SIGNALMENT:

Mitty, a seven-month-old female spayed Miniature Schnauzer weighing 7.38kg. Identification [redacted] Case log # 32.

HISTORY:

Mitty was presented to [redacted] on February 26, 2019, for acute lethargy, weakness and ataxia. Besides undergoing a routine spay procedure several months ago, she had no previous medical history. Prior to her acute ataxia, she had been eating and drinking normally, with no vomiting or diarrhea reported. There was no history of trauma.

INITIAL INTERVENTIONS:

The triage Registered Veterinary Technologist (RVT) immediately brought her to the treatment area with emergency consent obtained from the owners. Mitty was laterally recumbent and responsive, with a heart rate of 76 beats per minute (ref: 90-140 beats per minute[1]) and respiratory rate of 16 breaths per minute (ref: 10-30 breaths per minute[2]). Her gums were pink with a normal capillary refill time of less than two seconds. I placed an intravenous (IV) catheter and collected blood from the catheter. I used a drop of the blood in a portable hand-held glucometer which revealed Mitty was hypoglycemic, at 1.3mmol/L (ref: 3.44-9.55mmol/L[3]). I notified the veterinarian (DVM) and I administered a dextrose bolus (0.5ml/kg) of 50% dextrose diluted to make a 1:4 dilution with saline and administered IV. Her mentation rapidly improved and a recheck of her blood glucose read 8.1mmol/L. I continued to collect vital signs on Mitty, which included a body temperature and blood pressure, which were within normal limits. I performed an in-house blood panel which included a complete blood count, packed cell volume, chemistry panel and electrolytes. I suggested including an ammonia to help rule out a porto-systemic shunt (PSS; where an abnormal vein connects intestinal blood directly into circulation, bypassing the liver, causing a build up of ammonia in the blood stream), which is common in Miniature Schnauzers[4] and can lead to hepatic encephalopathy and hypoglycemia with symptoms similar to Mitty's.

Before putting Mitty into a kennel, I rechecked her blood glucose, and it was 5.1mmol/L. The bloodwork results revealed a normal complete blood count and chemistry, except hypoglycemia, which had already been addressed. Her hepatic values were normal. The ammonia level (via in house Idexx Catalyst) was zero (ref: 0-99umol/L), which made the diagnosis of a PSS less likely.

Mitty's owners informed the DVM there was gum in the house containing xylitol that she potentially could have ingested. Xylitol is an artificial sweetener used in many human products, including gum, and as a popular substitute for sugar in baking as well as toothpaste, as it is thought to decrease bacteria amounts in the mouth.[5,6] In contrast to in humans, xylitol causes a massive surge of insulin release in dogs, up to six times the amount released with an equal dose of glucose.[5] Hypoglycemia can be seen in 30 minutes or have a less common delayed response, taking up to 12 hours to see a hypoglycemic effect.[5] This surge of insulin can also cause electrolyte abnormalities, specifically hypokalemia and hypophosphatemia. Xylitol ingestion can also cause hepatopathy or hepatic necrosis. In

Mitty's case, emesis was not induced as it was unknown when she had ingested it (xylitol is usually absorbed within 30 minutes of ingestion[6]), and since she was already symptomatic of the xylitol ingestion (hypoglycemic) it could have led to aspiration. Activated charcoal, an adsorbent, was not given as it is not typically indicated for xylitol ingestion due to its low rate of binding it has to the substance.[5,6] N-acetylcystine (NAC) and S-adenosyl-methionine (SAMe) were prescribed. Both NAC and SAMe act as hepato-protectants by detoxifying and replenishing the antioxidant glutathione.[7,8]

FURTHER INTERVENTIONS:

Thirty minutes after the previous blood glucose, I rechecked her blood glucose and it had decreased to 5.1mmol/L. Mitty shortly after became very quiet and I noticed some twitching. Her blood glucose had dropped further and was again hypoglycemic at 2.7mmol/L. Her refractory hypoglycemia despite boluses of dextrose warranted a need for a constant infusion (CRI) of dextrose. I administered a dextrose bolus and suggested to the DVM that I start a 2.5% dextrose CRI. I made a 2.5% dextrose solution in a buretrol with her Plasmalyte R intravenous crystalloid fluids, which were being delivered at 40ml/hr. Though xylitol toxicity was the most likely diagnosis, pre and post prandial bile acids were collected to further rule out the differential diagnosis of a PSS (an increase in bile acids may indicate abnormal clearance of bile salts due to abnormal hepatic blood flow).

