Diagnosis and treatment of canine hypoadrenocorticism

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Canine hypoadrenocorticism (Addison's disease), the 'great pretender' of internal medicine, is a disease that should be frequently considered as a differential diagnosis of several clinical presentations, albeit it is less commonly the actual cause of the clinical signs. Hypoadrenocorticism cannot be diagnosed on clinical signs alone and further investigations are always required. There have been some interesting new ideas about diagnostic options for this condition and new treatment options are available for both acute and chronic therapy of the condition in dogs. It is therefore pertinent to review the causes, diagnosis and treatment of hypoadrenocorticism in dogs.

HYPOADRENOCORTICISM is the term used to describe the failure of glucocorticoid (primarily cortisol) and mineralocorticoid (aldosterone) secretion by the adrenal cortex. Cortisol has many roles within the body, all of which tend to protect the body from metabolic stresses (such as starvation and inflammation). It is important in the maintenance of the normal gastrointestinal barrier, as a counterbalance to insulin, and has a role in the regulation of calcium balance. Aldosterone has a more specific role as a long-term regulator of plasma volume, which it achieves by controlling the retention of sodium (and excretion of potassium) by the body.

Causes of hypoadrenocorticism

Hypoadrenocorticism may be primary (due to adrenal gland disease) or secondary (due to pituitary problems). The most common form of primary hypoadrenocorticism is an immune-mediated destruction of the adrenal cortex. Autoantibodies, which may be markers of this immune-mediated process, have been identified in some, although not all, affected dogs (Boag and others 2015). The condition is more common in certain breeds, such as the Portuguese water dog, standard poodle, bearded collie, cairn terrier and cocker spaniel (Hanson and others 2016). Genetic markers that may predispose dogs to this condition have been suggested but more research is required.

Primary hypoadrenocorticism may also be seen with the use of adrenal-suppressive drugs, such as trilostane and mitotane. Other causes, such as neoplastic infiltration of the adrenal gland and granulomatous inflammation, have been documented; however, these are regarded as rare.

Less commonly, cases of primary hypoadrenocorticism may be seen with isolated glucocorticoid deficiency (hypocortisolism) or, very rarely, isolated hypoaldosteronism. Isolated primary hypocortisolism is sometimes referred to as 'atypical hypoadrenocorticism'. However, this term is also sometimes (incorrectly) applied to dogs that have typical primary hypoadrenocorticism but have normal electrolyte concentrations (see Box 1). The underlying pathogenesis has not been determined.

Secondary hypoadrenocorticism usually results from the sudden cessation of long-term steroid therapy that has been sufficient to cause suppression of adrenocorticotrophic hormone (ACTH) secretion by the pituitary gland. This suppression leads to atrophy of the adrenal cortex, such that when the exogenous steroids are withdrawn, an acute secondary hypocortisolism results (aldosterone production is nearly always maintained). Spontaneous pituitary failure of ACTH secretion is very rare but can be detected in some dogs with congenital hypopituitarism and pituitary haemorrhage.

Diagnosis

Clinical signs

Hypoadrenocorticism is associated with a spectrum of clinical signs, which may be severe or mild, consistent or fluctuating, acute or chronic (Table 1, Fig 1). This can make diagnosis of the condition challenging and it is therefore important to include hypoadrenocorticism as a potential differential diagnosis of numerous non-specific signs.

Clinical signs may be vague, such as lethargy, weight loss and inappetence/anorexia, or patients may be presented with a history that appears to be more specific; for example, chronic gastrointestinal signs such as abdominal pain, melaena or haematochezia, or neurological abnormalities (episodic collapse) that can be confused with other conditions (Table 2). These signs often respond to symptomatic treatment but will then recur, although this may take a few weeks. Patients can present following acute collapse with no previously noted clinical signs. Occasionally, sudden deterioration can be a sequel to a stressful event, such as kennelling. It can be difficult to distinguish hypoadrenocorticism from other diseases based on clinical examination alone; however, there are a few findings which may increase the clinician's suspicion of disease:

- Bradycardia or a normal heart rate despite findings of clinical dehydration;
- More severe hypovolaemia dehydration than would be expected from the fluid losses (vomiting and diarrhoea) reported;
- Poor body condition despite only a recent history of disease.

Physical examination findings can be as variable as the history and, in some more chronic cases, there may be no significant findings on examination. Although hypoadrenocorticism may be a frequent differential diagnosis, it cannot be diagnosed solely on clinical examination and it

Box 1: What is atypical hypoadrenocorticism?

A few cases of hypoadrenocorticism (probably fewer than 10 per cent) have normal electrolyte concentrations – this has previously been referred to as 'atypical hypoadrenocorticism'; however, recent papers have suggested that this is an inappropriate use of this term (Baumstark and others 2014b) and, instead, these cases should be viewed as true primary hypoadrenocorticism. Regardless of what it is called, this situation poses a diagnostic challenge and the advice of a specialist endocrinologist should be sought in all such cases.

In these cases, it is useful to measure post-adrenocorticotrophic hormone (ACTH) aldosterone concentrations to distinguish between dogs with a mineralocorticoid deficiency that has not produced electrolyte abnormalities at the time of examination (due to compensatory mechanisms that are still unclear) and an isolated primary hypocortisolism (that will only need prednisolone treatment). Isolated primary hypocortisolism (ie, dogs with low cortisol and normal aldosterone, suggesting a selective destruction of the zona fasiculata of the adrenal gland) is now regarded by many authorities as being true 'atypical hypoadrenocorticism'. As this may also result from a pituitary problem rather than adrenal disease, measurement of endogenous ACTH may be useful and dogs with a low ACTH concentration (assuming that concurrent use of steroids is excluded) should be considered candidates for pituitary imaging.

