Intermittent hypoglycemia in a horse with anaplastic carcinoma of the kidney

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Clinically apparent hypoglycemia is rare in adult horses.

- Hypoglycemia is a well-recognized paraneoplastic syndrome in humans and dogs with non–insulin-secreting tumors and may occur in horses as well.
- Hypoglycemia associated with non–insulin-secreting tumors is believed to result from production of an abnormal form of insulin-like growth factor II.
- Neoplasia should be considered in the differential diagnosis for adult horses with hypoglycemia.

A 14-year-old Mustang gelding was referred to the University of California, Davis, Veterinary Medical Teaching Hospital for evaluation of a suspected episode of hypoglycemia and collapse. The horse had a 5-day history of mild colic and partial anorexia, chronic diarrhea of unknown duration, and a 2- to 3-week history of weight loss despite an increase in the amount of feed. On the morning of referral, the horse was examined by the referring veterinarian who reported that the horse was recumbent with hypoglycemia. At that time, the horse responded to IV administration of flunixin meglumine and dextrose and was standing and eating within a few minutes after treatment.

On initial examination at the veterinary teaching hospital, the horse was observed to be moderately thin and appeared slightly weak with noticeable muscle tremors. Temperature, heart rate, and respiratory rate were normal, and the horse passed soft formed feces followed by fluid feces during the examination. Examination per rectum did not reveal any clinically important abnormalities. Blood glucose concentration was 185 mg/dl (reference range, 59 to 122 mg/dl). Urine glucose concentration was initially estimated to be 230 mg/dl by use of a dipstick test, but results of a follow-up test approximately 24 hours later were negative. Total WBC count, PCV, and serum total protein, sodium, potassium, ionized calcium, and bicarbonate concentrations were within reference limits.

Abdominocentesis yielded a hazy yellow fluid with a total protein concentration of 1.2 g/dl and WBC count of 690 cells/µl. Evaluation of blood samples collected on days 3, 4, and 10 of hospitalization revealed moderate anemia (PCV = 22.5, 28.6, and 24.9%, respectively) and mild thrombocytopenia (98,000 platelets/µl) on day 3. Serum glucose, electrolyte, urea nitrogen, creatinine, total bilirubin, albumin, and globulin concentrations and sorbitol dehydrogenase, γ-glutamyltransferase, aspartate aminotransferase, alkaline phosphatase, and creatine kinase activities were within reference ranges the morning following admission.

Initially, financial constraints of the owner prevented thorough diagnostic evaluation, and the horse was treated conservatively on the basis of an assumption that it had colic of an unknown cause that was resolving. On the third day of hospitalization, the horse developed a large abscess on the left side of the neck consistent with infection of the site where the owner had injected flunixin meglumine multiple times during the week prior to admission. Bacterial culture of material from the abscess yielded Bacillus cereus, which was resistant to penicillin but susceptible to gentamicin. The abscess responded to treatment with gentamicin IV, hot packing, and drainage by needle aspiration and decreased in size considerably during the remaining 14 days of treatment. As the horse did not initially have any signs of acute illness following admission, treatment of this abscess was the reason for the prolonged hospitalization.

On the eighth day of hospitalization, the horse was found to be nonresponsive. It was standing but would not move, even when encouraged, or respond when offered food. Its pupils were dilated and did not respond to light, and its ears were twitching repetitively. Heart and respiratory rates were within reference limits. Blood glucose concentration was 13 mg/dl. The horse collapsed during examination, and 5 L of lactated Ringer’s solution was administered. The horse responded almost immediately and was standing and eating within 10 minutes after initiation of IV treatment. Blood glucose concentration was 296 mg/dl following administration of 5 L of lactated Ringer’s solution with 10% dextrose.