On 2.5% IV dextrose, Mitty became hypoglycemic. I increased her dextrose infusion to a 5% solution, but again, her blood glucose dropped to 2.7mmol/L. I confirmed that the IV catheter was patent, with no redness, swelling, or signs of pain or phlebitis. Confident in each of these checks, I increased the dextrose infusion to 7.5%.

Dextrose infusions can have consequences, especially at higher concentrations. Appropriate intravascular or intraosseous access is necessary. Dextrose has a high osmolarity, which only allows a certain percentage to be administered through a peripheral vein. Too high of an osmolarity can cause phlebitis, and if dextrose is infused perivascularly it can cause damage to the surrounding cells and cause tissue sloughing. If the concentration of the dextrose solution exceeds 7.5%, a central line should be placed to administer these fluids.[3] Dextrose supplementation in intravenous fluids can also cause fluid shifts within the patient, due to its high osmolarity. A patient should be adequately hydrated prior to a dextrose infusion. In a dehydrated state, dextrose will pull fluids into the intravascular space from the interstitial space, worsening the dehydration. This is due to the osmotic pull of dextrose.[3] Frequent blood glucose monitoring must be available to make sure adequate supplementation is being given, and that the patient is not becoming hyperglycemic. I obtained a blood glucose from Mitty's pinna every two hours, being read by a hand-held glucometer.

After five hours after being on 7.5% dextrose infusion and eating small, frequent meals, Mitty was still becoming hypoglycemic. Within this time, several IV boluses of dextrose (0.5ml/kg of 50% dextrose diluted 1:4 with saline) had to be given, which would only temporarily increase her blood glucose level. I then started her on a glucagon CRI. I prepared the glucagon by reconstituting the vile of powdered glucagon and added it to a one litre bag of 0.9% sodium chloride to produce a 1000 nanogram/ml

concentration and started the rate at 10 nanograms/kg/min. Her dextrose was weaned, and I continued to monitor her blood glucose every two hours, adjusting the glucagon CRI as needed, based on her blood glucose level.

Homeostasis of glucose is vital to provide energy for the brain and body to function and perform all tasks essential for mammalian life. Untreated hypoglycemia can lead to neuroglycopenia and neuronal death in the brain by disrupting the Na+K+ATPase pumps, causing swelling of brain cells.[3] Regulation between storing or utilizing glucose is constantly being monitored in the body and can change and adjust rapidly. Two main counter-regulatory hormones play an active role in this regulation, insulin and glucagon, which is determined by presence or lack of glucose.

In a post-prandial (hyperglycemic) state, glucose is delivered from the gastrointestinal tract to the liver and pancreas. Once glucose is at the pancreas it enters the beta cells, located in the islet of Langerhans of the pancreas. Glucose undergoes glycolysis, where each molecule becomes two pyruvates. Each pyruvate then undergoes oxidation, and becomes an enzyme called Acetyl Co-enzyme A (Acetyl CoA). This is the first enzyme to start the Krebs cycle. Acetyl CoA combines with oxalacetic acid to form citric acid, and then undergoes several more enzymatic reactions, which eventually enters the electron transport chain and creates the organic chemical called adenosine triphosphate (ATP), to be used by the cells for energy. The ATP now inside the cell triggers a chain of events, which end in insulin being secreted into the blood stream. The amount of insulin that is secreted is determined by the amount of glucose present. Insulin in the blood stream travels to all cells in the body and allows glucose to enter the cells to be utilized for energy. Insulin also travels to the liver where it stimulates the liver to undergo glycogenesis, where it changes glucose into a stored form called glycogen.[3,9]

During hypoglycemia, the body responds by secreting glucagon from the alpha cells also located in the islet of Langerhans inside the pancreas. Glucagon is a counter-regulatory hormone to insulin. Its primary target is the liver, in which it causes glycogenolysis; the breakdown of stored glycogen back into glucose. The adrenal glands also have a role in glucose homeostasis. The adrenal cortex secrets cortisol and the adrenal medulla secretes epinephrine. All three of these hormones stimulate gluconeogenesis, causing liposlysis of adipose tissue to release fatty acids and glycerol, as well as break down amino acids, all products of which are broken down into usable sources of glucose for cells. The glucose from both gluconeogenesis and glycogenolysis is utilized by body cells. Once the blood becomes normoglycemic, a negative feedback loop turns off the secretion of cortisol, epinephrine and glucagon. Administration of a CRI of intravenous glucagon stimulates glucose availability in the body just as endogenous glucagon does, to increase blood glucose levels.