Cases with true primary hypoadrenocorticism (ie, low cortisol and low aldosterone but normal electrolytes) can be successfully treated with just prednisolone provided their electrolytes are monitored. In such cases, clients should be counselled that electrolyte derangements may occur at any time, precipitating an acute crisis. Another strategy is to start desoxycortone pivalate (DOCP) in these cases (often at a lower starting dose). There have been no studies that report the long-term outcome of either of these management strategies.

Isolated mineralocorticoid deficiency has been reported in single case reports (either associated with increased renin concentrations, suggesting a failure of aldosterone synthesis, or decreased renin concentrations, suggesting a failure of aldosterone stimulation).

is sensible to carry out more routine diagnostic investigations before considering confirmatory tests.

Routine laboratory tests

Haematology

The 'classical' haematological finding in dogs that have hypoadrenocorticism is a reverse stress leucogram (low to normal neutrophil numbers with an increase in lymphocytes and eosinophils). These findings should prompt the clinician to consider hypoadrenocorticism, although it is not present in most cases. An absolute lymphocytosis is seen in only 10 per cent of cases, whereas eosinophilia is seen in 20 per cent (Scott-Moncrieff 2015).

Table 1: Summary of the common, and not so common, clinical signs and laboratory findings associated with hypoadrenocorticism*

	Clinical signs	Laboratory findings
Common	Lethargy Anorexia Vomiting Poor peripheral pulses Weakness Collapse Shock	Hypoalbuminaemia Hypercalcaemia Non-regenerative anaemia No stress leucogram Hyponatraemia Hyperkalaemia Azotaemia Minimally concentrated urine (USG <1.030)
Uncommon	Diarrhoea Gastrointestinal haemorrhage Weight loss Abdominal pain Polyuria/polydipsia Muscle cramps Regurgitation Seizures	Hypoglycaemia Neutropenia Lymphocytosis Eosinophilia Hypocholesterolaemia Isothenuric urine (USG <1.015)

* Adapted from Scott-Moncrieff 2015
USG Urine specific gravity

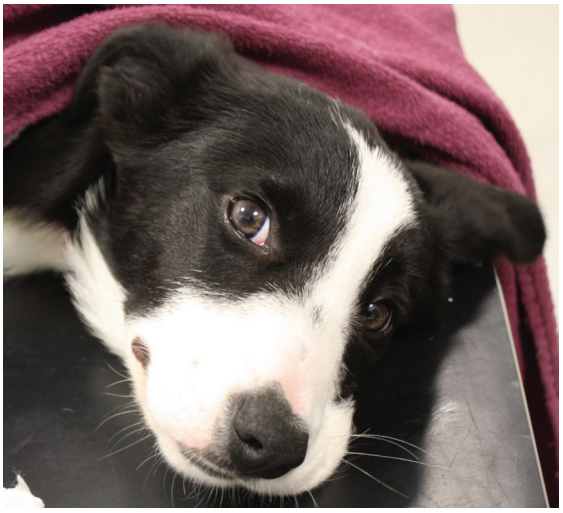


Fig 1: Hypoadrenocorticism is a disease of young to middle-aged dogs: this 12-week-old puppy was presented with a history of acute collapse and was subsequently diagnosed with hypoadrenocorticism

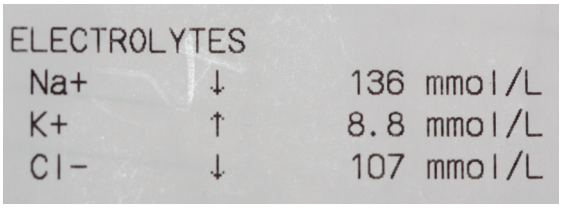


Fig 2: Typical example of electrolyte changes. Hyponatraemia, hyperkalaemia and hypochloraemia are all common in hypoadrenocorticism (reference intervals are Na = 144 to 160 mmol/l; K = 3.5 to 5.8 mmol/l; Cl = 109 to 122 mmol/l). This example is from the puppy in Fig 1

A more sensitive finding is the absence of a stress leucogram in an ill patient (which is the case in up to 92 per cent of patients with hypoadrenocorticism). There are descriptions of the use of ratios of white blood cell parameters as sensitive diagnostic aids; these are useful to exclude the diagnosis of hypoadrenocorticism but none is sufficiently specific to confirm the diagnosis (Seth and others 2011, Zeugswetter and Schwendenwein 2014).

Another common finding is a non-regenerative anaemia (normocytic normochromic), which can be seen in up to 25 per cent of patients. This is due to reduced red blood cell production but may be compounded by gastrointestinal blood losses. Less commonly, a patient may present with an increased packed cell volume due to hypovolaemia and haemoconcentration. As with clinical signs, haematological findings can be completely normal.

