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# Diagnosis and Treatment of Canine Hypoadrenocorticism

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## Introduction

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. The condition 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.

## Causes

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 gastro-intestinal 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.

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, though 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 (but this term is also sometimes (incorrectly) applied to dogs that have typical primary hypoadrenocorticism but have normal electrolyte concentrations). 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 secretion by the pituitary gland. This suppression leads to atrophy of the adrenal cortex such that when the exogenous steroids are withdrawn and 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 (see Figures 1 and 2). 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 e.g. chronic gastrointestinal signs such as abdominal pain, melena or haematochezia or neurological abnormalities (episodic collapse) which can be confused with other conditions (see Figure 3). 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 hypovolemia.
- More severe hypovolemia 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 exam and it is recommended to carry out more routine diagnostic investigations before considering confirmatory tests

## **Routine Laboratory Tests**

### ***Haematology***

The “classical” haematological finding in dogs which have hypoadrenocorticism is a reverse stress leukogram (low to normal neutrophil numbers with an increase in lymphocytes and eosinophils). These findings should prompt the clinician to consider hypoadrenocorticism, however it is not present in most cases. An absolute lymphocytosis is only seen in 10% of cases, whereas eosinophilia is seen in 20% (Scott-Moncrieff 2015). A more sensitive finding is the absence of a stress leukogram in an ill patient (which is the case in up to 92% of patients with hypoadrenocorticism). There are a couple of descriptions of using ratios of white blood cell parameters as sensitive diagnostic aids (which are useful to exclude the diagnosis of hypoadrenocorticism), however none are specific enough to rely on 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% of patients. This is due to a reduced red blood cell production but may be compounded by gastrointestinal blood losses. Less commonly a patient may present with an increased PCV 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 (see Figure 4). Historically, sodium:potassium ratios (<27:1) were used to assist in diagnosis of hypoadrenocorticism. However, some cases can be missed when using sodium potassium ratios and therefore we now prefer to consider the sodium and potassium concentrations separately, with respect to their individual reference ranges. There are several other causes of low sodium:potassium ratios including GI disease, renal disease and a variety of other conditions ((Nielsen and others 2008). Hypochloraemia and hyperphosphataemia may also be seen. Electrolyte abnormalities are due to mineralocorticoid (aldosterone) deficiency and therefore are not found in dogs with “atypical” hypoadrenocorticism (see separate box). Electrolyte abnormalities can correct rapidly following initiation of fluid therapy.

The second most common finding on biochemistry is azotaemia. This is predominantly pre-renal 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 pre-renal 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 hypoalbuminaemia is thought to be multifactorial with a reduction in appetite, gastro-intestinal 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***

Even though patients with hypoadrenocorticism often present with hypovolemia and pre-renal azotaemia, their urine specific gravity rarely exceeds 1.025. This can make differentiation from azotaemia due to renal insufficiency (e.g. 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. Patients with AKI frequently are anuric or have reduced renal output. In addition, patients with AKI usually have a stress leukogram (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 prior to starting fluid therapy.

### ***Diagnostic Imaging***

#### ***Radiography***

Abdominal radiography is not used in the diagnosis of hypoadrenocorticism; however 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, the authors do not routinely radiograph patients in which hypoadrenocorticism is suspected.

#### ***Abdominal Ultrasound***

This 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 utilised by the skilled clinician. Bilateral reduction in adrenal gland size and, in particular, left adrenal gland thickness less than 3.2mm is highly suggestive of hypoadrenocorticism, although this is not a sensitive test (see Figure 5). 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 due to concerns of 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 (e.g. as dilated cardiomyopathy). The changes in hypoadrenocorticism would be expected to improve with treatment.

### *Electrocardiographic Changes*

Patients may be presented with bradycardia and therefore electrocardiography (ECG) may be one of the first tests performed in an emergency. 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 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 cardio-protective and acidosis can cause increases in extracellular potassium levels.

