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Endocrinology Case Challenges Mini Series

Session One: Adrenal Disease

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Part 1: Adrenal Disease

Hyperadrenocorticism

Hyperadrenocorticism (HAC) is the term that is generally used to overproduction of cortisol by the adrenal cortex. The majority of the time that this condition is seen in dogs it is a naturally occurring disease associated with pathology of the hypothalamic-pituitary-adrenal axis (HPA). Within this, 85% of cases are due to overproduction of ACTH by the anterior pituitary (pituitary dependent HAC, PDH) with 15% being due to autonomous production of cortisol from an adrenal tumour (AT). Iatrogenic HAC refers to the same clinical signs as naturally occurring HAC but this is caused by exogenous glucocorticoid administration (typically prednisolone, methylprednisolone, dexamethasone or similar). It is technically inappropriate to refer to this condition as HAC as it is associated with suppression and atrophy of the adrenal cortex rather than overproduction. On rare occasions overproduction of cortisol has been described for other reasons too including ACTH secreting tumours in other regions of the body and food dependent hypercortisolaemia.

HAC does occur in cats but this is much less common than the disease in dogs. Broadly speaking, clinical signs, diagnosis and treatment are similar to that described in dogs but it is important to note that the sensitivity/specificity and dosing for the diagnostic tests is different. Clinically, HAC in cats most typically is recognised in association with insulin resistant diabetes mellitus, or occasionally in association with fragile skin syndrome. Due to the rarity of this condition in cats, it will not be discussed further within these notes.

Diagnosis

Diagnosis of HAC is straight forward in many cases but can be challenging in some. Many controversies exist around optimal testing strategy and in light lof this the American College of Veterinary Internal Medicine (ACVIM) produced a consensus statement on the diagnosis of canine HAC, which is freely available to download and also included with these course notes. Readers are referred to that manuscript for a more detailed commentary and rationalisation of diagnostic testing in HAC but some concise notes are included below.

One of the most important considerations in the diagnosis of HAC is that no test for the condition is close to 100% specific. This means that the positive predictive value of the test (the likelihood that a positive test result indicates true disease) is highly dependent on the prevalence of the disease within the tested population. In other words, tests for HAC are only likely to indicate the presence of HAC if testing animals where a reasonable clinical suspicion exists in the first instance and other diseases, which could result in appropriate increases in cortisol, are not present. With this in mind, it is important to know what signs are seen in dogs with HAC, with what frequency, so that the likelihood of this disease being present can be appropriately assessed. The following table lists clinical signs that can be attributed to HAC and the approximate prevalence reported in dogs when they are first diagnosed.

Clinical sign	Prevalence
Polydipsia	90
Polyuria	90
Polyphagia	50
Abdominal enlargement	70
Excessive panting	60
Alopecia	70
Lethargy	50
Muscle weakness	40
Nocturia	30
Hyperpigmentation	25
Muscle atrophy	35
Recurrent pyoderma	20
Comedones	30
Recurrent urinary tract infection	15
Calcinosis cutis	15
Facial nerve paralysis	5
Suspected ligament rupture	3
Pseudomyotonia	1
Anorexia	2

It can be seen from the above table that at the very least, the clear majority of dogs tested for HAC should have polyuria/polydipsia and if this is not present then serious consideration should be given to the merits of testing. As important as the clinical signs that are attributable to HAC are those that are not. Signs such as vomiting, diarrhoea, abdominal pain and inappetance do not feature on the above list and such signs may be associated with increases in cortisol as a manifestation of physiologic stress. It is therefore inappropriate to test dogs for HAC if such clinical signs are present as there is a relatively high likelihood of a false positive result.

If animals do present with clinical signs such as those listed in the table above, it is appropriate to conduct broad, routine screening tests before focussing exclusively on HAC. This should include a haematology, comprehensive serum biochemistry and urinalysis. Similar to clinical signs, there are some changes that are commonly seen in such labwork which should be evaluated when considering the likelihood of HAC and therefore the appropriateness of further testing. On haematology samples, erythrocytosis, a mature neutrophilia, monocytosis, eosinopenia and lymphopenia may all be seen. Thrombocytosis is seen in more than 90% of cases and the absence of this finding should again raise concern about further testing.

