

Hyperglycemia, hypernatremia, and hyperosmolarity in 6 neonatal llamas and alpacas

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- ▶ Neonatal camelids can develop hyperglycemia, hypernatremia, and hyperosmolarity in response to a combination of stress and inadequate water intake.
- ▶ Clinical signs of this syndrome include a fine head tremor, ataxia, and a base-wide stance of the hind limbs, but biochemical analyses are necessary to confirm the diagnosis.
- ▶ Camelids appear to be susceptible to this syndrome because of a poor insulin response to hyperglycemia; hypernatremia results from free water loss associated with glucose diuresis.
- ▶ Water loss associated with glucose diuresis may necessitate a higher rate of fluid administration in camelids with this syndrome than is typically used for treatment of hypernatremia in calves.

A 3-day-old 10-kg (22-lb) female llama cria was admitted to the Oregon State University Veterinary Teaching Hospital for evaluation of anorexia, weakness, hyperthermia (rectal temperature, 41.7 C [107.0 F]), and trembling. All signs had become progressively worse over a period of 6 hours. The dam had had dystocia, and the cria had never suckled the dam. Cow colostrum and llama plasma had been administered, and the cria had been fed 180 to 240 ml of goat milk replacer every 4 hours.

Initial examination confirmed the owner's findings and revealed tachycardia (132 beats/min), dehydration (dry mucus membranes and prolonged skin tent over the neck and eyelid), ataxia, and a base-wide stance of the hind limbs. Rectal temperature was 40 C (104 F), and respiratory rate was 24 breaths/min. The cria could not stand up or lie down without assistance. The trembling was further defined as a fine constant head tremor. Laboratory evaluation revealed high blood glucose (686 mg/dl; reference range for neonatal llamas,¹ 94 to 170 mg/dl), sodium (161 mEq/L; reference range,¹ 148 to 155 mEq/L), urea (47 mg/dl; reference range,¹ 10 to 21 mg/dl), and creatinine (3.6 mg/dl; reference range,¹ 1.1 to 2.9 mg/dl) concentrations. Calculated plasma osmolarity was 387 mOsm/L, and although a reference range has not been established for llamas, plasma osmolarity for most other domestic mammals typically ranges between 270 and 320 mOsm/L. Venous blood pH (7.23; reference range,² 7.35 to 7.5) and bicarbonate concentration (17 mEq/L; reference range,² 23 to 32 mEq/L) were low. Hematologic abnormalities included neutrophilic

leukocytosis (41,360 WBC/ μ l; neutrophil fraction, 91%) with a left shift and lymphopenia. Serum immunoglobulin concentration was > 800 mg/dl.

The llama was able to urinate and defecate without straining, helping to rule out stranguria and tenesmus as causes for the base-wide stance and allowing treatment efforts to focus on possible infectious and metabolic diseases. To correct metabolic abnormalities and treat presumptive sepsis, the llama was given 1 L of lactated Ringer's solution by rapid IV infusion, followed by additional 100-ml boluses every 2 hours. Blood sodium concentration was 159 mEq/L after the initial fluid bolus. The llama was also treated with flunixin meglumine (0.25 mg/kg [0.11 mg/lb] of body weight, IV, q 6 h), ceftiofur sodium (5 mg/kg [2.3 mg/lb], IV, q 12 h), and potassium penicillin G (22,000 U/kg [10,000 U/lb, IV, q 6 h). After 12 hours of treatment, blood sodium concentration had increased to 172 mEq/L, whereas blood glucose concentration had decreased to 504 mg/dl, and azotemia had lessened. Plasma osmolarity had increased to 400 mOsm/L. Cerebrospinal fluid had high sodium (175 mEq/L; reference range,³ 151 to 157 mEq/L), glucose (390 mg/dl; reference range,³ 66 to 73 mEq/L), and protein (140 mg/dl; reference range, 39 to 48 mg/dl) concentrations without cytologic evidence of infection of the CNS (2 WBC/ μ l; reference range,³ 0.3 to 1.5 WBC/ μ l). Urine glucose concentration was 1,000 mg/dl, and urinary fractional clearance of sodium was calculated to be 1.8% (reference range,⁴ < 1.5%). Serum cortisol concentration was 3.2 μ g/dl (reference range,⁵ 1.04 \pm 0.13 μ g/dl), and serum insulin concentration was < 5.0 μ U/ml (reference range,⁵ 5.6 \pm 0.1 μ U/ml), yielding an insulin-to-cortisol ratio of 156 μ U/ μ g (reference range,⁵ 768 \pm 34 μ U/ μ g). Serum concentrations of triglycerides (265 mg/dl; reference range,⁶ 8.3 to 55.8 mg/dl), nonesterified fatty acids (1.02 mEq/L; reference range,⁶ 0.91 \pm 0.17 mEq/L), and β -hydroxybutyrate (12.65 mg/dl; reference range,⁶ 0.12 to 0.75 mg/dl) were high. Bacterial culture of blood samples did not yield any organisms.

