Use of a constant rate infusion of insulin for the treatment of hyperglycemic, hypernatremic, hyperosmolar syndrome in an alpaca cria

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Case Description—A 3-day-old 9.5-kg (21-lb) female alpaca cria was examined because of lethargy and anorexia.

Clinical Findings—Physical examination revealed hyperthermia, muscle fasciculations, and tremors of the head. Seizures were also observed, which indicated CNS dysfunction. Hyperosmolar syndrome (HOS) was diagnosed on the basis of hyperglycemia, hypernatremia, azotemia, high plasma osmolarity, and metabolic acidosis.

Treatment and Outcome—A constant rate infusion of regular insulin was administered with hypo-osmolar fluids to treat HOS, and blood glucose and sodium concentrations were successfully lowered. Neurologic deficits resolved with treatment, and the cria was discharged 11 days after admission.

Clinical Relevance—Administration of insulin as a bolus in addition to hypo-osmolar fluids has been advocated in the management of neonatal camels with HOS. Administration of regular insulin via a constant rate IV infusion was used to successfully manage a neonatal camelid with HOS. This form of insulin administration may allow more control of glucose kinetics in these patients. (J Am Vet Med Assoc 2010;236:562–566)

A 3-day-old 9.5-kg (21-lb) female alpaca cria was referred to the University of Tennessee Veterinary Teaching Hospital for evaluation of signs of depression, anorexia, weakness, trembling, and hyperthermia (41.44°C [106.6°F]). The cria was presumed to have been born after a full-term gestation, but the owner was unable to provide the exact duration of the gestational period. The dam had a dystocia, and the delivery was assisted by the referring veterinarian (day of birth was designated as day 0). Supplemental colostrum was not administered because sucking appeared to be adequate. Birth weight of the cria was 10 kg (22 lb). Body weight was maintained for the first 48 hours after birth before decreasing by 0.45 kg (1.0 lb) on day 3. Lethargy and reduced sucking had been observed on the morning of referral. Treatments administered prior to referral included a single injection of cefiotur crystalline free acid (dose unknown) shortly after birth and then flunixin meglumine (1.1 mg/kg [0.5 mg/lb], IM) on day 3.

Seizures characterized by tremors, vertical nystagmus, and extensor rigidity were occurring during the initial examination at our hospital (day of examination was designated as day 1 of hospitalization). Seizures were successfully controlled by administering diazepam (0.5 mg/kg [0.23 mg/lb], IV, slowly over 2 minutes). Initial physical examination revealed dehydration, tachycardia (210 beats/min), tachypnea (84 breaths/min), an increase in intensity of the bronchovesicular sounds, and a rectal temperature of 39.67°C (103.4°F). The cria was unable to stand or maintain sternal recumbency and had no detectable suckle response. No abnormalities of the cranial nerves, patellar reflexes, or flexor reflexes were detected, but precise assessment of proprioception and postural reactions was not possible. Constant fine tremors of the head persisted and were detectable for 3 days after seizures were controlled.

Plasma biochemical abnormalities included severe hyperglycemia (1,300 mg/dL; reference range, 1 to 170 mg/dL), hypernatremia (176 mEq/L; reference range, 148 to 155 mEq/L), hyperchloremia (119 mEq/L; reference range, 101 to 116 mEq/L), hyperbilirubinemia (0.7 mg/dL; reference range, 0.0 to 0.6 mg/dL), and hypoalbuminemia (2.4 g/dL; reference range, 2.8 to 4.0 g/dL); high BUN (121 mg/dL; reference range, 10 to 21 mg/dL) and creatinine (4.5 mg/dL; reference range, 1.1 to 2.9 mg/dL) concentrations; high γ-glutamyltransferase activity (149 U/L; reference range, 8 to 29 U/L); and a high anion gap (44.2 mEq/L; reference range, 14 to 29 mEq/L). Calculated plasma osmolarity was 467.4 mOsm/L ([2 × sodium concentration] + [glucose concentration/18] + [BUN concentration/2.8]). Although a reference range for plasma osmolarity has not been established for camelids, the range for most other domestic mammals

