

119 HYPOADRENAL-GLAND DISEASE

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Hypoadrenocorticism can be one of the most diagnostically and therapeutically challenging, confusing and frustrating diseases that a companion animal practitioner must face. The first human cases were described in 1855 by Thomas Addison, thus this disease is often referred to in the literature as "Addison's" disease. About the same time, animal experiments verified that bilateral removal of the adrenal glands leads rapidly to death. It wasn't until the 1930's that crude aqueous extracts of adrenal glands were shown to prevent mortality in adrenalectomized cats.¹ It was still several more years before sources of glucocorticoids and mineralocorticoids became commercially available, so that affected humans could now survive this previously fatal disease.

Hypoadrenocorticism is an uncommon endocrine disorder in dogs and very rare in cats. The first canine case was reported in 1953² and the first reported case in a cat not until 1983.³ The prevalence in dogs at one large veterinary hospital is said to be less than 1/1000.⁴ Since its initial recognition, several case series of dogs with hypoadrenocorticism have been published.^{2, 5, 6, 7} Only one series of 10 cats with this disorder has appeared.⁸

ETIOLOGY

Hypoadrenocorticism in dogs and cats is most often associated with diseases of the adrenal gland that result in combined deficiencies of glucocorticoids and mineralocorticoids (**primary hypoadrenocorticism**). Less commonly, disruption of the hypothalamic-pituitary-adrenal axis occurs. This leads to deficient tropic hormone secretion of either corticotropin releasing hormone (CRH), or adrenocorticotrophic hormone (ACTH). Lack of pituitary stimulation of the adrenal cortex results in bilateral adrenal cortical atrophy, and is classified as **secondary hypoadrenocorticism**. Secondary hypoadrenocorticism is only associated with signs of glucocorticoid deficiency.

PRIMARY HYPOADRENOCORTICISM

Primary hypoadrenocorticism is most often classified as idiopathic, with histopathological findings usually characterized as bilateral adrenal atrophy with fibrosis.¹ In some cases significant infiltration of the adrenal cortex by lymphocytes and plasma cells has been seen, suggesting an immune mediated basis for the disease. Two recent reports have identified through indirect immunofluorescence the presence of anti-adrenal antibodies in the serum of 2 of 3 dogs with primary adrenal insufficiency.^{9, 10} The third dog had an infiltrate of lymphocytes and plasma cells in its adrenal cortex at necropsy. One of these dogs was also severely hypothyroid and had anti-thyroid antibodies detected in its serum as well. Up to 50 per cent of humans with hypoadrenocorticism are thought to have an immune mediated basis for their disease and multiple endocrine organs are often involved simultaneously.¹ In a survey of 45 dogs from the University of California,

six were found to have at least one additional endocrinopathy.² Four were hypothyroid, one had diabetes mellitus and one had partial gonadal failure .

Other less common causes for spontaneous primary adrenal failure include: infectious agents (coccidioidomycosis, blastomycosis, or tuberculosis), hemorrhagic infarctions, metastatic neoplasia, trauma, and amyloidosis.^{1, 11}

Genetic influences may play a role in some breeds of dogs. The only well documented cases of familial hypoadrenocorticism have occurred in standard poodles located on the East coast of the United States.^{4, 12} Labrador retrievers and Portuguese water spaniels are also said to have familial tendencies for this disease.¹³

Iatrogenic primary hypoadrenocorticism may follow the administration of the adrenocorticolytic drug o,p'-DDD (Mitotane), when treating dogs for hyperadrenocorticism (Cushing's disease). Relative cortisol deficiency is common after treatment for this disease, and is usually transient. However, combined mineralocorticoid and glucocorticoid deficiency occurs in approximately 5 per cent of treated dogs.^{14, 15, 16, 17} Dogs suffering severe adrenal cortical destruction following o,p'-DDD therapy often require supplemental mineralocorticoids and glucocorticoids for life.

Two other therapeutic agents that may interfere with adrenal cortical function are ketoconazole and megestrol acetate. Both only interfere with the synthesis of glucocorticoids. Ketoconazole impairs the normal response of the adrenal cortex to ACTH but leaves basal concentrations unchanged.¹⁸ Adrenal reserve, as measured by ACTH stimulation testing, returns to normal within three weeks of stopping ketoconazole administration.

Megestrol acetate has profound adrenal suppressive effects in cats.¹⁹ When given to normal cats at 5 mg/day for 16 days, ACTH response was severely impaired. Only three of seven cats had regained normal adrenal reserve capacity one month after stopping the drug. None of the cats showed signs of cortisol deficiency, however.

SECONDARY HYPOADRENOCORTICISM

Secondary hypoadrenocorticism may be either spontaneous, or iatrogenic. Spontaneous secondary hypoadrenocorticism occurs due to lack of normal adrenal stimulation via CRH or ACTH and implies primary hypothalamic or pituitary failure has led to adrenal malfunction. Most spontaneous cases have been due to inflammation, tumors, trauma or congenital defects of the hypothalamus or pituitary gland.^{1, 20}

Iatrogenic-secondary hypoadrenocorticism is the most common cause for adrenal cortical non-responsiveness in veterinary practice. It occurs following the administration of exogenous glucocorticoids. Exogenous glucocorticoids suppress normal pituitary ACTH production and lead to bilateral adrenal atrophy. Secondary adrenal atrophy may develop after the administration of virtually any glucocorticoid used by veterinarians, including oral, injectable and topical. Even otic and ophthalmic preparations can induce ACTH non-responsiveness quite rapidly.^{21, 22} Fortunately, the majority of dogs and cats receiving exogenous glucocorticoids do not develop signs of glucocorticoid deficiency when their medication is discontinued.

Although any glucocorticoid may inhibit ACTH release, long acting depot preparations cause the most severe adrenal atrophy and result in long periods of adrenal hypofunction. Dexamethazone containing preparations are 50 to 150 times as potent as endogenous cortisol in suppressing ACTH production.¹

Adrenal non-responsiveness may occur within a few days following daily or repositol glucocorticoid administration. Most dogs and cats have normal ACTH stimulation results within two weeks of steroid withdrawal.²³ However, those on potent preparations or who receive glucocorticoids for months or years may have very prolonged periods before ACTH stimulation results normalize(weeks to months).^{1, 5}

PATHOPHYSIOLOGY

The adrenal glands are essential for life. They secrete a number of hormones that are required for normal functioning of an animal as well as for survival in stressful situations (cortisol, epinephrine, norepinephrine). The adrenal cortex is composed of three layers, the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis. The zona glomerulosa is primarily involved with the synthesis and secretion of the mineralocorticoid, aldosterone. The zona reticularis is involved primarily with synthesis of glucocorticoids, of which cortisol is the most important in mammals. The inner zona reticularis secretes primarily adrenal sex steroids. The androgens and estrogens secreted by the zona reticularis are of unknown clinical significance in animals.¹ The adrenal medulla secretes the catecholamines, epinephrine and norepinephrine which are not effected in hypoadrenocorticism.

There is significant adrenal cortical functional reserve in animals and man. It is estimated that approximately 90 per cent of adrenal function must be compromised before clinical signs become evident.¹ Approximately ten per cent of animals with hypoadrenocorticism have waxing/waning clinical courses, with signs only becoming evident following stressful situations (disease, trauma, surgery, kenneling, etc.). This probably reflects slight residual adrenal reserve that maintains them at rest in a non-stressful environment. As their glandular reserve progressively declines, they ultimately may present in an adrenal crisis with no obvious precipitating event.

MINERALOCORTICIDS IN HEALTH AND DISEASE

Mineralocorticoids serve primarily to maintain sodium, chloride and water balance in the animal. The primary adrenal mineralocorticoid, aldosterone, promotes renal reabsorption of sodium and chloride and its accompanying water in exchange for potassium and hydrogen ions. Although this effect is mediated primarily via the kidneys, other epithelial tissues including the GI tract, skin and salivary glands undergo similar activities following aldosterone release.¹

Aldosterone release is controlled by three mechanisms working concurrently. The primary control is via the renin-angiotensin-aldosterone system. Minor modifications in aldosterone secretion occur in response to hyperkalemia, and also following an increase

in plasma ACTH concentrations. Renin is stored in the cells of the juxtaglomerular apparatus of the kidney. It is released in response to changes in extracellular volume. Anything that leads to hypotension or contraction in extracellular fluid volume will stimulate renin release (hemorrhage, dehydration, diuretic use, salt restriction). Renin acts on angiotensinogen in the circulation to release angiotensin-I, an alpha-2-globulin. Angiotensin-I is hydrolyzed by an angiotensin converting enzyme in the lung to angiotensin-II, a potent vasoconstrictor and the primary stimulus for aldosterone release. Angiotensin-II has a direct effect on vascular smooth muscle raising blood pressure. Aldosterone promotes active sodium, chloride, and water reabsorption which expands the extracellular fluid (ECF) volume. Once blood pressure and ECF volume normalize, further renin release is inhibited.^{1, 24}

An inability to release aldosterone has a number of adverse effects on the animal. The failure to conserve sodium and chloride leads to loss of these important electrolytes along with water. The resulting hyponatremia and hypochloremia are typical of primary hypoadrenocorticism. A continuing loss of sodium, chloride and water causes a progressive decline in ECF volume which results in dehydration, hypotension and prerenal azotemia. In association with hypotension and dehydration, pituitary ADH release may be increased promoting renal water reabsorption, further aggravating the hyponatremia. Untreated human patients have an impaired ability to excrete a free water load and are prone to water intoxication. Decreased tissue perfusion, prerenal azotemia, and failure to eliminate hydrogen ions in exchange for potassium, all lead to varying degrees of metabolic acidosis.

