Hypoadrenocorticism

Terry Bassett BVSc, MACVSc

Staff Veterinarian
Bundoora Veterinary Clinic/Northern Suburbs Animal Emergency Centre, Melbourne

Introduction

Hypoadrenocorticism is also known as Addison's Disease or acute adrenocortical insufficiency. The disease may vary from acute collapse with hypoperfusion to vague non-specific clinical signs. Hypoadrenocorticism is results from a deficiency in both glucocorticoid and mineralocorticoid secretion by the adrenal glands. Other diseases can present with similar clinical signs electrolyte disturbances to hypoadrenocorticism (HypoA).

Physiology and Anatomy of the Adrenal Gland

The adrenal glands are located in the retroperitoneal space craniomedial to each kidney. They are richly vascularised. These glands produce hormones essential for life and reproduction.

Eighty to ninety percent of gland is adrenal cortex which is the source of (1) glucocorticoids, essential to life due to their effects on carbohydrate and protein metabolism, (2) mineralocorticoid, aldosterone responsible for maintaining Na and K balance and ECF volume, and (3) sex steroids. The remaining 10-20% of the gland consists of the adrenal medulla, an enlarged specialised sympathetic ganglion, producing catecholamines.

Stimuli for hormone release from the adrenal gland include stress, pain, hypovolaemia, hypoglycaemia, and hypotension. The significant adrenal hormones involved in the pathogenesis of HypoA are glucocorticoids and aldosterone. The disease results from a deficiency of these hormones.

Normal physiological functions of glucocorticoids

1. Stimulation gluconeogenesis and glycogenolysis by the liver and muscle.
2. Suppression of peripheral cellular uptake and utilisation of plasma glucose.
3. Enhancement of protein and fat catabolism.
4. Stimulation of erythrocytosis.
5. Stimulation of caloric intake, favouring fat deposition.
6. Potent inhibitor of inflammation and lymphoid tissue.
7. Maintenance of normal blood pressure.
8. Counteract the effects of stress.

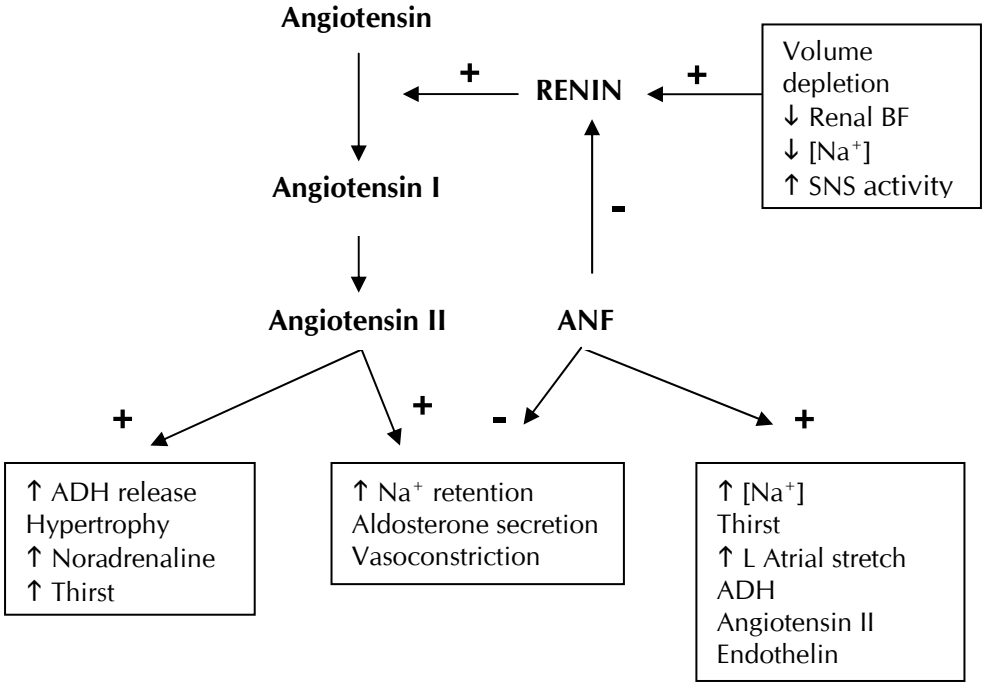
Glucocorticoid release is controlled by the hypothalamic-pituitary axis by negative feed back.

