ACHIEVING REMISSION IN DIABETIC CATS: WHAT DO WE REALLY KNOW?

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PATHOPHYSIOLOGY OF DM

Diabetes mellitus (DM) is a common endocrine disease in cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition the lack of insulin results in increased hepatic gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism. Factors that have been identified as predisposing factors in cats include obesity, advancing age and being male.

Two types of DM are recognized in man, and these classifications can be applied to the disease in cats as well. Type I DM (insulin dependent diabetes mellitus) is due to an absolute deficiency of insulin. This form of diabetes is characterized by minimal secretory response to β-cell secretagogues such as glucagon. Chronic pancreatitis appears to be a common cause of type I DM in cats. Other histopathologic changes reported include islet specific amyloidosis and beta cell degeneration. Type II DM (non insulin dependent diabetes) is characterized by an abnormal pattern of insulin secretion in combination with peripheral insulin resistance, and results in a stable reregulation of the blood glucose concentration at a higher concentration. The two types of diabetes are classically distinguished by characteristic responses to challenge by insulin secretagogues such as glucose, glucagon, or arginine. In type I DM, there is a decreased or negligible secretion of insulin compared to normal animals, whereas in Type II DM, total insulin secretion may be normal or increased, although the pattern of secretion is abnormal and the amount of insulin is insufficient to prevent hyperglycemia. The phenomenon of glucose toxicity complicates interpretation of glucagon tolerance tests in cats however, and the glucagon tolerance test is of little practical utility in clinical practice. Classification of diabetic cats as either insulin dependent or no insulin dependent may be more helpful clinically, recognizing that some cats can transition between the two states. Factors that likely influence the need for exogenous insulin in individual cats include the severity of pancreatic pathology, whether the pancreatic pathology is progressive or static, presence of concurrent disease that results in peripheral insulin resistance, presence of obesity, the caloric content of the diet and the ability to achieve good glycemic control.

DIAGNOSIS

The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss), and documentation of hyperglycemia and glycosuria. The presence of significant ketonuria together with hyperglycemia, is diagnostic for diabetes mellitus, however in cats without ketoacidosis, the diagnosis may be complicated by the occurrence of marked stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document <u>persistent</u> hyperglycemia and glucosuria, but also to rule out other diseases that may cause similar clinical signs. Measurement of fructosamine concentrations or glucose concentration of samples collected in the home environment may allow the clinician to distinguish between stress induced hyperglycemia (and resultant glycosuria) and persistent hyperglycemia due to diabetes mellitus.

INSULIN THERAPY

There are three insulin products that are commonly recommended for treatment of diabetes mellitus in cats, Protamine zinc insulin, Glargine insulin, and Lente insulin. NPH insulin tends to have a very short duration of action in cats and is not recommended as a first line insulin.

PZI insulin (ProZinc): There have been two large studies published regarding the use of PZI insulin in cats one using Beef/pork insulin (PZIVet) and the other using human recombinant PZI insulin (ProZinc). Both studies demonstrated good glycemic control in 85-90% of diabetic cats.Both newly diagnosed cats and cats who had had poor control with other insulin products were included in these studies. In the most recent study of 133 diabetic cats (120 cats with newly diagnosed DM, and 13 cats previously treated cats), PZI insulin was effective in decreasing BG concentration and improving clinical signs in 85% of the cats within 45 days of initiating treatment. All cats were treated with PZI twice daily, and the starting dose was 0.22 – 0.66 U/kg/injection. By the end of the study (day 45) the mean insulin dose was 0.59 U/kg/injection. The nadir of the blood glucose occurred at 5-7 hours post injection. Hypoglycemia occurred in 22% of the cats and sometimes occurred even when very low insulin doses were used. For this reason it is recommended that the starting insulin dose should be conservative (1U/cat/injection) with subsequent dose increases made based upon clinical response to treatment and blood glucose curves. Diabetic remission was not documented in these studies but the duration of evaluation was short (45 days).