Polydipsia, polyuria, and low urine specific gravities in the face of clinical dehydration and azotemia are frequent abnormalities in both dogs and cats with hypoadrenocorticism. These findings most likely reflect an ongoing solute diuresis of sodium, chloride and water secondary to hypoaldosteronism. Profound hyponatremia also impairs the renal concentrating capacity through medullary solute washout, decreasing the maximal renal concentrating ability significantly. This is because sodium and chloride account for approximately 50 per cent of the normal renal medullary solute gradient.

It has also been proposed that severe hyponatremia may impair normal renal concentrating ability by interfering with ADH release.²⁵ The primary stimulus for ADH release is an increase in serum osmolality. Since sodium and chloride account for the majority of ECF osmolality, severe decreases in these ions may impair normal osmotic stimuli for ADH release, promoting a dilute urine in the face of dehydration.

Failure to excrete potassium in exchange for sodium leads to hyperkalemia. One of the classical electrolyte abnormalities of adrenal insufficiency. Hyperkalemia is not only due to hypoaldosteronism, but is worsened by the decreased renal perfusion (impairs excretion) and accompanying metabolic acidosis (promotes shift of potassium from intracellular to extracellular space). Hyperkalemia leads to decreased neuromuscular excitability, and impaired myocardial contractility. This may result in signs of muscular weakness, bradycardia, and hypotension later in the disease course. As serum potassium concentrations approach 10 mEq/L, severe bradycardia, and atrial arrest are seen. Ultimately, ventricular fibrillation or cardiac standstill result in death of the patient.

GLUCOCORTICOIDS IN HEALTH AND DISEASE

Glucocorticoids are synthesized primarily in the zona fasciculata of the adrenal cortex and have effects on nearly every tissue in the body. Their synthesis and secretion are under a relatively simple negative feedback mechanism between the hypothalamic-pituitary axis and the adrenal gland (Fig. 119-1).^{1, 2, 24} When serum cortisol concentrations decline, hypothalamic CRH increases which stimulates increased production and release of pituitary ACTH. ACTH circulates to the adrenal cortex and increases production and release of cortisol. Increasing levels of cortisol inhibit CRH and ACTH release, which inhibits adrenal glucocorticoid production.

In primary hypoadrenocorticism, the lack of negative feedback by cortisol on the pituitary gland leads to chronically elevated concentrations of ACTH (Fig. 119-1). In secondary hypoadrenocorticism, whether iatrogenic or spontaneous, chronic lack of stimulation of the adrenal cortex by ACTH leads to severe adrenal cortical atrophy, and endogenous ACTH concentrations are very low (Fig. 119-1). Thus, endogenous plasma ACTH concentrations are the best diagnostic test for differentiating primary from secondary hypoadrenocorticism.

In normal animals, glucocorticoids promote a general sense of well being and stimulate appetite. They maintain fasting blood glucose values by promoting gluconeogenesis and hepatic glycogenesis, by impairing uptake of glucose by peripheral tissues, and by augmenting lipolysis. Glucocorticoids promote renal water elimination by increasing the GFR and inhibiting ADH effects on the kidney. They help to maintain normal serum calcium concentrations by augmenting renal excretion of calcium. They have anti-inflammatory and immunosuppressive effects on the white blood cells while stimulating erythrocytosis. They protect organisms against shock and maintain blood pressure by increasing vascular reactivity to catecholamines, preventing capillary dilatation and impairing protein extravasation from capillaries.

Cortisol deficiency is most often manifested by gastrointestinal signs and general signs of malaise. Animals are depressed, anorectic, lethargic, and have weight loss. They usually have vomiting and occasional diarrhea. Abdominal discomfort or pain is reported in humans and occasionally in dogs and cats with hypoadrenocorticism. It is thought to be cortisol related. Mild to moderate non-regenerative anemia, eosinophilia, lymphocytosis and relatively normal white blood cell counts in stressed animals all reflect the glucocorticoid deficiency. Hypoglycemia occurs in moderate numbers of adrenally insufficient animals, but is not often severe. Hypoglycemia may be associated with lethargy, tremors weakness, or other neurological signs. Hypercalcemia occurs in approximately 30 per cent of dogs with hypoadrenocorticism and appears to be related to cortisol deficiency.²⁶ Signs are typically exacerbated during periods of stress, and an adrenal crisis may follow some minor stress in the animals life.

CLINICAL FINDINGS

SIGNALMENT

Hypoadrenocorticism is primarily a disease of middle aged female dogs. Most surveys indicate that from 70 to 85 per cent of affected dogs are female.^{1, 2, 6, 7, 13} The age of presentation ranges from 2 months to 9 years with a mean of around 4 to 4.5 years of age. The majority of dogs are diagnosed under 7 years of age. Although there is no increased risk based on breed or size, some evidence for familial tendencies exist in standard poodles^{4, 12}, Labrador retrievers and Portuguese water spaniels¹³.

HISTORY^{1, 2, 6, 7, 13, 27}

The clinical signs exhibited by dogs with hypoadrenocorticism usually reflect combined mineralocorticoid and glucocorticoid deficiencies. Hypoadrenocorticism is typically a disease associated with vague, non-localized clinical signs such as depression, lethargy, weakness, anorexia and weight loss (Table 119-1)). In others, signs more typical of gastrointestinal diseases (vomiting, diarrhea), or renal diseases (polydipsia and polyuria), are seen. Additional abnormalities reported less often include shaking or tremors and a sensitive abdomen. The duration of clinical illness is generally around two weeks before presentation to a veterinarian. Although it is commonly considered a disease that has a waxing and waning course as animals get into and recover from stressful situations, this observation is actually made by only 10 per cent of owners. Some animals will have received, and generally responded well to supportive care for these signs in the recent past (fluids and glucocorticoids). Because signs of adrenal insufficiency mimic many other common diseases, the definitive diagnosis may be missed as animals are treated for these more commonly recognized disorders. They may ultimately present in what is perceived to be an "acute" adrenal crisis, when in actuality it is the end stage of progressively deteriorating adrenal gland disease.

PHYSICAL EXAM FINDINGS

Physical examination findings are generally unrewarding in terms of leading to a specific diagnosis of adrenal insufficiency. This is because of the non-specific nature of the abnormalities induced by mineralocorticoid and glucocorticoid deficiencies. Depression, weakness and dehydration are the most commonly identified physical exam findings. Dogs in an adrenal crisis are presented in shock, usually only vague signs of illness were noted previously. In approximately one third of the cases, bradycardia and/or weak pulses are identified.^{1, 2, 13, 27} Although bradycardia is not pathognomonic for hypoadrenocorticism, finding it in a dehydrated, hypotensive animal with GI signs should make you strongly suspicious that hypoadrenocorticism exists. Only occasionally will abdominal pain, hypothermia or emaciation be found.

LABORATORY DIAGNOSIS

The definitive diagnosis of hypoadrenocorticism requires a thorough history, a careful physical exam, and complete laboratory screening. In animals suspected to have hypoadrenocorticism, a CBC, serum chemistry profile (including an electrolyte panel), and a urinalysis will be very helpful in supporting the diagnosis. However, a definitive

diagnosis is only established through assessing adrenal reserve capacity (ACTH stimulation test).

Hemogram Alterations

Alterations in the hemogram are much discussed but only occasionally of value in the diagnostic process. The changes seen are all secondary to glucocorticoid deficiency. A mild normocytic, normochronic anemia is common in dogs. It may be masked initially by the dehydration associated with this disease, only becoming evident following volume expansion. The packed cell volume is usually in the 25 to 35 per cent range.

