

Canine hypoadrenocorticism: Part II

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Abstract – Dogs with chronic, vague gastrointestinal signs and those with signs and laboratory abnormalities suggestive of an Addisonian crisis should be tested for hypoadrenocorticism. A previous article (Part I; *Can Vet J* 2009;50:63–69) discussed the etiology, pathophysiology, clinical signs, and diagnostic abnormalities found in these patients. The present article discusses definitive diagnosis and treatment for both the acute and the chronic Addisonian patient. Expedient treatment remains the cornerstone of management for these patients, particularly those in the former category. The long-term prognosis is excellent for these patients, given well-educated, committed, and vigilant owners.

Résumé – **Hypoadrénocorticisme canin : Partie II.** Les chiens avec des signes gastro-intestinaux chroniques vagues et ceux avec des signes et des anomalies de laboratoire suggérant une crise addisonienne devraient être testés pour l'hypoadrénocorticisme. Un article antérieur (Partie I; *Can Vet J* 2009;50:63–69) a analysé l'étiologie, la pathophysiologie, les signes cliniques et les anomalies diagnostiques observées chez ces patients. Le présent article analyse le diagnostic et le traitement pour le patient addisonien aiguë et chronique. Un traitement opportun demeure le pilier de la gestion de ces patients, particulièrement dans la première catégorie. Le pronostic à long terme est excellent pour ces patients, pourvu qu'ils aient des propriétaires bien informés, dévoués et vigilants.

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Definitive diagnosis: The ACTH stimulation test

The gold standard for diagnosing hypoadrenocorticism is the adrenocorticotrophic hormone (ACTH) stimulation test that assesses the ability of the zona fasciculata and the zona reticularis to produce cortisol in response to a maximal stimulus (1–3). Dogs with hypoadrenocorticism do not possess adequate reserves to respond properly. In all ACTH stimulation tests, a baseline serum or plasma sample is obtained prior to the administration of ACTH. A second blood sample is obtained either 1 or 2 h later, depending on the type of ACTH used. Cortisol levels are then measured in both samples. Various types of ACTH exist, including synthetic ACTH, corticotrophic gel preparations from purified porcine pituitary extract, and compounded gel formulations. Purified ACTH extracts include the entire 39-amino acid

molecule, while synthetic ACTH contains the active portion (amino acids 1–24) (3).

Adrenocorticotrophic hormone stimulation results from synthetic or commercial gel preparations can be interpreted interchangeably (1). Cortisol levels in canine plasma or serum are measured in commercial laboratories by several assays, including radioimmunoassay (RIA) (1) and competitive chemiluminescence immunoassay (4). Each laboratory should establish its own reference range (1). Reference ranges vary slightly among laboratories, but the normal pre-ACTH cortisol level is about 13.8 to 137.9 nmol/L; the normal post-ACTH cortisol concentration is approximately 151.75 to 469 nmol/L (1,3).

Most dogs with hypoadrenocorticism show baseline cortisol levels ≤ 55.2 nmol/L (4). In a group of 407 dogs with primary hypoadrenocorticism, all dogs showed post-ACTH stimulation cortisol levels ≤ 55.2 nmol/L (1). In a separate group, 21 of 23 dogs with secondary hypoadrenocorticism showed post-ACTH stimulation cortisol levels ≤ 55.2 nmol/L (1). Two dogs in this group showed post-ACTH cortisol concentrations > 55.2 nmol/L, but their responses were still quite blunted and remained < 139.5 nmol/L (1).

The classic ACTH stimulation protocol with synthetic ACTH (cosyntropin, Cortrosyn; Amphastar Pharmaceuticals, Rancho Cucamonga, California, USA) uses 250 μg (1 vial) given intravenously (IV) or intramuscularly (IM); the second blood sample is taken 1 h later (1). An alternative protocol uses a lower dosage of cosyntropin at 5 $\mu\text{g}/\text{kg}$ IV, with a maximum

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250 µg/dog dosage (5–8). Use of a lower dosage of cosyntropin is attractive, given the cost and availability of this product over the past few years (3). Initial studies assessed maximal adrenal stimulation using lower ACTH dosages in normal dogs and in dogs with naturally occurring hyperadrenocorticism (6–10). A recent prospective clinical study evaluated whether a low-dose ACTH stimulation test would distinguish between dogs with hypoadrenocorticism and dogs with non-adrenal illness (5). This crossover design study compared the low dose (5 µg/kg) with the standard dose (250 µg/dog) ACTH stimulation test in dogs with clinical signs compatible with Addison's disease. Cortisol responses between these dosages were statistically equivalent, and the authors concluded that low-dose (5 µg/kg, IV) synthetic ACTH (cosyntropin or tetracosactrin) appears to be effective for diagnosing hypoadrenocorticism in dogs (5).

