

# Combined hyponatremia and hyperkalemia mimicking acute hypoadrenocorticism in three pregnant dogs

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- ▶ Differential diagnoses for hyponatremia with concurrent hyperkalemia should include hypoadrenocorticism.
- ▶ Renal failure, chylothorax, and gastrointestinal tract disorders may also cause abnormally low serum sodium:potassium ratios.
- ▶ The ACTH stimulation test is the gold standard for diagnosis of hypoadrenocorticism.

A 2-year-old 35-kg (77-lb) near-term (62 to 65 days of gestation) pregnant Greyhound was examined for the primary problems of acute weakness and collapse. The dog had been healthy and was 1 of several dogs in a Greyhound kennel. The dog had been vaccinated against common canine diseases and treated prophylactically for gastrointestinal parasites and heartworm infection. The owner reported that the dog had been inappetent and lethargic for 2 days before examination and had vomited water twice on the day of referral.

Physical examination revealed substantial signs of depression and severe muscle weakness. The dog was slightly dehydrated, rectal temperature was within reference range, and respiratory and heart rates were 60 breaths/min and 110 beats/min, respectively. Capillary refill time was 2 seconds. The abdomen was distended, and several puppies were palpated. Examination of the vaginal canal and the mammary glands revealed normal findings. The initial differential diagnoses included uterine torsion or rupture with hypovolemic shock, hypocalcemia, and hypoglycemia. The dog was admitted to the intensive care unit, and a saline (0.9% NaCl) solution<sup>a</sup> was administered IV (70 to 90 ml/kg [32 to 41 ml/lb] of body weight) during the first hour. Blood samples were taken and submitted for serum biochemical analyses. Electrocardiography revealed sinus tachycardia (110 beats/min), and abdominal radiography revealed 12 fetuses. The dog vomited blood and dark brown gastric contents within the first hour after admission.

Abnormal serum biochemical values included mild acidemia (pH 7.25; reference range, 7.35 to 7.45), hypobicarbonatemia (13 mEq/L; reference range, 20 to 27 mEq/L), mild hypocalcemia (8.8 mg/dl; reference

range, 9.0 to 10.8 mg/dl), substantial hyperkalemia (8.7 mEq/L; reference range, 3.7 to 5.3 mEq/L), hyponatremia (125 mEq/L; reference range, 145 to 157 mEq/L), and low sodium-potassium ratio (14:1; reference range, > 30:1). The dog was azotemic (BUN, 93 mg/dl [reference range, 7 to 25 mg/dl]; creatinine, 4.1 mg/dl [reference range, 0.5 to 1.4 mg/dl]). Serum phosphorus concentration was high (13.2 mg/dl; reference range, 2.4 to 6.1 mg/dl). Serum glucose concentration was slightly high (149 mg/dl; reference range, 66 to 116 mg/dl). Results of CBC included PCV within reference range (55%; reference range for Greyhounds, 45 to 60%), mild leukocytosis ( $23.7 \times 10^3$  cells/ $\mu$ l; reference range, 6.0 to  $17.0 \times 10^3$  cells/ $\mu$ l), and platelet count within reference range ( $369 \times 10^3$  platelets/ $\mu$ l; reference range, 200 to  $400 \times 10^3$  platelets/ $\mu$ l). Cystocentesis was not attempted because of the enlarged uterus.

Acute hypoadrenocortical crisis was suspected on the basis of signs of hypovolemia, hyponatremia, hyperkalemia, azotemia, and metabolic acidosis. Adrenal gland function was evaluated by use of an ACTH stimulation test. Blood samples were collected for baseline serum cortisol and aldosterone determinations, 0.25 mg of cosyntropin<sup>b</sup> was administered IV, and blood samples were collected 1 hour later. Because samples were analyzed elsewhere,<sup>c</sup> test results were unavailable until 4 days later. Baseline cortisol concentration was 4.8  $\mu$ g/dl (reference range, 0.5 to 3.9  $\mu$ g/dl), and cortisol concentration 1 hour after administration of cosyntropin was 16.23  $\mu$ g/dl (reference range, 7.97 to 19.9  $\mu$ g/dl). Serum aldosterone concentrations in samples obtained before and after administration of cosyntropin were high (2,793 and 3,329 pmol/L, respectively; reference range, 14 to 957 pmol/L).

