Relative Adrenal Insufficiency in Critically Ill Patients

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Relative adrenal insufficiency (RAI) is characterized by inadequate cortisol production during periods of severe stress such as critical illness, most notably sepsis or septic shock. Cortisol, which plays a pivotal role in metabolism, cardiovascular function, and the immune system, is normally produced to maintain homeostasis during stress. The normal physiologic response to illness consists of activation of the hypothalamic–pituitary–adrenal (HPA) axis to initiate increased secretion of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the anterior pituitary to produce adrenocorticotropic hormone (ACTH), causing production of cortisol by the adrenal cortex. Cortisol concentrations may be normal or high in critically ill patients; however, the concentrations are inadequate to appropriately compensate for the current illness.

The mechanisms for RAI are still unknown. Proposed mechanisms include blunted interleukin-6 responses, causing decreased release of ACTH secondary to understimulation of the HPA axis. Also, cytokines such as tumor necrosis factor α have been known to inhibit adrenal function by inhibiting the actions of ACTH and angiotensin II on adrenocortical cells and by impairing CRH-stimulated ACTH release, thus decreasing cortisol production. Corticostatin competes with ACTH by binding to its receptors on adrenal cells, thereby preventing the synthesis and release of cortisol and inhibiting the HPA axis. Migration inhibitory factor produced by macrophages has been shown to cause glucocorticoid resistance. In a rat cecal ligation and puncture, Koo et al found a 42% reduction in adrenal content of corticosterone (the primary glucocorticoid in rats), indicating impaired synthesis of glucocorticoid. Reduced plasma corticosterone and adrenal cAMP responses to exogenous corticotropin were also reported. These data confirm RAI-like syndromes in a specific animal model of sepsis and suggest resistance to corticotropic at the level of the adrenal glands as the mechanism.

RAI has been well documented in humans and is currently being investigated in dogs and cats. RAI has been noted in a foal and in rats. In human medicine, the most common causes of RAI are sepsis and systemic inflammatory response syndrome (SIRS). Information concerning RAI and the potential therapeutic use of corticosteroids in critically ill veterinary patients is extremely limited because only a few clinical randomized, controlled, prospective studies have been completed at this time.

Diagnostic Criteria

Historical Information

Gender, Age, Breed Predisposition
• None proven.

Owner Observations
• Clinical signs are dependent on the associated primary illness.
• Signs associated with hypoadrenocorticism (e.g., depression, weakness, vomiting, lethargy, collapse, shaking, weight loss, polyuria/polydipsia, anorexia). A waxing/waning course may or may not be seen.

Other Historical Considerations/Predispositions
• In humans: liver disease, immunodeficiency virus, traumatic brain injury, pancreatitis, burns, or cardiac surgery.
• In humans, the incidence of RAI is remarkably variable and depends on the severity of the illness and the underlying disease.
• The incidence increases with illness severity (sepsis > elective surgery > hospital ward admission); in high-risk critically ill patients (those with shock and sepsis), the incidence is approximately 30% to 45%. Most human studies report an incidence between 25% and 40%.
• Neoplasia: Prittie et al investigated the effects of critical illness on adrenocortical function in 20 critically ill cats. This study raised a high index of suspicion that critically ill cats with neoplasia develop RAI.
• Another study by Prittie et al that evaluated pituitary–adrenal function in cats with lymphoma also indicated that these cats were more likely to develop RAI compared with cats without neoplasia.
Boozer et al investigated endogenous ACTH levels and basal cortisol levels in dogs with neoplasia compared with the levels of healthy dogs. Dogs with lymphoma and nonhematopoietic neoplasia had decreased basal cortisol concentrations and a subnormal ACTH response. Endogenous ACTH levels were below the reference range in 10% of the dogs with lymphoma and 7% with nonhematopoietic neoplasia.

Shock (including septic shock), SIRS, sepsis, and severe sepsis: A case report by Durkan et al described a suspected RAi case involving all the currently accepted criteria for a diagnosis of RAi in a critically ill cat recovering from polytrauma.

Hemorrhage: Wang et al studied the occurrence of RAi after nonseptic insults in rats. The study of rats subjected to hemorrhage and resuscitation concluded that corticotropin-stimulated corticosterone release and adrenal concentrations of corticosterone and cAMP decreased significantly despite increased plasma concentrations of corticosterone. These results strongly suggest the presence of RAi.