In normal dogs, there is no difference between plasma cortisol levels 1 h post-injection by IV and IM routes using synthetic ACTH (8). However, in severely dehydrated animals, such as those experiencing an acute Addisonian crisis, absorption of an IM injection of ACTH may be delayed (11,12). In these situations, use of IV cosyntropin may be preferred to the IM protocol.

A reconstituted vial of cosyntropin can be refrigerated for up to 21 d without loss of efficacy (13). As the reconstituted cosyntropin does not contain preservatives, utmost care should be taken to prevent bacterial contamination during reconstitution. Cosyntropin can also be stored as frozen aliquots (–20°C) in plastic syringes for up to 6 mo without loss of efficacy (14). A frost-free freezer should not be used, due to thawing and freezing cycles that can cause destruction of the protein.

Two commercial ACTH gel preparations are available: HP Acthar Gel; Questcor Pharmaceuticals, San Francisco, California, USA; and ACTH Purified Corticotrophin; Virbac, Milperra, NSW, Australia. The dose is 2.2 U/kg IM, with the post-sample obtained at 2 h (1,3). The ACTH gel is stored under refrigeration and administered at room temperature. This gel is also available from several compounding pharmacies. There is concern about consistent bioavailability and lot variation among compounded products, and several studies have examined the response to compounded ACTH gel preparations (3,15). One study compared 4 compounded gel products (2.2 U/kg IM) with cosyntropin (5 µg/kg IV) in healthy dogs (15). The compounded gels appeared to maximally stimulate the adrenal cortex, and the 1-h post samples were comparable to those obtained with cosyntropin. However, the 2-h post values showed considerable variation, and the authors recommended serum cortisol measurements at both 1 and 2 h post-ACTH (15).

Measuring a single baseline cortisol level is not sufficient to confirm the diagnosis because cortisol levels fluctuate during the day (16). Although dogs with hypoadrenocorticism usually have very low basal levels, a single cortisol level does not measure adrenocortical reserves (1). Additionally, some dogs with non-adrenal illness show very low basal cortisol levels (4). However, a single cortisol level is cheaper and simpler to perform, as it does not involve the cost of ACTH as well as the cost of the full ACTH stimulation assay.

Given the difficulties in availability and the cost of ACTH, a recent study evaluated the use of basal serum or plasma cortisol levels as screening tools to rule out hypoadrenocorticism (4). This study found that basal cortisol levels ≤ 27.59 nmol/L had 100% sensitivity and 98.2% specificity in detecting dogs with hypoadrenocorticism. Cortisol levels ≤ 55.2 nmol/L showed 100% sensitivity but less specificity (78.2%) for hypoadrenocorticism (4). The study concluded that basal cortisol concentration has a high negative predictive value. That is, a dog not receiving corticosteroids, mitotane or ketoconazole, with a basal cortisol level ≥ 55.2 nmol/L is very unlikely to have hypoadrenocorticism (4). However, this study did recommend that a full ACTH stimulation test continue to be used to confirm hypoadrenocorticism in dogs with a basal cortisol level ≤ 55.2 nmol/L (4). Additionally, for dogs with basal cortisol levels ≥ 55.2 nmol/L in which hypoadrenocorticism still remains a leading differential, a full ACTH stimulation test should be performed (4).

The ACTH stimulation test is a simple, safe, short, reliable, and practical test that can be performed at any time of day prior to the administration of exogenous glucocorticoids (1). Exogenous glucocorticoids can cause erroneous results from detection as immunoreactive cortisol (prednisone, prednisolone, hydrocortisone), and from suppression of the pituitary-adrenal axis (prednisone, prednisolone, hydrocortisone, dexamethasone) (17,18). The ACTH stimulation test can be performed on an outpatient or an inpatient basis. Patient serum or plasma may be stored in refrigeration or at room temperature for up to 5 d without severe degradation of cortisol activity; samples that will be held for longer should be frozen as heparinized plasma (1).