On serum biochemistry, Alkaline Phosphatase is moderately elevated in most (>95%) cases (dogs, not seen in cats) with mild elevations in cholesterol, triglycerides, bile acids and ALT being common. Decreases in BUN and potassium may be noted in some cases. On routine urinalysis then specific gravity is commonly reduced but can be highly variable as most dogs with HAC can concentrate their urine to some degree, particularly when they are distracted such as when hospitalised or in the morning after sleeping. As such, USG may be hypo-, iso- or hyper-thenuric. Proteinuria is seen in most cases of HAC with a protein:creatinine ratio typically less than 5. Calcium oxalate crystals are occasionally seen. Urinary tract infections (UTIs) are seen in approximately 50% of newly diagnosed cases of HAC but this may not be associated with red/white blood cells as the patient may be immunosuppressed due to the hypercortisolaemia. As such, a UTI may be identified by bactiuria on sediment/culture but overlooked if just looking at a dipstick or for active sediment.

If the history, physical examination and routine labwork support a diagnosis of HAC then more focussed adrenal testing should be considered. There are several tests routinely available for this purpose, as described below. The position of the ACVIM guidelines is that the Low Dose Dexamethasone Suppression Test (LDDST) is the initial screening test of choice in most instances.

Low Dose Dexamethasone Suppression Test

This test investigates whether the HPA is appropriately suppressed in response to excessive exogenous glucocorticoids. The protocol involves giving 0.01mg/kg dexamethasone (0.013mg/kg Dexamethasone SP) intravenously and measuring serum cortisol before, 4 hours later and 8 hours later. In a normal animal cortisol should be below the laboratory threshold at both later measurements. In HAC the 8-hour sample will be above the threshold. If the 4-hour sample is below the threshold and the 8-hour is above then this indicates PDH. If the cortisol is above the lab threshold at 4 and 8 hours then PDH and AT cannot be distinguished. If the cortisol is increased at 4 hours but not at 8, this is considered a suspicious but equivocal result. The LDDST is reported to be 85-100% sensitive, meaning it can detect most cases of HAC, but its specificity is reported to be 45-70%, meaning that many dogs without HAC will also give a positive result. This highlights the importance of appropriate patient selection for this test.

ACTH Stimulation Test

The ACTH stimulation test investigates the maximal output of the adrenal cortex, which should be hypertrophied in HAC. The test involves giving 5μg/kg tetracosactide intravenously and measuring serum cortisol before and 1 hour later. Cortisol should be above the laboratory reported cutoff at the latter sample to make a diagnosis of HAC. This test is more specific for HAC (60-90% reported) but has a reported sensitivity of 60% for AT and 80% for PDH, meaning some cases will not be detected by this test. An advantage of the ACTH stimulation test is that it allows identification of iatrogenic HAC in those cases that have compatible signs but no measurable cortisol after exogenous ACTH stimulation, which demonstrates atrophy of the adrenal cortex.