Blood glucose concentration was monitored 1 to 3 times daily for the remaining 8 days of hospitalization. Nine of 12 samples had a blood glucose concentration between 63 and 136 mg/dl, and 3 had a concentration between 37 and 53 mg/dl. Blood glucose concentration was not obviously associated with time of blood sample collection or time since the horse was fed. For 3 samples, serum insulin concentration was measured at the same time blood glucose concentration was measured. For the first sample, insulin concentration was < 1.5 µU/ml (reference range, 1 < 300 µU/ml), and glucose concentration was 37 mg/dl. For the second sample, insulin concentration was 65.6 µU/ml, and glucose concentration was 136 mg/dl. For the third sample, insulin concentration was 14.6 µU/ml, and glucose concentration was 37 mg/dl. Insulin-to-glucose ratios for samples 1, 2, and 3 were 0.4, 0.48, and 0.4, respectively, which were within the range previously documented for healthy adult horses. Other than the episode of hypoglycemia on the eighth day of hospitalization...
EQUINE starvation. Hypoglycemia in horses with colic associ-
ated with strangulating lesions of the intestine has also
been reported. Hypoglycemia associated with excess-
ive secretions of insulin from an islet cell tumor in a
pony has been reported but, otherwise, is an unusual
finding in horses.

In dogs, several non–insulin-secreting tumors,
including leiomyoma, leiomyosarcoma, hepatoma,
lymphocytic leukemia, plasma cell myeloma, malign-
ant melanoma, salivary adenocarcinoma, hemangio-
sarcoma, and malignant lymphoma, have been asso-
ciated with hypoglycemia. Most of these tumors
have been malignant and associated with short survival
times. In many affected dogs, hypoglycemia resolved
following complete removal of the tumor. It is
currently thought that hypoglycemia associ-
ed with non–insulin-secreting tumors in dogs and
other species is associated with production of an
abnormal form of insulin-like growth factor (IGF)-II,
referred to as “big IGF-II,” and an alteration of its
interactions with other substances. In humans with
hypoglycemia secondary to non–insulin-secreting
tumors, there is impaired formation of serum com-
plexes of IGF, IGF-binding protein, and the acid-labile
subunit. These patients have high circulating concen-
trations of big IGF-II (which has insulin-like activity),
may have normal or high concentrations of normal
IGF-II, and have normal or low insulin concentrations.
The result is increased insulin-like activity and uptake
of glucose into tissues, primarily muscle, resulting in
hypoglycemia. Serum big IGF-II concentration returns
to normal and, as in dogs, hypoglycemia resolves fol-
lowing complete surgical resection of the tumor. Other
proposed causes of tumor-associated hypoglycemia
include increased metabolic demand for glucose by the
tumor itself, stimulation of increased glucose uptake
by tumor necrosis factor, and in the case of neoplasia
involving the liver, decreased hepatic gluconeogenesis
because of a decrease in the total number of functional
hepatocytes.

It is possible that hypoglycemia in the horse
described in the present report resulted from tumor-
related production of big IGF-II. Although the horse
had intermittent signs of mild colic and diarrhea, there
was no evidence of endotoxemia, strangulation of the
intestines, starvation, excessive exercise, or hyperlipi-
demia. Histologic examination of the tumor, serum
insulin concentration, and the insulin-to-glucose ratio,
which was evaluated on 3 separate occasions, did not
support a diagnosis of an insulin-secreting islet cell
tumor.

The horse did have moderate multifocal hepatocel-
lar necrosis and biliary hyperplasia, but most of
the liver was unaffected histologically. Serum albumin
and bilirubin concentrations and hepatic enzyme
activities were normal, and the horse did not have any
other clinical or laboratory evidence of compromised
liver function. In addition, episodes of hypoglycemia
were sporadic, and the horse had blood glucose con-
centrations within reference limits most of the time.
Thus, it is unlikely that persistent hepatic disease or
dysfunction was a major contributor to the hypo-
glycemia. Rather, the rapid decrease in blood glucose
concentration, coupled with the apparent lack of an
association between blood glucose and insulin concentrations, was suggestive of intermittent action of a substance with hypoglycemic or insulin-like activity in this horse.

To our knowledge, there has been only 1 other report of hypoglycemia associated with a nonislet cell tumor in a horse.11 This paraneoplastic condition may be more common in horses than presently recognized, and neoplasia should be included in the differential diagnosis for horses with hypoglycemia.

References