TYPICAL, ATYPICAL AND ‘RELATIVE’ ADRENAL INSUFFICIENCY IN DOGS - DO THEY REALLY EXIST?
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Naturally occurring hypoadrenocorticism is characterized by clinically significant loss of adrenocortical secretory capacity. In the overwhelming proportion of cases, hypoadrenocorticism is a direct result of inadequate adrenocortical function (primary hypoadrenocorticism) rather than a result of subnormal production of adrenocorticotropic hormone (secondary hypoadrenocorticism). Primary hypoadrenocorticism is generally a result of immune-mediated adrenocortical destruction with resultant mineralocorticoid and glucocorticoid deficiency. In a proportion of cases the clinical signs seem to predominantly reflect loss of only glucocorticoid secreting capacity although these patients frequently have concurrent subnormal aldosterone secreting capacity.

AETIOLOGY

Impaired adrenocortical function may develop as a result of disease of any part of the hypothalamic-pituitary-adrenal axis. However in dogs, hypoadrenocorticism is generally a result of substantial destruction of adrenocortical tissue. Although any destruction of adrenocortical tissue may impair adrenocortical reserve, in non-stressful situations approximately 90 % of the adrenal cortex needs to be non-functional before this impairment becomes clinically significant.

In most cases the underlying reason for adrenal destruction appears to be idiopathic or immune-mediated. Interestingly a marked genetic predisposition for hypoadrenocorticism has been demonstrated in Standard Poodles, Bearded Collies and Novo Scotia Duck Tolling Retrievers. Additionally there are a number of other breeds where hypoadrenocorticism is encountered more commonly than would be expected . In those breeds in which a marked breed predilection has not been reported, female dogs are more commonly affected with a ratio of approximately 2.3:1.

Overdosage and/or idiosyncratic reactions in dogs with hyperadrenocorticism treated with mitotane and trilostane have also resulted in both temporary and permanent hypoadrenocorticism. The most likely explanation for the development of hypoadrenocorticism in these animals is substantial adrenocortical destruction secondary to adrenal haemorrhage and necrosis brought about by increased adrenocortical blood flow in response to markedly elevated plasma adrenocorticotropic hormone (ACTH) concentrations.

The phenomenon of relative hypoadrenocorticism has been suggested as a syndrome which may be important in clinical practice. In essence this phenomenon may allegedly be an issue in situations where an unwell animal requires above-normal levels of glucocorticoid and is unable to deliver this as a consequence of a maladaptive response such as adrenal exhaustion, possibly due to chronic overstimulation. The scientific evidence to support the existence of this syndrome is lacking to non-existent and, in the author’s opinion, this is not a valid reason for an animal to be treated with glucocorticoid supplementation.

CLINICAL FEATURES

Hypoadrenocorticism has been reported in dogs ranging from 2 months to 14 years of age, although most affected animals present in young to middle age. The clinical features vary from acute collapse with generalized underperfusion to a variably present group of more non-specific signs that suggest the animal is unwell but do not focus the clinician’s attention on any particular body system or particular characterizing feature.

Patients presenting with acute collapse usually have evidence of generalized, marked hypovolaemia and dehydration, together with vomiting, diarrhoea, abdominal pain and hypothermia. Some may have severe gastrointestinal haemorrhage with melaena and occasional haematemesis. Although affected animals may have an inappropriately low heart rate for their degree of circulatory collapse and indeed some may even be bradycardic, the chronotropic drive induced by the hypovolaemia means many severely affected individuals will be tachycardic. These patients are obviously unstable and represent a true medical emergency that requires stabilization with rapid parenteral fluid therapy, at least initially.
It is not uncommon for dogs with primary hypoadrenocorticism to have a waxing and waning illness characterized by vague illness with variable gastrointestinal signs and depression/weakness interspersed with periods of apparent normality before they present in a collapsed state.

All dogs with primary hypoadrenocorticism are potentially unstable as they are variably hypovolaemic and are prone to marked hypotension. This hypotensive potential is due to a lack of aldosterone secretion and is possibly further exacerbated by concurrent decreased vascular responsiveness to normal pressor effects, mediated through the overproduction of nitric oxide. Consequently if primary hypoadrenocorticism is being considered in any patient, they should be treated as a potentially critical case until their adrenocortical function is clarified.