Aldosterone

Aldosterone is the principal endogenous mineralocorticoid. It is synthesised in the zona glomerulosa of the adrenal medulla by aldosterone synthase, which converts cortisone to aldosterone. Angiotensin II and hyperkalemia promote this conversion.

Aldosterone's principal function is to sustain extracellular fluid volume (ECFV) by the retention of sodium. Secretion is due to signals from the kidney by the renin-angiotensin-aldosterone system (RAAS) in response to a reduced circulating blood volume. Aldosterone affects sodium and potassium balance in the kidney.

Schematic representation of the renin-angiotensin-aldosterone system for sodium balance



Aldosterone and sodium balance

Changes in renal reabsorption of sodium in response to dietary changes in Na balance are mediated by aldosterone. Aldosterone secretion is stimulated by angiotensin II via the RAAS.

Renin is synthesised and stored in the granular cells of the JGA within the kidney and released by the following stimuli; (1) decreased renal perfusion pressure due to systemic hypotension or ECFV depletion; (2) stimulation of cardiac and arterial baroreceptors due to systemic hypotension increasing sympathetic neural activity that simulates α1-adrenergic receptors on the granular cells; and (3) changes in distal tubular flow and chloride delivery. Decreased ECFV and chronic NaCl depletion result in decreased distal tubular flow and delivery of chloride to the macula densa.

Renin release is inhibited by angiotensin II. Angiotensin II is a potent arterial vasoconstrictor increasing systemic blood pressure. Angiotensin II mediated renal arteriolar constriction (afferent > efferent) increases renal filtration fraction, decreases peritubular capillary hydrostatic pressure,

and increases capillary oncotic pressure favouring water and salt absorption. Aldosterone release increases sodium and chloride absorption in the cortical collecting duct of the kidney.

PGI_2 and PGE_2 are released by angiotensin II stimulation to minimise the harmful effects of vasoconstriction due to angiotensin II on the kidney.

Aldosterone increases the number and activity of Na channels in the luminal membranes of principal cells of the collecting ducts favouring sodium absorption. Both aldosterone and angiotensin II maintain blood volume and blood pressure due to vasoconstriction and sodium retention.

Aldosterone and potassium balance

The kidney is the primary regulator of K balance. Fine adjustments to potassium balance occur in the renal collecting duct, where 10-20% of filtered load is either secreted or reabsorbed. Aldosterone is important in potassium excretion by (1) increasing the reabsorption of Na^+ and the secretion of K^+ and H^+ ions in the distal nephron; (2) increasing the number of open sodium channels in the luminal membranes of the principal cells, making the duct lumen electronegative and potassium can leave the cell; (3) aldosterone increases basolateral Na^+/K^+-ATPase activity and increases the number of open potassium channels facilitating potassium excretion. An increased distal tubular flow further enhances potassium secretion by rapidly moving potassium ions downstream to maintaining a high chemical concentration gradient favouring potassium secretion.

Aldosterone facilitates potassium clearance from the ECF via the distal collecting duct in the kidneys.

Pathophysiology of Hypoadrenocorticism

Hypoadrenocorticism is a direct result of glucocorticoid and mineralocorticoid deficiencies.

As discussed, aldosterone controls sodium, potassium and ECF homeostasis. A deficiency of aldosterone results in excessive renal Na and Cl secretion and K and H^+ retention. The resulting hyponatraemia results in lethargy, depression, nausea, hypotension, a reduced cardiac output, poor renal perfusion, and hypovolaemia.

Urine concentrating ability is affected resulting in dilute urine.

Hyperkalemia causes muscle weakness, hyporeflexia, and impaired cardiac conduction. Hyperkalemia results from a reduced GFR and diminished cation exchange in distal convoluted tubule. Hyperkalemia decreases myocardial excitability, and increases the refractory period of myocardium slowing conduction in the heart. The cardiac arrhythmias are exacerbated by the hypoxia secondary to concurrent hypovolaemia.

The metabolic acidosis results from poor kidney perfusion resulting in an inability to excrete waste products and hydrogen ions and an impaired absorption of bicarbonate and chlorine in the distal renal tubules.