Ill animals with non-infectious diseases typically have a stress leukogram. This is characterized by a mature neutrophilia, eosinopenia, lymphopenia, and monocytosis. The patient with hypoadrenocorticism, lacking adequate cortisol reserve, would not be expected to develop this pattern in spite of being seriously "stressed". This would produce a hemogram characterized by a normal WBC count, with an eosinophilia, and a lymphocytosis. In actuality, a "non-stressed" hemogram is uncommon in dogs with hypoadrenocorticism. Eosinophilia and lymphocytosis occur in only 10 to 15 per cent of affected dogs.^{1, 2, 6, 7} However, seeing a normal white count and normal numbers of eosinophils or lymphocytes in a very ill animal is unexpected, and hypoadrenocorticism should be included in your rule-outs.

Electrolyte Abnormalities

Sodium and potassium abnormalities-The patient with hypoadrenocorticism may have abnormalities in all the commonly reported electrolytes (sodium, potassium, chloride, calcium, phosphorous). Typically, a presumptive diagnosis of hypoadrenocorticism is made based upon identifying the presence of hyponatremia, hypochloremia, hyperkalemia and a sodium/potassium ratio of less than 27:1 (Table 119-2). Normal sodium/potassium ratios are from 27:1 to 40:1 with a mean of 30:1.^{1, 2, 27} Most dogs with adrenal insufficiency have ratios of less than 20:1. Finding hyperkalemia and an abnormal sodium/potassium ratio warrants therapy to prevent life-threatening cardiac arrhythmias from developing, regardless of its cause. The most common diseases associated with hyperkalemia other than hypoadrenocorticism are acute oliguric or anuric renal failure and severe gastrointestinal disorders. All of these diseases benefit from judicious fluid administration while tests to discriminate between them are performed.

Unfortunately, neither the presence of normal electrolytes nor a normal sodium to potassium ratio can completely rule-out a diagnosis of hypoadrenocorticism. Approximately 10 per cent of dogs with this disease have a normal sodium, and/or a normal potassium.^{6, 7, 28, 29, 30} Clinical signs of so-called "atypical hypoadrenocorticism"³⁰ are due primarily to cortisol deficiency and may be caused by either primary or secondary hypoadrenocorticism.¹ Some dogs with **primary** hypoadrenocorticism initially have signs attributable only to severe cortisol deficiency, while mineralocorticoid secretion is adequate to maintain serum electrolytes in the normal range. Over time, electrolyte abnormalities will develop the expected pattern. If spontaneous or iatrogenic **secondary** hypoadrenocorticism is present, mineralocorticoid release is normal and electrolyte abnormalities never develop (Table 119-3). These latter

cases require an ACTH stimulation test and an endogenous ACTH concentration for definitive diagnosis.

Conversely, finding an abnormal sodium/potassium ratio is not pathognomonic for hypoadrenocorticism. Any disease associated with severe sodium depletion can cause the ratio to become subnormal, while other diseases associated with hyperkalemia also produce ratios of < 27:1 and may be misdiagnosed as hypoadrenocorticism (Table 119-4). It is important to differentiate non-adrenal from adrenal causes for hyperkalemia, as the therapy for primary hypoadrenocorticism is for life.

The most often recognized causes for non-adrenal associated hyperkalemia include acute oliguric/anuric renal failure, chronic oliguric renal failure (less commonly), uroabdomen secondary to a ruptured urinary bladder or ureter, post-renal uremia associated with urethral obstruction, severe gastrointestinal diseases, and metabolic acidosis (Table 119-4).^{1, 27, 31} Gastrointestinal diseases that may present with biochemical data resembling hypoadrenocorticism include infectious diarrheas (salmonellosis, trichuriasis, ancylostomiasis, parvovirus, distemper), perforated GI ulcers, gastric dilatation-volvulus, and severe malabsorption.^{1, 31}

Less commonly, hyperkalemia may be associated with the use of therapeutic agents (potassium sparing diuretics, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and potassium containing fluids). These causes should be readily identifiable.

Another less commonly recognized cause for both hyperkalemia and hyponatremia is seen in dogs with both chylous and non-chylous pleural effusions.³² The exact mechanism is unknown. Renal potassium excretion is impaired in spite of elevated serum aldosterone concentrations in these animals.

Massive release of potassium to the extracellular space can occur in severe crush injuries, in association with aortic thrombosis in cats or following rhabdomyolysis secondary to heat stroke or heavy exercise. It also occurs in association with severe hemolysis (rare), or in massive infections.¹

Pseudohyperkalemia has been seen in the Akita breed as a unique genetic abnormality. Their RBC's contain larger potassium concentrations than most dogs and potassium levels elevate in their serum when it is left in contact with RBC's for 4 hours or more following collection.³³ Pseudohyperkalemia may also occur in animals with severe leucocytosis (total WBC = > 100,000/mm³), or in cases of severe thrombocytosis (platelets = > 1,000,000/mm³).²⁷ The potassium elevates in the serum as blood is clotting and is an in-vitro phenomenon.

Hyponatremia can occur in many diseases other than hypoadrenocorticism (Table 119-4). Severe hyponatremic states often result in the sodium/potassium ratio being less than 27:1 and hypoadrenocorticism must be considered in the differential diagnosis of the patient. Diseases associated with hyponatremia include gastrointestinal losses secondary to vomiting, hemorrhagic gastroenteritis, and parvoviral enteritis, nephrotic syndrome and other edematous states, post-obstructive diuresis, congestive heart failure, myxedema, diabetes mellitus, primary polydipsia, and inappropriate secretion of ADH.^{1, 2, 25, 27, 31, 34, 35} All of these diseases are differentiated from hypoadrenocorticism by their response to

therapy and results of ACTH stimulation testing. Their clinical signs and other biochemical data overlap a great deal with dogs with primary hypoadrenocorticism and often cannot be differentiated based on these data alone.

Calcium Abnormalities - A somewhat unique biochemical abnormality seen in approximately one third of dogs with hypoadrenocorticism is hypercalcemia.^{2, 26} Although not pathognomonic for this disease, it aids, along with other electrolyte abnormalities, in establishing a presumptive diagnosis. In a review of 16 dogs with hypercalcemia associated with primary hypoadrenocorticism, the range of calcium concentrations was from 12.0 to 14.9 mg/dl.²⁶ The magnitude of the hypercalcemia correlates with the severity of their dehydration and other electrolyte abnormalities. Other causes for hypercalcemia must be considered as well and include pseudohyperparathyroidism, primary hyperparathyroidism, hypervitaminosis-D, acute and chronic renal failure, and intoxication with vitamin-D containing rodenticides.

The hypercalcemia further complicates the process of establishing a diagnosis since hypercalcemia is seen much more often in patients with malignancies, such as lymphosarcoma. Hypercalcemia induces polydipsia and polyuria and varying degrees of renal failure. These are all findings seen in hypoadrenocorticism as well.

Renal Function

Elevations in BUN, and creatinine and a reduction in renal concentrating ability are common in dogs with hypoadrenocorticism (Tables 119-2, 119-3). The mean BUN concentration in two large surveys was 83 mg/dl, with a range of 12 to 223.^{1, 5} This coupled with a urine specific gravity that is often less than 1.030,¹ and sometimes is isosthenuric in a dehydrated animal⁶ may lead to the erroneous conclusion that primary renal failure exists and is responsible for the clinical signs.

Serum creatinine values are typically less elevated than the BUN concentrations, supporting that a pre-renal component exists. Values for creatinine typically range from 0.9 to 3.8 mg/dl (mean = 2.2 mg/dl).⁵

The elevations in BUN and creatinine reflect the severe volume contraction, hypotension, and dehydration that are associated with hypoadrenocorticism. The decreased urine specific gravity is related to the hyponatremia, medullary solute washout, and solute diuresis seen in this disease. The BUN and creatinine usually return to normal in 24 to 48 hours if appropriate fluid therapy is utilized, even in cases with BUN concentrations over 200 mg/dl. Renal concentrating ability returns to normal in nearly all cases following appropriate medical management.

If hypotension is severe, renal ischemia may develop. The ischemia may induce a primary renal injury. Thus, a primary renal injury can be superimposed on a pre-renal component, confounding both management and diagnosis.

Acid Base Status

Mild to moderate degrees of metabolic acidosis exist in many dogs with hypoadrenocorticism.^{1, 2} The acidosis is secondary to decreased renal H⁺ excretion in the

mineralocorticoid deficient animal. Decreased renal perfusion and hypotension may also contribute to the acidosis. Fortunately, the majority of animals do not require specific therapy for the acidosis. Adequate fluid resuscitation and mineralocorticoid replacement corrects the abnormality in the most cases.

Blood Glucose

Hypoglycemia (blood glucose = < 70 mg/dl) is an uncommon laboratory finding in animals with hypoadrenocorticism in spite of the important role that cortisol plays in maintaining fasting blood glucose concentrations (Table 119-2). Hypoglycemia is reported in from 8⁶ to 37¹ per cent of dogs with this disease. It may be severe enough to cause weakness, tremors and even convulsions. Occasionally, hyperglycemia is seen as well.