The llama's condition did not improve during the first 12 hours, except that the hyperthermia resolved, and the llama would eat a little. Treatment was continued as before; in addition, 200 ml of milk replacer was offered every 2 hours by bottle. Appetite, including suckling of the dam and intake of milk replacer, frequency of urination, and clinical condition improved steadily during the next 48 hours, and IV fluid administration was discontinued in step-wise fashion during that period. Serum sodium concentration decreased from 165 mEq/L 36 hours after admission to 150 mEq/L 6 days after admission. Serum glucose concen-

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tration was > 500 mg/dl for 36 hours after admission, then decreased to < 200 mg/dl for the remainder of the hospitalization period. Plasma osmolality decreased approximately 20 mOsm/L each day, and hematologic values returned to reference ranges. The cria was discharged after 8 days.

Between January 1990 and December 1999, 81 llama and alpaca crias < 3 weeks old were examined at the veterinary teaching hospital, and 4 additional crias (9 hours to 2 weeks old) were found to have plasma glucose concentrations > 600 mg/dl at the time of initial examination. Another cria arrived dead, but the attending veterinarian reported that the blood glucose concentration had been > 600 mg/dl. Two of these 5 crias, including the youngest, were thought to be premature on the basis of known breeding dates, 1 had lost its dam as a result of a chronic disease, and 1 had been treated for 2 days with antibiotics and corticosteroids after getting its head caught in a fence. Two of these crias were dependent on bottle feeding, and the other 2 had been force-fed milk replacer or hypertonic oral electrolyte solutions because of inappetence. No extraordinary historical events were identified for the last cria. For all 5 crias, the owners sought veterinary attention because of lethargy and poor milk intake. Clinical abnormalities included hyperthermia (n = 2), dyspnea (2), and tremors (2). A base-wide stance of the hind limbs was interpreted to be a sign of straining by some owners.

Clinical and clinicopathologic abnormalities in these 5 crias resembled those of the first cria and included obtundation, dehydration, ataxia, base-wide stance of the hind limbs, hyperglycemia (maximum, 1,360 mg/dl), glycosuria (\geq 500 mg/dl), blood sodium concentration > 160 mEq/L (4 crias; maximum, 183 mEq/L), hyperchloremia, hyperkalemia, hypertriglyceridemia, hypercholesterolemia, azotemia, and metabolic acidosis. Calculated plasma osmolality was between 422 and 474 mOsm/L for the 4 crias with hypernatremia. Two crias had mature neutrophilia and lymphopenia; the other 3, including those with hyperthermia or dyspnea, had lymphopenia and high immature neutrophil counts. Bacterial culture of a blood sample from the cria that had previously been treated with corticosteroids yielded *Pseudomonas aeruginosa*.

Treatment of these 5 crias resembled that given the first cria, except that several were treated with fluids containing dextrose or sodium bicarbonate before laboratory results were available. The 2 most severely affected crias were treated with small volumes of fluid initially and given diazepam and dimethyl sulfoxide as hyperglycemia (> 500 mg/dl) persisted, hypernatremia worsened, and they started to seizure; 1 was also treated with regular insulin to aid in glucose clearance.

The 2 crias without evidence of sepsis survived treatment. Plasma osmolality decreased as much as 3.5 mOsm/h, but blood sodium concentration decreased no more than 0.5 mEq/h. Clinical recovery coincided with an increase in the frequency of urination and the volume of urine produced.