Urine Cortisol: Creatinine Ratio

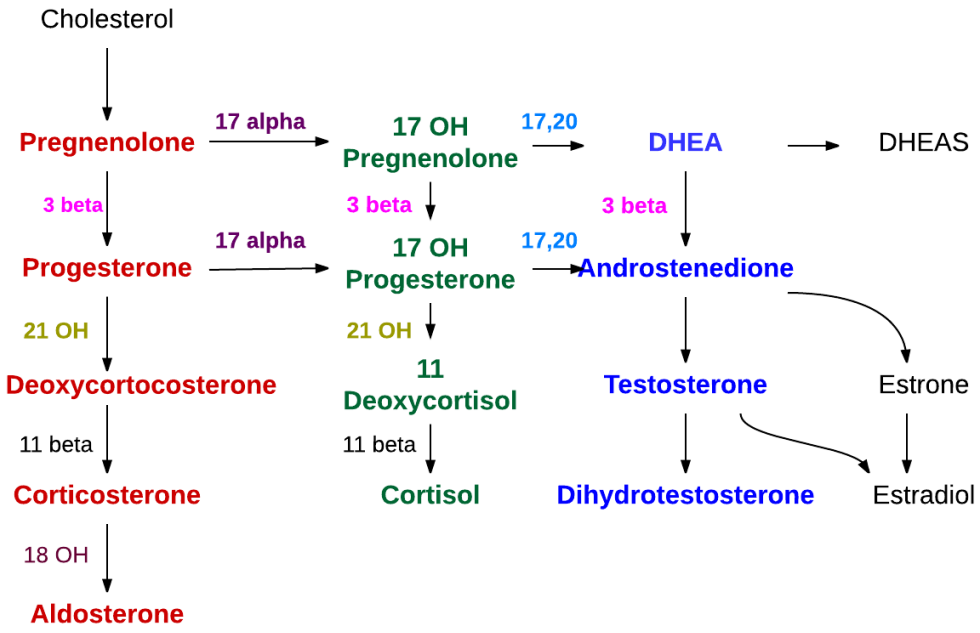
The urine cortisol: creatinine ratio (UC:Cr) has the advantage compared to the other tests that it can be run on a spot sample rather than being a dynamic, time consuming, test. It is reported to be moderately/highly sensitive (75-99%) but is very non-specific (15-25%), meaning it can be elevated in lots of dogs without HAC. The UC:Cr can therefore be used as a quick, outpatient test to determine if HAC is on the differential diagnosis list for a patient and if further testing is warranted.

Diagnosing cases after equivocal testing

None of the above tests are 100% sensitive (other than in 1 study of the LDDST) and as such it is a reasonably common occurrence that testing fails to achieve a definitive diagnosis despite high index of clinical suspicion. In such instances it is prudent to review the case and make sure that the suspicion is justified.

If it is then possibilities for this discrepancy include that the case is an “early” one that has not yet reached sufficient cortisol concentrations for our diagnostic criteria, or that another hormone, with cortisol-like-activity, is being excessively produced rather than cortisol itself.

Mechanistically, PDH should not elevations in other hormones without also causing a rise in cortisol but if an adrenal tumour is present then it may have dysfunction of the normal steroid hormone synthesis pathways:



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If an adrenal tumour is identified, which is suspected to be functional, then the other hormones in this pathway can measured during an ACTH stimulation test to see if they are elevated. These hormones are substantially less specific for HAC than cortisol and so their measurement should be interpreted cautiously.
It is thought that some dogs have PDH but cortisol measurements are within the laboratory normal or equivocal ranges. This is likely to be because our current understanding of HAC is evolving and laboratory cutoffs are inappropriately high in many instances. If HAC is suspected and the cortisol measurement is in the upper part of the normal/equivocal range then 17-OH progesterone, a precursor of cortisol, can be measured post-ACTH and it is reported that this is 91% sensitive for HAC but similar to other adrenal hormones, it is only 59% specific so it should be interpreted cautiously. If 17-OH and cortisol are both low then this should strongly push the clinician to consider alternative diagnoses.
If HAC is strongly suspected but cortisol measurement does not support it then one can also consider a cautious treatment trial, with or without 17-OH progesterone to justify this trial.

Further investigation of HAC

If a diagnosis of HAC is reached then further investigations should follow where financially possible. These include urine culture, given the high prevalence of UTIs, and measurement of blood pressure, given the high prevalence of hypertension within dogs with HAC and the fact that if this is identified, it warrants concurrent treatment. It is preferable to confirm if a dog has AT or PDH. Medical therapy is possible in either instance but if a dog has AT then adrenalectomy can be considered. Adrenalectomy is preferable in some instances as it can be curative, avoiding the need for long term therapy, and it may prevent spread of metastases. If a dog has PDH then advanced imaging of the pituitary (MRI or CT) should be considered as hypophysectomy may be curative in many cases (but would still require long term medication with other endocrine supplements) and large tumours (macroadenomas) may be associated with neurologic side effects and as such these cases may benefit from hypophysectomy or radiotherapy to minimise this risk.
The LDDST can be used to both diagnose HAC and identify PDH in 60% of cases but in many instances the test does not differentiate AT and PDH.
The test of choice for differentiating AT and PDH is endogenous ACTH, which should be low in AT and elevated in PDH. This sample requires special handling and cannot be taken after an ACTH stimulation test, LDDST or when a dog is on therapy so I prefer to collect and freeze a sample whenever taking the “pre-“ sample for HAC testing. Adrenal ultrasound is a poor test for differentiating AT and PDH as adrenal nodules are commonly present in older dogs but may not be functional.

