A Case of Presumptive Equine Primary Hypoparathyroidism

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Abstract

Hypoparathyroidism is an uncommon endocrine disorder in equine characterized by a transient or permanent parathyroid hormone insufficiency. Hypoparathyroidism is associated with hypocalcemia and hyperphosphatemia, primarily presenting with clinical signs consistent with hypocalcemia. Diagnosis is generally made by concurrently measuring parathyroid hormone and ionized calcium. Effective emergency treatment and maintenance of calcium levels results in a good prognosis for life, however long-term supplementation may be required.

History and Presentation

An approximately 17-year-old quarter horse gelding presented to Mississippi State University College of Veterinary Medicine on May 2, 2017 on emergency for shaking, tremors and stiffness. Earlier that day the horse was turned out to pasture and was noted to be acting abnormal upon his return to the barn for feeding time. The gelding was current on all vaccinations, Coggins testing, and deworming.

Upon presentation, the gelding was having generalized muscle fasciculations and significant abdominal movements associated with a diaphragmatic flutter ("thumps") as well as exhibited moderate facial swelling, a persistent grimace, difficulty swallowing, and a markedly hypermetric hindlimb gait. He was tachycardic with a heart rate of 64 beats per minute, tachypneic with a respiratory rate of 64 breaths per minute and had a normal rectal temperature of 100.3F. His mucous membranes were pink and moist with a normal capillary refill time of less than 2 seconds. His tongue was noticed to be a purplish color. Cardiac auscultation revealed marked tachycardia and an abnormal rhythm, although was difficult to discern due to the

significant diaphragmatic flutter. Thoracic auscultation, gastrointestinal auscultation and digital pulses were determined to be normal.

A complete blood count demonstrated no significant abnormalities. A serum chemistry revealed an elevated creatinine at 2.16 mg/dl (reference range: 1.2-1.9), a mildly elevated globulin at 4.1 g/dl (reference range: 2.5-4.0), a moderate hyperkalemia – 5.75 mmol/L (reference range: 2.4-4.7), a severe hypocalcemia – 5.7 mg/dL (reference range: 11.2-13.6), a moderate hyperphosphatemia – 5.7 mg/dl (reference range: 2.4-4.0), a moderate hypomagnesemia – 1.1 mg/dL (reference range: 1.6-2.5), and a markedly elevated CK – 1350 U/L (reference range: 57-283). An iSTAT confirmed a moderate hyperkalemia – 6.6 mmol/L (reference range: 3.8-5.0) and a severely decreased ionized calcium – 0.65 mmol/L (1.25-1.5). Initial rule-outs for the patient included canthardian toxicity, sepsis, severe gastro-intestinal disease, and hypoparathyroidism.

The patient was diagnosed with hypocalcemia, and due to the history of eating a mostly alfalfa diet, tentatively caused by canthardian toxicosis. Xylazine was administered intravenously to reduce anxiety and provide analgesia. Flow-by oxygen was provided to the patient, due to his synchronous diaphragmatic flutter and purple tongue coloration, until his respiration rate began to normalize. A nasogastric tube was passed, and 1 gallon of mineral oil was administered with 6 L of water to increase the passage rate of the suspected ingested toxin. At this time a bottle of 23% calcium gluconate (230 mg) was administered via the tube, followed by a calcium drench gel, before extubating. An intravenous catheter was placed, and the patient received an intravenous bolus of 230 mg of calcium gluconate with 5 L of Hartmann’s solution. Every 4 hours, the patient received an additional 50 mg of calcium gel orally throughout the night. Urine was collected for cantharidin testing through Texas A&M. Additionally, Ranitidine, at 7 mg/kg,

and Sucralfate, at 25 mg/kg, were added to daily treatments three times a day during hospitalization.

Twelve hours following presentation the patient had minimal muscle fasciculations and a blood sample was obtained to re-evaluate the patient's chemistry results. The serum chemistry revealed a resolution of the mildly elevated creatinine (1.49 mg/dl [1.2-1.9]), mildly elevated globulin (3.0 g/dl [2.5-4.0]), and moderate hyperkalemia (3.36 mmol/L [2.4-4.7]). A moderate hypocalcemia (9.3 mg/dL [11.2-13.6]), mild hyperphosphatemia (4.9 mg/dl [2.4-4.0]), a severe hypomagnesemia (0.7 mg/dL [1.6-2.5]), and markedly elevated CK (1066 U/L [57-283]) persisted in addition to a moderate hyperchloremia (109.1 mmol/L [98-106]), mild hyperglycemia (125 mg/dL [60-122]), mild hypoalbuminemia (2.6 g/dL [2.8-3.9]), and a mild hypoproteinemia (5.6 g/dL [6.1-8.4]). An iSTAT confirmed a normal ionized calcium (1.26 mmol/L [1.25-1.5]). The hypocalcemia and hypomagnesemia were attributed to a presumptive cantharidin toxicosis and were improving with supplementation of calcium. The hypoproteinemia was concerning as it could be possibly associated with acute inflammation, aggressive fluid therapy, or renal cantharidin toxicity. The patient was continued on a fluid therapy regiment of Hartmann's solution supplemented with calcium gluconate.