Serum Albumin

Over the past several years I have evaluated a number of dogs with primary hypoadrenocorticism that have had mild hypoalbuminemia noted in addition to other features typical for this disease. The serum concentration was usually between 2.0 and 2.6 g/dl (normal > 2.7 gm/dl). In all cases, no other cause for the hypoalbuminemia could be identified and it reversed with treatment for the hypoadrenocorticism. Hypoalbuminemia was noted in one of 6 dogs with hypoadrenocorticism in another review.³⁶ The exact mechanism remains speculative at this time, although it is known that glucocorticoids influence hepatic albumin synthesis, and a deficiency in cortisol may impair hepatic albumin production.³⁷

RADIOGRAPHIC FINDINGS

Survey radiographs are often taken in dogs in an adrenal crisis, both because of gastrointestinal complaints and the findings of bradycardia and hypotension on physical examination. Thoracic radiographs may identify the presence of microcardia due to the profound hypovolemia present in some patients. The cardiac silhouette appears small relative to the thoracic volume of the animal. The descending aorta will appear flattened and of decreased diameter. The caudal vena cava will also appear of very small diameter.¹ These findings are not diagnostic for hypoadrenocorticism. They reflect the presence of shock and the severity of ECF volume contraction seen in these animals.

One additional radiographic observation that may be made is that of megaesophagus. Several reports have identified this abnormality in recent years.^{1, 28, 29} Some dogs have been asymptomatic (no regurgitation history), while others were evaluated primarily for signs of regurgitation.²⁸ One animal had primary hypoadrenocorticism that was only associated with cortisol deficiency. Replacement glucocorticoid therapy was associated with resolution of the megaesophagus.

ELECTROCARDIOGRAPHIC ABNORMALITIES

The hyperkalemia associated with mineralocorticoid deficiency can have profound effects on myocardial contractility and the EKG of the patient (Fig. 119-2). An EKG is an easy, inexpensive and rapid way to assess changes in serum potassium concentrations in patients with hyperkalemia. When a bradycardia is identified on physical examination an EKG is an efficient way to determine if hyperkalemia may be causing it. This is particularly true once clinicians become familiar with the electrocardiographic changes typical for this electrolyte abnormality. Therapy can then be instituted to correct it while waiting for laboratory values to be returned. An EKG is also an efficient way to monitor the initial therapeutic response of the patient.

EKG changes tend to parallel the severity of the serum potassium concentration. However, since hyponatremia, hypercalcemia, hypoxia and metabolic acidosis can also effect myocardial performance, the severity of EKG changes for a given potassium concentration will vary from patient to patient. In general, if the serum sodium concentration is maintained near normal, the effects of hyperkalemia are less severe.¹

The primary effects of hyperkalemia are on electrical conduction through the myocardium and strength of contractions. Mild hyperkalemia (serum $K^+ = 5.5$ to 6.5 mEq/L) is generally associated with a tall, "peaked" T wave. As the K^+ concentration increases from 6.5 to 8.5 mEq/L there is widening and flattening of the QRS complex, a prolongation of the PR interval, a decrease in P wave amplitude and an increase in duration of the P wave. At potassium concentrations of > 8.5 mEq/L, atrial standstill, absence of P waves, and deviations of the ST segment from the baseline are expected. At serum potassium concentrations of 11 to 14 mEq/L ventricular asystole or ventricular fibrillation are common.

The frequency of occurrence of EKG abnormalities were quantified in a large group of dogs with primary hypoadrenocorticism.⁶ Tall peaked T waves (> 0.5 mV) in lead II occurred in 22 per cent of dogs. A decreased amplitude of the R wave (< 0.5 mV) in lead II was observed in 22 per cent, and absent P waves occurred in 50 per cent of cases. The serum potassium concentration associated with an absence of P waves ranged from 8.6 to 11.3 mEq/L.

ADRENAL FUNCTION TESTING

Although results of a CBC, biochemical profile, urinalysis and EKG may all be supportive of the diagnosis of hypoadrenocorticism, the definitive diagnosis requires assessing the integrity of the hypothalamic-pituitary-adrenal axis. This may be done in a number of ways, including; basal plasma cortisol concentrations, 24 hour urinary 7-hydroxycorticosteroid concentrations, ACTH stimulation testing, endogenous ACTH concentrations, and plasma aldosterone concentrations.

ACTH Stimulation Testing

Basal plasma cortisol concentrations are of little diagnostic value and should not be used as the sole criterion for establishing the diagnosis. Normal dogs can have basal cortisol values of zero, and dogs with hypoadrenocorticism occasionally have resting

values within the low normal range. Assessing adrenal reserve capacity is the only way not to mis-diagnose this disease.

Urinary 7-hydroxycorticosteroid determinations have been shown to be an accurate way to confirm the diagnosis of hypoadrenocorticism. However, they require 24 hour urine collections which limit their usefulness to academic institutions. They also only confirm that circulating cortisol values have been lower than normal for that time period, but do not assess adrenal cortical reserve.¹

Performing an ACTH stimulation test is currently the best method for confirming the diagnosis of hypoadrenocorticism in dogs and cats. The test is run as soon as the diagnosis is suspected, regardless of the time of day. It is important to get sample handling details from the laboratory performing your hormone assays prior to performing the test. Cortisol samples are generally fairly stable in serum or plasma for up to five days at room temperature.¹ If you suspect the diagnosis and must give some sort of glucocorticoid before the test is completed, it is recommended to give dexamethazone, as it does not interfere with the sample assay for glucocorticoids. Most other synthetic glucocorticoids will be measured by the RIA techniques and confound the diagnostic process. It is generally of no increased risk to the patient with hypoadrenocorticism to only administer fluids (saline) as you obtain plasma cortisol values and then give appropriate glucocorticoids as soon as your second sample is collected (one or two hours).

The test is performed in the following manner. Either animal origin ACTH gel (Cortigel 40, Savage Labs, Melville, NY 11747), or synthetic ACTH, tetracosactrin (Cortrosyn, Organon Pharmaceuticals, West Orange, NJ 07052) may be used. The repositol gel preparation is given at a dosage of 1 unit/lb (2.2 u/kg) IM in both dogs and cats, and plasma samples are collected at 0 and 2 hours post administration in dogs and at 0, 60 and 120 minutes in cats. Aqueous synthetic ACTH is given at 0.25 mg/dog or 0.125 mg/cat IM and plasma samples collected at 0 and 1 hour post injection in dogs, and 0, 30, and 60 minutes post injection in cats.

Results of ACTH stimulation testing in dogs and cats with hypoadrenocorticism typically have resting levels in the low normal range which fail to stimulate following ACTH (Fig. 119-3). Post-stimulation values are often similar to or below resting values in a given animal. Some animals will have a slight increase in post-stimulation values, but in all reported cases in dogs, values have been below the minimum normal post-stimulation value for the lab being used (Table. 119-5).^{1, 2, 6, 7} Post-stimulation cortisol values are consistently less than 50 ng/ml (5.0 µg/dl) in dogs with hypoadrenocorticism.

Endogenous ACTH Concentrations

The results of ACTH stimulation testing will not differentiate primary from secondary hypoadrenocorticism. This requires measurement of endogenous plasma ACTH concentrations. Sample handling is critical for this hormone as it is much more labile than cortisol. It is imperative that the lab processing the sample provide you with handling instructions before it is drawn. Samples generally must be drawn and centrifuged immediately and stored frozen in plastic test tubes.

Plasma endogenous ACTH concentrations are primarily of value in animals in which just glucocorticoid deficiency exists (ACTH stimulation test is non-responsive but electrolytes are normal). Some dogs with primary hypoadrenocorticism only have signs of glucocorticoid deficiency e.g. lethargy, depression, anorexia, vomiting, diarrhea and weakness. Their sodium, potassium and chloride values will be normal. Endogenous ACTH values should be very high in dogs with primary hypoadrenocorticism, since no negative feed back from cortisol occurs (Fig. 119-4). Finding very high endogenous ACTH concentrations confirms the pituitary is functioning and the primary lesion is located in the adrenal gland. These dogs should have serum electrolytes monitored every three to four months, as progressive destruction of adrenal tissue is the norm. They would be expected to eventually develop mineralocorticoid deficiency and need replacement therapy. Progressive destruction of adrenal function does not always occur, however. One dog has been reported with pure glucocorticoid deficient primary hypoadrenocorticism that failed to develop electrolyte abnormalities even after several years of monitoring.²⁸ It is being well managed with glucocorticoid replacement therapy alone.

The range of endogenous ACTH concentrations from 18 dogs with primary hypoadrenocorticism was reported as 554 to 4950 pg/ml. Normal values are from 20 to 100 pg/ml.² If both electrolytes and ACTH stimulation testing are abnormal, primary hypoadrenocorticism is confirmed and endogenous ACTH concentrations become of academic interest.