It is possible to have a non-functional adrenal nodule and PDH or to have bilateral nodules, which are functional on one side but not on the other, for instance. If a nodule/mass is present on one side and the contralateral side is <4mm thick then this suggests atrophy of that gland, likely indicating a functional nodule on the other side.

Treatment

Hyperadrenocorticism can be associated with many clinical sigs, as noted above, but many of them (PU/PD, polyphagia, thinning hair etc) are not life threatening for the dog and are mainly a quality of life issue for the dog/owner. It is certainly possible for more significant consequences (hypertension, thromboembolism, pancreatitis etc) to develop but these are rare. A recent study examined the fate of dogs where the owners elected not to treat HAC and those dogs survived approximately 18 months after diagnosis, despite the lack of specific treatment. This was less than those that were treated but it highlights that treatment is not necessarily mandatory in cases where it does not suit the dog/owner to treat.

As noted above, adrenalectomy or hypophysectomy can be considered for definitive treatment of HAC. A full description of these techniques and the risks involved is beyond the scope of these notes but they should be considered in any case where financial limitations do not apply, particularly in younger patients where very long term medications or clinical signs are the alternative.

Adrenalectomy is undoubtedly the treatment of choice for AT in many instances but AT only accounts for 15% of HAC and the procedure is complex, with a high risk of morbidity/mortality, particularly in inexperienced hands. Pre-operative CT is typically advised prior to adrenalectomy as size and invasiveness of the tumour have been associated with perioperative risk. If adrenalectomy is to be performed then it is important to realise that the contralateral adrenal gland is likely to be atrophied and so perioperative steroids will be required to prevent an Addisonion crisis. Hypohysectomy is performed at very few centres in the UK and again carries a significant risk with it. The long term outcome when successfully performed is good and it prevents the development of neurologic complications due to a space occupying intracranial lesion but endocrine supplementation (cortisol, thyroxine +/- ADH) are required for the rest of the patient's life.

Medical management of HAC

Regarding medical management, many drugs have been used to treat HAC but the only one licensed in the UK or recommended for routine use is trilostane, which reversibly blockades enzymes involved in the synthesis of cortisol. Dosing as per the data sheet (initially 2mg/kg PO SID) works in many instances but the duration of action of trilostane is less than 24 hours and several studies indicate a better clinical response to BID dosing (initially 1mg/kg BID). The aim of treatment is to control the clinical signs that led to a diagnosis and as such the drug should be uptitrated to effect, making dose adjustments no more often than once every 10 days. Labwork monitoring is recommended at 10d, 4w, 12w and then q3 months after any dose adjustment. Potassium should be measured as hyperkalaemia is a potential side effect. An ACTH stimulation test should be performed to test adrenal reserve. Although most labs will report a "target range" for this assay, individual clinical response is highly variable and the aim of such testing should be to ensure that some adrenal reserve still exists and the cortisol does rise in response to ACTH, preferably to more than 60nmol/L. A biochemistry is also routinely checked at the saem time as this monitoring is performed as it is informative to monitor normalisation of ALkP etc in association with improving control of HAC.

Trilostane should not be given if dogs are unwell/inappetant as it is important that they are able to mount a stress response with elevated cortisol in such instances and suppression of this may be contributing to the problem. If an ACTH stimulation test indicates oversuppression of the adrenals then trilstane should be stopped and then the test repeated in approximately 1 week or when clinical signs recur. In most instances trilostane can be safely restarted at that time but in a small minority of dogs then permanent adrenal necrosis can develop and dogs no longer need trilostane or may even require treatment for hypoadrenocorticism.