Depletion of glucocorticoids results in impaired gluconeogenesis and glycogenolysis, decreased sensitisation of blood vessels to catecholamines, impaired renal water excretion (hyponatraemia) and decreased vitality.

Gastrointestinal signs secondary to glucocorticoid deficiency include anorexia, vomiting, diarrhoea, and weight loss. Hypoglycaemia can occur due to altered glucose metabolism.

The development of adrenocortical insufficiency in humans requires 90% of the adrenal cortex to be destroyed.

Aetiology and Causes of Hypoadrenocorticism

Hypoadrenocorticism is a syndrome resulting from a deficiency of both glucocorticoid and mineralocorticoid secretion from the adrenal gland. Primary adrenocortical failure results from substantial destruction of the adrenal cortex. Secondary adrenocortical failure is due to any disease affecting the hypothalamic-pituitary axis leading to a reduced ACTH secretion and thus atrophy and decreased glucocorticoid and mineralocorticoid secretion.

Causes of Hypoadrenocorticism

Idiopathic adrenal atrophy	*o,p'*-DDD- induced adrenocortical destruction
Immune-mediated adrenocortical destruction	Mycotic or granulomatous disease Neoplasia
Glucocorticoid administration	Adrenalectomy
Haemorrhage or infarction of the adrenal glands	Anterior pituitary gland insufficiency (neoplasia, inflammation, or trauma)

Clinicopathologic Findings in Dogs with Hypoadrenocorticism

Dogs presented to the veterinary clinic vary from those with acute collapse and hypoperfusion to patients with vague signs suggesting an "ill dog". The majority of affected dogs have chronic intermittent signs, with approximately one third presenting in an acute adrenal crisis.

Signalment

Affected dogs are usually young to middle aged females. There is a genetic predilection in Standard Poodles and Bearded Collies. The disease is over represented in Great Danes, Rottweilers and West Highland White Terriers.

History

Dogs may have a history of weight loss, periodic vomiting and/or diarrhoea and lethargy. Polydipsia and polyuria may be present. The illness often has a waxing-waning nature with previous responses to symptomatic therapy. Check for previous glucocorticoid use and whether they are currently being treated for hyperadrenocorticism. The disease usually culminates to present in an acute hypotensive crisis often triggered by stress without prior signs. Boarding kennels are a common stress factor in these dogs.

Physical examination

Clinical findings may vary due the variation in presenting signs.

Dogs in an acute crisis may be hypothermic, dehydrated or hypovolaemic, hypotensive with weak pulses. Often these dogs have marked muscle weakness or collapse. Pale mucous membranes, a slow CRT, shallow respiratory pattern and cardiac arrhythmia's are also commonly identified. ***Bradycardia with hypovolaemia*** (generally tachycardia is present if hypovolaemic) should alert the clinician to hypoadrenocorticism. These dogs may have gastrointestinal haemorrhage. Acutely affected animals require immediate treatment.

Dogs presenting with vague clinical signs may have clinical signs attributable to impairment of the gastrointestinal tract, renal or nervous systems. Dogs may have a thin body condition, vomiting and diarrhoea, and lethargy. Regurgitation may be present secondary to a megaoesophagus. History is important when investigating these dogs.

ECG examination

Electrocardiography may detect hyperkalemia. Findings include flattened P waves, an increased P-R interval, increased positive or negative deflection in T waves, broadened QRS complexes, bradycardia, sinoventricular complexes and atrial standstill (absent P waves).

Electrolyte and blood gas assessment

Hyperkalemia and hyponatraemia (sodium: potassium ratio $<20:1$) are common findings. However, hyperkalemia and/or hyponatraemia are not present in all dogs. Approximately 10% of affected dogs will have normal electrolyte levels. Remember the disease has a slow and insidious onset. There is often a mild to moderate hypochloraemia. Similar electrolyte findings are also present in other conditions such as chronic urinary tract infections, pancreatitis, enteropathies, small bowel disease, and chronic end stage heart disease and liver failure.

Metabolic acidosis is common.