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CRI</td>
<td>Constant rate infusion</td>
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<td>GLUT4</td>
<td>Glucose transporter 4</td>
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<td>HOS</td>
<td>Hyperosmolar syndrome</td>
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is between 270 and 320 mOsm/L. Blood gas analysis of an initial sample obtained from the brachial artery indicated acidemia associated with metabolic acidosis (pH, 7.2; reference range, 7.35 to 7.50; and bicarbonate concentration, 6.4 mEq/L; reference range, 23 to 32 mEq/L) and hyperlactatemia (11.2 mmol/L; reference range not available for camelds). Results of hematologic analysis were within reference ranges, except for a high number of band cells (0.72 × 10⁹ cells/μL; reference range, 0 to 0.487 × 10⁹ cells/μL), many reactive lymphocytes, and hyperfibrinogenemia (600 mg/dL; reference range, 100 to 400 mg/dL).

Initial treatments were focused on correction of metabolic acidosis and hypernatremia. The cria received 250 mL of a balanced polyionic isotonic fluid by rapid IV infusion, followed by an additional 250-mL bolus of a solution that contained the same isotonic fluid diluted to a 50% concentration by the addition of sterile water and a sufficient amount of 5% sodium bicarbonate solution (calculated from the bicarbonate deficit of 104 mEq) to obtain 1 L of 50% isotonic fluid. The cria was administered the aforementioned 250-mL bolus of this solution, which provided 26 mEq of sodium bicarbonate. Blood sodium and lactate concentrations were evaluated 1.5 hours after treatment was initiated, and they decreased to 161 mEq/L and 6.3 mmol/L, respectively, after the initial 500-mL infusion. Administration of the remaining 750 mL of this solution (isotonic fluid diluted to a 50% concentration containing the remaining 78 mEq of sodium bicarbonate) was continued at a rate of 2.5 mL/kg/h (1.14 mL/lb/h). At this rate of administration, the cria should have received a sufficient amount of bicarbonate to replace the rest of the bicarbonate deficit during approximately a 30-hour period; however, frequent blood gas analysis of venous blood samples was planned.

Antimicrobial treatments included ceftiofur sodium (5 mg/kg [2.3 mg/lb], IV, q 12 h) and penicillin G (44,000 U/kg [20,000 U/lb], IV, q 6 h). Anticonvulsant treatment was also instituted in the form of phenobarbital (5 mg/kg, IV, q 12 h). After fluids had been administered for 4 hours, the blood sodium concentration exceeded 180 mEq/L, so sodium bicarbonate administration was discontinued. Fluid administration was continued with a solution of isotonic fluid diluted to a 50% concentration by the addition of sterile water. Twelve hours after initiation of treatment, the blood sodium concentration remained high (172 mEq/L), and hyperglycemia (> 700 mg/dL) and metabolic acidosis (blood pH, 7.29; bicarbonate, 18.5 mEq/L) had not resolved. Therefore, this treatment was discontinued and a solution of isotonic fluid, which was diluted to a 25% concentration by the addition of sterile water, was administered at a rate of 3.3 mL/kg/h (1.5 mL/lb/h), IV.

On day 2, the cria was able to maintain sternal recumbency with its head raised but fine tremors of the head persisted. To further investigate the underlying disease process, CSF was collected from the lumbosacral space. Cytologic examination revealed a total RBC count of 15,000 cells/μL and total nucleated cell count of 6 cells/μL, which were consistent with intrathecal peripheral blood contamination. The concentrations of sodium and glucose in the CSF were not evaluated. Blood gas analysis indicated that acidosis had resolved at that time.