The other 3 crias died, including the 2 with the highest initial blood glucose concentrations (> 1,100 mg/dl), blood sodium concentrations (> 175 mEq/L),

and plasma osmolality (> 470 mOsm/L). Both of these crias died within hours after initiation of treatment. The third cria, a premature neonate with initial hyponatremia, was euthanatized because of refractory seizures and hyperthermia 80 hours after admission. It had remained azotemic and hyperglycemic and had developed severe hypernatremia (186 mEq/L) along with clinical and hematologic signs of sepsis despite treatment. All 3 of these crias had hematologic evidence of sepsis and suppurative pneumonia on post-mortem examination, with little evidence of cerebral edema and no evidence of pancreatic disease. *Streptococcus* spp was recovered from postmortem lung and liver specimens from 1 cria, and *P aeruginosa* was recovered from multiple internal organs from the cria that previously had a positive blood culture sample.

All 6 of the crias described in the present report had hyperglycemia and hypernatremia. Clinical and clinicopathologic abnormalities in these crias were similar to those associated with hyperosmolar coma in people^{7,8} and small animals⁹ with diabetes mellitus in which the onset of neurologic signs coincides with an extremely high plasma osmolality, and the initial stimulus for the increase in plasma osmolality appears to be excess glucose. There are similarities and differences in the pathogenesis of hyperglycemia and, hence, hyperosmolality among species. People and dogs with impaired glucose clearance because of diabetes mellitus develop hyperosmolar coma after events (eg, severe infectious disease, ingestion of fluids with a high carbohydrate content, and accidental or intentional omission of an insulin injection) that stimulate hyperglycemia.^{8,9} In addition to promoting glucogenesis, these inciting events often also decrease water intake, leading to inadequate volume replacement during diuresis. Most crias described in the present report also had a history of a stressful event (eg, sepsis, trauma, premature birth, or death of the dam) prior to the onset of hyperglycemia and hyperosmolality, and most had direct (eg, history of exogenous glucocorticoid administration or oral administration of a glucose-containing electrolyte solution) or indirect (eg, stress leukogram, hyperlipidemia, or hypercortisolemia) evidence that the hyperglycemia was stimulated by glucogenic factors. Affected crias apparently did not have diabetes mellitus, as glucose homeostasis returned to normal in the 3 crias that recovered, but it is likely that they had a diabetes-like inability to clear excess glucose. Adult camelids have a minimal insulin response and prolonged hyperglycemia following administration of exogenous glucose.⁵ If the same is true for crias, then they would seem to be predisposed to develop hyperglycemia and hyperosmolality in response to glucogenic stimuli. In contrast, calves, which frequently are confronted by stressful events, have a much more vigorous pancreatic response to hyperglycemia and rarely or never develop pathologic hyperglycemic hyperosmolality.¹⁰ If this line of reasoning is correct, it is important to recognize that this degree of pancreatic function is normal in camelids; it is the glucogenic stimulus that is abnormal and stimulates development of hyperglycemia and hyperosmolality.

Insufficient water intake probably played an

important role in the development of hypernatremia in these crias. Persistent hyperglycemia leads to a redistribution of body water from the intracellular to the extracellular space, which may initially result in a decrease in blood sodium concentration secondary to dilution, as was seen in 1 cria described in the present report. Hypernatremia subsequently develops as extracellular water is lost during glucose diuresis and is not replaced through an increase in intake. Hypernatremia is an uncommon finding in people with hyperosmolar coma⁸ but was a consistent finding in these crias. Most of these crias had little opportunity to increase their fluid intake because of intermittent bottle feeding, the effort required to nurse the dam, or the lack of availability of water. Renal conservation of sodium to combat hypovolemia (as represented by the inappropriately low urinary fractional clearance),⁴ mineralocorticoid effects of glucocorticoids, and administration of sodium-containing electrolyte solutions may also have contributed to the hypernatremia. Because increases in sodium concentration typically have a greater effect on plasma osmolality than increases in glucose concentration, measuring blood sodium concentration may be the best way to assess the severity of the abnormalities in affected crias. Similar to people with hyperosmolar coma, severe hypernatremia (> 175 mEq/L) was associated with a grave prognosis.