Biochemistry and urinalysis findings

Prerenal azotemia, hyperphosphataemia are common secondary to hypovolaemia. Urine concentrating ability is impaired secondary to hypoaldosteronaemia, resulting in dilute urine. There may be a mild hypercalcaemia (second most common cause of canine hypercalcaemia) and hypoglycaemia.

Again these findings can be due to renal failure and non-adrenal causes such as vomiting.

Haematology

Often there is a mild non-regenerative anaemia, an increased haematocrit if dehydrated. There may be no stress leucogram.

Yes it does affect cats!

Cats have similar historical and clinical findings to dogs although it occurs in mixed breed cats 5-6 years old. Common signs are lethargy, weight loss, vomiting, waxing-waning course and a previous therapeutic response.

Tests of Adrenal Function

ACTH stimulation test

The electrolyte abnormalities and clinical signs/history are suggestive of HypoA. The ACTH stimulation test is confirmatory. Dogs and cats with HypoA will have a subnormal response to ACTH. Any animal in an acute adrenocortical crisis should be treated with IV fluid therapy before the test is performed (see treatment section).

Protocol

1. Collect baseline serum/plasma cortisol.
2. Give 250 µg synthetic ACTH IV/IM (synacthen).
3. Collect a second cortisol sample 1-hour later.
4. If the samples cannot be submitted to the lab immediately, the samples can be centrifuged and the serum harvested and frozen for later analysis at the laboratory.

Plasma cortisol will fail to rise in animals with primary hypoadrenocorticism. Pre and post cortisol levels may below normal resting range. There is a slight, but still subnormal rise in cortisol with secondary hypoadrenocorticism. Post ACTH serum cortisol <50 nmol/l are consistent with HypoA.

If glucocorticoid therapy is required before the ACTH stimulation test is performed, dexamethasone should be used, as it does not interfere with the cortisol assay (prednisone, prednisolone and hydrocortisone cross react with serum cortisol assays). If any other glucocorticoid other than dexamethasone has been used, the ACTH stimulation test must be delayed by 24 hours in dogs or 12 hours in cats.

Endogenous ACTH assay

The ACTH stimulation test does not differentiate between primary and secondary HypoA. Endogenous ACTH assays must be performed. History should assist in the differentiation of primary and secondary HypoA. Plasma endogenous ACTH assays require careful handling and preparation. They must be collected before glucocorticoid administration (suppresses ACTH release), the blood sample is collected into an EDTA tube, immediately centrifuged and the plasma harvested and frozen at -20°C (consult you diagnostic lab before submission, as dry ice is necessary). Errors in sample preparation and handling will affect the results.

The ACTH stimulation test confirms hypoadrenocorticism. Dogs and cats with HypoA will have a subnormal response to ACTH. Glucocorticoid administration prior to the test can affect the results. Remember to treat acutely hypovolaemic animals before undertaking the test.

Differential Diagnosis for Hypoadrenocorticism

The electrolyte and biochemical abnormalities and clinical signs/history are not pathognomic for HypoA.

Other possible causes of the abnormalities observed are:

- Renal failure
- Whipworm
- Salmonellosis
- Neoplasia
- Gastroenteritis
- Renal failure
- Any cause of vomiting and/or diarrhoea

