Diagnosis and treatment of canine hypoadrenocorticism

Susanna Spence, Eilidh Gunn, Ian Ramsey

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 hypoadrenosteronism. 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 adrenocorticotropic 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, melena 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
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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 hypotocisolism, lie, dogs with low cortisol and normal aldosterone, suggesting a selective destruction of the zona fasciculata 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. In such cases, clients should be counselled that electrolyte derangements may occur at any time, precipitating an acute crisis. Another strategy is to start desoxycorticosterone 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*

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

* Adapted from Scott-Moncrieff 2015

USG Urine specific gravity

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 Schwendewien 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 hypoponatremia) 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). Hyperkalaemia and hypophosphataemia 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-

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

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal disease (eg, irritable bowel disease, PLE, parvovirus)</td>
<td>Hypoalbuminaemia (PLE), Anaemia, Hypocholesterolaemia, Leucopenia (parvo)</td>
</tr>
<tr>
<td>Kidney disease (eg, AKI, CKD)</td>
<td>Anorexia, Dehydration, Weight loss (CKD), Polyuria/polydipsia (CKD)</td>
</tr>
<tr>
<td>Endocrine disease (eg, insulinoma)</td>
<td>Weakness, Episodic collapse, Seizures</td>
</tr>
<tr>
<td>Hepatic diseases (eg, chronic hepatopathy)</td>
<td>Anorexia, Vomiting, Diarrhoea, Weight loss, Lethargy, Polyuria/polydipsia</td>
</tr>
</tbody>
</table>

* See Table 1

**Intestinal disease**

- Vomiting
- Diarrhoea
- Gastrointestinal haemorrhage (parvo)
- Weight loss
- Lethargy

**Kidney disease (eg, AKI, CKD)**

- Anorexia
- Dehydration
- Weight loss (CKD)
- Polyuria/polydipsia (CKD)

**Endocrine disease (eg, insulinoma)**

- Weakness
- Episodic collapse
- Seizures

**Hepatic diseases (eg, chronic hepatopathy)**

- Anorexia
- Vomiting
- Diarrhoea
- Weight loss
- Lethargy
- Polyuria/polydipsia

**Laboratory findings**

- Hypoalbuminaemia (PLE)
- Anaemia
- Hypocholesterolaemia
- Leucopenia (parvo)
- Azotaemia
- Hyperkalaemia (AKI)
- Hypomagnesaemia (polyuric AKI)
- Anaemia (CKD)
- Hypercalcaemia (some CKD)
- USG <1.030 (CKD)
- Hypoglycaemia
- Increased liver enzymes
- Increased liver enzymes
- Hypoalbuminaemia
- Hypocholesterolaemia

**Other findings on biochemistry**

- Hypoglycaemia
- Polyuria/polydipsia
- Increased liver enzymes
- Hypercalcaemia (some CKD)
- Hypocholesterolaemia

**Maladies 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 hypcholesterolaemia. 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. Hypercholesterolaemia 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.

**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, megaesophagus 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 overinterpreted (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 T 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.
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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 adrenocorticotropic 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 hypona- 
tracemic; 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 hyponaemic 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 dexametha- 
sone, prednisolone and hydrocortisone. Hydrocortisone 
has the advantage of also providing short-acting miner-

**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 
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

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 electro-
lytes is necessary, especially in severely hyponaemic 
patients as excessively rapid correction of sodium concen-
trations may occur (see Box 4) (Gunn and others 2016).

Dexamethasone by contrast lacks mineralocorticoid 
activity but will provide a source of rapidly absorbable glu-
cocorticoid. 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 possi-
ble 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 dexa-
methasone 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 present-
ing 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 poten-
tial to reduce the excitability of cardiomyocytes. Neutral 
insulin and dextrose is commonly described in the man-
agement 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 facili-
ties 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 compro-
mised patients. Ideally, electrolytes should be rechecked 
every two to six hours (dependent on the severity of the 
patient’s hyperkalaemia/hyponaemia). 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, ambu-
latory and starting to eat voluntarily) then it is important 
to discuss the chronic management of hypoadrenocorti-
cism with the dog owner. The lifelong nature of this treat-
ment 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 glucocor-
ticoid and mineralocorticoid. The clinical targets for these 
cases should be ambitious – properly treated dogs should 
have a normal bodyweight, appetite, thirst and demean-
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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.

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.

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 unrelated 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-treat ed dogs in the UK have now made the transition to DOCP. However, fludrocortisone is available as a veterinary spe cial (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 2014).

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 reconstituted 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 desoxycorticosterone 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.

![Diagram](image-url)

<table>
<thead>
<tr>
<th>0 days</th>
<th>10 days after injection</th>
<th>28 days after injection</th>
<th>Actions required/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na high and/or K low</td>
<td>Na normal and K normal</td>
<td>Inject DOCP but decrease dose by 10 to 20 per cent</td>
<td></td>
</tr>
<tr>
<td>Na high and/or K low</td>
<td>Na high and/or K low</td>
<td>Do not inject DOCP</td>
<td></td>
</tr>
<tr>
<td>Na high and/or K low</td>
<td>Na low and/or K high</td>
<td>Inject DOCP but decrease dose by 10 to 20 per cent AND shorten interval to 21 days (NB, this is a rare pattern of results). Recheck electrolytes at day 10 and day 21</td>
<td></td>
</tr>
<tr>
<td>Na normal and K normal</td>
<td>Na low and/or K high</td>
<td>Do not inject DOCP</td>
<td></td>
</tr>
<tr>
<td>Na normal and K normal</td>
<td>Na high and/or K low</td>
<td>Inject DOCP but increase dose by 10 to 20 per cent</td>
<td></td>
</tr>
<tr>
<td>Na normal and K normal</td>
<td>Na normal and K normal</td>
<td>Do not inject DOCP</td>
<td></td>
</tr>
<tr>
<td>Na low and/or K high</td>
<td>Na low and/or K high</td>
<td>First set of normal results</td>
<td></td>
</tr>
<tr>
<td>Na low and/or K high</td>
<td>Na normal and K normal</td>
<td>Second set of normal results</td>
<td></td>
</tr>
<tr>
<td>Na low and/or K high</td>
<td>Na low and/or K high</td>
<td>Continue to inject DOCP every 28 days and recheck electrolytes preinjection in four months</td>
<td></td>
</tr>
</tbody>
</table>

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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References


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 adrenocorticotropic hormone (ACTH) was not available then which test 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 desoxycorticosterone valerate (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:** a, b, c, e