### *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 Figure 5). 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 (including some sex hormones as well as glucocorticoids) on the hypothalamic-pituitary-adrenal (HPA 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 ACTH is not available, and steroids are required in the short term (e.g over a

weekend), then dexamethasone does not interfere with the cortisol assay: however it will have to be withdrawn for 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 the 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 <55nmol/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% in this 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 who are not stable on presentation. Instead, in these patients a full ACTH stimulation test should be performed in attempt to obtain results sooner, to avoid delays in definitive therapy and thereby to minimise cost to clients.

### ***ACTH Stimulation Test***

This is the gold standard for diagnosis of hypoadrenocorticism, with a high sensitivity and specificity. This test is a function of adrenal reserve and hypoadrenocorticism can be diagnosed by demonstration that cortisol is not released in adequate quantities when exogenous ACTH is administered. To do this, a basal serum sample is taken before 5 µg/kg of ACTH is given intravenously (preferably) or intramuscularly. Post-ACTH blood samples can be 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. It is known that there can be considerable variation in cortisol results between laboratories and therefore we also recommend that clinicians use the same laboratory for familiarity.

As mentioned, this test should be performed before initiating steroid therapy. See box 2 for what to do when cases are presented having received steroid therapy.

### ***Cortisol / ACTH Ratio***

Measuring the cortisol/ACTH ratio may be useful in the diagnosis of primary hypoadrenocorticism as cortisol/ACTH ratios 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 (Boretta and others 2015, Javadi and others 2006, Lathan and others 2014) . 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 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. The measurement of aldosterone is indicated however 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**

### **Goals of Treatment**

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

### **Fluid Therapy**

The clinical status and degree of dehydration of the patient will dictate both the rate and volume of fluids administered. The authors recommend a 'goal-directed' approach to fluid resuscitation but it is possible that shock rates of crystalloids (~80 ml/kg/hr) may be required for the first 1-2 hours. Usually 0.9% sodium chloride is the fluid of choice as most affected dogs are hyponatraemic, however balanced potassium containing fluids (e.g. Hartmann's) are not necessarily contraindicated; the dilutional effects of fluid therapy will still outweigh the small additive effect of potassium. Care however, should be taken in severely hyponatraemic patients (see below) 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. The latter 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 it is also a cost-effective treatment option as it shortens hospitalisation. It should, however, be emphasized that close monitoring of electrolytes is necessary, especially in severely hyponatraemic patients as excessively rapid correction of sodium concentrations may occur (see below) (Gunn and others 2016). Dexamethasone by contrast lacks mineralocorticoid activity but will provide a course of rapidly absorbable glucocorticoid. There is a wide range of doses 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. The authors recommend a conservative bolus dose of 0.1-0.2 mg/kg IV dexamethasone (as dexamethasone disodium phosphate) given once daily.

## Ancillary Management of Hyperkalaemia

Ancillary management of hyperkalaemia in cases of hypoadrenocorticism is rarely necessary (especially where hydrocortisone is being used). However, for dogs presenting with associated cardiac complications (i.e. severe bradycardia of less than 40 bpm) then 10% calcium gluconate may be necessary (0.5-1.5 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 this approach in dogs with hypoadrenocorticism (where hypoglycaemic complications are more likely to be encountered).

## Patient Monitoring

The intensity of monitoring afforded to the patient is likely to be 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 1-2 hours in severely compromised patients. Ideally electrolytes should be rechecked every 2-6 hours (as dictated by 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).

### **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 (e.g. <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 lag by a couple of days behind 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, in patients presenting with severe hyponatraemia, treatment with 0.9% sodium chloride may not be appropriate and consideration should be given to low sodium-containing fluids (e.g. 0.45% sodium chloride). Similarly, if hydrocortisone is being used then a dose reduction (e.g. to 0.3mg/kg/hr) may be appropriate.