Since the ACTH stimulation assay measures cortisol levels, it only evaluates the ability of the adrenal cortex to produce glucocorticoids. It does not assess the ability of the adrenal cortex to produce mineralocorticoids, and so cannot differentiate primary from secondary adrenal insufficiency. In many situations, mineralocorticoid deficiency is inferred from abnormal sodium and potassium levels at initial diagnosis. If sodium and potassium levels remain normal; however, it is not clear whether mineralocorticoid supplementation will be required along with glucocorticoid supplementation. An endogenous ACTH level can help determine this, as dogs with primary hypoadrenocorticism have elevated endogenous ACTH levels while dogs with secondary hypoadrenocorticism have very low endogenous ACTH concentration (1,18). Careful sample handling is necessary, as ACTH is a labile substance and its activity can rapidly decrease in plasma (1,18). Consultation with the laboratory is recommended for best results, as some laboratories issue specific blood collection tubes and instructions for this assay. Some dogs will show normal electrolytes with an increased endogenous ACTH level; these dogs by definition have primary hypoadrenocorticism (atypical hypoadrenocorticism) and most will eventually develop electrolyte abnormalities (1).

Tests for plasma aldosterone levels (either basal or stimulated) are not easily available and may be unreliable (some healthy dogs may have low aldosterone levels), so this assay currently does not have widespread clinical use in canine hypoadrenocorticism (1,18). A recent study reported on the use of aldosterone-to-renin (ARR) and cortisol-to-adrenocorticotropic hormone

(CAR) ratios (19). The authors concluded that use of these ratios can reliably distinguish dogs with primary hypoadrenocorticism from healthy dogs (19). Since these methods involve difficult-to-perform hormone assays — particularly renin — they are unlikely to gain widespread utility in clinical veterinary medicine in the foreseeable future.

Treatment of acute adrenocortical insufficiency: The Addisonian crisis

An acute Addisonian crisis in a dog represents a true medical emergency, due to severe hypovolemia, dehydration, hypotension, electrolyte derangements, and acid-base abnormalities. Appropriate treatment should be instituted rapidly at the same time that the definitive diagnostic workup is begun. The goals of therapy include correcting hypovolemia, hypotension, electrolyte imbalances (particularly hyperkalemia and hypoglycemia), acid-base abnormalities, and providing corticosteroid supplementation (1,2,20).

Death in the Addisonian crisis is often ascribed to hypovolemia and shock. The first priority is therefore to rapidly correct hypovolemia and perfusion with large volumes of intravenous fluids (1,2,20). Subcutaneous or intraperitoneal fluid therapy is neither effective nor appropriate. An IV catheter should be placed at the same time that initial blood samples are taken for a packed cell volume/total solids (PCV/TS), blood glucose, venous blood gas (with electrolytes), complete blood (cell) count (CBC), and a chemistry panel. A baseline lactate may be considered. The pre-sample for an ACTH stimulation test should also be obtained at this time. The IV catheter may be peripheral or jugular; one may consider placing cephalic catheters in both forelimbs for additional access. Initially, a large-gauge, short catheter in a peripheral vein may be preferable to a jugular catheter because it can be placed more quickly and it can deliver larger volumes of fluid more rapidly than can a long catheter placed in a central vein (20). Venous cut-down or an intraosseous catheter may be necessary for access. Intravenous fluids should be started at an initial shock rate of 60 to 90 mL/kg/h for the first 1 to 2 h (1,2,20). The fluid rate can be adjusted according to the patient's perfusion parameters and as other vital signs improve. Ideally, 0.9% sodium chloride (NaCl) should be used because it will replace the sodium deficit, reduce hyperkalemia by dilution, and improve metabolic acidosis. If 0.9% NaCl is not available, other crystalloids such as lactated Ringer's solution or Normosol-R can be used. The small amount of potassium (K) present does not appear to cause harm, and the benefit of these fluids far outweighs the harm of giving **no** IV fluids (1,2,20).