Pork Lente insulin (Vetsulin): Pork Lente insulin been approved by the FDA for use in cats and it has been used successfully in cats in Europe for several years. Vetsulin is a pure pork insulin which has an intermediate duration of action. The average time from injection to to the BG nadir is 4 hours and the duration of effect (time for BG to return to baseline) is approximately 10 hours, so Lente insulin should be administered twice daily in cats. The starting dose for lente insulin in cats (0.25 -0.5 U/kg/injection) is similar to that of other insulins, and the median dose required for good glycemic control in a group of diabetic cats was 0.5 U/kg. In this same study 7 of 25 cats went into diabetic remission during the 12 months of the study and all the cats that remained diabetic had good or excellent control at the conclusion of the study. In another study using lente insulin in 46 cats, remission was reported in 15% of cats.

Insulin Glargine (Lantus): Glargine insulin is a long acting insulin analogue that has also been used for treatment of diabetes mellitus in cats. The pharmacokinetics of insulin glargine are very similar to those of PZI although the time to insulin nadir is longer. In a study of 13 diabetic cats fed a commercial high protein low carbohydrate diet and treated with either once daily Glargine insulin at a dose of 0.5 U/kg once a day or lente insulin (human recombinant) 0.5 U/kg, twice a day, there was a significant improvement in both groups of cats and no difference was detected in glycemic control between the two insulin groups. Of the four cats in remission at the end of the study, 3 had been treated with lente insulin and one with glargine. In a study of 24 newly diagnosed diabetic cats, treated with either glargine, PZI, or lente, and fed a low carbohydrate high protein diet, glargine treated cats tended to have lower blood glucose concentrations and fructosamine concentrations than those treated with PZI or Lente. In this study there was a higher rate of diabetic remission rate in the cats treated with Glargine insulin than in the cats treated with PZI or lente insulin.

Insulin treatment for a new diabetic patient:

The starting dose for insulin in a new feline diabetic patient is 0.25 – 0.5 Unit/kg or 1-3 U/cat. It is recommended that PZI and Glargine insulins are started at the lower end of this dose. It is

difficult to predict in advance which cats will do better with which insulin formulation. Cats should be carefully monitored for occurrence of hypoglycemia, because of the possibility of remission of diabetes mellitus in the cat. A blood glucose curve should be performed 5-14 days after making any change in insulin formulation. Whichever formulation is chosen, twice a day insulin therapy is more likely to result in good glycemic control than one a day therapy. If twice a day treatment is not possible, once a day therapy with PZI or Glargine can result in effective control of clinical signs in some cats.

DIABETIC REMISSON

A unique feature of diabetes mellitus in cats is that some diabetic cats become non insulin dependent after treatment has been initiated. From 15 to 70 % of cats with DM have been reported to go into spontaneous clinical remission after intiation of insulin treatment. This is termed diabetic remisison. Diabetic remission is typically defined as normoglycemia that persists for greater than 4 weeks without the use of exogenous insulin, although some studies have defined it as euglycemia for only 2 weeks. The duration of remission is variable with some cats requiring insulin treatment again within a few weeks to months and other cats remaining in remission for months to years. Factors that have been hypothesized to influence the likelihood of diabetic remission include the duration of diabetes mellitus, whether the cat initially presented in a ketoacidotic crisis, the carbohydrate content of the diet, the type of insulin used for treatment, the breed of cat, the presence of underlying disease, and how closely the blood glucose is maintained within the normal range with insulin treatment. Stimulation tests with secretagogues such as glucagon and arginine have also been investigated to identify cats who have residual insulin secretion from the pancreas, however the presence of glucose toxicity in cats complicates interpretation of these tests and they have not proved useful in predicting the likelihood of remission.

In a study of factors influencing diabetic remission in cats, remission was found to be more likely with increasing age,and increasing cholesterol concentration. (Zini 2010). A slightly higher percentage of cats (53%) treated with Glargine insulin went into remission than cats treated with Lente insulin (47%). Overall 21 cats treated with Glarine and 23 cats treated with Lente went into remission.

Influence of diet: it has been proposed that low carbohydrate diets increase the chance of diabetic remission in newly diagnosed diabetic cats. A prospective study comparing a low carbohydrate-low fiber diet to a moderate carbohydrate-high fiber diet in 63 diabetic cats showed improvements in glycemic control in both groups, but there was a higher rate of remission of diabetes mellitus in the low carbohydrate-low fiber diet. These findings support the clinical opinion that low carbohydrate diets in conjunction with good glycemic control increase the likelihood of diabetic remission. If diabetic remission occurs in cats it is most commonly in the first few months of treatment.