Animals with pituitary failure causing their adrenal insufficiency should have very low endogenous ACTH concentrations which leads to bilateral adrenal atrophy (Fig. 119-4). This is true in both spontaneous and iatrogenic secondary hypoadrenocorticism. Two dogs have been reported with spontaneous secondary hypoadrenocorticism in which endogenous ACTH concentrations were measured. Both dogs had values less than 20 pg/ml.² These animals need only cortisol replacement therapy to control signs of their disease.

Plasma Aldosterone Assay

Measurement of plasma aldosterone concentrations is rarely of diagnostic value and the assay is available commercially from very few sources. It may be of value in dogs suspected to have secondary hypoadrenocorticism and you want to validate that aldosterone secretion is normal. It could also be of value in the rare situation where an animal has hyperkalemia and hyponatremia, an abnormal sodium/potassium ratio, but normal ACTH stimulation results. Such an animal may have primary hypoadrenocorticism, but cortisol reserve is still normal.²⁷

Aldosterone release is measured as part of an ACTH stimulation test protocol. Limited numbers of dogs with primary hypoadrenocorticism have been tested, but all had very low to non-detectable basal aldosterone concentrations and no response following ACTH administration.^{38, 39} Normal serum aldosterone values are reported to be 20.3 ± 7 ng/dl before and 39.7 ± 9.4 ng/dl one hour after 0.25 IU/lb (0.5 IU/kg) synthetic ACTH

(Cosyntrosyn) was given IV³⁸, and 5-345 pg/ml before and 71-758 pg/ml, two hours after 1 unit/lb (2.2u/kg) IM ACTH gel was administered.³⁹

Modified Thorn Test

A modified Thorn test has been proposed as a rapid way to support or refute the diagnosis of hypoadrenocorticism during initial diagnostic evaluation of patients suspected to have this disease.⁴⁰ The test is performed at the same time as ACTH stimulation testing is done for cortisol assays. Because cortisol assays are relatively expensive and must be sent to commercial laboratories where several days may elapse prior to their analysis, this test may eliminate the need to have the cortisol assays performed. The test is based on monitoring the changes in neutrophils, eosinophils and lymphocytes that occur in response to IV synthetic ACTH administration. Cosyntropin is given at 0.25 mg/dog IV and absolute eosinophil, lymphocyte and neutrophil numbers calculated at 0 and 4 hours after administration. Normal dogs have an increase of greater than 30 per cent in the neutrophil to lymphocyte ratio and/or a greater than 50 per cent decrease in eosinophil numbers at 4 hours. If a dog suspected to have hypoadrenocorticism has a normal response, it has adequate adrenal reserve and the cortisol samples need not be processed. Other causes for the dog's clinical signs should be pursued. If the response is compatible with hypoadrenocorticism, then therapy is begun for the disease while waiting for results of cortisol assays.

THERAPY OF HYPOADRENOCORTICISM

ACUTE ADRENAL CRISIS MANAGEMENT

Patients with the clinical, biochemical and electrolyte abnormalities compatible with acute hypoadrenocorticism should be treated as if they have the disease until they respond appropriately or the diagnosis is refuted. To delay therapy pending cortisol assays may lead to death of the patient. Patients with non-adrenal causes for their hyperkalemia will not be harmed by therapy. The primary goals of therapy are to correct hypovolemia and hypotension, to reestablish vascular responsiveness, to replace glucocorticoid deficits, and to correct electrolyte abnormalities, hypoglycemia and acidosis (Table 119-6).

Management of Shock, Hypotension and Hypovolemia

Death from hypoadrenocorticism is usually secondary to vascular collapse and shock, not from profound hyperkalemia. As such, immediate intravenous fluid therapy is life-saving. Fluids not only increase the intravascular volume, raise blood pressure, and improve renal perfusion, they dilute out the extracellular potassium, reducing the risk of developing fatal cardiac arrhythmias.

Normal saline (0.9% sodium chloride) is the fluid of choice. The primary electrolyte deficits are sodium and chloride and the ideal fluid should be potassium free. An intravenous line is established, baseline samples are collected for a CBC, chemistry

profile, resting cortisol, and a urine analysis . Saline is initially administered at 20 to 40 ml/lb (40-80 mg/kg) during the first hour. Total fluid requirements and rates of administration are determined by the degree of dehydration, maintenance needs and ongoing losses, and adjusted accordingly. If the patient is found to be hypoglycemic, 50 per cent dextrose is added to the saline to make a 5 per cent solution (100 ml of 50 per cent dextrose per liter). Potassium containing fluids such as lactated Ringer's solution are relatively contraindicated ($K^+ = 4$ mEq/L). However, the serum potassium of the patient is usually much higher than the concentration in Lactated Ringer's solution and the volume expansion provided by LRS will dilute out the hyperkalemia. Lactated Ringer's is certainly preferable to giving no fluids at all. The patient's urine output needs to be monitored to be sure adequate urine production occurs once replacement fluids are begun.

Glucocorticoid replacement therapy can be delayed until a post-ACTH plasma cortisol sample is obtained (one hour for synthetic ACTH and two hours for ACTH gel). Rapid volume expansion provides therapy for nearly all the acutely fatal complications associated with hypoadrenocorticism. If a steroid is given during the time of ACTH stimulation testing, it should be dexamethazone (see below for dosages). This glucocorticoid is not measured by most RIA techniques for cortisol.

The ideal glucocorticoid to utilize in an acute hypoadrenal crisis would be hydrocortisone hemisuccinate or hydrocortisone phosphate.^{1, 27} These glucocorticoids possess both glucocorticoid and mineralocorticoid activity and are given at 1 to 2 mg/lb (2 to 4 mg/kg) IV initially, and repeated every eight hours. Prednisolone sodium succinate can be used as an alternative rapidly active glucocorticoid and is given at a dosage of 2 to 10 mg/lb (4 to 20 mg/kg) IV over 2 to 4 minutes. This dosage is repeated in two to six hours depending on how well the patient is responding. Prednisolone sodium succinate also possesses some mineralocorticoid activity. Dexamethazone sodium phosphate may also be used as replacement glucocorticoid therapy during initial treatment at dosages of 0.25 to 1.0 mg/lb (0.5 to 2 mg/kg) initially. This dosage is reduced once shock is reversed to 0.02 to 0.05 mg/lb (0.04 to 0.1 mg/kg) twice daily and is added to the patients intravenous fluids.

Mineralocorticoid Replacement

Correction of sodium, chloride and water deficits is accomplished by saline administration. Hyperkalemia is also improved by volume expansion and improved renal perfusion alone. There is no longer any rapidly acting parenteral mineralocorticoid preparation available. Desoxycorticosterone acetate has been taken off the market. Using hydrocortisone hemisuccinate or phosphate will provide adequate mineralocorticoid activity along with saline infusions to stabilize the hyperkalemia until oral daily mineralocorticoid or injectible monthly mineralocorticoids (desoxycorticosterone pivalate, Percorten-V) can be given. After initial shock dosages of hydrocortisone are administered, their dosage can be progressively reduced to 0.2 to 0.5 mg/lb (0.4 to 1.0 mg/kg) every six hours intravenously. They may be further reduced day two to 0.05 to 0.1 mg/lb (0.1 to 0.2 mg/kg) every six hours. By day three they may be given at the same dosage with the frequency reduced to every 12 hours. Supplemental mineralocorticoid

therapy will usually be needed when the dosage of hydrocortisone reaches this maintenance level.¹

Management of Life Threatening Hyperkalemia

In some animals the hyperkalemia is so severe that alternatives to volume expansion and mineralocorticoid replacement alone must be considered. In my experience, however, these alternative strategies for controlling hyperkalemia are rarely, if ever, needed. In addition to rapid volume expansion with 0.9% saline, intravenous glucose, glucose plus regular insulin, sodium bicarbonate therapy and intravenous 10% calcium bicarbonate therapy may be considered.^{1, 27}

Intravenous glucose is useful in managing hyperkalemia because as glucose enters cells, potassium follows, lowering its extracellular concentration. Glucose may be given as a 10 per cent solution at a dosage of 2 to 5 ml/lb (4 to 10 ml/kg) which may be added to the saline and given over 30 to 60 minutes.¹ Insulin is also known to promote the movement of extracellular potassium into cells. Regular insulin can be given either SQ or IV at a dosage of 0.03 to 0.06 units/lb (0.06 to 0.12 units/kg) to promote rapid potassium uptake by cells. For each unit of insulin given, 20 ml of 10 per cent dextrose are given to the patient to prevent hypoglycemia.

Alkalosis also promotes the transcellular movement of extracellular potassium into cells, reducing its cardiotoxic effects. It may be given at 0.25 to 0.5 mEq/lb (0.5 to 1.0 mEq/kg) as a slow IV bolus administration.²⁷ Again, this should not be necessary in most hypoadrenal patients.