Hypoglycemia should be treated with an initial bolus of 0.5 to 1.0 mL/kg of 50% dextrose if clinical signs are present. If clinical signs are not present, dextrose at 2.5% or 5% (depending on the severity of hypoglycemia) should be added to the saline. Ideally, 50% dextrose should be diluted or given through a central line to prevent phlebitis (20).

Hyperkalemia improves rapidly with aggressive IV fluid therapy through simple dilution, by improved renal perfusion and urine output, and by the shift of potassium from the extracellular space into cells as metabolic acidosis improves (1,20). It is not usually necessary to treat hyperkalemia. However,

specific therapy to counteract hyperkalemia may be indicated if life-threatening bradyarrhythmia is present, or if initial fluid resuscitation has failed to significantly improve hyperkalemia in the first 30 to 60 min (10,20). Regular insulin can be given at 0.2 U/kg, IV, followed by a dextrose bolus and addition of dextrose (5%) to IV fluids. Insulin drives potassium into cells; it effectively and rapidly lowers serum potassium level and its effects last for 15 to 30 min. The patient's blood glucose should be carefully monitored every 30 to 60 min after giving regular insulin, as the patient may have been presented with hypoglycemia and Addisonian patients predisposed to developing hypoglycemia (2,20). A second method of reducing serum potassium includes sodium bicarbonate at 1 to 2 mEq/kg as a slow IV push. This drives K⁺ ions into cells as hydrogen (H⁺) ions leave the cells to titrate the administered bicarbonate. Bicarbonate takes about 1 h to work and its effects last for several hours (2,20).

The most rapid cardioprotective agent is 10% calcium gluconate (0.5 to 1 mL/kg, or 2 to 10 mL/dog), which temporarily antagonizes the effects of hyperkalemia on the membrane potential of cells. It should be given as a slow infusion over 10 to 15 min, during which time ECG should be monitored. Calcium gluconate should be discontinued if the ECG shows worsening bradycardia, S-T segment elevation, or Q-T shortening. The calcium infusion may be re-started at a slower rate once these abnormalities resolve. Calcium gluconate's protective effects occur very rapidly but last only 15 to 30 min, although this window will give continued IV fluid therapy and insulin additional time to work (13,20). If specific therapy is required to counteract hyperkalemia, insulin and calcium gluconate are usually sufficient. Aggressive fluid support should continue during this time, as it represents the most important aspect of managing an Addisonian crisis.

Most dogs experiencing an Addisonian crisis have mild to moderate metabolic acidosis (HCO₃ or TCO₂ 13 to 17 mmol/L) (1). Fluid therapy alone generally resolves this problem. If, after initial fluid therapy, severe metabolic acidosis persists (pH < 7.1, or HCO₃ < 12 mmol/L), sodium bicarbonate may be administered. The bicarbonate deficit in mmol/L is estimated:

$$0.3 \times \text{body weight (kg)} \times (24 - \text{patient's HCO}_3)$$

Of this total, 1/4 to 1/2 is given over 2 to 4 h, after which a venous blood gas should be repeated to assess acid-base status. The goal of bicarbonate therapy is to increase the pH to 7.2 and the HCO₃ to 12 mmol/L, not to completely correct metabolic acidosis (20).

Glucocorticoid supplementation is of great importance during acute adrenocortical insufficiency. Use in an Addisonian crisis is aimed toward improving vascular integrity, GI integrity, aiding in maintenance of blood pressure, and helping to improve circulating volume. Supplementation should be given in conjunction with IV fluid therapy, but not in place of fluids (20). Glucocorticoids are initially supplemented parenterally at 3 to 10 times physiological requirements, although dose ranges in the veterinary literature vary tremendously. An initial dose should be followed by repeated dosages every 2 to 6 h. Ideally

the ACTH stimulation test should be completed prior to giving glucocorticoids, as they may confound test results. If this is not possible, use of rapidly acting dexamethasone sodium phosphate (Butler Animal Health Supply, Dublin, Ohio, USA), 0.5 to 4 mg/kg, IV, will decrease this problem. Other glucocorticoid choices include prednisolone sodium succinate (Solu-Delta-Cortef; Pfizer, Kalamazoo, Michigan, USA) at 15 to 20 mg/kg, IV, over 2 to 4 min, or hydrocortisone sodium succinate (Solu-Cortef; Upjohn, Kalamazoo, Michigan, USA) at 0.3 mg/kg/h, IV. Hydrocortisone can also be given as an initial 5 mg/kg IV bolus over 5 min, followed by 1 mg/kg IV every 6 h (1,13,20). Hydrocortisone possesses some mineralocorticoid activity in addition to glucocorticoid activity, but it remains unknown whether it has adequate physiological mineralocorticoid activity (1). Both prednisolone and hydrocortisone interfere with ACTH stimulation results and should not be given until the ACTH stimulation test has been completed.