Influence of insulin: It has been shown that strict glycemic control is important in achieving diabetic remission and it is clear that diabetic cats can go into remission with any insulin if good glycemic control is achieved. Most cats have better glycemic control with long acting insulin (PZI or Glargine) so most clinicians recommend these insulins as the insulin products of choice in diabetic cats. It is currently unclear whether some long acting insulin formulations are more likely to result in remission than others, or whether the critical factor is the glycemic control itself. In a study of 24 newly diagnosed diabetic cats, treated with either glargine, PZI, or lente insulin, and fed a low carbohydrate high protein diet, there was a higher rate of diabetic remission in the cats

treated with Glargine insulin than in the cats treated with PZI or lente insulin; however studies in larger groups of diabetic cats are required to confirm this finding.

Influence of clinical presentation: Although presentation in a diabetic ketoacidotic crisis is believed to be more common in cats with type I than type II diabetes mellitus, suggesting that cats with DKA should not go into remission; a recent study documented that some cats that initially presented with ketoacidosis can go into remission with adequate glycemic regulation and control of concurrent illness.

Other factors: Other factors that have been documented to increase the likelihood of diabetic remission in cats include short duration of diabetes mellitus (< 180 days), administration of glucocorticoids prior to diagnosis, low insulin dose required to achieve glycemic control, lack of polyneuropathy, older age, and lower cholesterol concentration. Sex, body weight, presence of renal failure, presence of hyperthyroidism, or presence of obesity at diagnosis have not been shown to influence the likelihood of remission. Diabetic remission tends to last for longer in cats of higher body weight. Serum concentrations of glucose, fructosamine, insulin, glucagon, and insulin growth factor I are not different between cats that do and do not achieve remission, but cats achieving remission have a higher glucagon to insulin ratio.

Table 1: How common is diabetic remission?

Number cats in remission	Percent cats in remission	Reference	Notes
7/17	41%	Tschuor JVIM 2011	
45/90	50%	Zini JVIM 2010	
13/24	54%	Marshall JFMS 2009	
35/55	64%	Roomp JFMS 2009	Intense protocol
2/12	17%	Hall JFMS 2009	
8/46	17%	Michiels JFMS 2008	
7/12	58%	Sieber-Ruckstuhl 2008	Cats with DKA
13/32	40%	Alt Vet Sci 2007	
35/63	55%	Bennett JFMS 2006	
4/13	31%	Weaver JVIM 2006	

Table 2: How long does remission last?

Reference	Time of onset (median and range)	Length remission	Relapses
Zini 2010	48 (8-216) days	28-3370 days	13/45
Roomp JFMS 2009	59 (6-306) days	84-1095 days	9/35
Sieber-Ruckstuhl 2008	7-35 days	35-720 days	4/7

Table 3: Insulin use in diabetic remission

	Number of cats in remission	Percent cats in remission	Type of insulin
Tschuor 2011	7/17	41%	Glargine/Lente
Zini 2010	45/90	50%	Glargine/Lente
Marshall 2009	13/24	54%	Glargine, PZI, Lente
Roomp 2009	35/55	64%	Glargine
Hall 2009	2/12	17%	Glargine
Michiels 2008	8/46	17%	Lente
Sieber-Ruckstuhl 2008	7/12	58%	Glargine/Lente
Alt 2007	13/32	40%	Lente
Rand 2007	7/25	28%	Lente
Bennett 2006	35/63	55%	PZI, Lente, Ultralente, NPH
Weaver 2006	4/13	31%	Glargine/Lente

Table 4: Insulin use in diabetic remission

Reference	Number cats in remission	Glargine	Lente	PZI	Other
Tschuor 2011	7/17	2	5		
Zini 2010	45/90	21	23		1
Marshall 2009	13/24	8	2	3	
Weaver 2006	4/13	1	3		
Nelson 1999	10/10			4	

Table 5: Diet in feline diabetic remission

Reference	Number cats in remission	Diet
Tschuor JVIM 2011	7/17	Purina DM
Zini 2010	45/90	Variable
Marshall JFMS 2009	13/24	Purina DM
Roomp JFMS 2009	35/55	Low carbohydrate various
Michiels JFMS 2008	8/46	Variable
Alt Vet Sci 2007	13/32	Not recorded
Bennett JFMS 2006	35/63	Low carb low fiber Mod carb high fiber