Biochemistry

Electrolyte abnormalities (hyperkalaemia and/or hyponatraemia) are the most commonly noted biochemical abnormality in hypoadrenocorticism (Fig 2). Historically, sodium:potassium ratios (<27:1) were used to assist in the diagnosis of hypoadrenocorticism. However, some cases can be missed when using sodium:potassium ratios and there are several other causes of low sodium:potassium ratios, including gastrointestinal disease, renal disease and a variety of other conditions. For this reason, it is preferable to consider the sodium and potassium concentrations separately, with respect to their individual reference ranges (Nielsen and others 2008). Hypochloraemia and hyperphosphataemia may also be seen. Electrolyte abnormalities are due to mineralocorticoid (aldosterone) deficiency and are therefore not found in dogs with 'atypical' hypoadrenocorticism (see Box 1). Electrolyte abnor-

Table 2: Similarities between the clinical signs and clinical pathology changes seen in hypoadrenocorticism* and intestinal, endocrine, kidney and hepatic diseases

	Clinical signs	Laboratory findings
Intestinal disease (eg, irritable bowel disease, PLE, parvovirus)	Vomiting Diarrhoea Gastrointestinal haemorrhage (parvo) Weight loss Lethargy	Hypoalbuminaemia (PLE) Anaemia Hypocholesterolaemia Leucopenia (parvo)
Kidney disease (eg, AKI, CKD)	Anorexia Dehydration Weight loss (CKD) Polyuria/polydipsia (CKD)	Azotaemia Hyperkalaemia (AKI) Hyponatraemia (polyuric AKI) Anaemia (CKD) Hypercalcaemia (some CKD) USG <1.030 (CKD)
Endocrine disease (eg, insulinoma)	Weakness Episodic collapse Seizures	Hypoglycaemia Increased liver enzymes
Hepatic diseases (eg, chronic hepatopathy)	Anorexia Vomiting Diarrhoea Weight loss Lethargy Polyuria/polydipsia	Increased liver enzymes Hypoglycaemia Hypoalbuminaemia Hypocholesterolaemia

* See Table 1
AKI Acute kidney injury, CKD Chronic kidney disease, PLE Protein losing enteropathy, USG Urine specific gravity

malities can correct rapidly following initiation of fluid therapy.

The second most common finding on biochemistry is azotaemia. This is predominantly prerenal in origin; however, intestinal blood losses can lead to proportionally higher increases in urea compared to creatinine. Dehydration due to water loss from the kidneys, secondary to aldosterone deficiency, leads to a prerenal azotaemia. In some cases, it may worsen pre-existing renal disease. Azotaemia in patients with hypoadrenocorticism normally corrects within 48 hours of intravenous fluid therapy.

Other findings on biochemistry include hypoglycaemia, hypoalbuminaemia, hypercalcaemia and hypocholesterolaemia. The hypoglycaemia is thought to be due to the reduction in the insulin antagonism of cortisol. The cause of the hypoalbuminaemia is probably multifactorial with a reduction in appetite, gastrointestinal malfunction and haemorrhage all being involved. Hypocholesterolaemia is linked to a reduction in fat absorption, which is known to occur. The cause of the hypercalcaemia remains unknown.

Urinalysis

Although patients with hypoadrenocorticism often present with hypovolaemia and prerenal azotaemia, their urine specific gravity rarely exceeds 1.025. This can make differentiation from azotaemia due to renal insufficiency (eg, due to chronic kidney disease [CKD]) difficult, but patients with CKD rarely present with hyperkalaemia or hyponatraemia. Acute kidney injury (AKI), however, can cause similar electrolyte changes to hypoadrenocorticism and therefore clinicians can often be faced with the challenge of distinguishing AKI from hypoadrenocorticism. Frequently, patients with AKI are anuric or have reduced renal output. In addition, patients with AKI usually have a stress leucogram (increase in neutrophils) and are rarely anaemic. If initial laboratory tests still fail to distinguish AKI patients from patients with hypoadrenocorticism, then response to treatment and clinical progression can be monitored. Diagnostic tests should always be performed before starting fluid therapy.

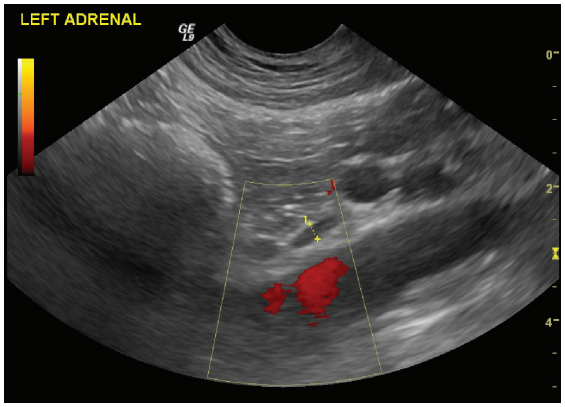


Fig 3: Adrenal ultrasound in a 50 kg great dane cross with hypoadrenocorticism. The left adrenal gland measures 2.5 mm across

Diagnostic imaging

Radiography

Abdominal radiography is not used in the diagnosis of hypoadrenocorticism, although it is sometimes indicated to investigate differential diagnoses such as obstructive gastrointestinal disease. Thoracic radiographs can be useful as the presence of microcardia and reduction in pulmonary vessel diameter can be suggestive of hypovolaemia. Rarely, megaoesophagus is seen as an anecdotal complication of hypoadrenocorticism (Lifton and others 1996). However, we do not routinely radiograph patients in which hypoadrenocorticism is suspected.

Abdominal ultrasonography

Examination by ultrasound is indicated to rule out other diseases, such as kidney disease, pancreatitis, gastrointestinal disease and liver disease, which can all present with similar clinical signs. Ultrasonography also allows assessment of adrenal size when performed by a skilled clinician. Bilateral reduction in adrenal gland size and, in particular, a left adrenal gland thickness less than 3.2 mm is highly suggestive of hypoadrenocorticism, although this is not a sensitive test (Fig 3). Previous treatment with steroids can also cause a reduction in adrenal thickness and so reduces the specificity of this test when the clinical history is unknown or includes steroid administration.

