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Case Report
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Heparin-Induced Hyperkalemia in a Dog Receiving Continuous Renal Replacement Treatment

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Key words: Aldosterone; Hypoadrenocorticism; Dialysis; Potassium.

Case Summary

An 11-year-old, male castrated Australian shepherd dog presented for evaluation of acute exacerbation of chronic kidney disease (CKD). The dog had a history of stage III CKD[a] (borderline proteinuric, blood pressure unknown) that had been stable for 4 years. The dog had last been evaluated 5 months earlier. At that time, blood urea nitrogen (BUN) concentration was 57 mg/dL, serum creatinine (SCr) concentration was 3.3 mg/dL, and serum potassium concentration was 5.5 mEq/L. The dog had been treated chronically with enalapril (0.56 mg/kg PO q24h), calcitriol (2.7 ng/kg PO q24h), omega fatty acids (unknown dose), aspirin (1.1 mg/kg PO q24h), and a prescription renal diet[b]. According to the owner, the dog had been doing well since its last evaluation with no changes in appetite, activity, or urinations.

A week before presentation, the dog's appetite and activity decreased markedly. It began having diarrhea, and water intake was decreased. No definitive toxin exposure had occurred but there was possible ingestion of raisin bread within 10 days of presentation. The dog weighed 17.8 kg and was markedly azotemic (SCr concentration: 12.6 mg/dL; BUN concentration: >130 mg/dL) with a urine protein:creatinine (UPC) ratio of 1.49. The dog was hospitalized and treated with antimicrobials, antacids, antiemetics, IV fluids, antihypertensive treatment, enteral nutrition (50% resting energy requirement [RER] for 2 days before referral), and 1 dose of epoetin alfa (101 U/kg SC). After a week of treatment, the dog was referred for continuous renal replacement treatment (CRRT) to manage refractory azotemia (SCr concentration: 8.2 mg/dL) and resolve fluid overload evidenced by peripheral edema and net weight gain (approximately 1.1 kg) although the dog had lost 1.2 kg in the 48 hours before referral.

Abbreviations:

ACE	angiotensin-converting enzyme
ACT	activated clotting time
ACTH	adrenocorticotropic hormone
BUN	blood urea nitrogen
CBC	complete blood count
CKD	chronic kidney disease
CRI	constant rate infusion
CRRT	continuous renal replacement treatment
CVVHDF	continuous venovenous hemodiafiltration
ECF	extracellular fluid
HIH	heparin-induced hyperkalemia
ICF	intracellular fluid
LMWH	low-molecular-weight heparin
RER	resting energy requirement
RI	reference interval
SCr	serum creatinine
UFH	unfractionated heparin
UOP	urine output
UPC	urine protein:creatinine

On presentation, the dog was quiet but responsive. Its mucous membranes were pale pink, vital signs were within normal limits, and body weight was 18.3 kg. The dog was mildly uncomfortable on abdominal palpation. Mentation was normal but occasional focal facial seizures were noted. A serum biochemistry profile and complete blood count (CBC) were obtained before initiating CRRT. Results indicated marked azotemia (BUN, 107 mg/dL; reference interval [RI], 7–27 mg/dL; SCr concentration, 7.9 mg/dL; RI, 0.4–1.8 mg/dL), hyperphosphatemia (serum phosphorus concentration, 11.6 mg/dL; RI, 2.2–7.9 mg/dL), hypoalbuminemia (serum albumin concentration, 1.9 g/dL; RI, 2.3–3.9 g/dL), hypernatremia (serum sodium concentration, 153 mEq/L; RI, 141–150 mEq/L), with normal serum chloride (112 mEq/L; RI, 109–119 mEq/L), and serum potassium (5.0 mEq/L; RI, 3.9–5.3 mEq/L) concentrations. The CBC results were consistent with a stress leukogram and disclosed a normocytic, hypochromic anemia (hematocrit, 19%). A dialysis catheter[c] was placed in the left jugular vein under anesthesia. The jugular sampling catheter on the contralateral side, nasogastric feeding tube, and urinary catheter placed before referral were evaluated for patency, cleaned, and maintained in place.