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HYPOADRENOCORTICISM IN DOGS AND CATS: UPDATE ON DIAGNOSIS AND TREATMENT

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INTRODUCTION

Hypoadrenocorticism (Addison's disease) results from failure of the adrenal glands to secrete glucocorticoids (primarily cortisol) and mineralocorticoids (primarily aldosterone). Most cases of hypoadrenocorticism are due to primary adrenal failure, resulting in deficiency of usually both cortisol and aldosterone from the adrenal cortex. More rarely, Addison's disease may be due to pituitary dysfunction resulting in a failure of ACTH secretion and pure glucocorticoid deficiency (secondary adrenal failure). In secondary hypoadrenocorticism, mineralocorticoid secretion is expected to be normal.

ETIOLOGY OF HYPOADRENOCORTICISM

Since most cases of hypoadrenocorticism either die with no necropsy or are successfully treated, the underlying cause is usually not known in individual patients. Primary adrenal failure is suspected to be immune-mediated in most cases. Other causes of primary hypoadrenocorticism include granulomatous destruction or hemorrhagic infarction of the adrenal gland, adrenalitis, neoplasia, amyloidosis and necrosis. Immune mediated destruction of the adrenal gland may also occur together with other immune mediated endocrine disorders such as hypothyroidism, diabetes mellitus, and hypoparathyroidism. Destructive lesions in the hypothalamus or pituitary due to neoplasia, inflammation, or trauma may cause secondary hypoadrenocorticism. Idiopathic ACTH deficiency may also occur.

Primary adrenal failure may also be caused by a number of drugs including mitotane, trilostane, and ketoconazole. Adrenal suppression caused by ketoconazole is reversible but adrenal failure caused by mitotane may be permanent. Although adrenal suppression caused by trilostane is reversible in most cases, adrenal gland necrosis associated with trilostane treatment has been reported in some dogs. Administration of glucocorticoid drugs may cause secondary adrenal failure. After corticosteroid administration (topical, oral, or injectable) suppression of ACTH production from the pituitary gland occurs within a few days. This results in secondary adrenal gland atrophy. How long the adrenal axis is suppressed depends on the potency and half-life of the administered glucocorticoid. Long acting depot drugs are the most potent adrenal suppressants and can cause suppression for 5 - 6 weeks or longer.

CLINICAL SIGNS

Signalment

Seventy percent of dogs diagnosed with hypoadrenocorticism are female, and most are young to middle-aged dogs (mean 4 - 5 years). The disease is heritable in the Standard Poodle, Bearded Collie, Portuguese water dog and the Nova Scotia Duck Tolling Retriever (NSDTR) and in these breeds no obvious sex predisposition is evident. In the Standard Poodle, Portuguese water dog, and NSDTR, the disease appears to be inherited as an autosomal recessive trait. Incidence of hypoadrenocorticism in the NSDTR is estimated to affect 1.4% of the population while in the Standard Poodle 8.6% of poodles in one study were affected.

History and Physical examination

Clinical signs may be either acute or gradual in onset and often wax and wane. Owners may not realize how long their dog has been ill until treatment results in a dramatic improvement in activity level. Since 85-90 % of adrenal reserve must be depleted before clinical signs are observed, it may require a stressful event to trigger clinical illness. Clinical signs may be very vague and are rarely pathognomonic for the disease. Anorexia, vomiting, lethargy/depression, weakness, weight loss, diarrhea, shaking/shivering, polyuria, polydipsia, and abdominal pain may be observed. Most of these clinical signs can occur due to glucocorticoid deficiency alone. If mineralocorticoids are also deficient, the clinical signs tend to be more severe and polyuria, polydipsia, hypovolemic shock, collapse and dehydration are often present. Less common clinical signs include acute gastrointestinal hemorrhage, and seizures due to hypoglycemia or electrolyte derangement. The physical examination may be normal or may reveal lethargy, weakness, dehydration, bradycardia, weak pulses, decreased capillary refill time, and other evidence of hypovolemic shock