Echocardiography

Echocardiography may be performed if there are concerns about cardiac function, particularly in bradycardic patients. A basic echocardiogram may subjectively indicate volume underload and demonstrate poor systolic function. It is important that the latter finding is not over-interpreted (eg, as dilated cardiomyopathy). The changes seen in hypoadrenocorticism would be expected to improve with treatment.

Electrocardiography

Patients may be presented with bradycardia and therefore electrocardiography (ECG) may be performed. Conduction abnormalities arise because of increases in potassium and reductions in sodium concentrations, making it more difficult to achieve threshold pacemaker potential. Changes seen range from widened QRS complexes to ectopic ventricular beats, and from low amplitude P waves to a complete absence of P waves. Spiked T waves may also be seen. It is important to note that the ECG gives no reliable indication of the plasma potassium levels. This is because concurrent hypercalcaemia can be cardioprotective, and acidosis can cause increases in extracellular potassium levels.

Box 2: Dealing with the patient that has received steroids

Sometimes clinicians are presented with a case of suspected hypoadrenocorticism that has been treated with one dose of dexamethasone. In this situation, patients should be supported with symptomatic treatment (such as fluid therapy) and an adrenocorticotrophic hormone (ACTH) test should be performed 36 hours later. Hypothalamic–pituitary–adrenal (HPA) axis suppression should have resolved by this time but results should still be interpreted with caution. Longer courses of steroids will have more effects that will last longer. Even topical steroid-containing preparations have the potential to cause HPA axis suppression. Studies have shown that 35 days of prednisolone at 0.5 mg/kg every 12 hours will suppress the ACTH stimulation test for a further month after cessation of the steroid and for the first two weeks this response could easily be confused with that of hypoadrenocorticism. A single dose of a long-acting methylprednisolone injection will affect ACTH stimulation tests for up to five weeks.

In addition, if steroids have been given very recently to any animal then it is worth remembering that some (eg, hydrocortisone and prednisolone) cross-react in the cortisol assay and therefore give false increases. For this reason, prednisolone should not be given during the 24 hours before an ACTH stimulation test.

Confirming the diagnosis

It is not appropriate for hypoadrenocorticism to be diagnosed on either electrolyte abnormalities or on response to steroids. There are many other conditions that can resemble hypoadrenocorticism (see Table 2). The long-term costs of management require that the diagnosis is properly established first. In addition, once steroid therapy has been initiated, it can be very difficult to obtain a diagnosis of hypoadrenocorticism due to cross reactivity of several steroid formulations with cortisol assays and the suppressive effect of many steroids on the hypothalamic–pituitary–adrenal axis. Steroid therapy should be withheld until pre- and post-ACTH serum blood samples have been obtained.

Steroid therapy is not required immediately for the emergency treatment of any collapsed patient and therefore an ACTH stimulation test can always be performed before starting steroid therapy. Patients that genuinely have hypoadrenocorticism can be stabilised in the short term with fluid therapy and management of electrolyte levels. If an ACTH stimulation test is not available, and steroids are required in the short term (eg, over a weekend), then dexamethasone does not interfere with the cortisol assay; however, it will have to be withdrawn before an ACTH stimulation test can be performed. In such circumstances it would be sensible to store freshly frozen EDTA and heparin plasma for ACTH and cortisol measurements at a later time.

Basal cortisol

Basal cortisol can be used as a screening test to rule out hypoadrenocorticism and is particularly useful in patients with a more chronic history or general signs such as intermittent weight loss or vomiting. Basal cortisol concentrations greater than 55 nmol/l are reliable for excluding a diagnosis of hypoadrenocorticism, meaning a full ACTH stimulation test is not required. It is important to appreciate that patients with many other diseases (or normal patients) can have basal cortisol levels of less than 55 nmol/l. Basal cortisol concentrations less than 5.5 nmol/l measured on a properly validated assay are a specific test for hypoadrenocorticism but only providing previous steroid therapy is excluded (Gold and others 2016). However, only some assays are validated at this low concentration and the sensitivity was only 81.6 per cent in the Gold and others study at this level.

Although basal cortisol may seem like a good 'rule out' test, it should not be used in patients where the clinical suspicion of hypoadrenocorticism is high or in patients that are not stable on presentation. Instead, to avoid delays in definitive therapy and thereby to minimise cost to clients, a full ACTH stimulation test should be performed.

ACTH stimulation test

This test of adrenal reserve is the gold standard for the diagnosis of hypoadrenocorticism, with a high sensitivity and specificity. To perform this test, a basal serum sample is taken before 5 µg/kg of ACTH is given intravenously (preferably) or intramuscularly. Post-ACTH blood samples are then taken 30 to 90 minutes later.

It is recommended that samples for cortisol measurement be sent to a reputable laboratory with known reliable sensitivity, specificity and repeatability for this assay as there can be considerable variation in cortisol results between laboratories. Hypoadrenocorticism is diagnosed if there is inadequate cortisol release following ACTH administration.

As mentioned above, this test should be performed before initiating steroid therapy. Box 2 explains what to do when cases are presented having already received steroid therapy.

Cortisol:ACTH ratio

Measuring the cortisol:ACTH ratio may be useful in the diagnosis of primary hypoadrenocorticism as this would be expected to be high when compared to healthy dogs and when compared to dogs with non-adrenal illness; however, some overlap may be seen (Javadi and others 2006, Lathan and others 2014, Boretti and others 2015). Currently, the costs and practical considerations of measuring endogenous ACTH make this approach relatively expensive when compared to an ACTH stimulation test and larger studies are required.