Continuous venovenous hemodiafiltration (CVVHDF) was initiated using an automated renal replacement treatment and continuous fluid management unit[d]. Before

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use, the hemofilter[e] and blood access lines were primed with heparinized saline (10 units/mL heparin in 0.9% saline). A commercial, electrolyte-balanced solution[f] was used as the dialysate and replacement solutions. A constant rate infusion (CRI) of unfractionated heparin (UFH) was utilized for anticoagulantion; dosages ranged from 22 to 38.5 U/kg/h to achieve an activated clotting time (ACT) between 180 and 220 seconds. During the initial CRRT session, extracorporeal blood flow rate was approximately 40 mL/min (2.2 mL/kg/min). Dialysate flow rates of 0–300 mL/h (0–16.5 mL/kg/h) and replacement rates of 300–350 mL/h (16.4–19 mL/kg/h) were utilized, with 200 mL/h predialyzer and 100–150 mL/h postdialyzer. A filtration fraction of 14–17% and a measured Kt/V[g] of 1.32–1.34 was achieved during the session. A commercial, electrolyte-balanced fluid[h] was administered through the jugular sampling catheter at a rate determined by urine output (UOP). There was no net fluid removal during the session. A packed red blood cell transfusion (450 mL total; 24.7 mL/kg) was administered on the first day of CRRT.

Medications administered during CRRT included ampicillin/sulbactam (24.7 mg/kg IV q8h), enrofloxacin (11 mg/kg IV q24h), diazepam (0.25–0.5 mg/kg IV as needed for seizure activity), levetiracetam (22 mg/kg IV q8h) for focal seizures, pantoprazole (0.9 mg/kg IV q24h), maropitant (1 mg/kg SC q24h), amlodipine (0.27 mg/kg PO q24h), and enteral nutrition (increased to 100% RER). The dog became tachycardic during CRRT and a fentanyl CRI was initiated (2–3 μg/kg/h) for analgesia. Because of decreasing UOP (2.8 mL/kg/h) which occurred 12 hour after beginning the first CRRT session, and concurrent weight gain (0.5 kg), furosemide (1 mg/kg IV) was administered followed by a fenoldopam CRI (0.5 μg/kg/min). After 46 hour of CRRT, SCr concentration was 1.9 mg/dL, well below the patient's baseline SCr concentration. In addition, UOP appeared stable, with no evidence of fluid overload, and the session was discontinued. Serum potassium concentration (4.6 mEq/L) was normal at that time. After cessation of CRRT, the dog was continued on IV fluids to match UOP plus estimated insensible losses. Because of the risk of thromboembolism (given the presence of bilateral jugular catheters, recent extracorporeal treatment, and proteinuria), UFH CRI (22–30 U/kg/h) was continued. Fentanyl was discontinued after CRRT. Fenoldopam was discontinued because UOP had increased (>4.0 mL/kg/h).

The patient's demeanor, UOP and weight appeared stable with fluid treatment alone despite gradual worsening of azotemia. Two days later, SCr concentration had increased to 4.2 mg/dL and hyperkalemia (6.2 mEq/L) was noted. A limited renal replacement session of 10 hours was performed in an attempt to managed worsening azotemia and hyperkalemia. A shorter session was elected because of owner constraints. Similar fluid flow parameters were used during this second session. Despite improvement of SCr concentration (2.2 mg/dL), minimal improvement of hyperkalemia (5.7 mEq/L) occurred and hyponatremia (138 mEq/L) and hypochloremia (106 mEq/L) developed. At this point, nutritional support had been occurring for 5 days, including 3 days of 100% RER. On day 5 of hospitalization, heparin-induced hyperkalemia (HIH) was considered as a differential diagnosis for the persistent hyperkalemia, and heparin was discontinued. Before cessation of the heparin CRI, blood was collected for measurement of plasma aldosterone concentration (0 pmol/L; RI, 14–957 pmol/L). Fludrocortisone (0.01 mg/kg PO q12h) was initiated 3 days later because of persistent hyperkalemia. Hyperkalemia resolved (4.9 mEq/L) within 2 days of starting fludrocortisone. SCr concentration stabilized between 4.2 and 4.7 mg/dL, and the dog was discharged with the following medications: benazepril (0.19 mg/kg PO q24h), aluminum hydroxide (8.8 mg/kg PO q6h), amlodipine (0.27 mg/kg PO q24h), levetiracetam (6.9 mg/kg PO q8h), metoclopramide (0.1 mg/kg PO q8h), maropitant (1.6 mg/kg PO q24h), and fludrocortisone (0.005 mg/kg PO q12h). A prescription renal diet[b] was administered via an esophagostomy tube placed 24 hours before discharge in preparation for home care.