Approximately 20 hours after treatment was initiated, a solution of 8.5% amino acids without dextrose was added to provide a partial nutrient supplement of 30 g of protein/d parenterally; via CRI at a rate of 2 mL/h (approx 50 mL/d). This treatment was calculated on the basis of the estimated nutritional requirement of 50 kcal/kg/d (22.7 kcal/lb/d) for healthy crias, which included 3 g of protein/kg/d (1.36 g of protein/lb/d). A CRI of insulin was also initiated to address ongoing hyperglycemia (993 mg/dL at 18 hours after admission). The insulin solution was prepared by adding 100 U of regular insulin to 500 mL of saline (0.9% NaCl) solution to yield a concentration of 0.2 U/mL, and this solution was administered at an initial rate of 1 mL/h (0.02 U/kg/h [0.009 U/lb/h]). The rate of insulin infusion and total fluid rate were adjusted according to blood glucose concentrations (Figure 1) and hydration status. The peak insulin rate was 10 mL/h. Blood glucose concentrations were measured at intervals of 30 minutes to 2 hours, depending on the status of the cria and the need for reassessment after adjusting the infusion rate, with the goal of maintaining blood glucose concentrations between 100 and 250 mg/dL. The insulin infusion rate was adjusted in increments of 0.02 U/kg/h to avoid rapid alterations in blood glucose concentrations. Within 4 hours after insulin treatment, the blood glucose concentration decreased to 580 mg/dL. At 24 hours after admission, blood electrolyte evaluation revealed hypernatremia (175 mEq/L) and hypokalemia (2.5 mEq/L; reference range, 4.6 to 5.9 mEq/L). Hypokalemia was attributed to the intracellular shift of potassium in response to insulin, and fluids administered IV were supplemented with potassium chloride.

![Figure 1](https://example.com/figure1.png)

**Figure 1**—Changes in blood glucose (white circles) and sodium (black triangles) concentrations over time in a cria admitted to a veterinary medical teaching hospital at 3 days of age for treatment of HOS.
CAMELIDS

By day 3 of hospitalization, clinical improvement was observed and the rectal temperature of the cria was within the reference range (38.56°C [101.4°F]; reference range, 37.78° to 39.17°C [100° to 102.5°F]). The cria was maintaining its head in an upright position and attempting to stand. An IgG concentration < 400 mg/dL (lower reference limit, 800 mg/dL) was detected by use of a sodium sulfite turbidity test, and approximately 600 mL of plasma was administered to address this deficiency. Fluid treatment consisted of the isotonic fluid diluted to 25% by the addition of sterile water with added dextrose, potassium chloride, and amino acids. Regular insulin was also administered via a separate CRI, so fluids were administered at a total rate of 4 mL/kg/h (1.82 mL/lb/h). Thiamine (10 mg/kg [4.5 mg/lb], SC, q 12 h) was initiated for its neuroprotective effects. An indwelling nasogastric tube was placed to facilitate feeding, and milk replacer diluted to 50% by the addition of water was fed in a total daily amount equivalent to 5% of body weight. The volume of diluted milk replacer was included in the total daily fluid requirement of 100 mL/kg/d (45.5 mL/lb/d). Periodic monitoring revealed that the cria was maintaining blood glucose concentrations between 76 and 239 mg/dL.

On day 4 of hospitalization, the cria was able to stand for short periods without assistance, although ataxia was evident and a wide-based stance in the pelvic limbs was observed. Insulin treatment was discontinued, and the cria remained normoglycemic while receiving fluids IV that contained 5% dextrose. Total fluid intake was lowered to 80 mL/kg/d (36.4 mL/lb/d), and enteral feeding was adjusted to provide a volume equivalent to 8% of body weight. Phenobarbital treatment was discontinued, and no further seizure activity was detected.

By day 5 of hospitalization, the cria was able to walk and to suckle the dam. Physical examination revealed mild tachypnea, and auscultation of the thorax revealed moist lung sounds. Thoracic radiography revealed diffuse areas of nonstructured interstitial and bronchial patterns, which coalesced in places to form an alveolar pattern in the caudodorsal lung fields. Noncardiogenic pulmonary edema, atypical cardiogenic pulmonary edema, hematogenous bacterial pneumonia, and viral pneumonia were considered differential diagnoses for this mixed lung pattern. Because pulmonary edema was a differential diagnosis, the total IV and enteral fluid volume was decreased to 40 mL/kg/d (18.2 mL/lb/d), which was administered to supplement milk consumed through suckling of the dam. On day 6 of hospitalization, the enteral feeding was increased to 10% of body weight and IV administration of fluids was discontinued, including the parenteral nutrients. The enteral feedings were decreased as the cria’s suckling frequency increased, and enteral feeding was discontinued on day 9 of hospitalization.