Overnight Mitty remained on the glucagon CRI, continued to eat small frequent meals and had no further episodes of hypoglycemia. She was weaned off of the glucagon infusion and remained normoglycemic. The bile acid test results returned which were normal, ruling out the differential diagnosis of a PSS. Electrolytes and liver values were not rechecked.

CASE DISCUSSION:

It is suspected that Mitty ingested gum containing xylitol, which the owners found in their household within her reach. It is unclear how much or when she could have ingested it. It is suggested that a dose as small as >0.1mg/kg of xylitol can cause hypoglycemia, and at >0.5mg/kg, xylitol may cause hepatic failure and necrosis.[5] Though there are several theories, the exact cause of hepatic failure is not known.[5,6] Mitty did not show any indication her liver was affected. Her skin, mucous membranes and sclera did not become icteric, nor did any petechia or ecchymosis appear on her body. Her abdomen remained non-painful.

Jaundice is seen when increased liver values are circulating, particularly total bilirubin. The liver is responsible for conjugating bilirubin (a metabolite of the breakdown of hemoglobin) for it to be excreted into bile. This conjugation process makes the bilirubin water soluble, and then able to be excreted. If this process is not done in the face of hepatic pathology, there will be an increase of total bilirubin (unconjugated bilirubin), causing the visual markers of jaundice, potentially indicating hepatic abnormalities.[10] Other increased blood serum values that could indicate hepatic damage include alanine aminotransferase (ALT; an enzyme present in hepatocytes which may indicate cell damage), alkaline phosphatase (ALP; an enzyme within hepatic biliary ducts that could indicate hepatitis), as well as increased clotting times.[6]

The liver, along with playing a large part in glucose homeostasis, also is involved with producing clotting factors, necessary for coagulation.[10] Clotting times can be measured in clinic by testing PT and aPTT (prothrombin and activated partial thromboplastin time, respectively). Prothrombin is a globulin that is produced by the liver, important for the extrinsic pathway to allow normal coagulation. An increase in PT can indicate hepatic disease (damaged hepatocytes are not producing prothrombin appropriately).[10] aPTT tests the intrinsic clotting pathway and determines how long it takes a blood sample to form a clot. Thromboplastin is a blood clotting factor necessary to change prothrombin into thrombin.[10] Both tests involve a 'clean poke' using a peripheral vein. If clotting factor production is interrupted, bleeding within the body and skin may occur, resulting petechia or ecchymosis, as well as active bleeding from anywhere in or on the body.

Due to the surge of insulin released during xylitol toxicity, serum potassium or phosphorus levels may become depleted. As insulin allows glucose to enter cells, it also stimulates Na+-K+-ATPase pumps, which move potassium intracellularly. Phosphate enters intracellularly, as insulin causes the cells to become more permeable to the ion.[5] Symptoms of severe hypokalemia can be seen when potassium drops below 2.5mEq/L (ref: 3.5-4.6mEq/L).[11] Hypokalemia causes membranes to become less excitable resulting in the action potential being prolonged (harder to stimulate depolarization). Skeletal weakness, most commonly displayed by a ventroflexed neck and head, or a plantigrade stance ('dropped hock') can be seen in the pelvic limbs. Cardiac abnormalities seen on electrocardiograph may include a bradyarrhythmia with an increased P wave, a depression in the ST segment, with a depressed T wave, sometimes referred to as a U wave.[11,12] An infusion of potassium may be required to re-establish normal potassium levels, though should not exceed