The dog was treated for suspected hypoadrenocortical crisis. In addition to infusion with saline solution, other medications administered IV included dexamethasone phosphate<sup>d</sup> (2.4 mg/kg [1.09 mg/lb]), 10% solution of calcium gluconate<sup>e</sup> (0.5 ml/kg [0.23 ml/lb]), sodium bicarbonate<sup>f</sup> (1.1 mEq/kg [0.5 mEq/lb]), and cimetidine hydrochloride<sup>g</sup> (5 mg/kg [2.3 mg/lb]). Sucralfate<sup>h</sup> (1 g, PO, q 8 h) and fludrocortisone acetate<sup>i</sup> (0.01 mg/kg [0.005 mg/lb]) were administered orally later that day after vomiting had ceased. After clinical stabilization, ovariohysterectomy was performed. Eleven of 12 puppies survived, and the dog recovered from anesthesia without complications.

On the first postoperative day, all abnormal serum biochemical values returned to or near reference ranges. Two episodes of diarrhea with dark brown feces occurred; fecal examination for parasites was inadver-

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tently omitted. The dog otherwise appeared well enough to go home and was released with instructions for treatment with sucralfate (1 g, PO, q 6 h for 14 days) and famotidine (20 mg, PO, q 24 h for 14 days). Fludrocortisone was given orally for 1 week and subsequently discontinued when adrenal function test results were determined to be within reference ranges; the dog remained healthy.

A 3-year-old 37-kg (81-lb) near-term pregnant Greyhound was examined for acute onset of weakness, inappetence, and vomiting of 24 hours' duration. The vomitus was described as watery. Vaccinations and intestinal parasite prevention measures were reported as current.

Physical examination revealed findings that were almost identical to those of the first dog. Treatment with saline solution and lactated Ringer's solution (70 ml/kg) was initiated. Results of ECG were similar to the first dog's, and abdominal radiography revealed 8 fetuses.

Abnormal serum biochemical values included metabolic acidosis, hyperkalemia, hyponatremia, azotemia, hyperphosphatemia, and low sodium-potassium ratio. The PCV and serum total protein concentration were high. Serum cortisol concentration before administration of cosyntropin was 7.6 µg/dl and 1 hour after administration of cosyntropin was 19.6 µg/dl, but these results were unavailable for the first 48 hours.

Initial treatment was prescribed for an assumed hypoadrenocortical crisis. Additional treatments given IV included dexamethasone phosphate (4 mg/kg [1.8 mg/lb]), cephalothin<sup>i</sup> (20 mg/kg [9.1 mg/lb]), and cimetidine (5 mg/kg).

The dog underwent an exploratory laparotomy after vital signs and serum biochemical values improved. An extensive uterine tear was identified, 8 puppies were delivered, and an ovariohysterectomy was performed. The dog recovered without major complications except for occasional vomiting and semi-fluid feces that occurred for 2 days after surgery; the dog was discharged 1 day later. Fludrocortisone acetate administration was begun orally (0.006 mg/kg [0.003 mg/lb]) on the second postoperative day after vomiting had ceased and was discontinued without complications when serum cortisol values were found to be within reference ranges. Results of repeat blood tests performed on the first postoperative day were within reference ranges.

An 8-year-old 27-kg (59-lb) pregnant Greyhound was examined for anorexia, vomiting, and progressive weakness of 2 days' duration. The dog's vomitus was watery. Labor had begun that morning. History revealed no prior illnesses, and vaccinations and parasite treatments were current.

At referral, the dog had signs of depression and was in lateral recumbency. Rectal temperature was 102.2 F (39 C), heart rate was 16 beats/min, and respirations were rapid and shallow. Several fetuses were detected by use of abdominal palpation. Rectal examinations revealed melena, but diarrhea was not reported to have occurred prior to admission. The dog was admitted to the intensive care ward, an IV catheter was placed, and blood samples were collected for serum biochemical analyses.