Physical Examination Findings
- Signs for human cases are nonspecific. Because this syndrome is still being studied in veterinary medicine, the full range of clinical signs and laboratory findings has not been determined.
- Hypotension refractory to appropriate fluid and vasopressor therapy.
- Weakness, anorexia, lethargy.
- Some patients may present with nonspecific gastrointestinal signs (abdominal discomfort, nausea, vomiting, diarrhea).
- Clinical features of RAi may be masked by the signs of the primary disease process responsible for causing RAi.

Laboratory Findings
- Classic electrolyte abnormalities of primary hypoadrenocorticism (low sodium and high potassium) are thought to be absent.
- Complete blood count:
  - A stress leukogram may be absent.
  - Eosinophilia may be present. A human study found that the relative and absolute numbers of eosinophils were significantly higher in high-risk surgical patients with RAi compared with patients with a normal ACTH response. Thus, eosinophilia in critically ill patients is uncommon and, if present, should raise the index of suspicion for RAi.
- Chemistry: Hypoglycemia may be seen.

Other Diagnostic Findings
- Standard-dose ACTH stimulation test:
  - Obtain blood sample for determination of baseline serum or plasma cortisol and then administer 250 µg or 5 µg/kg IV of cosyntropin up to a maximum of 250 µg.
  - Obtain blood for assessment of postinjection serum or plasma cortisol level 60 minutes after cosyntropin administration.
  - In critically ill humans, a response to 250 µg of cosyntropin does not rule out RAi because this is a supraphysiologic dose (100-fold greater than a normal endogenous stress-induced ACTH level) of corticotropin. This supraphysiologic dose may override adrenal resistance to ACTH, resulting in a normal cortisol response from the adrenal reserve.
  - A “normal” response to an ACTH stimulation test may not rule out RAi in every case. However, little is known about how the HPA axis functions in serious illness or how critically ill veterinary patients respond to traditional ACTH stimulation testing.
  - Two separate studies by Farrelly et al and Prittie et al that investigated RAi in cats with neoplasia indicated that critically ill cats with neoplasia had a smaller change in cortisol concentration compared with control animals and had inadequate cortisol concentrations after ACTH stimulation testing.
  - A case report described a suspected case of RAi in a critically ill cat recovering from polytrauma that developed hypotension that was nonresponsive to intravenous fluid and vasopressor therapy. An ACTH stimulation test was conducted by administering 125 µg IM of cosyntropin. Test results indicated an inadequate response: a baseline cortisol concentration of 1.1 µg/dL (reference range: 0.5 to 5.0 µg/dL), and poststimulation cortisol levels of 4.3 and 4.2 µg/dL (reference range: 5 to 15 µg/dL) at 30 and 60 minutes, respectively. The change...
SUMMARY OF DIAGNOSTIC CRITERIA

- Clinical signs, especially hypotension refractory to fluid and vasopressor therapy in a critically ill animal.
- Response to treatment: The ability to wean a previously vasopressor-dependent patient from vasopressors after glucocorticoid administration is the gold standard for diagnosing RAI.
- Diagnostic tests:
  - Standard-dose ACTH stimulation test: An ACTH-stimulated cortisol concentration below the reference range.
  - Low-dose ACTH stimulation test: An ACTH-stimulated cortisol concentration below the normal reference range.
  - Change in cortisol concentration: ≤3 µg/dL in dogs with sepsis.

- Exact diagnostic criteria are still being debated in human medicine and have yet to be completely defined in veterinary medicine.

DIAGNOSTIC DIFFERENTIALS

- SIRS without adrenal dysfunction.
- Primary hypoadrenocorticism.
- Neoplasia of the adrenal glands (lymphoma): Diagnose by ultrasound-guided aspiration or biopsy.
- Adrenal hemorrhage secondary to septicemia or coagulopathy: Diagnose by abdominal ultrasonography and/or coagulation profile, with or without biopsy.
- Etomidate or ketoconazole administration: These medications have been found to inhibit the enzymes involved in cortisol synthesis.
- Traumatic brain injury affecting the pituitary may cause hypoadrenocorticism.
- In humans, other causes include immunosuppression (resulting from human immunodeficiency virus, tuberculosis, or fungal disease) and rifampin therapy (which may produce signs similar to those of RAI).

TREATMENT RECOMMENDATIONS

INITIAL TREATMENT

- After an ACTH stimulation test, volume-resuscitated vasopressor-dependent animals may be started on low-dose glucocorticoid therapy. Hydrocortisone has been the glucocorticoid of choice for critically ill humans, as it also has mineralocorticoid activity. Mineralocorticoid insufficiency has never been proven to occur in critically ill humans or animals with RAI.
• In humans, hydrocortisone is administered at 100 mg IV q8h (or 200 to 300 mg/day) or, alternatively, if the cortisol assay needs to be delayed, dexamethasone at 0.08 mg/kg IV q24h, which is equivalent to administering 0.5 mg/kg q24h of prednisone in cats.