Three days after discharge, the patient was reevaluated. Fludrocortisone administration had undergone planned dose reduction and was discontinued the morning of reevaluation. The serum potassium concentration was 5.3 mEq/L at that time and SCr concentration level had increased to 4.9 mg/dL. Benazepril, amlodipine, and aluminum hydroxide were continued. Several days later, the dog was evaluated at an emergency clinic after an episode of vomiting. Serum cortisol and plasma aldosterone concentrations were measured before and after ACTH administration, 2 days after discontinuing fludrocortisone. The baseline serum cortisol concentration was 5.9 μg/dL (RI, 1.0–5.0 μg/dL) and post-stimulation was 24.8 μg/dL (RI, 8.0–17.0 μg/dL). The baseline plasma aldosterone concentration was 92 pmol/L, and the post-stimulation concentration was 376 pmol/L (RI, 197–2,103 pmol/L). At reevaluation 3 days later, serum potassium concentration was 4.5 mEq/L, and SCr concentration was 6.4 mg/dL. A month later, because of declining quality of life, the dog was euthanized.

This case report is consistent with a unique clinical syndrome, HIH. The associated aldosterone concentrations and resolution of hyperkalemia upon cessation of heparin treatment are documented, and support HIH as a cause of the hyperkalemia. HIH has not previously been described previously in veterinary medicine.

Hyperkalemia has been reported as an uncommon adverse effect in humans treated with heparin.[1–5] Hyperkalemia has been attributed to transient suppression of aldosterone synthesis that resolves with cessation of heparin administration.[4–6] This phenomenon has been reported in humans receiving UFH as well as those treated with low-molecular-weight heparins (LMWH).[4,7–9] Reports suggest that 7–8% of human patients receiving heparin treatment may experience some degree of HIH.[5,6] Heparin is used frequently in both human and veterinary medicine, but HIH is reported uncommonly in humans and has not been reported previously in veterinary patients. Clinically

relevant HIH in humans has been associated primarily with concurrent renal insufficiency, diabetes mellitus, metabolic acidosis, or concurrent use of other drugs (eg, angiotensin-converting enzyme [ACE] inhibitors) that can contribute to hyperkalemia.[4,6] These concurrent conditions are thought to impede compensation for aldosterone suppression.[6] In HIH in humans, hyperkalemia often is detectable within 2–3 days and becomes marked by days 4–6 of heparin treatment.[5,6] Concurrent hyponatremia is reported in 6–50% of cases.[5,6] Studies from humans and rats identified subclinical decreases in plasma aldosterone concentration associated with heparin administration.[3,5] Heparin does not alter metabolic clearance of aldosterone but instead decreases its production in a dose-dependent manner.[3,5,6] In HIH, aldosterone suppression may be mediated through inhibition of the adrenal response to angiotensin II, because both the number and affinity of angiotensin II receptors are decreased.[5,6] In addition, there is evidence of a direct inhibitory effect on adrenal aldosterone production; steroidogenesis is inhibited at the 18-hydroxylase step.[6,9] Aldosterone synthase (18-hydroxylase) is the final step in aldosterone synthesis, which converts corticosterone to aldosterone. Evidence of adrenal zona glomerulosa atrophy from chronic heparin treatment also has been reported on necropsy.[5,6,9]

Our patient had confirmed hypoaldosteronism during heparin treatment that resolved after cessation of heparin treatment. At that time, no other inhibitors of aldosterone had been administered and the dog was hyperkalemic and hyponatremic. Hyperkalemia normally stimulates aldosterone secretion,[5,10] thus making this patient's hypoaldosteronism inappropriate. In addition to hyperkalemia, the other major stimulus for aldosterone secretion is the renin-angiotensin system, in response to hypovolemia.[10] At the time of aldosterone sample collection, the patient showed no evidence of volume overload, and body weight had remained stable. It is unlikely that a subclinical change in volume status would suppress aldosterone to this extent, particularly in the face of clinically relevant hyperkalemia. Furthermore, hypoadrenocorticism was later ruled out by ACTH stimulation testing. Primary hypoaldosteronism without hypocortisolism has been reported in dogs[11,12] but in this patient hypoaldosteronism and hyperkalemia resolved after discontinuation of heparin treatment.

In veterinary medicine, hyperkalemia has been associated with a variety of different conditions resulting in a shift of potassium to the extracellular fluid (ECF) or decreased renal excretion. The majority of body potassium is stored intracellularly and translocation of potassium from the intracellular fluid (ICF) to the ECF, as seen in patients with acute hyperchloremic acidosis, insulin deficiency, and hyperosmolality, can result in hyperkalemia.[10,13] None of these conditions were present in this patient. Hyperkalemia also has been associated with renal injury, but occurs uncommonly unless oliguria, anuria or urinary tract obstruction is present.[13] Our patient's OUP reached a nadir of 1.7 mL/kg/h, and the dog was normokalemic (4.3 mEq/L) at that time. For the majority of hospitalization, UOP averaged between 3.0 and 4.5 mL/kg/h concurrent during periods of hyperkalemia. Based on this finding, the cause of hyperkalemia was not consistent with oliguric renal failure. Additionally, an abdominal ultrasound examination disclosed no evidence of postrenal obstruction.