0.5mEq/kg/hour, as it can cause cardiac arrest if infused too quickly or cause over supplementation, causing hyperkalemia.[12] Though in severe hypokalemia, potassium infusions can be increased to 1mEq/kg/hour if monitored appropriately, including a continuous ECG.[12]

Since most of phosphorus exists intracellularly (less than 1% exists extracellularly and available to measure in serum), the value obtained in a serum or plasma measurement does not reflect the total amount of phosphorus in the body.[13] Despite this, having adequate plasma phosphorus measurements is important, as phosphorus is required for contraction of muscles, acid-base balance, conduction of nerve impulses as well as a component for energy and ATP production.[13] A serum phosphorus level less than 1mg/dL is considered significant and may need supplementation.[13]

If Mitty did not improve, or began to show signs of hepatic failure, hypokalemia, hypophosphatemia or coagulopathy, repeat bloodwork including liver values, clotting times and electrolytes may require frequent checking. IV infusions of potassium and phosphorus may be warranted. If there was a coagulopathy, fresh frozen plasma to restore clotting factors may be given, as well as a packed red blood cell or whole blood, if there is active bleeding causing anemia or hemorrhagic hypovolemia. Hypoglycemia in the face of liver failure is due to the hepatic cells not able to properly perform gluconeogenesis and glycogenolysis, which may persist even when the xylitol is no longer the contributing factor.[5] Continued glucagon or dextrose administration would be necessary during hypoglycemia.

Mitty was discharged after 27 hours in hospital, with prescriptions for NAC and SAMe to be continued at home. She was to follow up with her rDVM in 24 hours to have repeat bloodwork to ensure her hepatic values and electrolytes remained normal.

REFERENCES:

1. Ford R, Mazzaferro E, editors. Vet. Procedures and Emergency Treatment. 9th edition. Missouri: Saunders; 2012, p. 94
2. Ford R, Mazzaferro E, editors. Vet. Procedures and Emergency Treatment. 9th edition. Missouri: Saunders; 2012, p. 373
3. Natara Loose. Glucose. In: Kirby R, Linklater A, editors. Monitoring and Intervention for the Critically Ill Small Animal Rule of 20. Iowa: Wiley & Sons; 2017, p.55-71
4. Watson P, Bunch S. Hepatobiliary Diseases in the Dog. In: Nelson R, Couto C. Small Animal Internal Medicine. 4th edition. Missouri: Elsevier; 2009, p. 541-568
5. Eric K. Dunayer. New Findings on the Effects of Xylitol Ingestion in Dogs: 2006. Veterinary Medicine. 2006, p. 791-797
6. Matthew S. Mellema. Xylitol. In: Peterson M, Talcott P, editors. Small Animal Toxicology. 3rd edition. Missouri: Saunders; 2013, p. 841-846
7. Deborah C. Mandell. Acute Liver Failure. In: Drobatz K, Hopper K, Rozanski E, Silverstein D, editors. Textbook of Small Animal Emergency Medicine. Volume 1. New Jersey: Wiley and Sons; 2019, p.566-577
8. Justine A. Lee. Approach to Drug Overdose. In: Silverstein DC, Hopper K, editors. Small Animal Critical Care Medicine. 2nd ed. Missouri: Saunders; 2015, p. 385- 389
9. Bassert J. Nutrients and Metabolism. In: Colville T, Bassert J, editors. Clinical Anatomy and Physiology. 2nd edition. Missouri: Mosby, Inc; 2008, p. 283-313
10. Amy Newfield. Hepatic Emergencies. In: VECCS/ AVECCT Technician Multidisciplinary Review; 2018: New Orleans, USA p. 1-10
11. Riordan L, Schaer M. Potassium Disorders. In: Silverstein DC, Hopper K, editors. Small Animal Critical Care Medicine. 2nd ed. Missouri: Saunders; 2015, p. 269-273
12. Cowan D. Disorders of Potassium. In: Randels-Thorp A, Liss D, editors. Acid-Base and Electrolyte Handbook for Veterinary Technicians. Singapore: Wiley & Sons; 2017, p. 44-56
13. O'Dwyer L. Disorders of Phosphorous. In: Randels-Thorp A, Liss D, editors. Acid-Base and Electrolyte Handbook for Veterinary Technicians. Singapore: Wiley & Sons; 2017, p.66-78