No additional problems were encountered. The cria maintained blood glucose and electrolyte concentrations within reference ranges until discharged from the hospital 11 days after admission. Microbial culture results of blood samples were negative for aerobic and anaerobic bacterial growth at 7 days after the sample culture was initiated, but ceftiofur sodium (5 mg/kg, SC, q 12 h) was continued for an additional 4 days after discharge. At the time of discharge, the cria weighed 10.9 kg (24 lb) and no abnormalities were detectable during physical examination or neurologic evaluation. The referring veterinarian reported that the young alpaca was clinically healthy 7 months after discharge.

Discussion

An alpaca cria that had clinicopathologic abnormalities and CNS derangement consistent with HOS was successfully treated. This disorder has been described in neonatal camelids, and clinical signs of lethargy, anorexia, hyperthermia, tremors of the head, seizure activity, and wide-based stance of the pelvic limbs have been reported. These neurologic signs are presumed to result from cerebral edema or cerebral dehydration caused by severe hypernatremia, which is attributed to excessive renal loss of water secondary to hyperglycemia-induced osmotic diuresis. Hyperglycemia is thought to be initiated by endogenous glucocorticoids released during a stressful event such as premature birth, trauma, sepsis, or death of the dam. In the cria described here, HOS was diagnosed on the basis of clinical signs and analysis of biochemical results that indicated severe hyperglycemia and hypernatremia. Other differential diagnoses that were considered included sepsis, bacterial meningitis, metabolic encephalitis, metabolic encephalopathy, and diffuse cerebral cortical disease.

Glucosuria is an important component of HOS because it results in osmotic diuresis, which induces hypernatremia. Crias that develop HOS are often consuming an inadequate volume of milk to meet the demands of glucosuric osmotic diuresis, and water is lost at a rate that exceeds intake. This problem is exacerbated if the affected cria has sepsis or other underlying medical conditions that induce anorexia and reduce milk intake. This was identified as a compounding factor for the cria reported here because suckling of the dam had not been observed for approximately 10 hours prior to referral.

It is advisable to correct severe chronic hypernatremia slowly to avoid the detrimental effects of osmotic disequilibrium within brain tissues. Rapid IV administration of fluids that are hypotonic relative to a patient’s serum can cause swelling and lysis of brain cells and the development of cerebral edema. In the cria described here, neurologic derangements were apparent and abnormalities appeared to develop quickly. It was assumed that hypernatremia had developed acutely, which left insufficient time for the brain to adapt to the hypertonic state.

Treatment of neonatal camelids with HOS is challenging because of concurrent hyperglycemia. Fluids
containing dextrose can be administered IV to provide free water without directly increasing sodium concentrations but would have been contraindicated in this situation because of hyperglycemia. Therefore, solutions administered IV to the cria were prepared by diluting isotonic fluid (140 mEq/L) with sterile water.

Despite initial treatment efforts to reduce the sodium concentration and rehydrate the cria, blood sodium concentrations transiently increased and peaked at > 180 mEq/L 30 hours after admission. This alteration was attributed to the administration of sodium bicarbonate for the treatment of metabolic acidosis. Sodium bicarbonate has been administered to calves with hypernatremia without complications, but those affected calves had chronic hypernatremia, rather than acute hypernatremia. The authors acknowledge that metabolic acidosis, which was attributed to a lactic acidosis with a high anion gap that was detected in the cria, should have been corrected through rehydration with IV administered fluids without sodium bicarbonate. Persistent hypovolemia, and possibly the administration of insulin prior to correction of hypovolemia, was also considered a potential explanation for the increase in the blood sodium concentration. Hypotonic fluids were being administered IV; thus, < 10% of the infused volume would be expected to remain in the intravascular space 1 hour after infusion. The fluid dose of 80 mL/kg/d selected for the patient may therefore have been too low to accomplish rehydration in these circumstances. This possibility was supported by the reduction in blood sodium concentration detected at 30 hours after admission in response to bolus IV administration of fluids. In the cria described here, hypernatremia did not improve until hyperglycemia was treated.

Camelids have a poor endogenous insulin response to hyperglycemia, and partial insulin resistance has been reported. Therefore, insulin administration was incorporated into the treatment regimen to facilitate movement of glucose into cells. Insulin stimulates glucose uptake by binding cell surface receptors, which promotes movement of GLUT4 proteins to the cell membrane and facilitates the transport of glucose into cells. In which investigators examined the response to insulin in camelids determined that cell membranes of these species possess insulin receptors and GLUT4 proteins and can respond to exogenous insulin; however, insulin sensitivity is reduced. Healthy cria treated with insulin have an initial glucose turnover rate that is closer to that of monogastric animals than that of adult camelids. A physiologically adequate pancreatic response is detected in healthy cria, but it has been suggested that pancreatic function is compromised in certain circumstances, which contributes to the development of HOS.