DIAGNOSTIC TESTING

Clinical Pathology

A complete blood count may reveal a nonregenerative normocytic normochromic anemia, or the hematocrit may be increased due to dehydration. Eosinophilia, neutrophilia or lymphocytosis occur in only 20-30% of dogs with hypoadrenocorticism, but lack of a stress leukogram in a dog with systemic illness is common. A chemistry profile may reveal hyponatremia, hypochloremia, hyperkalemia, hypercalcemia, and hyperphosphatemia. These changes occur due to aldosterone deficiency with a resultant failure of the kidneys to conserve sodium. This is accompanied by profound fluid loss, shift of K^+ ions to the extracellular compartment, pre-renal azotemia due to decreased renal perfusion and hypovolemia. A mild to moderate metabolic acidosis may also occur because lack of aldosterone impairs renal tubular hydrogen ion secretion. Other serum biochemical abnormalities that may occur in dogs with hypoadrenocorticism include hypoalbuminemia, hypocholesterolemia, hypoglycemia, and increased liver enzymes. Specific gravity of the urine is commonly less than 1.030 due to loss of the normal medullary concentration gradient and impaired water reabsorption by

the renal collecting tubules. The changes on the minimum data base in dogs with hypoadrenocorticism may initially mimic other disorders such as renal failure, hepatic disease, gastrointestinal disease, or insulinoma.

Serum electrolyte abnormalities
The majority of dogs with hypoadrenocorticism have the classic electrolyte changes of hyponatremia and hyperkaelina due to aldosterone deficiency. It is now recognized however, that a subset of dogs with hypoadrenocorticism does not have the classic electrolyte changes typically observed in dogs with hypoadrenocorticism. In a retrospective study of dogs with hypoadrenocorticism, 24% of dogs lacked hyponatremia and hyperkalemia. In a study of 25 NSDTR, 32% lacked electrolyte abnormalities at the time of diagnosis. Reasons for normal electrolytes include secondary hypoadrenocorticism due to decreased ACTH secretion, selective destruction of the zona fasciculata and reticularis, or early stage disease in which there has not yet been complete destruction of the zona glomerulosa. Dogs with glucocorticoid deficient hypoadrenocorticism tend to be older, have a longer duration of clinical signs, and are more likely to be anemic, hypoalbuminemic and hypocholesterolemic. It is important for clinicians to recognize that an absence of the characteristic electrolyte changes does not exclude a diagnosis of hypoadrenocorticism. Conversely reliance on measurement of electrolytes alone for diagnosis of hypoadrenocorticism can be misleading, because there are many other causes of these electrolyte changes.

Na:K ratio
The Na:K ratio is usually low in dogs with hypoadrenocorticism, and this ratio may be useful to guide emergency diagnosis and treatment while waiting for definitive test results. Use of a Na:K ratio cut off of <27 or 28 for predicting a diagnosis of hypoadrenocorticism resulted in correct classification of disease state 95% of the time in a retrospective study of 76 dogs with hypoadrenocorticism and 200 dogs with other disorders. It is important to remember however, that this ratio is only useful in dogs which have electrolyte changes. As discussed above, electrolyte concentrations and therefore the Na:K ratio may be completely normal in dogs with both primary and secondary hypoadrenocorticism.

Imaging studies
Most untreated dogs with hypoadrenocorticism have one or more radiographic abnormalities on thoracic and abdominal radiographs including microcardia, small cranial lobar pulmonary artery, narrow posterior vena cava, or microhepatica. These changes reflect the degree of hypovolemia, therefore they are more likely to be present in dogs with electrolyte abnormalities. Occasional dogs may have evidence of megaesophagus. Most dogs with hypoadrenocorticism have a measurable reduction in size of the adrenal glands, and sometimes the adrenal glands cannot be identified on ultrasound. There is overlap however with the adrenal size of normal dogs. The presence of small adrenal glands on ultrasound, although supportive of a diagnosis of hypoadrenocorticism, is not adequate for confirmation.

Electrocardiogram
In dogs with hyperkalemia, abnormalities may be present on the electrocardiogram. These include a peaked T wave and shortening of the QT interval in mild hyperkalemia, widening of the QRS complex, decreased QRS amplitude, increased duration of the P wave, and increased P-R interval in moderate hyperkalemia, and loss of P waves and ventricular fibrillation or asystole in severe hyperkalemia.

Basal cortisol
Measurement of a basal cortisol concentration is not adequate for confirmation of a diagnosis of hypoadrenocorticism, because some dogs have a low basal cortisol concentration but have an appropriate response to ACTH administration. Measurement of a basal cortisol of >2μg/dl had a negative predictive value of 100% in a study of 123 dogs evaluated for hypoadrenocorticism. Thus a basal cortisol of >2μg/dl is a useful test to exclude a diagnosis of hypoadrenocorticism.