The patient continued to improve throughout the day. Thirty-six hours after presentation, the patient appeared to be markedly improved. No muscle fasciculations were noted and his appetite had returned. Due to his improvement, fluids were discontinued, and the patient was scheduled for discharge later that day. Just prior to discharge, the patient was noted to again have a synchronous diaphragmatic flutter. Blood was rapidly obtained for an iSTAT which revealed a mild hypokalemia (3.5 mmol/L [3.8-5.0]) and a severely decreased ionized calcium (0.71 mmol/L [1.25-1.5]). The patient immediately received a fluid bolus containing calcium gluconate

and an oral calcium drench gel. The patient was monitored throughout the night for muscle fasciculations and a synchronous diaphragmatic flutter. The patient developed oral edema attributed to the caustic nature of the oral calcium drench and was given flunixin meglumine during the night.

Forty-eight hours after presentation, the patient was bright and alert; however, he had a decreased appetite due to oral edema. The patient was offered feed grade ground limestone (calcium carbonate) in addition to his morning grain. Blood was submitted for a send-out parathyroid hormone and ionized calcium test performed by Michigan State University. Additional blood was submitted for a serum chemistry which revealed a mild hypoproteinemia (5.6 g/dL [6.1-8.4]), a moderate hypocalcemia (9.3 mg/dL [11.2-13.6]), a mild hyperphosphatemia (4.1 g/dL [2.4-4.0]), a mild hypomagnesemia (1.5 mg/dL [1.6-2.5]), and a mildly elevated CK (695 U/L [57-283]). With the reoccurrence of the hypocalcemia without renal signs, the main differential shifted from cantharidin toxicity to hypoparathyroidism. The patient was transitioned from intravenous calcium to oral calcium in the form of feed grade calcium carbonate.

The patient showed marked improvement and readily ate the grain and calcium carbonate presented. The patient was tentatively scheduled for discharge from the hospital that afternoon. A blood sample was obtained at noon to monitor the patient's calcium which revealed a normal calcium (11.4 mg/dL [11.2-13.6]). The patient was discharged with instructions to feed 100 g of limestone daily in addition to a vitamin AED supplement to aid in the absorption of the calcium from the calcium carbonate.

A week after discharge, the patient's cantharidin screening returned as negative and the parathyroid hormone returned as 1.40 pmol/L (reference range: 0.6-11) with an ionized calcium

of 0.81 mmol/L (reference range: 1.58-1.9). While the parathyroid hormone is within normal limits, with an ionized calcium that low, there should be a compensatory increase in the parathyroid hormone. With this result, the patient was presumptively diagnosed with primary hypoparathyroidism.

Pathophysiology

Calcium regulates muscle contraction, hormone secretion, enzyme activation, cell division, cell membrane stability, neuromuscular excitability, and blood coagulation[1,2]. Due to the number of functions that rely on calcium, the body maintains tight regulation over the quantity of calcium available.

In the equine body, calcium is found in the skeleton, soft tissues, and extracellular fluids. The skeleton contains approximately 99% of the total body calcium as hydroxyapatite crystals. The crystalline structure provides structural support, protection for vital organs, regions for blood forming elements, and serves as a reservoir for calcium. Soft tissues, such as cell membranes, mitochondria, and the endoplasmic reticulum, contain about 0.9% of the body's calcium. The remainder of the calcium, approximately 0.1%, is found within the extracellular fluid, mostly within the blood plasma. The biologically active form of calcium, also known as ionized or free calcium, composes about 50 to 55% of the total calcium within the plasma. Approximately 40% of plasma calcium is bound to protein, of which 80% is bound to albumin and the remaining 20% with globulins. The remaining 5 to 10% is complexed with anions found in the plasma. For horses, ionized calcium represents 55 to 58% of serum calcium concentrations[1,2].