### **Chronic Management**

Once a dog has been stabilised then it is important to discuss the chronic management of hypoadrenocorticism. The lifelong nature of this treatment and the importance of not missing doses must be emphasised. It is also important to make sure that the clients understand that it may take several visits and multiple monitoring blood tests to find the right doses of glucocorticoid and mineralocorticoid. Our clinical targets for these cases should be ambitious – properly treated dogs should have a normal body weight, appetite, thirst and demeanour 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.

### **Glucocorticoid supplementation**

All dogs must receive daily glucocorticoid treatment titrated to effect based on clinical signs. The starting dose of prednisolone is 0.1-0.2 mg/kg q24h for newly diagnosed cases. The final dose varies considerably between individual animals and whilst a good proportion of dogs will ultimately be

stable at 0.05-0.1 mg/kg q24h, some may be even lower. 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 ask owners if their 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 unless asked. 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  $\pm$ 25 to 50% of the previous dose. At times of metabolic stress or illness, the glucocorticoid dose should be increased (2 to 4-fold). In dogs on low doses of glucocorticoid then even greater increases (such as 10 fold) may be used for short periods. 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 desoxycortone pivalate (DOCP) (Zycortal®; Dechra Veterinary Products Ltd.) was released on to the UK market in 2016. Shortly afterwards, in a completely 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 now available as a veterinary special (Summit pharmaceuticals) and this may be useful for specific patients but this requires specific individual justification, according to the cascade. As there is mounting evidence that DOCP is superior in many respects to fludrocortisone and as this is the authorised drug, so 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 SC given approximately every 25 days. Many authorities however use a starting dose of 1.5 mg/kg SC given every 28 days. 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 (e.g. 35 days) increase the risk of instability (but may be cheaper for the client). There is no evidence that there is an extended duration of action but many dogs, if their 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 (see Figure 7). 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 post injection after every dose until stable. Monitoring electrolytes at 10 days post injection enables assessment of the peak effect of the dose whereas the 28 day sample enables assessment of the duration of the dose. If the peak effect is too great (or too little) at 10 days post injection then the subsequent dose should be reduced (or increased). If the potassium is below and/or sodium is above their respective reference range at 28 days then DOCP should not be administered and electrolytes should be checked every 7 days until they are within their respective reference ranges and then DOCP administered (at a reduced dose of about 20 % 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 post injection for at least two consecutive treatment cycles using that same dose. Once the correct dose has been determined, dogs should be reassessed every 4-6 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 over-interpretation 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 post injection. This is usually associated with a mild overdose of DOCP and a dose reduction at the next injection usually 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 important to be aware that electrolyte measurements vary between laboratory machines and their reference ranges vary. Electrolytes may also fluctuate day to day. 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 Ltd. and the authors encourage their use). It is also important that owners are 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 however our experience is still limited and it is important that experiences are shared and discussed with relevant specialists and the company who supply the product.

### **Summary**

The current recommended doses of drugs suggested by the authors in this paper are summarised in figure 6.

***Declaration of conflict of interest.*** Two of the authors participated in a clinical trial funded by and one author continues to receive clinical research funding from Dechra Veterinary Products Ltd.

## Figures

### Figure 1

Hypoadrenocorticism is a disease of young to middle aged dogs. The picture shows a 12-week-old puppy that was presented with a history of acute collapse that was subsequently diagnosed with hypoadrenocorticism.



**Figure 2**

A table summarising the common, and not so common, clinical signs and laboratory findings that are associated with hypoadrenocorticism (Scott-Moncrieff 2015)

	Clinical signs	Laboratory findings
<b>Common</b>	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)
<b>Uncommon</b>	Diarrhoea GI haemorrhage Weight loss Abdominal pain PU/PD Muscle cramps Regurgitation Seizures	Hypoglycaemia Neutropenia Lymphocytosis Eosinophilia Hypocholesterolaemia Isosthenuric urine (USG < 1.015)

**Figure 3**

A table demonstrating the similarities between the clinical signs and clinical pathology changes seen in hypoadrenocorticism and intestinal endocrine kidney and hepatic diseases.