Treatment was initiated by IV administration of saline solution. The PCV was slightly low (44%), whereas total protein concentration and platelet count were within reference ranges. Metabolic acidosis, mild hypocalcemia, hyperkalemia, hyponatremia, and moderate azotemia were detected. The sodium:potassium ratio was low (14:1). Electrocardiography revealed substantial bradycardia (16 beats/min) and lack of P waves (atrial standstill).

Hetastarch<sup>k</sup> (20 ml/kg) was administered IV with the saline solution to help reverse hypovolemic shock. The dog also received prednisolone sodium succinate<sup>l</sup> (10 mg/kg [4.5 mg/lb]), cimetidine (5 mg/kg), and sodium bicarbonate (0.5 mEq/kg [0.23 mEq/lb]). Desoxycorticosterone acetate<sup>m</sup> (4 mg) was also given IM.

The dog was taken to surgery after 1.5 hours of medical treatment; an ovariohysterectomy was performed, and 8 live puppies were delivered. The dog remained in the intensive care ward for 3 additional days after surgery because of persistent weakness and onset of diarrhea with dark brown fluid feces; however, the dog's condition progressively improved. An ACTH stimulation test was not performed until the fourth day of hospitalization, at which time baseline serum cortisol concentration was 2.2 µg/dl. Cortisol concentration 1 hour after administration of cosyntropin was 7.11 µg/dl, which was interpreted as within reference range, considering the negative feedback inhibition caused by the fludrocortisone treatment the dog had been receiving (0.3 mg, PO, q 24 h). This mineralocorticoid treatment was subsequently discontinued when serum cortisol concentrations were determined to be within reference ranges, and the dog continued to do well. All of the abnormal serum biochemical test results had returned to reference ranges by the third hospital day.

Concurrent hyponatremia and hyperkalemia in dogs is commonly associated with adrenocortical insufficiency. Before the ACTH stimulation test became the gold standard for diagnosing adrenocortical insufficiency,<sup>1,2</sup> diagnosis of this disease was usually made on the basis of clinical signs, hyponatremia, and hyperkalemia. However, other syndromes reported in dogs have been associated with hyponatremia and hyperkalemia, including various gastrointestinal tract disorders,<sup>3,5</sup> chylothorax,<sup>6</sup> and renal failure.<sup>7</sup> Although the pathophysiology of the electrolyte disturbances in these disorders remains obscure, their clinical identification has emphasized the importance of the continued use of the ACTH stimulation test for confirming the diagnosis of hypoadrenocorticism.

Hyponatremia and hyperkalemia that are associated with primary gastrointestinal tract disorders are attributed primarily to loss of sodium and bicarbonate ions from the gastrointestinal tract and metabolic acidosis.<sup>3,5</sup> The fluid lost from the circulation because of diarrhea is usually isotonic; if it is replaced by orally administered water, hyponatremia results. Hyperkalemia is thought to be caused by translocation of intracellular potassium to the extracellular fluid space as a result of metabolic acidosis. Metabolic acidosis is attributed to intestinal loss of bicarbonate ions and tissue hypoperfusion. A clinical study<sup>4</sup> of dogs with whip-

worm-associated diarrhea, hyponatremia, and hyperkalemia revealed normal adrenocortical function; serum sodium concentration was as low as 113 mEq/L, and serum potassium concentration was as high as 7.3 mEq/L, with sodium:potassium ratio ranging from 15 to 26.7. In the dogs reported here, diarrhea was not detected prior to hospitalization, although it became a problem for all 3 dogs after the first day of hospitalization. Furthermore, the vomiting that occurred prior to hospitalization did not appear severe enough to cause such profound biochemical abnormalities. Therefore, it is difficult to incriminate the delayed onset of the diarrhea and the mild vomiting as major causes of the serum electrolyte abnormalities in these 3 dogs.