The key factors of calcium homeostasis are parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D_3. A decrease in extracellular calcium concentrations results in an

increase in PTH secretion from the chief cells in the parathyroid gland. Increased PTH results in upregulation of osteoclast activity resulting in calcium resorption from bone, increased renal absorption of calcium and increased 1,25-dihydoxyvitamin D_3 synthesis. Parathyroid hormone also acts on the kidney to increase the urinary excretion of phosphorus. Increased 1,25-dihydoxyvitamin D_3 results in increased renal reabsorption and intestinal absorption of calcium and phosphate. Conversely, an increase in extracellular calcium concentration leads to the secretion of calcitonin by the C cells of the thyroid gland to inhibit osteoclast activity and inhibit PTH secretion. Magnesium is also involved in calcium homeostasis as PTH release, action, and 1,25-dihydoxyvitamin D_3 synthesis are magnesium dependent[2,3,4]. Hypomagnesemia will affect calcium concentrations in the body since magnesium is a cofactor for enzymatic activity[4].

There are a few unique attributes of horses pertaining to calcium regulation. Horses normally have a high serum total and ionized calcium concentration, poorly regulated intestinal calcium absorption, high urinary fractional clearance of calcium, a low serum concentration of vitamin D metabolites, and increased calcium set-point[2,5]. The calcium set-point is higher in horses compared to humans and dogs indicating that the equine parathyroid gland cells are less sensitive to extracellular calcium concentrations[3]. The calcium set-point is defined as the serum calcium concentration corresponding to 50% of the maximal PTH secretion during hypocalcemia and is an indicator of the serum calcium concentration at which PTH secretion is stimulated. Knowing the calcium set-point indicates the sensitivity of the parathyroid gland to calcium concentrations.

Hypocalcemia is an abnormally low concentration on calcium in the blood. Clinical signs of hypocalcemia include depression, ataxia, stiff gait, hyperexcitability, inability to chew/swallow, sweating, normal-high temperature, synchronous diaphragmatic flutter,

tachycardia, tachypnea with flared nostrils, muscle fasciculation, and ileus cardiac arrhythmias, recumbency, convulsions, death[1,2,6].

Etiologies of hypocalcemia include lactational tetany, cantharidin toxicity, prolonged exercise, sepsis, and idiopathic hypoparathyroidism. Lactational tetany is commonly seen in food animals and lactating females. These animals may be fed an inadequate dietary calcium or vitamin D concentration to meet their calcium demands leading to an acute onset of tetany or flaccid paralysis and other clinical signs associated with hypocalcemia[7]. Cantharidin toxicity is caused by ingestion of blister beetles (*Epicauta sp.*) with clinical signs being related to abdominal pain caused by the vesicant effect of Cantharidin on mucosal surfaces. Patients may appear similar to horses with colic but will have clinical signs consistent with hypocalcemia and hypomagnesemia[8,9]. Prolonged exercise can lead to hyperventilation and excessive chloride loss in sweat resulting in alkalosis, ionized hypocalcemia, and hypomagnesemia; however, calcium and magnesium concentrations in these patients tend to be normal[4]. Critically ill horses with enterocolitis, intestinal strangulation, and/or sepsis may present with an ionized hypocalcemia and hypomagnesemia resulting from a cytokine-induced hypoparathyroidism[4]. With cytokine-induced hypoparathyroidism, interleukins 1 and 6 decrease PTH mRNA expression in the equine parathyroid cells causing a decrease in PTH secretion. The decrease in PTH results in an increase in calcium-sensing receptor mRNA expression which causes parathyroid chief cells to become more sensitive to extracellular calcium thereby resetting the calcium set-point to a lower value[10]. Idiopathic hypoparathyroidism is characterized by hypocalcemia, hyperphosphatemia, hypomagnesemia, and decreased serum PTH concentrations. Patients present with clinical signs consistent with hypocalcemia[4].

Diagnostic Approach/Considerations

To identify the definitive cause of hypocalcemia, specific differentials, such as, lactational tetany, cantharidin toxicity, prolonged exercise, sepsis, and idiopathic hypoparathyroidism, must be ruled out. Lactational tetany was ruled out due to the patient's gender and non-lactational status. To definitively rule out cantharidin toxicity, a send out test is required to detect and quantify catharidin in biological specimen. Either, 5 mL of urine, 5 mL of serum, or 500 g of stomach/cecal content or feed is required[11]. Currently, the sole laboratory testing for cantharidin is Texas A&M Veterinary Medical Diagnostic Laboratory with a turnaround time between 2 and 10 days[11]. While waiting for the results to return, it is imperative to treat the patient as if the result were positive for cantharidin toxicity to allow for the best possible outcome. Prolonged exercise results in a patient with clinical signs like hypocalcemia, but serum calcium and magnesium tend to be normal. The patient's serum chemistry results and history ruled out prolonged exercise. The patient's clinical signs and bloodwork were inconsistent with sepsis and the patient, at the time of presentation, did not appear critically ill.