**ROUTINE CLINICAL PATHOLOGY**

**Haematology:** In the presence of appropriate clinical signs, suspicion for hypoadrenocorticism is dramatically increased by the presence of lymphocytosis and/or eosinophilia or simply the absence of a stress leukogram (i.e. lymphopenia and eosinopenia) in a clearly “unwell” patient.

Acute hypoadrenocorticism commonly results in a non-regenerative or variably regenerative anaemia which may be profound in those cases with severe concurrent gastrointestinal haemorrhage.

**Biochemistry:** the most consistent biochemical abnormalities include azotaemia, hyponatraemia, hyperkalaemia, hypochloraemia and less commonly hypoglycaemia and hypercalcaemia.

Hyponatraemia and hyperkalaemia with a sodium:potassium ratio of less than 23:1 are considered characteristic features of primary hypoadrenocorticism although these changes can occur in a variety of other conditions. In addition, artefactual hyperkalaemia may be a confusing consequence of post-collection haemolysis, particularly in Japanese Akitas, or of marked leukocytosis or thrombocytosis.

Additionally, approximately 10 – 30% of dogs with primary hypoadrenocorticism have reference range circulating electrolyte concentrations or only mild hyponatraemia without hyperkalaemia at the time of diagnosis. These animals have either early or mild primary hypoadrenocorticism or, more commonly, selective “glucocorticoid deficient hypoadrenocorticism”. Consequently the diagnosis of hypoadrenocorticism cannot be precluded in animals with normal or mild electrolyte changes.

As with all hypovolaemic conditions, animals with primary hypoadrenocorticism develop azotaemia as a consequence of renal underperfusion. However unlike other hypovolaemic conditions where renal concentrating ability is maintained, dogs with primary hypoadrenocorticism are generally unable to concentrate their urine effectively. Impaired urine concentrating ability is due to mineralocorticoid deficiency and resultant chronic renal sodium loss, depletion of normal renal medullary sodium concentration gradient and impaired water resorption from the renal collecting ducts. As a consequence, azotaemia is usually accompanied by inappropriately dilute urine increasing the potential for affected animals to be mistakenly diagnosed with severe primary renal disease.

Other biochemical abnormalities commonly encountered in dogs and cats with hypoadrenocorticism include hypercalcaemia, hypoglycaemia and varying levels of hypoalbuminaemia or hypoproteinaemia. As with anaemia, the severity of the hypoproteinaemia may be masked by the hypovolaemia/dehydration. Hypoproteinaemia is presumably a consequence of gastrointestinal haemorrhage.

**CONFIRMATION OF DIAGNOSIS**

None of the above potential abnormalities, either alone or in concert, could be considered sufficient evidence to confirm a diagnosis of hypoadrenocorticism. Consequently the use of adrenal function tests is invariably required to confirm a diagnosis of hypoadrenocorticism. As untreated hypoadrenocorticism is both a critical and potentially fatal disease, it is reasonable to expect that clinicians with even a low index of suspicion for clinically significant impaired adrenocortical function will perform an adrenal function test, especially if the test is safe, easy to perform and relatively inexpensive.

**ACTH stimulation test:** A definitive diagnosis of spontaneous hypoadrenocorticism requires the demonstration of subnormal basal and post-ACTH plasma cortisol concentrations in an animal that has not recently received exogenous glucocorticoid therapy. In dogs the ACTH stimulation test can be performed by sampling before and
one hour after the administration of the ACTH analogue tetracosactrin (cosyntropin) either given intravenously at a dose of 5 µgm/kg, or intramuscularly at a dose of 250 µgm per animal.

As hydrocortisone, prednisolone and prednisone all cross-react in cortisol assays it is essential that the ACTH stimulation test be performed before these agents are administered to the dog. In contrast, dexamethasone does not cross-react in cortisol assays and consequently can be used to provide glucocorticoid support to critically ill patients if the clinician is concerned about leaving the patient without glucocorticoid supplementation until the ACTH stimulation test has been completed. It is worth noting dexamethasone does directly inhibit endogenous cortisol production, however this usually takes at least 4-6 hours to take effect. Consequently any artefactual lowering of post ACTH cortisol levels can be avoided by insuring the ACTH stimulation test is completed within 2-3 hours of dexamethasone’s administration.