Pheochromocytomas

Pheochromocytomas are neuroendocrine tumours of the adrenal medulla that produce excessive catecholamines. They occur in middle-aged to older dogs and no gender/breed predisposition is recognised. The clinical signs associated with these tumours is very variable with some dogs having quite suggestive signs such as tachycardia, panting, hyperthermia and collapse, whereas others can have much more vague signs such as vomiting, diarrhoea, PU/PD or lethargy. Occasionally they may present with spontaneous intra-abdominal or retroperitoneal bleeding or as incidental findings.

Signs may also be secondary to hypertension such as seizures or blindness. Labwork findings associated with these tumours can include anaemia, hypoproteinaemia and thrombocytopenia, secondary to bleeding, azotaemia or mild alterations to AlkP, ALT and cholesterol.
Many of the findings, such as adrenal mass, PU/PD, hypertension and AlkP elevation can be readily confused with an adrenocortical tumour and so careful consideration is warranted in these cases. The diagnostic test of choice is measurement of normetanephrine, which can be assessed in urine (as a ratio to creatinine) or in plasma (where free and total can be measured). Studies indicate that urine and plasma free normetanephrine perform reasonably well for differentiating pheochromocytomas from AT. Both assays require meticulous sample handling and unusual requirements and so they should be discussed with your laboratory prior to submitting samples.
Medical management of pheochromocytomas is aimed at controlling hypertension and the other signs secondary to catecholamines using alpha blockers (phenoxybenzamine or prazosin). These drugs have only been studied for short term pre-operative use where their use for 1-2 weeks prior to surgery has been associated with a reduced perioperative mortality. The treatment of choice for these tumours is adrenalaectomy. This is more risky than for cases of AT as noted above as vascular invasion is more common, they are more friable tumours and the anaesthetic is more challenging due to the variable catecholamine release. Long term outcome in cases that do not have metastases identified at staging and that survive the perioperative period is generally good. Less is known about long term outcome for those patients that are medically managed without undergoing surgery. This is likely to depend on the clinical signs present at the time of diagnosis and the severity of disease but in some instances where signs were mild at the time of diagnosis then anecdotally they have been managed long term over many months successfully.

Incidentalomas

As noted above, adrenal nodules are common in older dogs and they may/may not be functional. They are increasingly recognised as a problem as abdominal imaging is more commonly performed than it used to be where unexpected adrenal nodules may be fund during an investigation for other purposes (a so called “incedentaloma”). If an incidentaloma is found then the 2 most pertinatn clinical questions are whether it is likely to be malignant and whether it is likely to be functional, producing cortical or medullary hormones.
If the mass is greater than 2cm in diameter then it is likely to be malignant and studies indicate that it will be associated with a shortened life expectancy if left untreated and so this should prompt a recommendation for surgical excision, after thoroughly investigating if it has already metastasised and if it is functional (which will affect perioperative management). The presence of vascular invasion or confirmation of a pheochromocytoma are similarly indicators of malignancy that should lead to a discussion of surgical excision, although the risk associated with excision should be carefully considered.
In terms of the functionality of the tumour, then the same mantra as noted above holds true. HAC should not be too thoroughly investigated unless there is reason to suspect it. Blood pressure should be measured as this may go up with HAC or pheochoromocytomas but if this is normal, there are no other signs of HAC and the contralateral gland is not atrophied then testing for HAC should not be pursued and the nodule can be monitored for future growth or the development of clinical signs. If hypertension is present or there are other clinical signs that may be attributable toa pheochromocytoma then investigation for that, as noted above, should be carried out.