In a recent review<sup>7</sup> of low sodium:potassium ratios in 34 dogs, renal failure or urinary tract disease leading to decreased urine excretion accounted for this abnormality in most of the dogs, with sodium:potassium ratios ranging between 19.9 and 15. These low ratios were more strongly associated with high serum potassium concentrations than with low serum sodium concentrations. Four of the dogs in that study had sodium:potassium ratios of < 15, and each had hypoadrenocorticism. The authors were careful to avoid implicating sodium:potassium ratios of < 15 as diagnostic of hypoadrenocorticism. This is in agreement with results obtained in 2 dogs reported here, which included sodium:potassium ratios of 14 and responses to ACTH stimulation tests within reference ranges.

Renal and gastrointestinal tract dysfunction likely contributed to the hyponatremia and hyperkalemia in the dogs reported here, although it is unlikely that renal tubular damage was severe, because abnormal renal values returned rapidly to reference ranges in the 2 dogs in which follow-up values were measured, and all 3 dogs resumed normal activity at or soon after discharge from the hospital. The exact cause of the renal dysfunction was never determined, although prerenal azotemia was likely a contributing factor. In addition, consideration must be given to the hormonal and hemodynamic mechanisms in pregnancy that may influence renal function and electrolyte balance.<sup>8</sup>

High aldosterone concentration in the first dog of this report and sustained serum electrolyte concentrations within reference ranges for all 3 dogs after discharge and discontinuation of fludrocortisone treatment were evidence that hypoaldosteronemia in these dogs was not present, despite hyponatremia and hyperkalemia. In contrast, pregnancy may actually result in high concentrations of aldosterone. Pregnant women have increased serum concentrations of renin and aldosterone during the last trimester,<sup>9</sup> and urinary concentrations of free 18-hydroxycorticosterone, plasma aldosterone, and urinary aldosterone metabolites are also high during normal pregnancy.<sup>10</sup>

Much is known about the effects of estrogen and progesterone on sodium and potassium metabolism and adrenocortical function during pregnancy, and it seems unlikely that pregnancy caused the serum biochemical abnormalities detected in the 3 dogs of our report. Pregnancy protects adrenalectomized animals against volume depletion, which suggests that progesterone, estrogen, or both have a mineralocorticoid effect dur-

ing pregnancy.<sup>8</sup> In female dogs, estradiol and estriol cause sodium retention that seems independent of the effect of aldosterone, because a concurrent change in potassium excretion does not develop.<sup>11</sup>

Pregnant women secrete increased amounts of aldosterone and desoxycorticosterone without kaliuresis.<sup>12</sup> This is attributed to progesterone's activity as a competitive inhibitor of aldosterone, which facilitates natriuresis and attenuates the kaliuretic action of mineralocorticoids. Thus, if this mechanism occurs in dogs, aldosterone inhibition may have contributed to hyperkalemia in the 3 Greyhounds reported here.

<sup>a</sup>0.9% sodium chloride solution, injection USP, Baxter Healthcare Corporation, Deerfield, Ill.

<sup>b</sup>Cortrosyn, cosyntropin, Organon Inc, West Orange, NJ.

<sup>c</sup>Animal Health Diagnostic Laboratory, East Lansing, Mich.

<sup>d</sup>Dexamethasone sodium phosphate injection, American Regent Laboratories Inc, Shirley, NY.

<sup>e</sup>Calcium gluconate injection USP, 10%, American Regent Laboratories Inc, Shirley, NY.

<sup>f</sup>Sodium bicarbonate injection USP, 8.4%, American Regent Laboratories Inc, Shirley, NY.

<sup>g</sup>Cimetidine hydrochloride injection, SK-Beecham, Philadelphia, Pa.

<sup>h</sup>Carafate, Hoechst Marion Roussel, Kansas City, Mo.

<sup>i</sup>Florinef acetate, Apoteco, A Bristol-Myers Squibb Co, Princeton, NJ.

<sup>j</sup>Cephalothin sodium injection, Eli Lilly Co, Indianapolis, Ind.

<sup>k</sup>6% Hetastarch in 0.9% sodium chloride injection, Abbott Laboratories, North Chicago, Ill.

<sup>l</sup>Prednisolone sodium succinate (Solu Delta Cortef), Pharmacia and Upjohn Company, Kalamazoo, Mich.

<sup>m</sup>Desoxycorticosterone acetate, Organon Inc, West Orange, NJ.

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