Endogenous plasma ACTH concentration: Estimating the plasma ACTH concentration is the most reliable means of differentiating primary from secondary hypoadrenocorticism and can also alert the clinician to the likelihood of a prior undisclosed glucocorticoid injection.

TREATMENT

Because of the combination of a potentially critical patient and the inability to confirm a diagnosis by cortisol estimation within hours of hospitalization, there are frequently times when suspected hypoadrenocorticism requires treatment before a diagnosis has been reliably confirmed. Initially most affected animals require concurrent intravenous fluid and parenteral glucocorticoid/mineralocorticoid replacement therapy.

Initial stabilising therapy: Fluid therapy should be started as soon as possible in the acutely sick patient. Patients with hypoadrenocorticism are susceptible to fluid overload and additionally rapid correction of the hyponatraemia may result in structural neurological disease and myelinolysis characterized by a variety of variably reversible neurological signs (Brady et al 1999, MacMillan 2003). There is thus a conflict between the need to rapidly correct the severe hypovolaemia while insuring the serum sodium concentration does not increase rapidly. Consequently the fluid of choice is normal saline (0.9%) either with a loading dose with an initial rate of 10-30 ml/kg/hr with a subsequent reduction to no more than twice maintenance levels (120 ml/kg/24 hours) after 2-3 hours or starting with the lower rate from the beginning. The latter option is certainly preferable if hydrocortisone is the steroid replacement used.

Because of the potential for excessively rapid correction of the hyponatraemia, plasma sodium concentration should be monitored closely. Experimental and clinical observations suggest the degree of correction over the first 24 hours is more important than a rate over any given period and problems are unlikely if the plasma sodium does not increase by more than 10 to 12 mmol/L in the first 24 hours.

Although fluid therapy alone generally results in a marked reduction in plasma potassium, restoration of renal perfusion and correction of acidosis it should be complemented by treatment with a parenteral agent possessing both glucocorticoid and mineralocorticoid activity. Currently, hydrocortisone sodium succinate (HSS) is the only commercially available parenteral steroid with equipotent glucocorticoid and mineralocorticoid activity. Although soluble dexamethasone or prednisolone preparations can be used, the lack of mineralocorticoid activity make them less attractive alternatives to HSS.

Hydrocortisone sodium succinate is the succinate ester of hydrocortisone or cortisol, the principal steroid produced by the adrenal cortex in dogs. It has equipotent glucocorticoid and mineralocorticoid activity. However, it has only 25% of the glucocorticoid potency of prednisolone and less than 1% of the mineralocorticoid potency of fludrocortisone. At the recommended doses it provides sufficient glucocorticoid and mineralocorticoid activity to treat the clinical consequences of primary hypoadrenocorticism and consequently can be effectively used in the short-term management of these patients (Church et al 1999).

Hydrocortisone sodium succinate is administered as an intravenous infusion at a dose of 0.5mg/kg/h until normal gastrointestinal function has returned, the dog is eating and drinking normally and can be changed to oral steroid supplementation. In a dog with clinically significant hypoadrenocorticism this dose is likely to produce plasma cortisol concentrations of approximately 1000 nmol/L within 2 to 3 hours. Such a cortisol concentration is likely to provide adequate glucocorticoid and mineralocorticoid replacement in stressed dogs with impaired adrenocortical function.
As there is potential for HSS to adhere to plastic or glass at low concentrations it is best to administer it in its own fluid bag made up to a concentration of 1mg/mL. It is incompatible with a variety of different solutions including ampicillin sodium and it is therefore best to dilute the HSS in normal saline.

**Maintenance therapy:** Once the patient is stabilised, glucocorticoid and mineralocorticoid replacement therapy is almost always needed to be maintained for the remainder of the animal’s life. Traditionally, a semi-selective mineralocorticoid, fludrocortisone and a semi-selective glucocorticoid (cortisone acetate or prednisolone) are initially used together. The former is discontinued in a proportion of patients after one to two months.

In the USA a proportion of patients are maintained on a combination of a selective mineralocorticoid, deoxycorticosterone pivalate (DOCP) (Percorten®, Novartis) and a semi-selective glucocorticoid (cortisone acetate or prednisolone). Some of the pertinent features of the most effective drugs used to maintain hypoadrenocorticism patients are given below.