Hypoadrenocorticism

Hypoadrenocorticism (Addison’s disease) refers to insufficient production of hormones by the adrenal cortex. Typically, this refers to both cortisol and aldosterone but in rare instances it may be one hormone or the other. The most common cause of Addison’s disease is described as idiopathic but it is thought to be an immune mediated destruction of the adrenal cortex and is most commonly identified in young to middle aged female dogs. Several breeds, including Poodles, Soft Coated Wheaten Terriers and Nova Scotia Duck Tolling Retrievers are recognised to be predisposed to the condition.
Cortisol has many functions throughout the body but 2 of the most important in the context of Addison’s disease are a role in maintaining gastrointestinal mucosal health and in regulating vascular tone. Aldosterone’s role is in stimulating sodium/water retention to maintain perfusion and simultaneously excreting potassium. It is certainly possible for dogs with Addison’s disease to present with chronic and vague signs of malaise with/without gastrointestinal signs but the commonest presentation is of collapsed patients with haemorrhagic gastrointestinal signs in crisis. Treatment is highly specific and as such prompt recognition is important.

Diagnosis

Definitive diagnosis of Addison's disease is based on measurement of cortisol, which is less than 55nmol/L 1 hour after ACTH. This result must be specifically requested and it is often not available quickly so other clues are used to raise the index of suspicion. The most notable of these is the sodium: potassium ratio.

Aldosterone is responsible for sodium retention and potassium excretion and so in the absence of this hormone hyponatraemia and hyperkalaemia develop. This is seen in about 75% of cases of Addison's but aldosterone deficiency is actually present in >95% of cases. The majority of dogs with Addison's have a ratio <28 and a ratio <24, which is seen in ~60% of cases, is strongly suggestive for this condition. Although the ratio can be strongly suggestive it should never be used for definitive diagnosis as other conditions, including acute kidney injury and whipworm, can cause similar clinical signs and similar electrolyte imbalances.

The majority of dogs with other conditions that present with collapse and haemorrhagic gastrointestinal signs have markedly elevated cortisol and as such they develop a stress leukogram, including a lymphopenia. A study has indicated that a normal lymphocyte count in such dogs is suggestive of Addison's disease.

Resting cortisol levels can be measured as a screening test for Addison's in dogs where the index of suspicion is low and if this is >55nmol/L it rules out this condition. If the cortisol is <55nmol/L then an ACTH stimulation test is needed to see if Addison's is present or not so if the index of suspicion is high this test should be requested in the first instance.

Treatment

Fluid therapy

Patients with Addison's disease typically present with signs of shock and severe electrolyte imbalances. As such, intravenous fluid therapy is a lifesaving treatment that should be started without delay, and certainly before worrying about definitive diagnosis etc. The greatest priority should be to restore volume/perfusion and any isotonic crystalloid solution available is suitable for this purpose. This should be given as boluses to effect, typically starting with a dose of ~20ml/kg over 10-15 minutes unless contraindications exist, and then repeated as required.

Hyperkalaemia is often present and may be associated with bradycardia or ECG changes. Restoration of perfusion/GFR and initial dilution will go a long way towards correcting this and again the choice of isotonic crystalloid is unlikely to matter in this regard. In fact, Hartmann's solution, which contains small amounts of potassium, is generally preferred for this purpose owing to its buffering and lower sodium concentration. If bradycardia/ECG changes are noted in association with hyperkalaemia then calcium gluconate should be given to temporarily protect the myocardium while potassium is lowered. Additional strategies to lower the potassium such as intravenous glucose (with/without insulin) can also be considered.

Hyponatraemia is often present in dogs presenting with Addiosnion crisis. Whilst there are usually no clinical signs associated with mild to moderate hyponatraemia, if the hyponatraemia is severe (<120 mEq/l), neurological signs including depressed mentation, seizures, coma and death may occur. Clinical signs are secondary to cell and neuronal swelling caused by free water movement from the relatively hypo-osmolar extracellular space to the relatively hyperosmolar intracellular space. The cells of the central nervous system are least tolerant to such changes in volume. In the face of hyponatraemia, neurons rapidly expel intracellular electrolytes and more slowly expel organic osmoles in order to reduce intracellular osmolarity and limit further cellular swelling.