ACTH stimulation test
An ACTH stimulation test is necessary to confirm a diagnosis of hypoadrenocorticism because not all dogs with hypoadrenocorticism have the expected electrolyte changes, and because many other disorders may mimic the characteristic findings of Addison's disease. It is acceptable to base emergency treatment upon a tentative diagnosis (based on electrolyte abnormalities), however an ACTH stimulation test should always be performed prior to initiating long term treatment. In dogs with hypoadrenocorticism, both the pre- and post- ACTH cortisol concentrations are usually less than 1μg/dl, and both values should be less than the reference range for basal cortisol (usually 2 μg/dl) to confirm the diagnosis. Although there is usually a clear distinction between the response to ACTH in a dog with hypoadrenocorticism and that of a dog with adequate adrenal reserve, sometimes borderline results can occur (post ACTH cortisol concentrations between 2 and 6 μg/dl). Other causes of inadequate response to ACTH stimulation include prior glucocorticoid administration (other than recent use of IV dexamethasone), lysodren, trilostane or ketoconazole administration, loss of activity of the ACTH product administered, and errors in administration of ACTH. Rarely dogs with sex hormone secreting adrenal tumors will have a flat line response to ACTH, however these dogs usually have overt signs of hyperadrenocorticism. Interpretation of such test results is difficult if no other underlying cause of adrenal suppression can be identified. It is possible that dogs with early adrenal gland dysfunction may initially have borderline results, but this is currently poorly documented. Whether inadequate adrenal reserve in a dog with another underlying disease (relative adrenal insufficiency) can contribute to clinical signs is also not established. Recommendations for further evaluation in dogs in which the ACTH stimulation test is borderline include repetition of the ACTH

stimulation test, and measurement of concurrent ACTH concentration. Measurement of aldosterone and renin activity might also be useful in dogs with electrolyte abnormalities. Whether dogs with apparent relative adrenal insufficiency benefit from administration of glucocorticoids is unknown.

Aldosterone-to-renin and Cortisol-to-adrenocorticotrophic hormone ratios

Measurement of cortisol:ACTH ratio (CAR) and aldosterone:renin ratio (ARR) has been proposed as an alternative diagnostic test for hypoadrenocorticism in dogs. Advantages of measuring these ratios include the need for collection of only one blood sample, and avoiding the cost of performing the ACTH stimulation test. Disadvantages include the lack of availability of the renin and aldosterone assay, and the issues of sample handling with regard to measurement of endogenous ACTH.

Feline hypoadrenocorticism

Hypoadrenocorticism is a rare diagnosis in the cat. The majority of reported cases have been caused by primary adrenal failure. In most cases the underlying cause is suspected to be immune-mediated, although bilateral adrenal infiltration due to lymphoma, and permanent or transient adrenal failure secondary to trauma have also been reported. There are no published reports of spontaneous secondary hypoadrenocorticism in cats although iatrogenic hypoadrenocorticism due to rapid withdrawal of corticosteroids as been reported. There is no breed or sex predisposition and affected cats have ranged in age from 1.5 to 14 years of age. Clinical signs and laboratory abnormalities associated with hypoadrenocorticism in the cat are similar to those reported in the dog. Clinopathologic abnormalities include hyperkalemia, hyponatremia, azotemia, hyperphosphatemia, anemia, lymphocytosis, and eosinophilia. Atypical hypoadrenococrticism in which electrolyte abnormalities are absent has yet to be reported in the cat. The diagnosis of feline hypoadrenocorticism is confirmed by lack of cortisol response to ACTH administration. The most common protocol utilizes a dose of 125µg of cortrosyn administered IM or SQ with samples collected at 0, 30 minutes and 60 minutes. It is important to recognize that the reference range for the post ACTH cortisol is lower in cats than in dogs. To confirm a diagnosis of hypoadrenocorticism both the pre and post cortisol concentrations should be < than 2 µg/dl. Treatment of feline hypoadrenocorticism is with either fludrocortisone at a dose of 0.02 mg/kg per day or with DOCP at a dose of 10 -12.5 mg per month.[55] Either oral prednisone or prednisolone (1.25 mg/cat PO q 254 hours) may be used for glucocorticoid replacement. In cats that are difficult to handle, IM injectable methylprednisolone acetate can be administered monthly at the same time as DOCP administration. Response to treatment is similar although clinical signs such as anorexia, lethargy, and weakness may sometimes take longer to resolve than in dogs. Prognosis for long-term survival is good with the exception of cats in which the underlying cause is neoplasia.