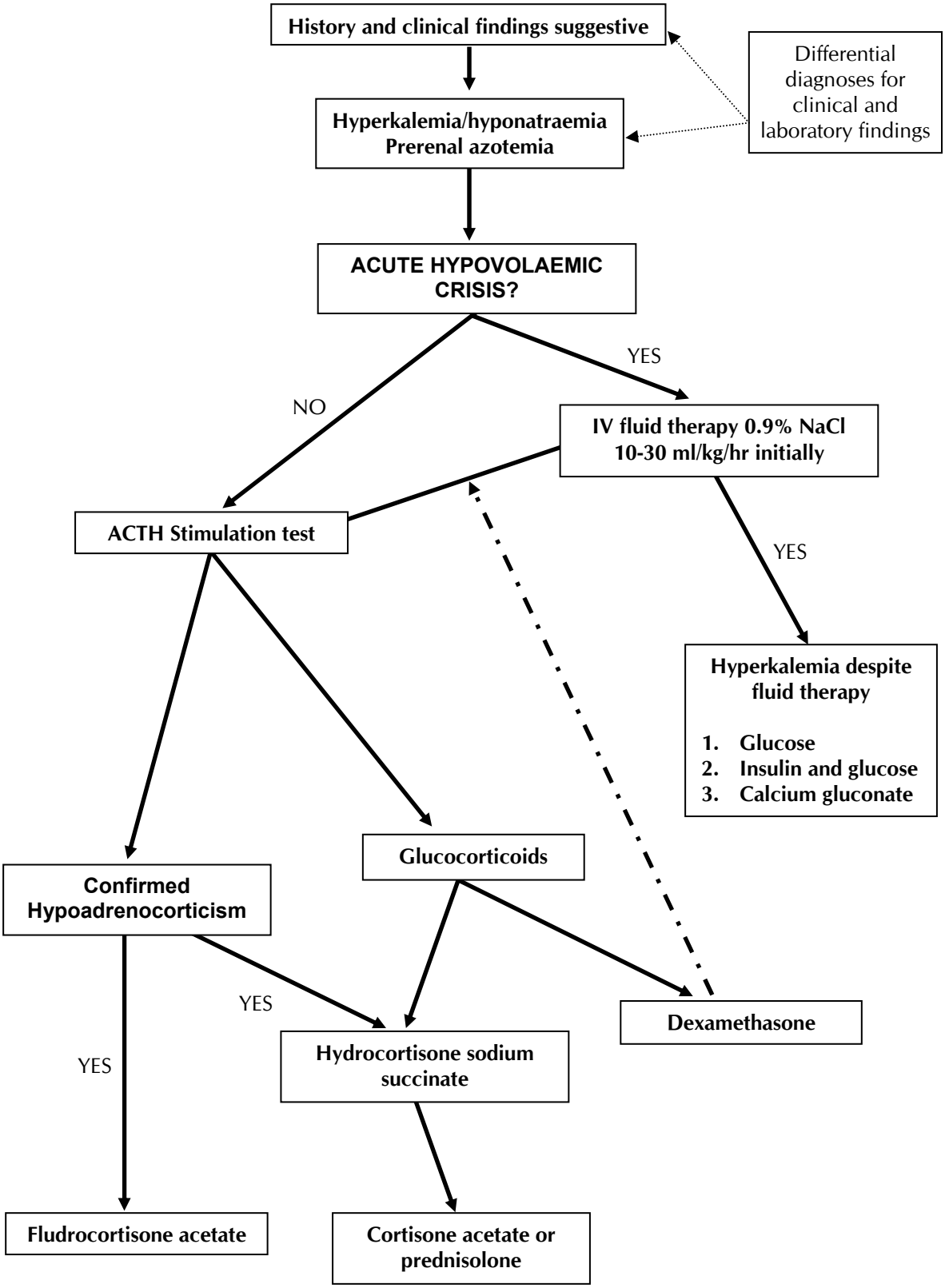
The ACTH stimulation test is required to confirm the diagnosis of hypoadrenocorticism.

Treatment

The goals of therapy are (1) the restoration of intravascular fluid volume; (2) correction of hyponatraemia, hyperkalemia, and metabolic acidosis; (3) recognition and treatment of the detrimental effects of hyperkalemia on the heart; (4) and replacement of glucocorticoids and mineralocorticoids.

IV fluid therapy is the most important treatment in acute hypoadrenocortical crisis. Start at 10-30 ml/kg/hr to restore circulating volume, dilute potassium and improve renal perfusion.

Suggested flow chart for the treatment and diagnosis of hypoadrenocorticism



Management of acute adrenocortical crisis

1. Fluid therapy

This is the ***first priority*** as shock and circulatory collapse is a common cause of death in acute adrenocortical insufficiency. Fluid therapy should be commenced before the ACTH stimulation test is performed. It is an emergency! Collect blood for CBC, biochemistry, electrolyte later analysis and urine for urinalysis.

Start with a rapid infusion of 0.9% NaCl IV. Initially commence at a rate of 10-30 ml/kg/hr for the first two hours to correct the hypovolaemia, and then decrease the fluid rate to 2-3 times maintenance (5-7.5 ml/kg/hr). The rate is dependent on the patient's volume status and urine output. Animals with hypoadrenocorticism are at risk of volume overload due to the concurrent renal alterations, and rapid correction of sodium deficits may result in neurological signs and demyelination. The goal is not to raise the sodium concentration by greater then 10-12 mmol/kg for the first 24 hours.