The aim of treatment of hyponatraemia is to increase the blood sodium concentration towards the lower end of the normal range as a rate no greater than 0.5-1mEq/l/hr. The exception to this is in cases of symptomatic or severe hyponatraemia (<120mEq/l) when an initial rapid increase in sodium is preferable. Sodium must be carefully monitored during the initial boluses that are used to correct hypoperfusion as there is the potential for rapid fluctuations to occur.

A fluid with a [Na] close to the patient's initial [Na] should be sued for this purpose to avoid large shifts and if needed, isotonic and hypotonic fluids can be mixed to achieve something with a closer matching concentration.

For asymptomatic patients with moderate hyponatraemia (<130mEq/l), fluid therapy with a fluid containing a higher level of sodium than blood sodium can be cautiously given after restoration of perfusion.

The most concerning complication in the treatment of hyponatraemia is cerebral haemorrhage and myelinolysis resulting from neuronal shrinking as water moves out of the cell. Clinical signs resulting from this may not become evident for several days after the initial insult and may include paresis, ataxia, obtundation, dysphagia and other neurologic abnormalities. Some dogs recover with time and intensive supportive therapy. Given the potential delay, it cannot be assumed that a rapid increase in [Na+] is being well tolerated at the time of treatment, hence the conservative recommendation for correction.

Glucocorticoid replacement

Cortisol is important for maintenance of blood pressure and gastrointestinal health. As such replacement should be started as soon as possible in dogs with Addison's. It should not be started prior to definitive diagnosis and administration of exogenous steroids may interfere with diagnostic tests. Dexamethasone is generally used in the first instance and this can be started simultaneously with an ACTH stimulation test in highly suspicious cases as it will not be measured by cortisol assays. The initial dose is 0.1mg/kg IV SID and this is generally continued until dogs are sufficiently recovered that they start to eat. Thereafter I typically transition them onto prednisolone at a dose of 0.5mg/kg SID. Ultimately, this dose is excessive but in the first instance it is more cautious to give too much rather than too little.

The majority of dogs require 0.05-0.25mg/kg prednisolone daily to control their clinical signs and this therapy is required lifelong. There are no good tools available for the monitoring and adjustment of this medication and it is largely based on owner reports of clinical signs. If signs of iatrogenic HAC develop then dogs are likely receiving too much. If dogs are down-titrated and they start to become lethargic or develop gastrointestinal signs then they are likely receiving too little. Dose adjustments should not be any more frequent than once per week to allow for proper assessment.

The maintenance dose of prednisolone that a dog receives is the correct dose for "normal" circumstances. The body requires more glucocorticoids at times of stress, which include mental stress (kennels, trips to the vet etc) and physiologic stress (illness, anaesthetic procedures etc). In such instances a short-term increase in prednisolone, typically to 0.5mg/kg SID), is generally required and owners should be aware that they are to give the higher dose in the short term if they are in any doubt.

Mineralocorticoid supplementation

Aldosterone is responsible for potassium excretion and sodium/water retention. Much has been discussed on the need for this during an acute crisis and therefore the need for short acting mineralocorticoids, such as hydrocortisone, but this requirement can be met with fluid therapy alone and early aggressive mineralocorticoid therapy risks rapid sodium fluctuations, which can be deleterious to the patient.

Mineralocorticoid therapy, therefore, should be viewed as a long-term requirement. Based on license/availability, the only currently sensible choice for this in the UK is DOCP. This can be started as soon as a diagnosis is confirmed. The initial dose is 2.2mg/kg SC. The dose and duration are quite variable and as such the electrolytes should be checked 10 days after dosing, with subsequent doses adjusted based on these findings, as listed in the data sheet. Because the duration of therapy is also variable, many dogs require dosing less than once a month and the manufacturer recommends monitoring electrolytes every 5-9 days after day 25 to see when the effect wears off. While it is possible to get dosing intervals >40 days in some cases by doing this it tends to confuse/frustrate owners and so I prefer to stick to a monthly or 4 weekly dosing strategy in most instances (checking from day 25 onwards that the duration is at least that long). Once a dose and interval has been established then owners can be taught to give the injections at home although electrolyte monitoring every 3-6 months is still recommended as dosing requirements can gradually change over time.