Administration of insulin is established for the treatment of hyperglycemia and hyperlipemia disorders in camelids and has been advocated for the prevention and treatment of HOS in neonatal camelids. Regular and long-acting insulins have been studied in camelids. Regular insulin enhances glucose clearance for < 1 hour, whereas long-acting insulin improves clearance of exogenous glucose in alpacas for up to 10 hours. Unfortu-

nately, administration of long-acting insulin increases the risk of hypoglycemia even in alpacas receiving dextrose. Insulin has been used to treat HOS in llamas and alpacas, but to the authors' knowledge, the information reported here is the first description of the successful management of hyperglycemic, hypernatremic HOS in a cria through a CRI of regular insulin.

An initial insulin infusion rate of 0.02 U/kg/h was selected on the basis of the authors' prior experiences, and the rate was titrated to maintain normoglycemia. The response to the insulin infusion was not detected immediately. The blood glucose concentration decreased from > 700 to 414 mg/dl approximately 6 hours after initiation of the infusion and was within the reference range < 9 hours after the CRI was initiated. Urine glucose concentrations were not monitored in the cria because of the difficulty in obtaining a free-catch urine sample; however, urine glucose concentrations would have been helpful to determine whether the osmotic load dissipated after glucosuria resolved. Hydration status improved once the cria became normoglycemic, and this coincided with a decrease in the blood sodium concentration. Clinical signs also improved as the blood sodium concentration decreased to < 160 mEq/L, and the cria was able to stand without assistance. In another report, it was recommended that fluid deficits be replaced prior to insulin administration to avoid worsening of hypernatremia as water follows glucose into cells, and this phenomenon may have contributed to the sodium peak observed at 30 hours. Because the persistent hypovolemia was attributed to hyperglycemia-induced osmotic diuresis in this cria, insulin treatment was initiated before adequate hydration could be achieved.

In the cria with HOS in this report, hypernatremia did not improve until insulin treatment was initiated and clinical signs improved in response to treatment. Therefore, IV administration of regular insulin via CRI may be considered as an alternative to bolus administration for the treatment of hyperglycemic, hypernatremic HOS in neonatal camelids.

References
Effects of exercise training on adiposity, insulin sensitivity, and plasma hormone and lipid concentrations in overweight or obese, insulin-resistant horses

Rebecca A. Carter et al

**Objective**—To determine effects of exercise training without dietary restriction on adiposity, basal hormone and lipid concentrations, and glucose and insulin dynamics in overweight or obese, insulin-resistant horses.

**Animals**—12 overweight or obese (body condition score ≥ 7), insulin-resistant (insulin sensitivity ≤ 1.2 X 10^-4 L/min/mU) geldings.

**Procedures**—4 horses remained sedentary, and 8 horses were exercised for 4 weeks at low intensity and 4 weeks at higher intensity, followed by 2 weeks of detraining. Prior to and after each training period, frequently sampled IV glucose tolerance tests with minimal model analysis were performed and baseline plasma insulin, glucose, triglycerides, nonesterified fatty acids, and leptin concentrations were analyzed. Adiposity was assessed by use of morphometrics, ultrasonic subcutaneous fat thickness, and estimation of fat mass from total body water (deuterium dilution method).

**Results**—Body weight and fat mass decreased by 4% (mean ± SD, 20 ± 8 kg) and 34% (32 ± 9 kg), respectively, compared with pre-exercise values, with similar losses during low- and higher-intensity training. There was no effect of exercise training on subcutaneous fat thickness, plasma hormone and lipid concentrations, or minimal model parameters of glucose and insulin dynamics.

**Conclusions and Clinical Relevance**—Results suggested that moderate exercise training without concurrent dietary restriction does not mitigate insulin resistance in overweight or obese horses. A more pronounced reduction in adiposity or higher volume or intensity of exercise may be necessary for improvement in insulin sensitivity in such horses. (Am J Vet Res 2010;71:314–321)

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