Aldosterone

In typical hypoadrenocorticism, there is reduced production of both cortisol and aldosterone from the adrenal cortex. Aldosterone can be measured from serum samples, similar to the measurement of cortisol. However, this test should not be run routinely in the diagnosis of hypoadrenocorticism as it is relatively expensive compared to the measurement of cortisol. Nonetheless, the measurement of aldosterone is indicated in cases of 'atypical' hypoadrenocorticism. Aldosterone is also less likely to be affected by exogenous glucocorticoids but how useful this might be in distinguishing iatrogenic hypercortisolism from primary hypoadrenocorticism has not been investigated.

Acute management

In the event of an adrenal crisis, the main goals of emergency management are to restore fluid volume, correct electrolyte abnormalities and provide a rapidly acting source of glucocorticoid support. Long-term mineralocorticoid support (eg, desoxycortone pivalate [DOCP], fludrocortisone) is not indicated at this point, and may even be harmful, until these objectives have been met.

Box 3 summarises the treatments that we use for acute management of hypoadrenocorticism.

Fluid therapy

The clinical status and degree of dehydration of the patient will dictate both the rate and volume of fluids administered. We recommend a 'goal-directed' approach to fluid resuscitation but it is possible that shock rates of crystalloids (~80 ml/kg/hour) may be required for the first one to two hours. Usually 0.9 per cent sodium chloride is

the fluid of choice as most affected dogs are hyponatraemic; however, balanced potassium-containing fluids (eg, Hartmann's solution) are not necessarily contraindicated as the dilutional effects of fluid therapy will still outweigh the small additive effect of potassium. Particular care should be taken in severely hyponatraemic patients (see Box 4) with a sodium concentration less than 120 mmol/l. In patients presenting with concurrent hypoglycaemia then fluids should also be supplemented with dextrose.

Glucocorticoid replacement

The glucocorticoids that are the most commonly cited in the management of acute Addisonian crises are dexamethasone, prednisolone and hydrocortisone. Hydrocortisone has the advantage of also providing short-acting mineralocorticoid support and is therefore likely to provide rapid correction of hyperkalaemia (Gunn and others 2016). An infusion of hydrocortisone sodium succinate at a dose rate of 0.5 mg/kg/hour is likely to confer sufficient glucocorticoid and mineralocorticoid support for the treatment of adrenal insufficiency. Hydrocortisone is not only clinically effective, but is also inexpensive and has a long shelf-life. It should, however, be emphasised that close monitoring of electrolytes is necessary, especially in severely hyponatraemic patients as excessively rapid correction of sodium concentrations may occur (see Box 4) (Gunn and others 2016).

Dexamethasone by contrast lacks mineralocorticoid activity but will provide a source of rapidly absorbable glucocorticoid. A wide range of doses is currently reported in the literature ranging from near-physiological doses of ~0.05 mg/kg up to significantly higher doses of 4 mg/kg (Kintzer and Peterson 2014, Scott-Moncrieff 2015). There is no evidence to suggest that extremely high doses of dexamethasone are warranted and indeed it is possible that such doses could contribute to gastrointestinal haemorrhage. We recommend a conservative bolus dose of 0.1 to 0.2 mg/kg intravenous dexamethasone (as dexamethasone disodium phosphate) given once daily.

Ancillary management of hyperkalaemia

Ancillary management of hyperkalaemia in cases of hypoadrenocorticism is rarely necessary (especially when hydrocortisone is being used). However, for dogs presenting with associated cardiac complications (such as severe bradycardia of less than 40 beats per minute) then 10 per cent calcium gluconate may be necessary (0.5 to 1.5 ml/kg given as a slow intravenous infusion). While this will not lower serum potassium concentrations, it has the potential to reduce the excitability of cardiomyocytes. Neutral insulin and dextrose is commonly described in the management of hyperkalaemia (insulin encourages movement of potassium into cells, thus lowering the extracellular potassium concentration). However, while this approach is often successfully employed to manage hyperkalaemic complications of urinary obstruction, caution is advised when considering it in dogs with hypoadrenocorticism since hypoglycaemic complications are more likely to be encountered.

Patient monitoring

The intensity of monitoring is dictated by both the degree of patient compromise and, at least in part, by practice facilities and owner finances. Physiological parameters such as temperature, pulse rate and quality, respiration rate and non-invasive blood pressure measurement should be monitored every one to two hours in severely compromised patients. Ideally, electrolytes should be rechecked every two to six hours (dependent on the severity of the patient's hyperkalaemia/hyponatraemia). Continuous ECG monitoring is advisable; however, it should be noted that ECG changes do not always correlate with serum potassium concentrations (and should therefore not be used in lieu of direct electrolyte measurement).

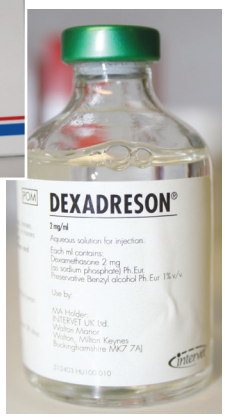
Chronic management

Once a dog has been stabilised (ie, is rehydrated, ambulatory and starting to eat voluntarily) then it is important to discuss the chronic management of hypoadrenocorticism with the dog owner. The lifelong nature of this treatment and the importance of not missing doses must be emphasised. It is also important to make sure that clients understand that it may take several visits and multiple monitoring blood tests to find the right doses of glucocorticoid and mineralocorticoid. The clinical targets for these cases should be ambitious – properly treated dogs should have a normal bodyweight, appetite, thirst and demean-