Excessive dietary potassium intake is another potential cause for hyperkalemia. This patient received a balanced critical care diet[i] via a nasogastric tube during the majority of hospitalization. The dog received a total of 894 mg of potassium per day using this diet, which contained 1.3 g potassium per 1,000 kcal of metabolizable energy, and received the same volume of food consistently. Because the dog had a poor appetite in the hospital, an esophagostomy tube was placed to facilitate adequate caloric intake. The dog was transitioned to a prescription renal diet[b] after esophagostomy tube placement. The dog received a total of 494 mg of potassium per day in this diet (0.8 g potassium/1,000 kcal of ME), with minimal supplemental PO feeding. The suggested dietary potassium intake for dogs with CKD is 0.8–1.2 g/1,000 kcal of ME.[14] Although slightly above the suggested intake for a CKD patient, the potassium intake in the hospital was well below the minimum for normal dogs (1.7 g/1,000 kcal of ME[14]) and unlikely to be excessive. Although subsequent reduction in dietary potassium intake may have contributed to the eventual normalization of the dog's serum potassium concentration, improvement in hyperkalemia preceded the dietary transition. Furthermore, diet-induced hyperkalemia should stimulate, rather than suppress, production of aldosterone,[13] and is therefore inconsistent with the hyperkalemia in this patient.

The patient previously had been treated with an ACE inhibitor, but it was discontinued because of inappetence. Hyperkalemia was not observed at the time of presentation and developed several days after ACE inhibitor treatment was suspended. Furthermore, benazepril was initiated before discharge, and hyperkalemia continued to improve despite re-administration of an ACE inhibitor.

Fludrocortisone, a steroid with potent mineralocorticoid activity, was used to promote potassium excretion and sodium retention.[2,6] This drug has been used previously in human patients with HIH, resulting in rapid correction of hyperkalemia.[2,6] In our patient, hyperkalemia improved substantially within 24 hours of fludrocortisone administration. Hyperkalemia may have resolved spontaneously, however, after cessation of heparin treatment, based on the clinical course observed in human patients. The time from cessation of heparin treatment to resolution of hyperkalemia varied from 1 to 30 days in humans, but was $\leq$5 days in 9 of 11 patients.[5,6]

In patients with HIH, fluid diuresis and loop or thiazide diuretics to manage hyperkalemia may be considered if cessation of heparin is not an option.[13] Hyperkalemia also can be managed by promoting potassium shifts from ECF to ICF by administration of glucose alone or glucose with insulin, or with sodium bicarbonate.[13] Gastrointestinal absorption of potassium also can be decreased by administration of oral

potassium binders such as polystyrene sulfonate[j].[13] In addition, although LMWH also has been associated with hyperkalemia, it may pose a lower risk and therefore may be preferable in patients potentially at risk for HIH.[4]

In conclusion, the laboratory changes in this patient were consistent with HIH, a condition that has not been described previously in a veterinary patient. HIH does not appear to be of prognostic relevance, but could be easily misinterpreted as indication of declining renal function. Clinicians should be aware of this syndrome in veterinary patients receiving heparin that have unexplained or unexpected hyperkalemia.

Footnotes

[a] http://www.iris-kidney.com/guidelines/staging.shtml.
[b] Canine k/d, Hill's Science Diet; Topeka, KS
[c] Mahurkar acute dual lumen catheter kit; Covidien, Mansfield, MA
[d] Prismaflex; Gambro, Lakewood, CO
[e] Prismaflex M60 Set with Acrylonitrile (AN 69) membrane, Lakewood, CO
[f] Prismasate 4K+/2.5Ca++; Gambro, Lakewood, CO
[g] $Kt/V = K_{del} \times 1{,}320$ minutes/[0.6 × body weight (kg)]; where K_{del} = Ultrafiltrate urea concentration × (ultrafiltation rate + dialysate rate/predialyzer blood urea concentration)[15]
[h] Plasma-Lyte A; Abbott, Abbott Park, IL
[i] Oxepa; Abbott Nutrition, Columbus, OH
[j] Kayexalate; Covis, Cary, NC

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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