**Fludrocortisone acetate:** Fludrocortisone acetate is a synthetic adrenocortical steroid with a fluoride ion substituted at the 9α position and an 11β-hydroxyl group giving it both glucocorticoid and mineralocorticoid potency. Because of the 9α fluoride substitution, fludrocortisone has potent mineralocorticoid activity while the 11-hydroxylation confers significant glucocorticoid activity. By comparison, fludrocortisone has 10 times the glucocorticoid activity and 125 times the mineralocorticoid activity of cortisol.

The dose of fludrocortisone is 10 to 30μg/kg administered orally once daily. Typically a lower dose is used initially with subsequent titration based on clinical impression and plasma electrolyte concentrations. Dose adjustments are usually made after weekly electrolyte evaluations. Once these are stable and within the normal range adjustments can be made every 3 to 4 months.

In patients receiving concurrent long-term fludrocortisone and prednisolone, it is not uncommon for the dose of fludrocortisone to gradually increase, as there appears to be a reduction in its mineralocorticoid efficacy over time (Kintzer and Peterson 1997). Although many possible mechanisms for this exist, it is tempting to speculate that this represents accelerated metabolism of both steroids in response to the chronic “supraphysiological” state created by long-term daily prednisolone administration. In the author’s opinion, this “fludrocortisone creep” is not a feature of patients treated with concurrent cortisone acetate and fludrocortisone. In such treated patients, the fludrocortisone dose required to maintain normal electrolyte levels is generally at the lower end of the suggested dose range.

**Desoxycorticosterone pivalate:** is a potent mineralocorticoid analogue. As it has neither 11β or a 17β hydroxylation, it theoretically has little if any glucocorticoid activity. The pivalate ester means the preparation will be relatively long-acting.

The recommended dose of DOCP is 2.2 mg/kg by deep intramuscular injection every 25 days although subcutaneous injection has been shown to be an effective alternative (McCabe et al 1995). Plasma electrolyte, urea and creatinine concentrations are monitored every two weeks to determine the duration of action and help individualize the dose. Once stabilised it is prudent to check electrolytes every 3 to 6 months. Most dogs are well controlled on 1.1 to 2.2 mg/kg every 3 to 4 weeks although it has been suggested that occasional individuals will require more frequent dosing. As DOCP has no glucocorticoid activity it is essential that patients receive concurrent glucocorticoid supplementation with either cortisone acetate or prednisolone.

**Cortisone acetate:** Cortisone is a synthetic steroid with an 11-keto substitution. Once absorbed, it is rapidly activated to hydrocortisone by a distinct 11β-hydroxysteroid dehydrogenase operating in a reductive mode. As cortisone is rapidly 11-hydroxylated to cortisol, it provides a complete replacement for any form of cortisol deficiency. As it has equipotent glucocorticoid and mineralocorticoid activity it will also provide more mineralocorticoid activity than other synthetic glucocorticoids such as prednisolone. In addition, its shorter half-life and lower overall activity means it may be less likely to create iatrogenic hyperadrenocorticism with long-term administration.

In patients with hypoadrenocorticism, orally administered cortisone acetate can be used as an effective long-term cortisol replacement. The dose of cortisone acetate must be individualized according to the severity of the condition, the response obtained and what other glucocorticoid or mineralocorticoid is being concurrently administered. In the change over period as animals recover from an acute crisis, start eating and drinking and are changed from parenteral to oral medication most hypoadrenocortisocortic dogs are started on a dose of 0.5-1.0mg/kg/12-24hr. However once they are stable, generally a dose of 0.5mg/kg/12-24 hr provides adequate additional glucocorticoid supplementation.
Prednisolone: Prednisolone is a synthetic adrenal steroid with moderately potentiated glucocorticoid activity (approximately 5 times that of hydrocortisone) and less than 10% of hydrocortisone’s mineralocorticoid activity. Some clinicians advocate its use as a glucocorticoid supplement in the long-term management of hypoadrenocorticism at a dose rate of between 0.2- 0.5 mg/kg/24hr. In the author’s opinion cortisone acetate is a more effective alternative.