	Clinical signs	Clinical pathology
Intestinal disease (e.g. IBD, PLE, parvovirus)	Vomiting Diarrhoea GI haemorrhage (parvo) Weight loss Lethargy	Hypoalbuminemia (PLE) Anaemia Hypocholesterolaemia Leucopenia (parvo)
Kidney disease (e.g. AKI, CKD)	Anorexia Dehydration Weight loss (CKD) PU/PD (CKD)	Azotaemia Hyperkalaemia (AKI) Hyponatraemia (polyuric AKI) Anaemia (CKD) Hypercalcaemia (some CKD) USG < 1.030 (CKD)
Endocrine disease (e.g. insulinoma)	Weakness Episodic collapse Seizures	Hypoglycaemia Increased liver enzymes
Hepatic disease (e.g chronic hepatopathy)	Anorexia Vomiting Diarrhoea Weight loss Lethargy PU/PD	Increased liver enzymes Hypoglycaemia Hypoalbuminaemia Hypocholesterolaemia



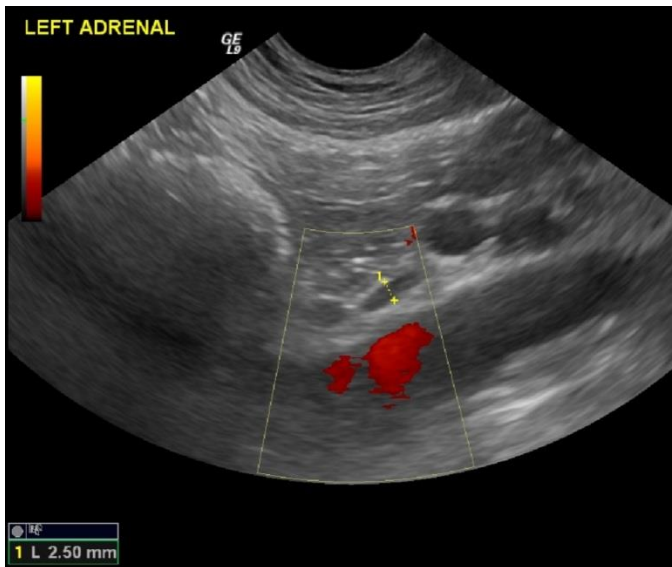
**Figure 4.**

Typical example of electrolyte changes. Hyponatraemia, hyperkalaemia and hypochloraemia are all common in this condition. This example was from the puppy shown in Figure 1. The reference intervals are Na = 144-160, K = 3.5-5.8, Cl = 109-122.

ELECTROLYTES		
Na <sup>+</sup>	↓	136 mmol/L
K <sup>+</sup>	↑	8.8 mmol/L
Cl <sup>-</sup>	↓	107 mmol/L






### Figure 5

Adrenal ultrasound in a 50 kg Great Dane cross with hypoadrenocorticism. The left adrenal measures 2.5 mm across.



**Figure 6**

The main drugs and their starting doses that are used to treat hypoadrenocorticism

Acute management	Chronic Management
<p><b>A) 0.9% saline</b> As calculated but often 80 ml/kg/hr for 1 to 2 hours then reduce</p> 	<p><b>C) Desoxycortone pivalate:</b> 1.5-2.2 mg/kg q25-28d SC then titrate to required dose</p> 
<p><b>B) Hydrocortisone sodium succinate</b> 0.5 mg/kg/hour IV</p> 	<p><b>D) Prednisolone</b> 0.1-0.2 mg/kg q24h PO then titrate to required dose</p> 
<p><b>Or:-</b> <b>Dexamethasone disodium phosphate</b> 0.1-0.2 mg/kg IV q24h</p> 	

**Figure 7**

The adjustment of DOCP dose is based on a combination of clinical signs and electrolyte changes. Clinical signs are usually more important than electrolytes and are covered in the text.