ATYPICAL PRESENTATIONS OF ADDISONS DISEASE

Although diagnosis of a typical case of hypoadrenocorticism is usually straight forward, many cases have a less typical presentation with normal electrolyte concentrations.

Pure glucocorticoid deficiency

Although most cases of Addison's disease present with typical electrolyte abnormalities, in some cases the biochemical profile reveals normal electrolytes. This is always the case in secondary hypoadrenocorticism, but may also occur with early primary adrenal failure. Some dogs with primary adrenal failure will initially have glucocorticoid deficiency alone and later progress to mineralocorticoid deficiency. Interestingly, in one retrospective study of 11 dogs with glucocorticoid deficient hypoadrenocorticism, only one dog ultimately developed mineralocorticoid deficiency, despite the fact that the majority of the dogs (9/11) were diagnosed as having primary hypoadrenocorticism.

Measurement of an endogenous ACTH concentration will allow differentiation of primary versus secondary hypoadrenocorticism in these dogs and thus allow the clinician to decide whether long-term monitoring of electrolyte concentrations is necessary. Measurement of an increased ACTH concentration confirms a diagnosis of primary hypoadrenocorticism, while an ACTH concentration within or below the reference range this is consistent with a diagnosis of secondary hypoadrenocorticism. Assays for measurement of aldosterone are also available; however they are unreliable in identifying those dogs that will go on to require mineralocortiocoid as well as glucocorticoid supplementation. In one study of dogs with pure glucocorticoid deficiency dogs without electrolyte abnormalities were more likely to be anemic, hypoalbuminemic, and hypocholesterolemic.

Hypoglycemia: Hypoglycemia severe enough to cause a seizure disorder may occur in hypoadrenocorticism. Other more classic electrolyte changes may or may not be present. Hypoadrenocorticism should always be considered in the differential diagnosis of dogs presenting with hypoglycemia. It is possible that some cases of hunting dog hypoglycemia reported in the past were actually cases of atypical Addison's disease.

Severe gastrointestinal hemorrhage: Severe gastrointestinal hemorrhage may be a feature of hypoadrenocorticism. Causes of gastrointestinal hemorrhage in hypoadrenocorticism may include ischemia due to severe hypovolemia, and the effect of cortisol deficiency on the mucosa of the gastrointestinal tract. Interestingly in one report, dogs with gastrointestinal hemorrhage initially had typical Addisonian electrolyte changes, but by the time of referral had either normokalemia, or hypokalemia. Electrolyte changes typical of hypoadrenocorticism may also occur in dogs with other causes of severe gastrointestinal disease due to hypovolemia and acidosis. Differentiation of Addison's from other causes of gastrointestinal disease can only be made by the ACTH stimulation test. Dogs with severe gastrointestinal hemorrhage may require blood transfusion(s), and may have prolonged recovery.

Hepatopathy: Thirty percent of dogs with Addison's disease have increased hepatic enzymes, and in addition, hypoalbuminemia, hypocholesterolemia, and hypoglycemia are common in this disease. Hypoadrenocorticism may therefore mimic hepatic failure. Abnormalities in liver function tests have also been reported in some Addisonian dogs. It has been speculated that immune mediated

hepatitis may occur concurrently with hypoadrenocorticism in some dogs. Alternatively the liver could be secondarily affected due to hypotension and impaired tissue perfusion. Regardless, hepatic abnormalities detected in Addisonian dogs resolve with no specific treatment other than that for hypoadrenocorticism.

Renal failure: Azotemia is common in hypoadrenocorticism due to hypovolemia, hypotension, and decreased renal perfusion. Usually renal abnormalities are rapidly corrected with treatment, however a delay in treatment may cause secondary renal damage. Permanent renal failure is uncommon. Hypoadrenocorticism should always be considered in the differential diagnosis of animals presenting with evidence of acute renal failure.