There is debate on mineralocorticoid supplementation during an Addisonian crisis. Some authors believe that intensive fluid and glucocorticoid therapy is sufficient to stabilize these patients (2,11). Others prefer to begin parenteral mineralocorticoid supplementation during the crisis (1,18,22). A short-acting parenteral mineralocorticoid formulation is no longer available in the United States (desoxycorticosterone acetate, DOCA). The parenteral mineralocorticoid of choice in the United States is desoxycorticosterone pivalate (DOCP, Percorten-V; Novartis Animal Health, Basel, Switzerland), although this drug may not be available in all countries. A long-acting pure mineralocorticoid, DOCP is given IM once every 25 d (13,23). The starting dosage is 2.2 mg/kg IM; DOCP should **not** be given IV, as acute collapse and shock could result (13). At least 2 authors have not observed harmful side effects when DOCP was given to a suspected Addisonian crisis dog whose ACTH stimulation test later proved normal (1,11). Toxicity studies support this finding (24). In the rare non-vomiting shocky patient, oral or rectal fludrocortisone (Florinef; Monarch, Bristol-Myers-Squib, Princeton, New Jersey, USA) could be given as some of the medication may be absorbed.

Additional supportive care for the Addisonian crisis patient should be directed at symptomatic relief. Many of these dogs have vomiting or nausea as a historical complaint, so antiemetics such as metoclopramide (Reglan; Wyeth-Ayerst, Philadelphia, Pennsylvania, USA), ondansetron (Zofran; GlaxoSmithKline, Brentford, United Kingdom), or Cerenia (maropitant citrate; Pfizer) may be used if vomiting does not resolve with initial therapy. Prochlorperazine (Compazine; GlaxoSmithKline) is contraindicated in a shocky animal. In addition to its anti-emetic effects, metoclopramide possesses intestinal motility activity that can help prevent or treat ileus. Significant gastrointestinal ulceration and blood loss can occur in these patients (1); gastroprotectants such as sucralfate (Carafate; Sanofi-Aventis, Bridgewater, New Jersey, USA) and H-2 blockers (Pepcis, famotidine; Merck and Company, Whiteside Station, New Jersey, USA; ranitidine; GlaxoSmithKline) or proton-pump inhibitors (omeprazole, Prilosec; Kremers-Urban, West Seymour, Indiana, USA) can be used. Specific anti-diarrhea medications are not indicated.

If severe enough, anemia may need to be corrected by blood transfusion (packed red cells or fresh whole blood). Finally, since GI ulceration and a gut compromised by shock may lead to bacterial translocation and sepsis, broad-spectrum antibiotics should be used.