Box 3: Main treatments for hypoadrenocorticism and their starting doses

Acute management

A: 0.9 per cent saline
As calculated but often 80 ml/kg/hour for the first one to two hours, then reduce



B: Hydrocortisone sodium succinate
0.5 mg/kg/hour intravenously
OR: Dexamethasone disodium phosphate
0.1 to 0.2 mg/kg intravenously every 24 hours

The change from acute to chronic management should be made once the patient is clinically stable (ie, is rehydrated, ambulatory and starting to eat voluntarily)

Chronic management

C: Desoxycortone pivalate
1.5 to 2.2 mg/kg subcutaneously every 25 to 28 days then titrate to required dose

D: Prednisolone
0.1 to 0.2 mg/kg orally every 24 hours then titrate to required dose

Box 4: Overcorrection of hyponatraemia

While the focus in managing patients in acute adrenal crisis is often directed at resolving hyperkalaemia, it is imperative to also pay close attention to changes in sodium concentration. In patients with severe hyponatraemia (<120 mmol/l), too rapid a correction of sodium can lead to loss of the neuronal myelin sheath within the pons and other regions of the brain. This is known as osmotic demyelination syndrome (or central pontine myelinolysis) and can be associated with dramatic neurological signs, such as ataxia, postural deficits, dysphagia and decreased mentation. It should be noted that these signs often appear a couple of days after the initial acute presentation and treatment event.

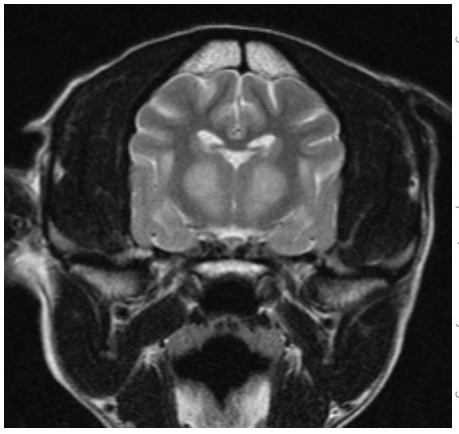


Image: Small Animal Hospital, University of Glasgow

T2 weighted image of a dog with osmotic demyelination syndrome associated with early injection of desoxycortone pivalate

Guidelines extrapolated from human medicine suggest sodium concentration should not increase by more than 12 mmol/l/day (or >0.5 mmol/l/hour). To prevent such complications, treatment with 0.9 per cent sodium chloride may not be appropriate in patients presenting with severe hyponatraemia, and consideration should be given to low sodium-containing fluids (eg, 0.45 per cent sodium chloride). Similarly, if hydrocortisone is being used, then a dose reduction (eg, to 0.3 mg/kg/hour) may be appropriate.

our without signs of glucocorticoid excess. Medications should be adjusted to achieve this and nothing less than this should be accepted. It is also desirable that treated dogs have normal concentrations of electrolytes but the consequences of mild abnormalities are not known.

The current doses of drugs that we use ourselves are summarised in Box 3.

Glucocorticoid supplementation

All dogs must receive daily glucocorticoid treatment titrated to effect based on clinical signs. The starting dose of prednisolone is 0.1 to 0.2 mg/kg every 24 hours for newly diagnosed cases. The final dose varies considerably between individual animals and while a good proportion of dogs will ultimately be stable at 0.05 to 0.1 mg/kg every 24 hours, some may be stable at even lower doses. For dogs requiring particularly small doses of glucocorticoid, cortisone acetate could be considered as an alternative.

Overdosing with glucocorticoids is common and it is important to check if dogs are showing any signs of polyuria/polydipsia, poor hair regrowth or increased bodyweight. In particular, poor hair regrowth at sites of venepuncture, in the absence of polyuria/polydipsia, can be seen in long-term mild overdosing and owners may not notice this.

Glucocorticoid deficiency causes lethargy (which can be severe), inappetence, weakness and gastrointestinal signs. Glucocorticoid dose adjustments should be made no more frequently than twice monthly and dose increments should be 25 to 50 per cent of the previous dose. At times of metabolic stress or illness, the glucocorticoid dose should be increased two- to four-fold. Even greater increases (such as 10-fold) may be used for short periods in dogs on low doses of glucocorticoid. Appetite, demeanour and blood pressure are the most useful parameters to assess the glucocorticoid requirement of such patients.

Mineralocorticoid supplementation

An authorised long-acting formulation of DOCP (Zycortal; Dechra Veterinary Products) was released on to the UK market in 2016. Shortly afterwards, in an unconnected move, the formulation of fludrocortisone authorised for medical use was sold from one company to another, resulting in a marked change in price. Most fludrocortisone-treated dogs in the UK have now made the transition to DOCP. However, fludrocortisone is available as a veterinary special (Summit Pharmaceuticals) and this may be useful for some patients but requires specific individual justification, according to the prescribing cascade. As there is mounting evidence that DOCP is superior in many respects to fludrocortisone, and as this is the authorised drug, DOCP should always be regarded as first choice for mineralocorticoid supplementation (Baumstark and others 2014a). Guidelines are available for transferring dogs from fludrocortisone (Ramsey and others 2016). If using fludrocortisone then it is important to be aware that some dogs stabilise better with twice daily doses (Roberts and others 2016).

The authorised initial dose of DOCP is 2.2 mg/kg given subcutaneously approximately every 25 days. However, many specialists use a starting dose of 1.5 mg/kg given subcutaneously every 28 days. This should only be administered once the patient is rehydrated. It is very important to make sure that the product is properly resuspended before drawing up the injection (and the syringe should continue to be gently rotated after drawing up the dose before injection to avoid precipitation in the needle and subsequent pain reaction on injection).