Cats should be started on 40 ml/hr as they have a smaller intravascular volume than dogs.

Fluid therapy not only restores the intravascular fluid deficit present, it also dilutes extracellular potassium and enhances urinary potassium excretion secondary to improvements in renal perfusion.

Lactated ringers can be used even though it contains 4 mEq/L potassium because the large volume of fluid administered will dilute the potassium in the circulation. If the animal is hypoglycaemic add dextrose to make a 5% final solution.

Maintenance fluids should be continued until the animal is eating and drinking Cats take longer to recover following treatment of an acute hypoadrenocortical crisis compared to dogs, taking up to 3-5 days.

Monitor urine output (closed system best) and treat oliguria aggressively (see treatment of acute renal failure) once intravascular deficits corrected. Central venous pressure is useful to monitor fluid therapy and to avoid hypervolaemia.

2. Management of hyperkalemia

Rapid volume expansion alone is usually sufficient to dilute extracellular potassium.

If serum potassium is greater than 7.5 mEq/l and atrial standstill or bradycardia is present it will require further prompt treatment. After commencing IV fluids give 10% glucose @ 1-4 ml/kg IV over 30-60 minutes. This drives K intracellularly due to interactions with insulin. Alternatively, give regular insulin @ 0.1-0.2 U/kg SQ, IM followed by at least 2 g dextrose for every unit of insulin given. This again drives K intracellularly but hypoglycaemia is a common risk factor. Remember these animals are very sensitive to the hypoglycaemic actions of insulin, due to the glucocorticoid deficiency. Using IV dextrose will achieve the same effect using endogenous insulin and it will not predispose the patient to hypoglycaemia.

If the hyperkalemia is immediately life threatening such as atrial standstill give 10% calcium gluconate IV over 10-20 minutes (watching the ECG!) in order to protect myocardial cells form hyperkalemia while other treatments take effect.

See table below for summary of treatments for hyperkalemia.

Therapy	Mechanism of Action
Mild Hyperkalemia (< 6.0 mEq/l)	
IV fluids	Plasma volume expansion, dilutes K, and increased GFR and renal potassium excretion
Moderate Hyperkalemia (6.0-8.0 mEq/l)	
Sodium bicarbonate (1-2 mEq/kg IV slowly over 20 min)	Translocates K into intracellular space in exchange for hydrogen ions
Dextrose (20-50%) (1.5 q/kg IV bolus)	Stimulates insulin release; insulin plus dextrose promotes transcellular entry of potassium into cells
Regular insulin and dextrose (0.1-0.25 U/kg + 1-2 g/kg dextrose IV)	
Severe Hyperkalemia (> 8.0 mEq/l)	
Calcium gluconate (10%) (0.5-1.0 ml/kg over 10-15 min; monitor ECG)	Specific antagonist against cardiotoxic effects of potassium

3. Correction of metabolic acidosis

This is usually corrected with fluid therapy alone due improvements in perfusion.

If the pH < 7.1 or bicarbonate < 10 mEq/l you can use sodium bicarbonate according to standard protocols. The goal is to raise pH to 7.2 or bicarbonate to 12 mEq/l.

4. Immediate short term glucocorticoid replacement

Intravenous fluids will dilute potassium and restore renal perfusion and correct the acidosis. Glucocorticoids and mineralocorticoids are required. However, mineralocorticoids are necessary to enhance distal tubular sodium absorption and potassium excretion and restore normal electrolyte balances. Give following IV fluid therapy initiation and once the ACTH stimulation test is completed. Use a rapidly acting agent:

(a) **Hydrocortisone sodium succinate** 2-4 mg/kg IV

(b) Dexamethasone sodium phosphate 1-2 mg/kg IV

(c) Dexamethasone 0.5-1.0 mg/kg IV (cats and dogs)

(d) Prednisolone sodium succinate 15-20 mg/kg IV (cats and dogs)

Hydrocortisone sodium succinate is an ester of cortisol that has equipotent glucocorticoid and mineralocorticoid activity. It has only 25% glucocorticoid potency of prednisolone and <1% mineralocorticoid potency of fludrocortisone, but at recommended dose rates it will provide sufficient activity to treat the consequences of hypoadrenocorticism. Hydrocortisone can be given as a CRI @0.5 mg/kg/hr in a separate IV fluid bag made up to 1 mg/ml as it binds to plastic and glass.

