideally:</th>
<th>0.9% Saline 20-40 ml/kg/hour for first 1-2 hours (up to 60-80 ml/kg/hr if necessary)</th>
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<tr>
<td>Alternative:</td>
<td>Glucose if hypoglycaemic</td>
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### Glucocorticoid preparations

<table>
<thead>
<tr>
<th>Ideally:</th>
<th>Hydrocortisone sodium succinate/phosphate 0.5 - 0.625 mg/kg/hour as an intravenous infusion</th>
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<tr>
<td>Alternative:</td>
<td>Dexamethasone 0.5-4.0 mg/kg as an intravenous bolus. Can be repeated after 2-6 hours</td>
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### Treatment of unresponsive hyperkalaemia

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<tr>
<th>Or</th>
<th>10% glucose solution 4-10 ml/kg intravenously over 30-60 mins</th>
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<tr>
<td>Or</td>
<td>Sodium bicarbonate 1-2 mmol/kg intravenously over 5-15 mins</td>
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<tr>
<td>Or</td>
<td>10% Ca gluconate 0.5-1.0 ml/kg intravenously slowly over 10-20 mins. (Continuous ECG monitoring required)</td>
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<tr>
<td>Or</td>
<td>Regular (crystalline) insulin 0.25 – 0.5 IU/kg intravenously. For each unit of insulin supplement with 20 ml of 10% glucose, with half as a bolus and half as an intravenous infusion over 6 – 8 hours.</td>
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**Table 1.** Initial emergency therapy for the dog with acute hypoadrenocortical crisis.