• The 2008 Surviving Sepsis Campaign recommends that humans in septic shock not receive dexamethasone if hydrocortisone is available. It also recommends that corticosteroids not be administered to treat sepsis in the absence of shock.

• The use of short-course, low-dose hydrocortisone has not been studied in dogs with RAI, and it is unknown whether this treatment would improve blood pressure and survival as in humans.

• Clinical conditions of humans with sepsis or in septic shock do not appear to improve with pharmacologic or high-dose glucocorticoid therapy.

• Recent studies have demonstrated that administration of “stress” (low) doses of glucocorticoids has beneficial effects in critically ill humans with RAI and a variety of other medical and surgical conditions, including sepsis.

Supportive Treatment
• Intravenous fluid therapy with a crystalloid or colloid.
• Vasopressor therapy such as dopamine or norepinephrine as the first line of defense; vasopressin therapy should then be initiated if the initial pressor agent is not improving blood pressure adequately.
• Electrolytes, nutrition, pertinent medications, and organ support, depending on the underlying problem.

Patient Monitoring
• Continuous blood pressure measurements after glucocorticoid administration.
• Lactate measurements or blood gas evaluation to monitor perfusion and metabolic status.
• Repeat the ACTH stimulation test once the patient has fully recovered from the illness to rule out primary adrenal insufficiency or to confirm normalization of adrenal function. Recommend repeating in 5 to 7 days; if the ACTH stimulation test result is within the reference range at this time, glucocorticoid administration can be discontinued. However, if the ACTH stimulation test result is low, continue administration of glucocorticoids and repeat the ACTH stimulation test in 5 to 7 days.
• Glucocorticoid administration could affect the ACTH stimulation test result by suppressing cortisol production and making it seem as though RAI is still present. To accurately assess the patient’s adrenal function after discontinuing corticosteroid administration, it is probably best to wait 7 days to repeat the stimulation test. The discontinuation of corticosteroid administration may also be based on response to therapy and resolution of hypotension.

Home Management
• Prednisone or prednisolone at a physiologic dose (0.25 mg/kg/day PO).
• Medication for the underlying disease process.

Milestones/Recovery Time Frames
• Removal of vasopressor support should be possible 24 to 48 hours after administration of dexamethasone or hydrocortisone.

Treatment Contraindications
• Ketoconazole.
• Etorphine.
• Spironolactone.
• In humans, megestrol acetate, rifampin, phenytoin, metyrapone, and mitotane can cause adrenal insufficiency.

PROGNOSIS

Favorable Criteria
• Improvement in blood pressure following glucocorticoid administration after previously being refractory to vasopressor therapy.
• Maintaining blood pressure after removal of vasopressor therapy.

Unfavorable Criteria
• Continued hypotension after glucocorticoid administration.

RECOMMENDED READING


ARTICLE #2 CE TEST

1. What is the gold standard of diagnosis for RAI?
   a. high-dose ACTH stimulation test
   b. the ability to wean a previously vasopressor-dependent patient from vasopressors after glucocorticoid administration
   c. change in cortisol concentration: >3 μg/dL in dogs with sepsis
   d. low-dose ACTH stimulation test

2. Which of the following is not a mechanism considered to cause RAI?
   a. increased response to interleukin-6
   b. understimulation of the HPA axis secondary to decreased release of ACTH
   c. migration inhibitory factor produced by macrophages
   d. competitive inhibition of ACTH by corticostatin

3. Which is not a common clinical finding in patients with RAI?
   a. weakness
   b. depressed spinal reflexes
   c. abdominal discomfort
   d. hypotension refractory to appropriate fluid and vasopressor therapy

4. What is the appropriate therapy for at home management?
   a. prednisone (0.25 mg/kg/day PO)
   b. prednisone (0.25 mg/kg/day PO) and fludrocortisone acetate
   c. prednisone (0.5 mg/kg/day PO) and desoxycorticosterone pivalate
   d. prednisone (0.5 mg/kg/day PO)

5. Which is the most unlikely laboratory finding in patients suspected of having RAI?
   a. eosinophilia
   b. absence of a stress leukogram
   c. hyponatremia and hyperkalemia
   d. hypoglycemia

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