Recheck electrolytes 10 days and 28 days post-injection

0 days	10 days post injection	28 days post injection	Actions required / Comments
<b>Inject DOCP at a starting dose of 1.5 to 2.2. mg/kg SC*</b>	Na high and/or K low	Na normal and K normal	Inject DOCP but decrease dose by 10-20%.
	Na high and/or K low	Na high and/or K low	<b>Do not inject DOCP.</b> Recheck electrolytes every 7 days until Na normal and K normal. At this point, inject DOCP but decrease dose by ~20%.
	Na high and/or K low	Na low and/or K high	Inject DOCP but decrease dose by 10-20% AND shorten interval to 21 days. [NB: This is rare pattern of results] . Recheck electrolytes at d10 and d21.
	Na normal and K normal	Na low and/or K high	Inject DOCP but increase dose by 10-20%.
	Na normal and K normal	Na high and/or K low	<b>Do not inject DOCP.</b> Recheck electrolytes every 7 days until Na normal and K normal. At this point, inject DOCP but decrease dose by ~20%.
	Na normal and K normal	Na normal and K normal	<b>First set of normal results</b> Inject DOCP at the same dose.
	Na low and/or K high	Na low and/or K high	<b>Second set of normal results</b> Continue to inject DOCP every 28 days and recheck electrolytes pre-injection in 4 months
			Inject DOCP but increase dose by ~20%.

\*Ensure product is properly re-suspended before use

## BOX 1

### What is atypical hypoadrenocorticism?

A few cases of hypoadrenocorticism (probably less than 10%) 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). 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-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 (i.e. dogs with low cortisol and normal aldosterone suggesting a selective destruction of the zona fasciculata) is now regarded by many authorities as being true ‘atypical hypoadrenocorticism’. As this may also result from a pituitary rather than adrenal disease measurement of endogenous ACTH may be useful and those 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 (i.e. low cortisol and low aldosterone but normal electrolytes) can be successfully treated with just prednisolone providing 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 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).

## BOX 2

### What to do 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 ACTH test should be performed 36 hours later. HPA 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 q12h will suppress the ACTH stimulation test for a further month after cessation of the steroid and for the first 2 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 5 weeks.

In addition, if steroids have been given very recently to any animal then it is worth remembering that some (e.g. 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 as it may cross react with cortisol in the assay.

**Figure for Box 2 – a long acting methylprednisolone**



## Self Assessment Quiz

(answers highlighted)

- 1) What breed of dog has the highest risk of hypoadrenocorticism?
  - a) Boxer
  - b) French Bulldog
  - c) German Shepherd
  - d) Portuguese Water dog
  - e) Yorkshire terrier
  
- 2) 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
  
- 3) What are the most common changes seen in biochemistry and haematology in hypoadrenocorticism?
  - a) Hypercalcaemia and lymphocytosis
  - b) Hyperkalaemia and anaemia
  - c) Hyponatraemia and neutropenia
  - d) Hypoalbuminemia and eosinopenia
  - e) Hypoglycaemia and neutrophilia
  
- 4) If synthetic 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
  
- 5) When on night duty, you are strongly suspicious that a collapsed 3 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 IV of dexamethasone 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 GI 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

6) A client wishes to reduce the cost of managing their dog with hypoadrenocorticism using 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 Zycortal to 1.0 mg/kg SC 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 6 months for a physical check and electrolyte monitoring**

7) A dog is presented to you for a DOCP injection, its previous injection was given at 1.8 mg/kg. It is 3 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 = 31

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 SC
- b) Do not inject and retest at 7 days but a decrease in the dose to 1.2 mg/kg SC is likely
- c) Do not inject and retest at 7 days but a decrease in the dose to 1.5 mg/kg SC is likely.**
- d) Inject the DOCP today but decrease the dose to 1.6 mg/kg SC
- e) Inject the DOCP today but increase the dose to 2.2. mg/kg SC



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Note to editors: We have only included recent references and a couple of recommended texts but we can supply a larger reference list if required.