Clinical signs in the crias described in the present report were related to the loss of intra- and extracellular water, with resultant circulatory failure and cellular dysfunction. The most common clinical signs were lethargy, anorexia, weakness, hyperthermia, base-wide stance of the hind limbs, head tremor, and eventually coma, with more severe signs seen in crias with the highest glucose and sodium concentrations. Because of osmotic extraction of water from the brain, CNS abnormalities were more common than would be expected for animals that were dehydrated but did not have hyperosmolality. Important differential diagnoses for crias with similar signs include prematurity, sepsis, meningoencephalitis, peritonitis, congenital nervous system lesions, meconium impaction, and other congenital or acquired large-intestine obstructions.¹¹⁻¹³ Laboratory analysis was necessary to establish the diagnosis. Severe hyperglycemia, glucosuria, hypernatremia, metabolic acidosis, and azotemia were the most frequent abnormalities.

The goal of treatment of these crias was to restore normal blood osmolality without causing cerebral edema. Treatment, therefore, consisted mainly of IV administration of isotonic fluids, followed by oral administration of hypotonic fluids. When treating crias with these signs, it is logical to avoid using fluids containing glucose or supraphysiologic concentrations of sodium and to avoid using glucocorticoids. The choice between isotonic and hypotonic fluids in people with hyperosmolar coma is less important than giving a sufficient volume of fluids to restore renal function while avoiding rapid changes in osmolality.¹⁴ Slow administration of hypertonic fluids is advocated to treat hypernatremia in calves,¹⁵ because calves often have had the condition long enough to generate osmotic molecules (idiogenic osmoles) in their brains to protect the CNS

against dehydration. Also, affected calves typically do not have renal sodium retention and free water loss. Thus, slow restoration of normal systemic and CNS osmolality is preferred. In contrast, abnormalities appeared to develop quickly in the crias described in the present report, giving them less time to produce idiogenic osmoles in their brains. Because these crias were continuing to lose water secondary to glucose diuresis, slow administration of fluids may have restored renal output without correcting the hyperosmolality, and even though isotonic, rather than hypertonic, fluids were used, hypernatremia worsened in 3 crias, 2 of which received only small volumes of fluid and died. Even with administration of relatively high volumes of isotonic fluids, hypernatremia resolved at a slower rate (up to 0.5 mEq/h) than has been recommended for neonatal cervids (< 1.7 mEq/h)¹⁶ and other species¹⁷; however, changes in plasma osmolality were similar. The slower correction rate was selected on the basis of concerns that rapid unforeseen changes in glucose concentration associated with a loss of glucogenic stimulation could have caused unanticipated changes in plasma osmolality. The inability to reduce blood sodium concentration to a value < 160 mEq/L while blood glucose concentration was > 500 mg/dl further highlighted the importance of correcting hyperglycemia in these crias.

Although all 6 of these crias had severe hyperglycemia, only 1 was treated with insulin. At the time, it was thought that hyperglycemia in camelids was attributable to the stress response and concurrent insulin resistance and that hyperglycemia would resolve spontaneously with time and treatment of the primary disorder. In addition, the detrimental effects of hyperglycemia in camelids had not been reported. It is now known that camelids have low baseline insulin concentrations and a poor pancreatic response to hyperglycemia.⁵ Insulin is used routinely to treat hyperglycemic hyperosmolality in people, and there appears to be less concern about the rate at which blood glucose concentration is returned to reference limits with this disorder than in people with diabetic ketoacidosis.⁸ Therefore, it is likely that insulin administration would have been helpful in the treatment of these crias. It is recommended that fluid deficits be replaced prior to insulin administration, otherwise hypernatremia and the extracellular fluid deficit may worsen as water follows glucose into cells. Also, the blood glucose concentration should be monitored to avoid hypoglycemia. Frequent monitoring of sodium and glucose concentrations will help prevent rapid shifts of water into the CNS.

An additional goal of treatment of the crias described in the present report was to prevent or manage sepsis, which was presumed to be a contributory stressor in several of these animals. Infectious diseases are also considered an important risk factor for hyperosmolar coma in people⁸ and are known to induce hyperglycemia in llamas.^{11,18} Sepsis could contribute to hyperosmolality by stimulating cortisol release, decreasing fluid intake, and affecting renal function. For these reasons and because of the poor prognosis for crias with sepsis and hyperosmolality, veterinarians

should exercise care when treating sick crias with sodium- or glucose-containing fluids or with glucocorticoids and should monitor sick crias for hyperglycemia, hyperosmolarity, and hypernatremia.

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