A dog experiencing an Addisonian crisis represents a critically ill patient, so diligent and frequent monitoring is necessary, particularly in the early stages of resuscitation. Mentation, color, heart rate, respiratory rate, pulse quality, capillary refill time, core temperature/extremities temperature, and blood pressure should be checked regularly. Initially, fluid therapy should be adjusted if perfusion parameters do not improve and normalize. After initial stabilization, fluids can be adjusted on the basis of ongoing losses and dehydration estimates using physical examination findings, especially serial body weight measurements. Ideally, continuous ECG monitoring should occur, especially in those patients with severe hyperkalemia. Urine output (“ins and outs”) can be measured with an indwelling urinary catheter; inadequate urine production may result from inadequate fluid therapy or from development of oligo-anuric renal failure. If a jugular catheter is present, central venous pressure can also be measured to help guide fluid therapy. Serial lactate measurements can be considered, as this parameter has recently gained favor in monitoring therapeutic response to treatment for shock (20). As already discussed, blood glucose should be monitored frequently, especially in patients that were presented with hypoglycemia and patients that require insulin/dextrose to counteract hyperkalemia. Persistent hypoglycemia despite adequate glucocorticoid supplementation should prompt the clinician to consider other causes of hypoglycemia, including sepsis or hepatopathy. Ideally, electrolyte concentration and a venous blood gas to assess acid-base status should be obtained prior to the start of therapy. These tests should be repeated at frequent intervals (every 30 to 60 min) during initial resuscitation, particularly when severe hyperkalemia exists. After the patient has stabilized hemodynamically and the potassium level has reached the non-life-threatening level (< 6.5 mmol/L), electrolyte concentration and venous blood gas measurements can be performed every 6 to 8 h. Serum sodium should be assessed and the rate of correction monitored carefully. Serum sodium should not rise more than 10 to 12 mmol/L per day. A rapid rise in serum sodium concentration — particularly in situations of chronic and severe hyponatremia (< 110 mmol/L), can lead to neurological complications called central pontine myelinolysis, a non-inflammatory demyelination disorder. This syndrome was initially described in humans in 1959; the first veterinary report occurred in 1994 (24). Clinical signs of myelinolysis are reported rarely in the veterinary literature (20,25–27). They occur several days after too-rapid correction of chronic hyponatremia, and consist of lethargy, weakness, dysphagia, trismus, decreased menace response, and ataxia progressing to hypermetria and spastic quadriparesis (20,25–27). Magnetic resonance images in these cases appear similar to those in humans (25,27), as do histopathological findings (25). Neurological signs take weeks to months to resolve.

With adequate fluid resuscitation and glucocorticoid supplementation, Addisonian crisis patients often improve dramatically

within several hours. Fluid therapy should be continued as long as necessary to re-hydrate the animal, and then should be tapered slowly. Generally fluid therapy will be continued for at least 48 h, especially in the critical patients. Medications, particularly glucocorticoids, should be given parenterally until vomiting ceases, and then should be introduced PO. Water and a bland diet can be introduced after the initial shock crisis abates, and after vomiting ceases. Additional supportive care should be given as necessary. In most patients, electrolytes and other blood abnormalities return to normal quickly, generally within 24 to 48 h. The patient should be monitored as described above; severe complications such as sepsis, acute renal failure, or disseminated intravascular coagulation (DIC) are rare but can occur. The patient should be weaned from fluids, parenteral medications, and other supportive care very slowly to prevent a relapse. It is ideal to be sure that the patient remains stable for 24 h off fluids and parenteral medications prior to discharge.

Treatment of chronic adrenocortical insufficiency: Maintenance therapy

Dogs with primary hypoadrenocorticism that are presented with classic electrolyte abnormalities (hyperkalemia, hyponatremia, hypochloremia) will require lifelong mineralocorticoid and glucocorticoid supplementation. Those that are presented with normal electrolytes may have secondary hypoadrenocorticism or atypical primary hypoadrenocorticism. Dogs that have secondary hypoadrenocorticism will require lifelong glucocorticoid supplementation but not mineralocorticoid supplementation. Dogs with atypical primary hypoadrenocorticism (10% of dogs with primary hypoadrenocorticism) will require lifelong glucocorticoid supplementation and will likely require mineralocorticoid supplementation in the following days to weeks to years (1). Serum electrolytes must be judiciously monitored in these patients (1).

Mineralocorticoid replacement in primary hypoadrenocorticism is essential for maintaining electrolyte homeostasis. Desoxycorticosterone pivalate (DOCP) is a long-acting ester of desoxycorticosterone acetate (DOCA), a short-acting synthetic corticosteroid that was developed in the 1940's, but is no longer available in the United States (1,11). Like DOCA, DOCP, which was developed for humans in the 1950's, possesses pure mineralocorticoid activity (1,13). Percorten-V, DOCP for veterinary use, is formulated in a microcrystalline suspension for IM or subcutaneous (SC) injection; it should not be given IV. Its onset of action is rapid and occurs within hours (1). The initial recommended dosage is 2.2 mg/kg every 25 d; dose and interval adjustments depend on follow-up chemistry values and physical examination findings (13). In the first several months following the initial diagnosis, DOCP injections should occur in conjunction with recheck examinations. Once stabilized on this medication, owners can be taught to give the injection at home (1).

