Proceedings of the Southern European Veterinary Conference
- SEVC -

Sep. 30-Oct. 3, 2010, Barcelona, Spain

Next SEVC Conference:

Sep. 30-Oct. 2, 2011 - Barcelona, Spain

Reprinted in the IVIS website with the permission of the SEVC - AVEPA
www.ivis.org
Small animal medicine

Hypoglycemia – causes, diagnosis, and treatment
Michael Schaer, DVM, Diplomate ACVIM, ACVECC

University of Florida, College of Veterinary Medicine

Definition and Adverse Effects:

Normally, the whole blood concentration of glucose is 10 to 15% less than that found in the serum or plasma. This is due to a dilutional effect caused by the red blood cells in whole blood that contain little glucose. Hypoglycemia is a symptom complex associated with an abnormally low (< 60 mg/dl) blood glucose concentration. The brain is the main organ that is adversely affected by this metabolic abnormality since it primarily depends on glucose as an energy substrate, but brain dysfunction rarely occurs until the blood glucose level declines to < 40 mg/dl. With protracted severe hypoglycemia, the cerebrum and the brainstem will eventually undergo autolytic changes that is pathologically described as pseudolaminar necrosis.

Pathophysiology:

Normally a highly sophisticated regulatory system maintains glucose concentrations within a very narrow range. This is a steady state system where the rate of production does not equal the rate of utilization at any given moment. The brain, RBC-s, lymphocytes and platelets are nearly totally dependent upon glucose for their metabolism. In the adult fasted human, up to 80% of the glucose produced by glycogenolysis and gluconeogenesis is used for brain metabolism. Nearly all of the rest is used by the formed elements of the blood. The heart, other muscles, and the kidneys can use other substrates quite efficiently. During periods of inadequate glucose supply to the brain, alternate sources of energy such as ketones and Krebs cycle intermediates will be utilized for the short term.

Carrier-mediated transport is responsible for shuttling glucose through the blood-brain barrier and moving it from the CSF into the extracellular space (ECF) where it can be utilized by the individual cells of the brain. The CSF glucose concentration is maintained at about 65% of that found in the blood while that of the brain–s ECF is maintained at about one-third the CSF glucose concentration. When the plasma glucose level drops to about 30 mg/dl, the supply to the brain cells becomes dangerously low causing neuronal metabolism to fail. Acute changes in the plasma glucose concentration do not immediately affect that of the CSF and brain. Changes here lag behind those in the plasma by a few hours thereby giving the brain a chance to benefit by the systemic counter-regulatory changes that might ensue. Once neuroglycopenia occurs and the patient is given exogenous glucose, it often takes a few hours for normal mentation to return. Cerebral damage from hypoglycemia is thought to be due to the release of excitotoxins, which lead to neuronal necrosis. The neuronal necrosis mostly involves the cerebrum.
In the starving state, the body becomes dependent on gluconeogenesis and ketogenesis for energy production. These alternate pathways provide many tissues their necessary energy supply, thus allowing the brain more access to endogenously produced glucose. These counter-regulatory effects are brought about from decreases in insulin production and increases in epinephrine, glucagon, growth hormone, and cortisol production. Glucagon causes gluconeogenesis and glycogenolysis, epinephrine causes glycogenolysis, glucocorticoids cause gluconeogenesis, and growth hormone causes insulin antagonism thereby promoting lipolysis and ketogenesis. Patients with glycogen storage defects such as those with hepatic portasystemic shunts will not benefit from the counter-regulatory actions of glucagon and epinephrine as far as glycogenolysis is concerned.

Glucagon's release is normally stimulated by hypoglycemia as well as elevated levels of growth hormone, epinephrine, and cortisol. Glucagon release is impaired by certain drugs such as Ca\(^{2+}\)-channel blockers, β-blockers, and anticholinergics.

**Clinical Signs:**

The signs relate to both the rapidity and severity of the decline in glucose levels. These are further influenced by the augmentation of epinephrine release from the sympathetic nervous system and the cerebral cortical effects. Postprandial hypoglycemia is more likely to present with signs of adrenergic excess whereas fasting hypoglycemia commonly presents with neuroglycemic signs. The signs include: bizarre behavioral changes, palpitations, hunger, anxiety, dementia, weakness, seizures, coma, and hypothermia. The hypoglycemic signs associated with stressed immature puppies and kittens and that associated with sepsis are characteristically progressive in nature. However, hypoglycemia associated with insulin secreting tumors characteristically has episodic signs.

Hypoglycemic encephalopathy may characterize as four different forms: 1) delirium manifested by mental changes, 2) coma accompanied by signs of multifocal brainstem dysfunction, 3) stroke-like disorder with focal neurological signs with or without coma and 4) epileptic seizures.

The manifestations of hypoglycemia ultimately depend on the nature of the agent or stimulant responsible for the fall in blood glucose, the rate at which hypoglycemia develops, the structure and functional integrity of the CNS, and the competence of the counter-regulatory hormone mechanisms.