Dexamethasone is often the initial choice, as it does not interfere with cortisol assays. However, both dexamethasone and prednisolone lack mineralocorticoid activity making these less attractive treatment options.

Parenteral glucocorticoid therapy should be continued until vomiting has ceased. Glucocorticoids can be given every 2-6 hours as required. As the dog improves slowly reduce glucocorticoid dose to maintenance oral prednisone or cortisone acetate.

Hydrocortisone sodium succinate is the best rapidly acting glucocorticoid to use as it has glucocorticoid and mineralocorticoid effects Give @ 2-4 mg/kg IV

Maintenance glucocorticoid and mineralocorticoid therapy

Once stabilised the animal will require glucocorticoid and mineralocorticoid replacement therapy for the remainder of the patient's life.

Glucocorticoid replacement therapy

1. Prednisolone: This drug has no mineralocorticoid activity.

   Cats should continue on prednisolone at 1.25 mg/cat/day.

   In dogs, if prednisone is to be used for long term maintenance slowly taper from 1.0 mg/kg PO q 12 hrs to 0.25-0.5 mg/kg PO q 12 hrs while in hospital.

   Approximately 50% of dogs may require daily dosing with prednisolone @ 0.2 mg/kg/day. This may be able to be tapered over time. However, the dog will need additional glucocorticoids when they are under a period of stress such as surgery, trauma, or illness.

   If the dog has documented secondary hypoadrenocorticism glucocorticoids alone will only be required for maintenance, use prednisolone @ 0.2 mg/kg/day.

2. Cortisone acetate: This is a synthetic steroid with an 11-keto substitution. It is rapidly activated to hydrocortisone and then cortisone correcting the hypocortisolaemia. Like hydrocortisone succinate, cortisone acetate has equipotent glucocorticoid and mineralocorticoid activity, with more mineralocorticoid activity than other synthetic glucocorticoids, including prednisolone. It has a shorter half-life and lower overall activity reducing the risk of iatrogenic hyperadrenocorticism. It is able to be used long term. It may work synergistically with fludrocortisone.

   Treatment is individualised to each dog based on electrolyte therapy and clinical signs.

   0.5-1.0 mg/kg q 12-24 hours initially reducing to 0.5 mg/kg q-12-24 hours once stable.

Mineralocorticoid replacement therapy

There are no rapidly acting mineralocorticoids available.

Fludrocortisone acetate (Florinef): This is a synthetic adrenocortical steroid that has both mineralocorticoid and glucocorticoid properties. It has 10 times the glucocorticoid activity and 125 times the mineralocorticoid activity of cortisol.

Cats can be maintained on fludrocortisone @ 0.1 mg/cat/day.

In dogs use fludrocortisone acetate @ 0.01-0.02 mg/kg daily rounded to the nearest 0.05-0.1 mg increment. Dogs may require gradual incremental dose adjustments. These adjustments are based on serial electrolyte determinations. Most adjustments occur during the first 6-24 months and appear to be related to ongoing destruction or atrophy of the adrenal glands.

Dogs on concurrent long-term prednisolone and fludrocortisone therapy often require gradual increases of fludrocortisone, as mineralocorticoid therapy appears to reduce over time. However, dogs on cortisone acetate do not appear to show the same trend, and the dose of fludrocortisone required to maintain normal electrolyte levels is at the lower end of the suggested dose range.

In dogs long term therapy consists of a combination prednisolone and fludrocortisone or a combination of cortisol acetate and fludrocortisone, with the latter possibly being better. Cats are maintained long term on prednisolone and fludrocortisone.

All dose adjustments in mineralocorticoids must be made following assessment of electrolytes.