Lastly, calcium gluconate is known to be cardioprotective against the effects of hyperkalemia on the myocardium.¹ It can be given intravenously as a 10 per cent solution at 0.2 to 0.5 mg/lb (0.4 to 1.0 mg/kg) over a 10 to 20 minute period. Administration of calcium gluconate may provide time for other slower acting therapies for hyperkalemia to have time to be effective. Patients receiving intravenous calcium gluconate must have continuous EKG monitoring. If any new arrhythmias are seen, the infusion should be stopped.

Acidosis Management

The metabolic acidosis seen in patients with hypoadrenocorticism is usually mild and rarely needs to be treated specifically. Volume expansion, increased tissue perfusion and improved renal function, all usually lead to correction of preexisting metabolic acidosis. If the total CO₂ is less than 12 mEq/L, judicious sodium bicarbonate therapy may be indicated.¹ The base deficit is calculated as body weight (kg) x 0.5 x base deficit (mEq/L). In the absence of blood gas analysis for determination of the base deficit, it can be estimated as: base deficit = 22 - TCO₂. One fourth of the calculated bicarbonate deficit is given to the patient in the first six to eight hours of therapy. It would be rare for any more alkalization therapy to be needed. Sodium bicarbonate therapy has an additional benefit in that it will help promote the intracellular movement of potassium from the extracellular space, reducing its adverse physiologic effects.

Most patients improve significantly within hours after administering appropriate fluid, electrolyte and glucocorticoid replacement therapy. Within 24 to 48 hours most

have stopped vomiting and diarrhea will cease. Gradual reintroduction of oral food, water and medications can now be safely done. A rapid reversal of severe renal compromise, hypercalcemia and hyperkalemia lends further support for the diagnosis if results of ACTH stimulation testing are still pending. Most other causes for these biochemical abnormalities will not respond this rapidly to the therapy described above.

In rare cases, renal function may not return rapidly to normal. In such animals it is likely that the shock associated with hypoadrenocorticism induced severe renal ischemia, or some pre-existing primary renal disease was present that was aggravated by hypovolemia and hypotension. In this situation, a rapid return to normal of the BUN or creatinine is not expected. These patients require much more judicious fluid administration, especially if they become oliguric.

MAINTENANCE THERAPY OF HYPOADRENOCORTICISM

Once patients stabilize following initial aggressive fluid, electrolyte, glucocorticoid and acidosis therapy, maintenance therapy can be begun (Table 119-7). In most animals with primary hypoadrenocorticism, both glucocorticoid and mineralocorticoid replacement therapy will be needed for life. In the rare animal with only glucocorticoid deficiency, no mineralocorticoids will be needed. Low dosages of glucocorticoids will control signs of their disease.

Oral glucocorticoid replacement therapy is continued for three to four weeks in most animals after the crisis is over. Prednisone or prednisolone may be given initially at 0.25 to 0.5 mg/lb/day (0.5 to 1 mg/kg) in divided dosages every twelve hours. This dosage is gradually tapered off (decrease by 50 per cent per week) until it is discontinued entirely. In my experience, the majority of dogs do fine on replacement mineralocorticoid alone after the first few weeks of therapy if fludrocortisone acetate is used (Florinef). If dogs show signs of cortisol deficiency (anorexia, lethargy, depression), then low dosages of prednisone or prednisolone can be started again. Daily maintenance needs for prednisone or prednisolone are approximately 0.1 mg/lb/day (0.22 mg/kg) in most dogs. All owners should be given a prescription of some sort of glucocorticoid to use in times of stress, irregardless of whether the patient needs them daily or not.

Long-term mineralocorticoid replacement therapy can be provided by a number of means including, oral fludrocortisone acetate, injectable desoxycorticosterone pivalate (DOCP) or surgically implanted DOCP-pellets. The drug used most commonly is fludrocortisone acetate (Florinef). Fludrocortisone is a potent oral mineralocorticoid that is useful as daily replacement therapy. It comes as a 0.1 mg tablet. It has mineralocorticoid potency equivalent to natural aldosterone.²⁴ It also has significant glucocorticoid activity. On a milligram basis, it is ten times as potent as cortisol.²⁴ Thus, it provides for both the glucocorticoid and mineralocorticoid needs of most patients once the high cortisol needs of an adrenal crisis are managed. It is administered at approximately 0.1 mg/10 lbs body weight (0.1 mg/5 kg) in divided dosages every twelve hours.^{1, 27, 41} Dosages are adjusted based on normalization of serum sodium and potassium concentrations. Electrolytes should be monitored every 4 to 7 days during the first week or two and then every three to four months during the first year of therapy.

Dogs generally develop increased need for fludrocortisone during the initial six to eighteen months of therapy.^{1, 41} After that time, most have very stable mineralocorticoid dosages. This increasing drug need may be due to progression of adrenal inflammatory disease that was on-going at the time of initial diagnosis.

My goal is to maintain the serum potassium concentration in the high normal range. The drug's cost and side effects (polyuria) are limiting factors in the treatment of some dogs with hypoadrenocorticism. Particularly in giant breeds, the cost of daily fludrocortisone can be several dollars a day. By maintaining the serum potassium in the high normal range, you are sure the minimal amount possible is being given which helps control long-term drug costs for the owner and is not associated with any increased clinical risk of relapse for the dog.

In some animals on large fludrocortisone dosages, polyuria can be profound and intolerable for owners. This is most likely due to the glucocorticoid activity inherent in this product. It has been suggested that this may be controlled by using oral hydrocortisone as replacement therapy for both glucocorticoids and mineralocorticoids. Hydrocortisone may be given at 0.0612 mg/lb (0.125 mg/kg) with 2/3 given in the morning when steroid needs are greatest and 1/3 given 12 hours later. In some dogs supplemental fludrocortisone will still be needed, but at reduced dosages (0.05 to 0.2 mg/day).¹

In occasional animals, hyponatremia will persist in spite of having normal serum potassium concentrations. In such cases, adding supplemental table salt to the diet should normalize the sodium concentrations without necessitating increasing fludrocortisone dosages (a more costly alternative).

An alternative to daily oral fludrocortisone therapy is the use of injectable desoxycorticosterone pivalate (DOCP). DOCP is a long-acting ester of desoxycorticosterone in a microcrystalline suspension. Several recent reports have discussed its use as a replacement for daily fludrocortisone tablets.^{13, 41, 42, 43} It was available commercially as Percorten pivalate up until 1987 when commercial production was discontinued. Since that time it has only been available from the manufacturer upon individual request. The drug, Percorten-V, has gone through initial clinical trials and is awaiting approval by the FDA for use in dogs. The manufacturer anticipates approval of the drug for general use by veterinarians sometime in 1994 or 1995. At this time, it can only be obtained from the manufacturer by individual request. Write CIBA Animal Health at P.O. Box 18300 Greensboro, NC 27419-1180 for information about obtaining DOCP for selected animals. Current costs are \$62.00 per 100 mg vial (25 mg/ml).

DOCP is useful for dogs that develop significant polydipsia and polyuria when receiving Florinef, for those who require large dosages, and thus incur high costs for control of their disease, or for animals in which fludrocortisone appears ineffective even in large dosages. DOCP is initially given at 1 mg/lb (2.2 mg/kg) IM once every 25 days. Serum should be collected after fourteen days and again at twenty five days for the first two to three months of therapy to determine if dosage adjustments are needed. There are significant individual dosage variations with DOCP and frequent monitoring, at least during the first few months of therapy, is important to stress to owners. The goal is to get the dog on the smallest dosage possible that maintains normal electrolytes and prevents

clinical signs of disease. If the sodium and potassium are normal at day 25 (the day of injection), you may decrease the dosage by 0.1 mg/lb (0.2 mg/kg) at each subsequent dosing interval until the lowest dosage that maintains normal electrolytes is obtained.¹³ As an alternative, the dosing interval may be increased to 30 days and an electrolyte panel evaluated at the end of the new 30 day inter-injection interval.

In some dogs the duration of action is less than 25 days. If electrolytes are normal at 14 days, but too low at day 25, the dosing interval should be shortened. Shorten the inter-injection interval to 21 days first. Rare animals need DOCP as often as every fourteen days.