Following resolution of the initial Addisonian crisis, dogs receiving DOCP should have a recheck evaluation that includes a history, a physical examination (including body weight), and a serum chemistry panel at about 12 and 25 d following each DOCP injection. This should be continued after the first 2 to

3 injections, especially if dose adjustments are made. If a full chemistry panel is not possible, sodium, potassium, and BUN/creatinine should be checked. A CBC or, at least, a PCV/TS should be included, particularly in those patients that experienced anemia. The 12-day recheck assesses DOCP's peak effects and therefore the DOCP dose amount given each time. If hyperkalemia and/or hyponatremia occur, the DOCP dose should be increased by 5% to 10% next time. If hypokalemia and/or hypernatremia occur, the next DOCP dose should be decreased by 5% to 10% (13). The 25-day recheck evaluates DOCP's dose frequency; if hyperkalemia and/or hyponatremia exist, the dosing frequency should be decreased by 1 d (13).

Since DOCP is a pure mineralocorticoid, glucocorticoid supplementation is necessary. One benefit of using DOCP and prednisone is that these medications can be titrated individually. Prednisone should be given at physiological dosages (0.22 mg/kg BID initially). This dosage can be tapered to decrease polyuria and polydipsia, as some dogs show exquisite sensitivity to prednisone's effects. The amount of prednisone that enhances the patient's well-being but prevents side effects (PU/PD, panting, polyphagia) may be very small. The owner should be instructed to increase the prednisone dosage in times of stress; the amount of extra prednisone needed ranges from 2 to 10 times the physiology dose (1).

Fludrocortisone acetate offers a second chronic management option for dogs with primary hypoadrenocorticism. Fludrocortisone is a synthetic glucocorticoid with significant mineralocorticoid activity that is administered PO daily (13). The starting dosage is 0.02 mg/kg, divided and given twice daily (1,13). It is often necessary to increase the dosage during the first 6 to 18 mo of therapy (1). During follow-up after initial diagnosis, the pet should be evaluated as above (progress report, body weight, physical examination), including a serum chemistry panel or at least electrolytes every 1 to 2 wk until the patient stabilizes. Ideally, the goal is normal electrolyte concentrations. Fludrocortisone possesses significant glucocorticoid activity, so less than 50% of patients will require additional supplemental prednisone (1).

One drawback of fludrocortisone results from its combined glucocorticoid and mineralocorticoid activity. This combination may make it difficult to find an optimal drug dosage. It is possible that the fludrocortisone dosage may be increased to correct electrolytes, but the glucocorticoid activity of that dosage may result in signs of hypercortisolism (polyuria, polydipsia, hair loss) (1). In these patients, switching to DOCP may prove necessary. Some authors have advocated providing supplemental table salt to dogs that receive fludrocortisone in order to correct mild hyponatremia without resorting to a very high dosage (11). Others have not found this necessary and do not recommend it (1).

Dogs with secondary hypoadrenocorticism require glucocorticoid supplementation only. This can be achieved with prednisone, as described above.

Regardless of which chronic therapy the pet receives, the goal is a clinically normal and healthy pet with normal blood parameters. It is particularly important to monitor the dog's weight and to medicate according to weight, as most Addisonian

dogs regain the weight that they lost. Once the patient has stabilized on its chronic therapy, the frequency of rechecks and follow-up laboratory work can be decreased to 3 to 4 times yearly. However, if the pet is doing poorly prior to one of the scheduled rechecks, he/she should be re-evaluated sooner and a chemistry panel should be done. Abnormal electrolytes indicate that the mineralocorticoid needs adjustment; vomiting, diarrhea, inappetence, or lethargy suggests that the glucocorticoid dose should be increased.

Prognosis

With committed and vigilant caregivers, the long-term prognosis is generally excellent in Addisonian patients. A study evaluating long-term treatment of 225 dogs with hypoadrenocorticism (1979–1993) reported that there was a good to excellent response to treatment in more than 80% of the dogs, and a fair response to treatment in 12.5% (28). The median survival time for the dogs in this study was 4.7 y, and many of these dogs were still alive at the end of the study period. There was no difference in survival time between dogs treated with fludrocortisone versus DOCP. Of the 124 dogs that died, 120 expired for reasons unrelated to hypoadrenocorticism (28). With proper medication and monitoring, dogs with hypoadrenocorticism can lead normal lives and enjoy their regular activities. CVJ

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