Summary

Hypoadrenocorticism encompasses a myriad of disease syndromes often with a waxing-waning progression, making diagnosis difficult. However approximately one third will present in an acute adrenocortical crisis requiring prompt treatment and diagnosis. Diagnosis must be performed during the initial work up and treatment period. Treatment involves IV fluids, glucocorticoid and mineralocorticoid replacement.

Finally, don't forget cats, they do suffer from hypoadrenocorticism.

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Appendix A: Differential Diagnosis for Electrolyte Abnormalities

Causes of Hyponatraemia

With Normal Plasma Osmolality Hyperlipaemia Hyperproteinaemia **With High Plasma Osmolality** Hyperglycaemia Mannitol infusion	**With Low Plasma Osmolality** And hypervolaemia Severe liver disease Congestive heart failure Nephrotic syndrome Advanced renal failure And normovolaemia Psychogenic polydipsia Syndrome of inappropriate ADH secretion Antidiuretic drugs Myxoedema coma of hypothyroidism Hypotonic fluid admin. And hypovolaemia Gastro-intestinal loss Vomiting Diarrhoea Third-space loss Pancreatitis Peritonitis Uroabdomen Pleural effusion Peritoneal effusion Cutaneous loss Burns Hypoadrenocorticism Diuretic administration

Causes of Hypoglycaemia

Insulinoma Insulin overdose Sepsis Extrapancreatic neoplasia Adrenocortical insufficiency End-stage liver disease Pregnancy Artifactual – poor sample handling	Glycogen storage diseases Congenital portosystemic shunts Malnutrition Paediatric metabolic enzyme deficiency Hunting dog hypoglycaemia Polycythemia

Causes of Hyperkalemia

Pseudohyperkalemia
- Thrombocytosis
- Haemolysis

Increased Intake
- Unlikely to cause hypokalemia in the presence of normal renal function unless iatrogenic.

Translocation (ICF γ ECF)
- Acute mineral acidosis
- Insulin deficiency (DKA)
- Acute tumour lysis syndrome
- Reperfusion of extremities after aortic thromboembolism in cats with cardiomyopathy
- Hyperkalemic periodic paralysis
- Non-specific βblockers (propanalol)

Decreased Urinary Excretion
- Urethral obstruction
- Ruptured bladder
- Anuric or oliguric renal failure
- Hypoadrenocorticism
- Selected GIT disease (Trichuriasis, salmonellosis, perforated duodenal ulcer)
- Chylothorax with repeated pleural fluid drainage
- Drugs
  - ACE inhibitors
  - Potassium sparing diuretics
  - Prostaglandin inhibitors
  - Heparin

Differential diagnosis of hypercalcaemia

Nonpathologic
- Nonfasting (Minimal)
- Physiologic growth of young
- Laboratory error
- Spurious
  - Lipaemia
  - Detergent contamination of sample or tube

Transient or Inconsequential
- Haemoconcentration
- Hyperproteinaemia
- Hypoadrenocorticism
- Severe environmental hypothermia

Pathologic or Consequential – Persistent
- Malignancy associated
  - Humoral hypercalcaemia of malignancy
    - Lymphoma
    - Anal sac apocrine gland adenocarcinoma
    - Carcinoma (sporadic)
    - Thymoma (rare)
  - Haematologic malignancies (bone marrow osteolysis)
    - Lymphoma
    - Multiple myeloma
    - Myeloproliferative disease (rare)
    - Leukaemia (rare)

Pathologic or Consequential (cont.)
- Chronic renal failure
- Hypervitaminosis D
  - Iatrogenic
  - Plants
  - Rodenticide
- Granulomatous disease
  - Blastomycosis
  - Dermatitis
- Primary hyperparathyroidism
  - Adenoma
  - Adenocarcinoma (rare)
  - Hyperplasia (uncommon)
- Acute renal failure
- Skeletal lesions (non-malignant) (uncommon)
  - Osteomyelitis
  - Hypertrophic osteodystrophy
  - Disuse osteoporosis
- Excessive calcium-containing intestinal phosphate binders
- Excessive calcium supplementation
- Hypervitaminosis A
- Hypercalcaemic conditions in human medicine
  - Milk-alkali syndrome (rare (D))
  - Thiazide diuretics
  - Acromegaly
  - Thyrotoxicosis
  - Postrenal transplantation
  - Aluminium exposure