Current data suggests that approximately 15 per cent of dogs will require 0.5 mg/lb (1.1 mg/kg) every 25 days, 30 per cent will require between 0.5 and 1.0 mg/lb (1.0 and 2.2 mg/kg). Over 50 per cent are well maintained on 1.0 mg/lb (2.2 mg/kg) every 25 days. Few require greater than 1.0 mg/lb/injection (2.2 mg/kg).^{13, 41, 43}

Because DOCP has little or no glucocorticoid activity, supplemental glucocorticoid therapy should be combined with DOCP, at least initially. Interestingly, approximately 50 per cent of dogs do well with no supplemental glucocorticoids when maintained on DOCP alone.^{13, 41} Initially, dogs are given approximately 0.1 mg/lb/day (0.22 mg/kg) of prednisone or prednisolone. This dosage may be gradually reduced and eliminated after several weeks if the dog has no clinical signs of disease in the absence of glucocorticoid supplementation (anorexia, lethargy, depression). Some dogs do well when glucocorticoids are given only once every two to three days. Owners should have a supply of glucocorticoids available to give during stressful situations even if they are not needed on a daily basis. Glucocorticoid demands during stress are two to ten times those needed for maintenance.⁴¹

Side effects associated with DOCP have been infrequent. Polydipsia and polyuria are occasionally seen. This most often results from combining glucocorticoids with the DOCP and responds to lowering the glucocorticoid dosage. In rare animals, lowering of the DOCP dosage results in elimination of these signs. One animal was reported to have a less favorable response to DOCP than Florinef, and one dog had an acute adrenal crisis in spite of receiving the drug, and was considered a drug failure.¹³ Mild hypoalbuminemia has been noted in occasional dogs receiving DOCP.(serum albumin 2.0 to 2.5 g/dl).²⁷

The main disadvantage for owners to the use of DOCP is the need to return monthly for an injection and the costs of repeat exams and laboratory work. Owners can be taught to give the injections at home and are seen only every 3 to 4 months once the patient is stable, to be sure electrolytes are well maintained. Recent data also suggests that subcutaneous injections are as effective as IM injections, simplifying at home management for owners.⁴⁴

The last method for mineralocorticoid replacement is that of DOCP pellets. DOCP pellets contain 125 mg of DOCP and are surgically implanted subcutaneously. They release approximately, 0.5 mg of desoxycorticosterone acetate per implanted pellet per day and have a duration of action of approximately ten months. They are costly,

require more technical manipulations (surgery) and are the least reliable of the three methods available. They are not recommended for use at this time.

Therapy of Secondary Hypoadrenocorticism

Animals with spontaneous or iatrogenic secondary hypoadrenocorticism need only glucocorticoids to reverse their clinical signs. Dosages utilized are similar to those recommended previously. Starting at 0.25 to 0.5 mg/lb/day (0.5 to 1 mg/kg) initially and tapering the dosage to the lowest needed to control clinical signs of disease. Periodic reevaluation of serum electrolytes are indicated in animals thought to have spontaneous secondary hypoadrenocorticism (pituitary disease) because some animals may actually have primary disease and have been mis-diagnosed initially. They develop electrolyte abnormalities only late in their disease course. This is particularly true if endogenous ACTH concentrations are not available for analysis. In cases of iatrogenic hypoadrenocorticism, glucocorticoid dosages are gradually reduced to alternate day therapy at very low dosages until eventually no supplemental therapy is needed.

PROGNOSIS

The long-term prognosis for animals with hypoadrenocorticism, once an adrenal crisis is controlled, is excellent. With appropriate glucocorticoid and or mineralocorticoid replacement dogs and cats should be expected to live a normal life. Good communication between the veterinarian and the owner is critical for success, however. The importance of life-long therapy, and the need for periodic physical examinations and biochemical evaluations must be emphasized to owners. In addition, owners need to know that their pet may deteriorate in high stress situations if glucocorticoids are not increased. They also need to be educated about how to recognize signs of glucocorticoid deficiency.

HYPOADRENOCORTICISM IN CATS^{1, 3, 8, 11, 45, 46}

Primary hypoadrenocorticism is a rare disease in cats, being first described in 1983.³ Since that time only 11 additional cases have been described in the veterinary literature. There have been seven cats with primary hypoadrenocorticism diagnosed at the author's practice between 1985 and 1993. The cause is generally idiopathic adrenal atrophy, although one case of traumatic hypoadrenocorticism has been described.¹¹ Spontaneous secondary hypoadrenocorticism has not been described as a clinical entity in cats. Iatrogenic secondary hypoadrenocorticism may occur following long-term use of either exogenous glucocorticoids or megestrol acetate.

Cats have ranged from 1.5 to 14 years of age. All have been domestic short or long-haired breeds. There is no sex predisposition in contrast to dogs with hypoadrenocorticism in which females predominate.

Clinical signs are similar to those described for dogs. The duration of signs prior to diagnosis ranged from five to 100 days with a mean of fourteen days.⁸ Anorexia, lethargy, depression, weight loss, and weakness have been seen in nearly all cases.

Approximately one third of cats had vomiting, or polyuria and polydipsia. Diarrhea was not reported in any case to date. Some response to symptomatic and supportive care (fluids with or without glucocorticoids), was noted in a few cases prior to the diagnosis being established.

Physical exam findings of note included dehydration, weakness and hypothermia in nearly all cases. Less common observations include prolonged capillary refill, weak pulses, collapse and sinus bradycardia (100 to 120 bpm). A painful abdomen was detected in one cat.

The diagnosis is established similarly to that described for dogs. A CBC, chemistry profile, urinalysis and ACTH stimulation test will verify the cause in all cases. Hematological abnormalities are infrequent, but include mild anemia, rare lymphocytosis and eosinophilia. Significant biochemical abnormalities include hyponatremia, hyperkalemia, hypochloremia, azotemia and hyperphosphatemia in nearly all cats. Abnormal sodium/potassium ratios were present in every case, all being less than 24:1. The hyperkalemia was milder than that seen in dogs ranging from 5.4 to 7.6 mEq/L. Hypercalcemia appears to be less common in cats than dogs, being identified in only one animal. Metabolic acidosis, based on a decreased TCO₂, was identified in three of ten cats from one report.⁸

Confusion about renal functional status occurs in cats with hypoadrenocorticism as with dogs. The urine specific gravity was less than 1.030 in seven of ten dehydrated azotemic cats from one study.⁸ This observation confuses the diagnostic picture providing some support that primary renal disease may be the cause for clinical signs. The BUN concentration ranged from 31 to 80 mg/dl in these ten cats with a mean of 55 mg/dl.

Cardiovascular abnormalities are infrequently detected in cats with hypoadrenocorticism. Microcardia was noted in five cats on thoracic radiographs. EKG abnormalities have been limited to sinus bradycardia in two animals and atrial premature contractions in one.

ACTH stimulation testing is the basis for a definitive diagnosis. The expected results in cats with hypoadrenocorticism are a low to low normal resting concentration with no or minimal response following exogenous ACTH. ACTH stimulation testing requires a slightly different protocol from that utilized in dogs (see section on adrenal reserve testing). Resting cortisol values from ten cats with hypoadrenocorticism ranged from 0.1 to 0.8 µg/dl (normal = 0.5 to 5.0 µg/dl). Following 1 unit/lb (2.2 units/kg) of ACTH gel one and two hour plasma cortisol values were 0.1 to 1.1 µg/dl (normal = 4.5 to 13.0 µg/dl), and 0.1 to 1.3 µg/dl (normal = 4.0 to 14.5 µg/dl) respectively.⁸

Endogenous ACTH concentrations were measured in seven of these ten cats and were dramatically elevated in all seven (mean = 3767 pg/ml, range = 500 to 8,000, normal = < 10 to 125 pg/ml), supporting a diagnosis of primary hypoadrenocorticism.

Principles of therapeutic management for cats with hypoadrenocorticism are similar to those described previously for dogs. Initial therapy involves intravenous 0.9 per cent saline at 20 ml/lb (40 ml/kg) in order to replace deficits in two to six hours. After that time, maintenance intravenous saline is given at approximately 30 ml/lb (60 ml/kg) per day. Intravenous dexamethazone can be administered at 0.25 to 0.5 mg/lb (0.5

to 1 mg/kg) while performing an ACTH stimulation test. The glucocorticoid can be switched to prednisone or prednisolone given IM, IV or per os depending on the cats hydration status. Prednisone can be given at 1 mg/lb (2.2 mg/kg) per day for the first 5 to seven days and then tapered off to maintenance dosages (1.25 mg/day) after the cat has responded fully. Long-term maintenance glucocorticoid therapy has also utilized 10 mg of injectable methylprednisolone acetate given IM every month, in place of daily oral glucocorticoids.

Mineralocorticoid replacement is provided by oral fludrocortisone acetate at 0.1 mg/day or intramuscular DOCP at 10 to 12.5 mg once a month.⁸ Periodic electrolyte monitoring is necessary, as with dogs, to determine the optimal dosage of mineralocorticoid for each cat.

The one unique feature about treating cats with hypoadrenocorticism is that they do not generally respond as rapidly to fluids, glucocorticoid and mineralocorticoid replacement as dogs usually do. They may remain weak, lethargic and depressed for three to five days after appropriate therapy is instituted.⁸ Three of ten cats in one report were euthanatized after two to five days of therapy because of poor initial responses. It is possible that they may have improved and survived their initial crisis if longer therapeutic intervention had been allowed.