**Causes in the Dog and Cat:**

These include pancreatic beta cell carcinoma, extrapancreatic cancer, prolonged starvation, Addison's disease, insulin overdose, glycogen storage diseases, sepsis, and portacaval vascular anomalies. The following table provides the likely mechanisms of hypoglycemia with its particular cause:

<table>
<thead>
<tr>
<th>1. Pancreatic beta cell tumor</th>
<th>1. Production and secretion of abnormally large amounts of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Extrapancreatic cancer</td>
<td>*(a) Production of nonsuppressible insulin-like growth factors (IGF I and II)</td>
</tr>
<tr>
<td></td>
<td>(b) Tumor production of gluconeogenic inhibiting substances</td>
</tr>
<tr>
<td></td>
<td>(c) Tumor's excess glucose consumption</td>
</tr>
<tr>
<td>3. Starvation</td>
<td>*(a) Depleted tissue reserves</td>
</tr>
</tbody>
</table>

Proceedings of the Southern European Veterinary Conference & Congreso Nacional AVEPA, 2010 - Barcelona, Spain
4. Addison’s disease
   4. Glucocorticoid insufficiency decreasing gluconeogenesis

5. Insulin overdose
   5. (a) Excessive amount
   (b) Reduced need
   (c) Recovery from stress states

6. Glycogen storage disease
   6. Abnormal hepatic intermediary metabolism

7. Sepsis
   7. (a) Endotoxin and metabolic acidosis associated inhibition of gluconeogenesis
   (b) Increased glucose requirements to fulfill energy needs in the hypotension-induced anaerobic tissue environment, causing depleted liver glycogen stores

8. Portacaval vascular anomalies
   8. Impaired gluconeogenesis and glycogenolysis

(*) most common mechanism

**Diagnostic Workup:**

In a diabetic animal receiving insulin, the symptoms of hypoglycemia alone should alert the pet owner and the clinician to the obvious cause, especially when signs of neuroglycopenia occur at the approximate peak action time of the particular insulin used.

Hypoglycemia in a puppy or kitten is related to depleted glycogen stores and the inability of gluconeogenesis to fulfill the young animal’s energy needs during a period of stress and anorexia.

In the above two situations the obvious signs call for the immediate administration of glucose intravenously. A blood glucose determination will confirm the clinical impression. The blood glucose reagent strips (Dextrostix, Bayer or Chemstrip Bg, Boehringer Mannheim) are most helpful when laboratory facilities are unavailable.

In the middle-aged and geriatric canine not receiving exogenous insulin, the symptoms of neuroglycopenia and the demonstration of concomitant low blood glucose levels require the investigation for extrapancreatic neoplasia and/or a pancreatic beta cell tumor. The diagnostic workup should include: chest and abdominal radiographs, complete blood count, complete blood biochemical panel, serum electrolytes, and a urinalysis. When an islet cell carcinoma is suspected, the demonstration of hypoglycemia and coexisting inappropriate hyperinsulinemia is essential for diagnosis. When the above tests results are equivocal, certain provocative tests such as the glucagon tolerance and leucine tolerance tests can be performed. Simply fasting the patient under ICU conditions will usually bring about an insulinoma-induced hypoglycemia.

**Treatment of Hypoglycemia:**

If the patient is conscious, Karo syrup containing 1 gm of carbohydrate per 1 ml can be given orally at a dose of 0.5 to 1 ml/kg. When oral treatment is not an option, the intravenous route should be used. Boluses of 0.25-0.5 g/kg are most commonly used. This is equivalent to 2.5 to 5 ml/kg 10% D/W, 1 to 2 ml/kg 25% D/W or 0.5 to 1 ml/kg 50% D/W. If no response is seen within 5 minutes, this should
be repeated and the blood glucose re-evaluated. If euglycemia is restored, maintenance treatment can consist of 10% dextrose in 0.9% NaCl (or 10% Dextrose in 0.45% NaCl) with KCl added. This solution can be infused at a rate of 3 ml/kg/hr. Patients who are hyperinsulinemic can be maintained at a rate of 10 to 12 ml/kg/min or more.

Glucagon works only if the patient has intact glycogen stores. Its use should be considered, especially, in the prehospital setting, when an intravenous line cannot be placed as seen with the seizuring diabetic pet suffering from insulin overdose. The usual dose is 1 mg glucagon for large dogs and 30 μg/kg (or 0.03 mg/kg) for the smaller patient. It may be given IV, SQ or IM. The IM route is probably the best route in the hypoglycemic seizuring patient in its home environment.

For those patients with refractory hypoglycemia, there is a special protocol using glucagon by constant rate infusion. A 1 μg/ml solution is prepared by adding 1 mg of lyophilized glucagon, which has been reconstituted with its diluent, to one liter of 0.9% NaCl. The rate of infusion will vary depending on the dosage needed which can range from 5-13 ng/kg per minute.

Other drugs that can be used are hydrocortisone, prednisone, or dexamethasone; diazoxide; amlodipine; verapamil; and octreotide. Octreotide inhibits insulin secretion and can be given at a dose of 2 to 4 μg/kg SQ Q8-12 hours. Its use in dogs warrants further study. The glucocorticoids will promote gluconeogenesis and be essential in cases where adrenocortical insufficiency is the cause of the hypoglycemia. The calcium channel blockers, amlodipine (0.2-0.4 mg/kg bid) and verapamil (1-5 mg/kg tid), inhibit insulin secretion from the beta-cell (insulin secretion is a calcium-dependent process). It is best to begin the calcium channel blockers at the lower dose and titrate to effect.

Feedings of raw cornstarch at night can maintain safe glucose levels for a number of hours with little or no rebound.

Diazoxide inhibits insulin release and activity. The oral starting dose is 10 mg/kg divided twice daily. This can be doubled if there is minimal response. Although once easily available in the U.S., diazoxide is usually obtained through a compounding pharmacy. Other drugs that might palliate insulin secretion by an insulinoma are propranolol (dog 0.5-1.0 mg/kg PO tid) and phenytoin (dog 20-35 mg/kg PO Q6h).

IT IS ESSENTIAL TO REMEMBER THAT ANY PATIENT SUSPECTED OF HAVING HYPOGLYCEMIA SHOULD HAVE ITS BLOOD GLUCOSE MEASURED IMMEDIATELY SO THAT TREATMENT CAN BE GIVEN IN A TIMELY MANNER BEFORE BRAIN DAMAGE EnsUES.

References