Longer intervals between doses (eg, 35 days) increase the risk of instability (but may be cheaper for the client). There is no evidence that DOCP has an extended duration of action but many dogs, if the dose is delayed, do not show electrolyte abnormalities for some time (Jaffey and others 2017). This is consistent with the long period between the onset of clinical signs and the development of electrolyte abnormalities seen before diagnosis in many cases.

Most dogs require adjustments to their initial dose and it is more likely that dogs will require a dose reduction than a dose increase if using a starting dose of 2.2 mg/kg. The decision to change the dose is made by assessing electrolytes and clinical signs (Fig 4). The aim is to keep potassium and sodium within their reference intervals throughout the dosing interval. To assess this, it is necessary to check at 10 (+/-3) and 28 (+/-3) days after injection after every dose until stable.

Monitoring electrolytes at 10 days after injection enables assessment of the peak effect of the dose, whereas the 28-day sample enables assessment of the duration of action of the dose. If the peak effect is too great (or too little) at 10 days after injection then the subsequent dose should be reduced (or increased). If potassium is below and/or sodium is above their respective reference ranges at 28 days then DOCP should not be administered and electrolytes should be checked every seven days until they are within their respective reference ranges and then DOCP administered (at a reduced dose of about 20 per cent less than the previous dose). If the dog still has electrolyte abnormalities consistent with hypoadrenocorticism at 28 days, then DOCP must be injected at a higher dose (or the interval shortened).

A dog can be regarded as being on the correct dose of DOCP when it is clinically well and has electrolytes within their respective reference ranges on days 10 and 28 after

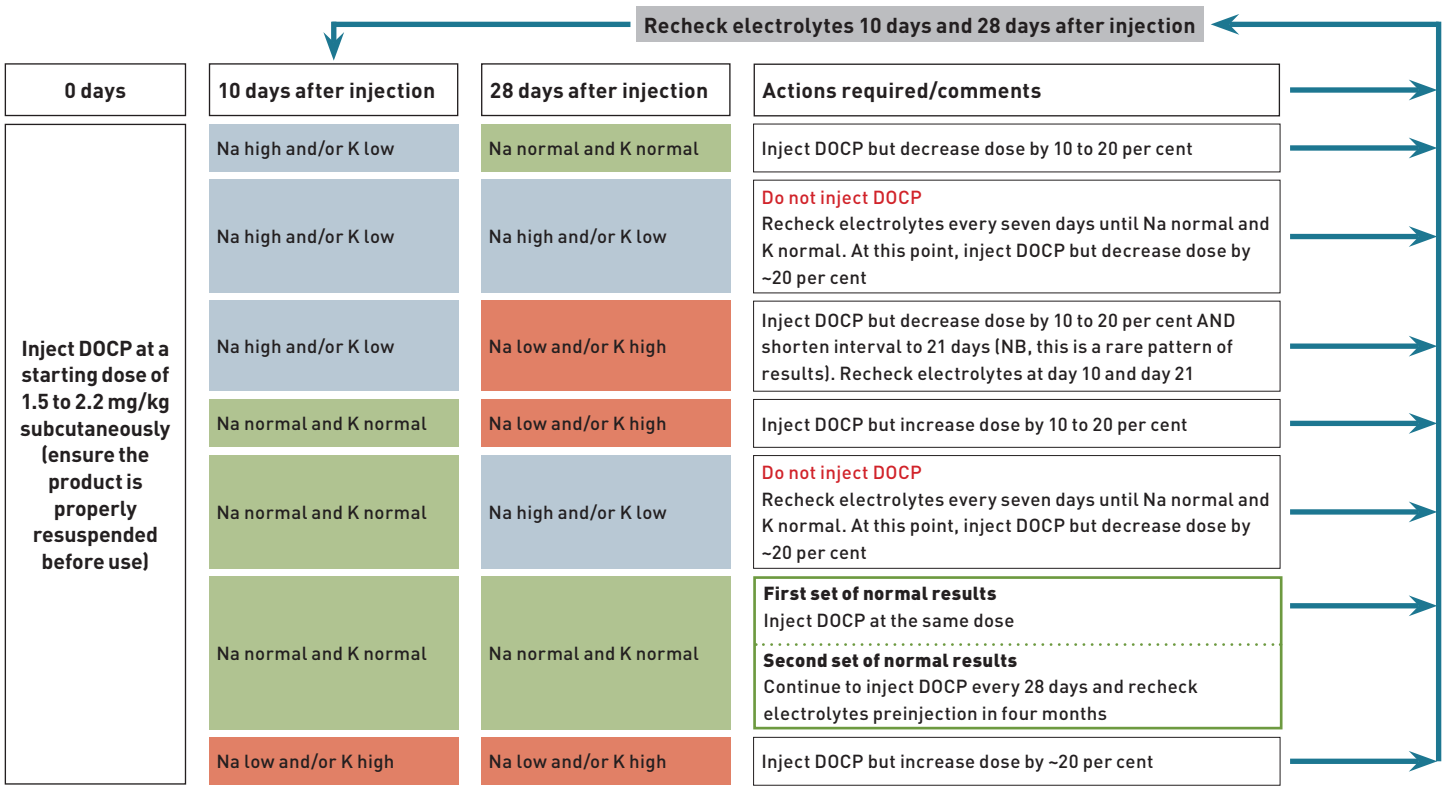


Fig 4: Adjustment of desoxycortone pivalate (DOCP) dose is based on a combination of clinical signs and electrolyte changes. Clinical signs are usually more important than electrolytes and these are covered in the text

injection for at least two consecutive treatment cycles using that same dose. Once the correct dose has been determined, dogs should be reassessed every four to six months at the time of (or just before) injection. Frequent monitoring of electrolytes is not necessary and, given the day-to-day variation in sodium and potassium concentrations, risks overinterpretation and excessive dose adjustments. Average stability is likely to be safer (and certainly cheaper) than constant re-titration.