Megaesophagus: Reversible megaesophagus associated with hypoadrenocorticism has been reported in dogs. The cause of megaesophagus has been suggested to be the effect of abnormal electrolyte concentrations on neuromuscular function, however in some affected dogs electrolyte concentrations are normal.

Multiple endocrinopathies: Hypoadrenocorticism may occur in conjunction with other endocrine deficiencies such as hypothyroidism, diabetes mellitus, and hypoparathyroidism. A series of 10 dogs with concurrent hypoadrenocorticism and hypothyroidism have been reported. Hypothyroidism should be considered in any dog with hypoadrenocorticism that has a poor clinical response to initial treatment. In some cases profound hypothyroidism may mask the typical electrolyte changes of Addison's disease. Conversely a diagnosis of concurrent hypothyroidism may be the cause of a poor response to treatment in an Addisonian patient.

ACUTE TREATMENT

Rapid treatment of dogs with suspected Addison's disease is vital especially if profound electrolyte abnormalities are present. Aims of treatment include correction of hypotension/hypovolemia, correction of electrolyte imbalances, provision of an immediate source of glucocorticoids, and correction of acidosis, hypoglycemia, and hypercalcemia.

The suggested procedure for dogs presenting with signs of hypovolemia in which Addison's disease is suspected is to immediately: Place an IV catheter in cephalic or jugular vein, and collect a blood sample for measurement of electrolytes, and cortisol. Synthetic ACTH is then administered IV, and a second blood sample for measurement of cortisol collected 1 hour later. Fluid therapy (0.9% saline IV, 30 - 80 ml/kg/24 hours plus correction for dehydration) should be started immediately. Once the second blood sample has been collected, administer prednisolone sodium succinate at a dose of 4-20 mg/kg IV, or hydrocortisone hemisuccinate or hydrocortisone phosphate at dose of 2-4 mg/kg IV or dexamethasone 0.5 to 2.0 mg/kg as an initial dose. Then add dexamethasone 0.05 - 0.1 mg/kg q 12 hours into fluids until can switch to oral glucocortiocoids. If animal is in shock, administration of steroids should be at shock doses and this should take precedence over establishing an immediate diagnosis. For dogs with hyperkalemia consider IV glucose and insulin to rapidly lower serum potassium, and calcium gluconate to protect the heart from the cardiosuppressive effects of hyperkalemia.

Options for mineralocorticoid supplementation include fludrocortisone, desoxycorticosterone pivalate, or hydrocortisone. The choice of mineralocorticoid depends upon the clinical status of patient (oral versus injectable), product availability, and confidence in diagnosis. In most cases electrolytes normalize with fluid therapy and glucocorticoids alone and immediate mineralocorticoid supplementation is not necessary. Long-term mineralocorticoid therapy can be initiated once the animal is stable and the diagnosis is confirmed. Other treatments that may be indicated in individual patients include synthetic colloids, blood transfusion, and IV dextrose. Parameters that should be monitored during treatment include serum electrolytes and acid-base status, urine output, ECG, blood pressure, and if possible central venous pressure. IV fluid therapy should be continued until the animal is fully rehydrated and oral intake is possible. Injectable medication should be continued until oral medications can be substituted.

MAINTENANCE THERAPY

Options for long term mineralocorticoid treatment include fludrocortisone (0.1 mg/5 kg body weight divided bid) or desoxycorticosterone pivalate (2.2 mg/kg IM q 25 days initially). For both of these mineralocorticoids the dose should be titrated to effect. The dose of fludrocortisone typically needs to be increased over time whereas in many cases the dose of DOCP can be decreased over time. In our clinic we reduce the dose of DOCP by 10% a month provided the electrolytes remain in the normal range at 30 days. In one study the range of doses needed for good control of hypoadrenocorticism ranged from 1.65 to 2.2 mg/kg at intervals ranging from 21-30 days. Dogs without electrolyte derangements do not require mineralocorticoid treatment, although electrolytes should be monitored frequently.

Prednisone is typically recommended for glucocorticoid replacement. The starting dose is 0.1 to 0.22 mg/kg initially, but this dose should then be tapered to the lowest dose that will control the clinical signs. It is important to avoid excess prednisone supplementation because this may result in manifestations of hyperadrenocorticism. Only 50% of dogs on fludrocortisone require supplemental prednisone, whereas most dogs on DOCP require prednisone at least every other day.

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