XYLITOL TOXICITY

Key points:

1. Mechanism of acute hepatic necrosis is unknown and
2. While elevated liver enzymes seem to be dose dependant the occurrence of necrosis may be idiosyncratic

Acute hepatic failure and coagulopathy associated with xylitol ingestion in 8 dogs

1 case – 4yo ingested muffins with 7.23g/kg xylitol

DAY 1: BG 18 on presentation. Hypophosphatemic, hypokalemic, elevated ALT (144), Crea 3.0 with low BUN. Thrombocytopenic 159

DAY 2: Vomiting, still hypoglycemic, icteric serum tbili 3.0, ALP 284, ALT > reference range. Went to specialty hospital, Developed epistaxis, oral hemorrhage, hematochezia. Thrombocytopenic 98 (140 manual). PT/PTT elevated (>4x, >3x). Did not improve with FFP. Developed seizures, inappropriate mentation. Started metronidazole and lactulose enemas for possible HE.

DAY 3: Severe tachycardia, hypoxemic, febrile – suspect aspiration pneumonia vs reaction to FFP, hypotension. Euthanized.

NECROPSY:

- Multifocal hemorrhage. Histo – severe acute periacinar and midzonal hepatic necrosis with periportal vacuolar degeneration – consistent with hepatotoxin.
- Mild, subacute neutrophilic lymphoplasmacytic cholangiohepatitis, mild biliary hyperplasia - suspect chronic

Additional ASPCA Cases: 'developed clinical signs similar to those of the previously described case'

3yo Standard poodle, 1.4-2g/kg – clinical signs 24hr post, died 2 days after ingestion

5yo Scottish terrier 7g/kg, clinical signs 24hr post, euthanized 5d post as not responding to treatment

6yo mn lab 13.9g/kg – clinical signs 24hr post, death 36hr after ingestion

7yo miniature dachshund 16g/k – clinical signs 72hrs post, recovered

4yo Aust shepherd – dose unknown (12 cupcakes) clinical disn 8hr after ingestion, euthanasia 4 days post

8yo lab 4.1g/kg, clinical sings 2hr post, lost to followup

6yo Dalmatian, 5g/kg. clinical signs hr post, recovered

Presenting signs: lethargy, vomiting, one was recumbent and non responsive

4 developed coagulopathy, one had late seizures. All cases had mild to moderate hyperbilirubinemia, elevated ALT, moderate to marked prolonged PT. Mild to moderate thrombocytopenia (6/6), marked prolongation of PTT, mild to moderate ALP elevation in 5/6.

4/7 died or euthanized. 2x necropsy - widespread hemorroghage (hemoabdomen, petechiation, ecchymoses, GI bleeding) in both. Findings consistent with hepatotoxicosis in both.

DISCUSSION:

Dogs that ingested the highest dose survived. Lowest dose died within 2 days - perhaps hepatic failure is idiosyncratic rather than dose dependant? Many of these dogs did not develop signs of hypoglycemia. Signs of acute hepatic failure occurred within 9-72hrs post ingestion.

Study of 16 beagles were fed up to 12g/kg/day of xylitol in their diet and di not develop liver lesions, but dose was gradually increased over time. They did have mild intermittent elevations in ALT suspected to be secondary to glycogen accumulation in periportal hepatocytes -> swelling -> altered membrane permeability.

No studies in other species (rabbits, mice) have shown an hepatic necrosis after oral administration of xylitol. Has been demonstrated in multiple species after IV administration.

People given IV xylitol developed nausea, abdominal pain, elevated tbili, ALT AST ALKP and LDH – normalized after 9 days

Proposed mechanisms:

1. Metabolism -> intermediates -> depletion of ATP, ADP and inorganic phosphorus reserves -> cellular necrosis
2. Metabolism -> nicotinamide adenine dinucleotide which produces ROS when metabolized in mitochondria

Doses as little as 0.15g/kg can cause hypoglycemia.

Both hyperphosphatemia and hypophosphatemia have been seen in these patients and in humans in acute hepatic failure – release of inorganic phosphate from liver during cellular necrosis, decreased uptake from the liver or concurrent renal impairment. In humans hyoperphosphatemia is associated with increased mortality, hypophosphatemia increases survival.

Recommendations:

Emesis if not hypoglycemic

Activated charcoal is suspected not to be useful

Dextrose if hypoglycemic, or if not

Monitor liver enzymes, tbili, platelet counts, and clotting times should be monitored for 48 to 72hrs or more after ingestion

Plasma/whole blood as needed, hepatic protectants (early!)

Experimental acute toxicity of xylitol in dogs

18 pekingese: Control, low dose (1g/kg), high dose (4g/kg), administered orally

FINDINGS:

- Insulin increased from 20mins, peaked at 40mins
- Glucose started decreasing at 30mins, started rising to control levels at 1.5hrs, then higher than control, back to baseline 3-4hrs after dosing. Minimum glucose levels occurred 10-20mins after peak hyperinsulinemia
- Clinical signs of weakness and depression – suspect secondary to hypoglycemia
- Dose related increase in ALT & AST (ALT 3x higher in low, 10x higher in high)
- TBili increased at 1-2hr post dosing but no increase in direct bilirubin
- Also associated with hypokalemia (3.07 at 60mins on high dose) and hypophosphatemia
- Insulin stimulates NaKaTPase so there is intracellular transfer of potassium
- NO mortality in 4g/kg dose

DISCUSSION:

- Mechanism of hyperinsulinemia unknown – suspect action of xylitol not its metabolites
- Mainly metabolized by the liver by pentose phosphate pathway -> intermediate metabolite -> glucose
- Process requires ATP. When large amounts ingested then hepatocyte ATP becomes depleted -> hepatocyte necrosis and increased ALT + AST
- No effect on biliary system – suspect increase in indirect bili was secondary to hemolysis (loss of glucose leads to erythrocyte membrane rupture)
- Increased Ca – xylitol is suspected to promote calcium absorption from small and large intestines

QUESTIONS:

3. Which of the following is NOT a common finding secondary to xylitol toxicity?

    A. Hyperkalemia

    B. Hyperphosphatemia

    C. Hypophosphatemia

    D. Increased AST activity

4. Discussed two proposed mechanisms acute hepatic failure secondary to xylitol ingestion in dogs.

5. What is the mechanism for hypokalemia secondary to xylitol ingestion in dogs?

ANSWERS:

1. hyperkalemia
2. Activation of NaKATPase -> depletion of hepatocyte ATP -> necrosis. OR production of metabolites results in release of ROS -> necrosis. OR production of metabolites uses hepatocyte ATP -> depletion -> necrosis
3. increased insulin -> increased activation of NaKATPase -> transport of K intracellularly