Few side effects have been seen with DOCP but one that should be noted is that dogs may show polyuria/polydipsia from days 7 to 10 after injection. This is usually associated with a mild overdose of DOCP and a dose reduction at the next injection normally resolves this problem. It is important to distinguish this short-term side effect from the long-term polyuria/polydipsia seen with excessive doses of glucocorticoids.

It is also important to be aware that electrolyte measurements vary between laboratory machines and their reference ranges vary. Electrolytes may fluctuate day to day and any sample haemolysis or ageing can lead to artefactual changes in electrolytes. Therefore, very small or inconsistent changes may not be clinically significant. If in doubt it is entirely appropriate to repeat the measurement and/or give the same dose as previously.

Owners should be encouraged to keep their own records of doses administered (support materials are available from Dechra Veterinary Products and we encourage their use). In many cases the owners can be taught to give the injections themselves. Owners should be reminded regularly that should a dog become ill then additional glucocorticoids are rarely wrong, but veterinary advice should be sought as soon as possible.

Many UK practitioners are becoming very familiar with DOCP but our experience is still limited and it is important that experiences are shared and discussed with relevant specialists and the company that supplies the product.

Summary

Although lifelong treatment will be needed, dogs with hypoadrenocorticism can be managed successfully and lead mainly normal lives. Many dogs can be managed in general practice, with specialist help required for only some individual cases.

Declaration of conflict of interest

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Self-assessment quizzes

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Self assessment: Diagnosis and treatment of canine hypoadrenocorticism

1. What are the two most common clinical signs of hypoadrenocorticism?
   a. Abdominal pain and seizures
   b. Diarrhoea and weight loss
   c. Polyuria and polydipsia
   d. Regurgitation and melaena
   e. Vomiting and anorexia

2. What are the most common changes seen in biochemistry and haematology in hypoadrenocorticism?
   a. Hypercalcaemia and lymphocytosis
   b. Hyperkalaemia and anaemia
   c. Hypernatraemia and neutropenia
   d. Hypoalbuminaemia and eosinopenia
   e. Hypoglycaemia and neutrophilia

3. If synthetic adrenocorticotrophic hormone (ACTH) was not available then which would be the next best test for diagnosing hypoadrenocorticism?
   a. Basal aldosterone
   b. Basal cortisol
   c. Cortisol: ACTH ratio
   d. Neutrophil:lymphocyte ratio
   e. Sodium:potassium ratio

4. When on night duty, you are strongly suspicious that a collapsed three-year-old female standard poodle recently admitted with melaena and hyperkalaemia and hyponatraemia has hypoadrenocorticism. A senior colleague suggests you should immediately give a 'shock' dose of 0.5 mg/kg of dexamethasone intravenously and do the ACTH stimulation test in the morning if the dog is no better. Which of the following reasons should you give for not following this advice?

   I. Dexamethasone may suppress the ACTH stimulation test, thereby leading to a false positive diagnosis of hypoadrenocorticism in dogs that do not have the condition
   II. High doses of glucocorticoids may increase the risk of gastrointestinal haemorrhage
   III. Dexamethasone does not provide any mineralocorticoid support
   IV. Such low doses of dexamethasone may not be sufficient to suppress the immune-mediated adrenalitis
   V. Dexamethasone cross reacts in the cortisol assay so next morning the cortisol will be artefactually increased

   a. All of the above reasons
   b. Reasons I, II and III
   c. Reasons I and IV
   d. Reasons II and V
   e. Reasons II, III and V

5. A client wishes to reduce the cost of managing their dog with hypoadrenocorticism using desoxycortone pivalate (DOCP) (currently at 1.8 mg/kg every 28 days) and prednisolone (currently 0.05 mg/kg). What is likely to be the safest and most effective way of doing this?
   a. Decrease the dose of DOCP to 1.0 mg/kg subcutaneously every 28 days and increase the dose of prednisolone if the dog looks unwell
   b. Increase the interval of administration from 28 days to 35 days
   c. Stop electrolyte monitoring but continue veterinary injections every 28 days
   d. Switch to fludrocortisone and titrate the dose to effect
   e. Teach the owner to inject the dog and only see the dog once every six months for a physical check and electrolyte monitoring

6. A dog is presented to you for a DOCP injection; its previous injection was given at 1.8 mg/kg. It is three months since diagnosis, it is clinically very well and the electrolytes are as follows:
   - Sodium 163 mmol/l (reference range = 145 to 158)
   - Potassium 5.1 mmol/l (reference range = 3.8 to 5.5)
   - Sodium:potassium ratio = 32

   What advice should you give the owner with regards to the DOCP dose?
   a. Inject the DOCP today but decrease the dose to 1.0 mg/kg subcutaneously
   b. Do not inject and retest at seven days but a decrease in the dose to 1.2 mg/kg subcutaneously is likely
   c. Do not inject and retest at seven days but a decrease in the dose to 1.5 mg/kg subcutaneously is likely
   d. Inject the DOCP today but decrease the dose to 1.6 mg/kg subcutaneously
   e. Inject the DOCP today but increase the dose to 2.2 mg/kg subcutaneously

Answers: e, b, c, b, e, c