After ruling out other causes of hypocalcemia, idiopathic hypoparathyroidism remained. Diagnosis could be made through a surgical biopsy and histology of the gland, anti-parathyroid antibody assay, or a serum PTH test. A biopsy of the parathyroid gland could reveal degradation of the chief cells. In other species, the detection of anti-parathyroid antibodies could be used to diagnose autoimmune destruction of the glands; however, no equine assay is available[12]. To confirm the diagnosis, serum was sent to Michigan State University Veterinary Diagnostic Laboratory for a parathyroid hormone and ionized calcium test. The test measures the amount of PTH and ionized calcium in the blood which can aid in the diagnosis of hypoparathyroidism. Alternatively, to make a presumptive diagnosis, empirical treatment of the patient with calcium supplementation and monitoring for regression of clinical signs. Once the patient has returned to

a clinically normal state, discontinue the calcium supplementation and monitor for the reoccurrence of clinical signs. This would rule out the other causes of hypocalcemia, leaving only hypoparathyroidism to be confirmed.

Treatment and Management

In emergent conditions, the first requirement is to stabilize the patient by correcting the hypocalcemia. Plumb's proposes using either calcium gluconate, intravenously slowly at 150-250 mg/kg to effect, or calcium borogluconate, 50-150 mL of 23% calcium borogluconate in 5 L lactated ringer's solution at twice maintenance[13]. Alternatively, 500 mEq of calcium gluconate as a 23% solution till effect has been found to also be effective[12]. Rapid intravenous injection of calcium can cause hypotension, cardiac arrhythmias, and cardiac arrest therefore, frequent auscultations for cardiac arrhythmias are recommended. An adverse effect of calcium supplementation may be hypercalcemia, especially in patients with cardiac or renal disease. If hypercalcemia occurs, calcium supplementation should be discontinued and administration of IV normal saline and a loop diuretic in encouraged to increase the excretion of calcium and sodium. Potassium and magnesium may need to be replaced as well[13]. If the hypocalcemia becomes refractory or chronic, lifelong oral supplementation of 100-300 grams/horse/day of calcium carbonate or 100-200 grams/horse/day of dicalcium phosphate may be needed[13]. The addition of low dose vitamin D may benefit horses with decreased calcium absorption and reabsorption but may result in the mineralization of soft tissue[13,14].

Without knowing the etiology of the hypocalcemia, it is pertinent to treat all potential etiologies while correcting the hypocalcemia. If the physical exam reveals signs of infection, a broad-based antimicrobial should be added to the initial treatment. With the potentially fatal cantharidin toxin, overall treatment goals should aim at eliminating exposure and reducing

absorption, pain management, correction of fluid electrolyte deficits, and gastrointestinal mucosal protection. Administration of activated charcoal (1-3 g/kg) or mineral oil may encourage toxin elimination and prevent absorption. Fluid therapy corrects dehydration, electrolyte abnormalities, and promotes diuresis. Gastrointestinal lesions are another main concern with cantharidin toxicity so the addition of sucralfate (10 g) and omeprazole (4 mg/kg) may reduce the severity. With aggressive treatment, most horses with cantharidin toxicosis recover[15].

Long term prognosis is variable and depends upon clinical signs. Generally, prognosis is good as horses may show improvement with medical treatment though signs reoccur after discontinuation of calcium supplementation making long-term supplementation necessary. Horses that require frequent intravenous administration of calcium have a poorer prognosis[14]. Of the 3 adult horses in literature diagnosed with primary hypoparathyroidism, one was euthanized after 12 months, two remained on ground limestone for over 6 months before being lost to follow-up[6,12]. Potentially, calcium supplementation could be tapered to a lower dose; however, reoccurrence of clinical signs may deter a clinician from tapering dosing[12].

Case Outcome

The patient returned to the MSU-CVM to measure his serum calcium levels 30 days post discharge which revealed him to be hypocalcemic (9.4 mg/dl [11.2-13.6]) but improved from his discharge date with no clinical signs of hypocalcemia. He continues to receive 100 g of feed grade limestone and 500 U/kg of vitamin AED supplement. The gelding was reported to be doing well and, according to the owners, is back to his normal self.

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