The long-term prognosis for cats that survive the initial crisis stage appears to be good. Of ten cats from the only published series of cases, three were euthanatized within 5 days, one died after 47 days of unknown causes and the remaining six have survived for a mean of 34 months.⁸

BIBLIOGRAPHY

- 1 Feldman EC : Adrenal gland disease. In Ettinger S J (ed): Textbook of Veterinary Internal Medicine. Philadelphia, WB Saunders, 1989, pp1721-1724.
- 2 Feldman EC, and Nelson RW : Hypoadrenocorticism. In Feldman EC and Nelson RW: Canine and Feline Endocrinology and Reproduction. Philadelphia, WB Saunders, 1987, pp 195-217.
- 3 Johnessee J, et. al. : Primary hypoadrenocorticism in a cat. J Amer Vet Med Assoc 183:881-882, 1983.
- 4 Shaker E, et. al. : Hypoadrenocorticism in a family of standard poodles. J Amer Vet Med Asso 192:1091-1092, 1988.
- 5 Schaer M, Chen C: A clinical survey of 48 dogs with adrenocortical insufficiency. J Amer Anim Hosp Asso 19:443-452, 1983.
- 6 Willard M, et. al. : Canine hypoadrenocorticism: Report of 37 cases and review of 39 previously reported cases. J Amer Vet Med Asso 180:59-62, 1982.
- 7 Rakich P, and Lorenz M: Clinical signs and laboratory abnormalities in 23 dogs with spontaneous hypoadrenocorticism. J Amer Anim Hosp Asso 20:647-649, 1984.
- 8 Peterson M, et. al. : Primary hypoadrenocorticism in ten cats. J Vet Internal Med 3:55-58, 1989.
- 9 Bowen D, et. al. : Autoimmune polyglandular syndrome in a dog: A case report. J Amer Anim Hosp Asso 22:649-654, 1986.
- 10 Schaer M, et. al. : Autoimmunity and Addison's disease in the dog. J Amer Anim Hosp Asso 22:789-794, 1986.
- 11 Berger S, and Reed J: Traumatically induced hypoadrenocorticism in a cat. J Amer Anim Hosp Assoc 29:337-339, 1993.
- 12 Auge P: Addison's disease in littermates. Vet Med 80:43-45, 1985.
- 13 Feldman E, et. al. : Desoxycorticosterone pivalate (DOCP) treatment of canine and feline hypoadrenocorticism. Current Veterinary Therapy, Small Animal Practice XI:353-355, 1992.
- 14 Berry C, et. al. : ECG of the Month: Iatrogenic hypoadrenocorticism due to 0,p'-DDD. J Amer Vet Med Asso 190:158-159, 1987.

- 15 Kintzer P, and Peterson M. : O,p'-DDD treatment of 200 dogs with pituitary dependent
hyperadrenocorticism. Proceedings of the 8th Annual Veterinary Medical Forum of the American College of
Veterinary Internal Medicine, Washington, DC: 1990: p 1116.
- 16 Peterson M: Canine hyperadrenocorticism. In Kirk R (ed): Current Veterinary Therapy, Small Animal
Practice, Philadelphia, WB Saunders, 1986, pp 963-973.
- 17 Willard M, et. al. : Hypoadrenocorticism following therapy with o,p'-DDD for hyperadrenocorticism in four
dogs. J Amer Vet Med Asso 180:638-641, 1982.
- 18 Willard M, et. al. : Ketoconazole induced changes in selected canine hormone concentrations. Amer J Vet
Res 47:2504-2509, 1986.
- 19 Middleton D, et. al. : Suppression of cortisol response to exogenous adrenocorticotrophic hormone, and the
side effects of glucocorticoid excess in cats during therapy with megestrol acetate and prednisolone.
Canadian J Vet Res 51:60-65, 1987.
- 20 DeBowes L: Pituitary dwarfism in a German Shepherd puppy. Comp Cont Educ 9:931-936, 1987.
- 21 Moriello K, et. al. : Adrenocortical suppression associated with topical administration of glucocorticoids in
dogs. J Amer Vet Med Assoc 193:329-331, 1988.
- 22 Roberts S, et. al. : Effect of ophthalmic prednisolone acetate on the canine adrenal gland and hepatic
function. Amer J Vet Res 45:1711-1714, 1984.
- 23 Moore G, and Hoenig M: Duration of pituitary and adrenocortical suppression after long-term administration
of anti-inflammatory doses of prednisone to dogs. Am J Vet Res 53:716-720, 1992.
- 24 Stabenfeldt G: The Endocrine System. In Cunningham J (ed): Textbook of Veterinary Physiology.
Philadelphia, W B Saunders, 1992, pp 369-424.
- 25 Tyler R, et. al. : Renal concentrating ability in dehydrated hyponatremic dogs. J Amer Vet Med Asso
191:1095-1100, 1987.
- 26 Peterson M, and Feinman J: Hypercalcemia associated with hypoadrenocorticism in sixteen dogs. J Amer
Vet Med Asso 181:802-804, 1982.
- 27 Nelson R: Disorders of the Adrenal Gland. In Nelson R, and Couto C (eds): Essentials of Small Animal
Internal Medicine. St. Louis, Mosby Year Book, 1992, pp 587-605.
- 28 Bartges J, and Nielson D: Reversible megaesophagus associated with atypical primary hypoadrenocorticism
in a dog. J Amer Vet Med Asso 201:889-891, 1992.
- 29 Burrows C: Reversible megaesophagus in a dog with hypoadrenocorticism. J Small Anim Pract 28:1073-
1078, 1987.
- 30 Rogers W, et. al. : Atypical hypoadrenocorticism in three dogs. J Amer Vet Med Asso 179:155-158, 1981.
- 31 DiBartola S, et. al. : Clinicopathologic findings resembling hypoadrenocorticism in dogs with primary
gastrointestinal disease. J Amer Vet Med Asso 187:60-63, 1985.
- 32 Zenger E: Persistent hyperkalemia associated with non-chylous pleural effusion in a dog. J Amer Anim Hosp
Asso 28:411-414, 1992.
- 33 Degen M: Pseudohyperkalemia in Akitas. J Amer Vet Med Asso 190:541-543, 1987.
- 34 Crow S, and Stockham S: Profound hyponatremia associated with glucocorticoid deficiency in a dog. J
Amer Anim Hosp Asso 21:393-400, 1985.
- 35 Houston D, et. al. : Syndrome of inappropriate antidiuretic hormone secretion in a dog. Can Vet J 30:423-
425, 1989.
- 36 van den Broek, A: Serum protein values in canine diabetes mellitus, hypothyroidism and
hypoadrenocorticism. Brit Vet J 148:259-262, 1992.
- 37 Center C: Pathophysiology and laboratory diagnosis of liver disease. In Ettinger S J (ed): Textbook of
Veterinary Internal Medicine. Philadelphia, W. B. Saunders, 1989, pp1421-1478.
- 38 Golden D, and Lothrop CJ: A retrospective study of aldosterone secretion in normal and adreopathic dogs.
J Vet Internal Med 2:121-125, 1988.
- 39 Willard M, et. al. : Evaluation of plasma aldosterone concentrations before and after ACTH administration in
clinically normal dogs and dogs with various diseases. Amer J Vet Res 48:713-718, 1987.
- 40 Chastain C, et. al. : A screening evaluation for endogenous glucocorticoid deficiency in dogs: A modified
Thorn test. J Amer Anim Hosp Asso 25:18-22, 1989.
- 41 Kintzer P, and Peterson M. Clinical spectrum of hypoadrenocorticism in dogs. Proceedings of the 11th
Annual Veterinary Medical Forum of the American College of Veterinary Internal Medicine. Washington,
DC, 1993, pp 325-326.
- 42 Lynn R, and Feldman E: Treatment of hypoadrenocorticism with microcrystalline desoxycorticosterone
pivalate. Brit Vet J 147:478-483, 1991.
- 43 Lynn R, et. al. : Efficacy of microcrystalline desoxycorticosterone pivalate for treatment of
hypoadrenocorticism in dogs. J Amer Vet Med Assoc 202:392-396, 1993.

- 44 McCabe M, Lynn R, Feldman E. Subcutaneous desoxycorticosterone pivalate (SC-DOCP) for treatment of canine hypoadrenocorticism. Proceedings of the 11th Annual Meeting of the American College of Veterinary Medicine. Washington DC, 1993, p 925.
- 45 Greco D, and Peterson M: Feline hypoadrenocorticism. In Kirk R (ed): Current Veterinary Therapy, Small Animal Practice. Philadelphia, WB Saunders, 1989, pp 1042-1045.
- 46 Mawhinney A, et. al. : Primary hypoadrenocorticism in a cat. Aust Vet Pract 19:46-49, 1989.