Toxins Affecting the Liver

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Aflatoxins

Aflatoxins are mycotoxins produced by *Aspergillus flavus, Penicillium* spp. and possibly other fungi. The most commonly affected crops are corn, peanuts, and cottonseed, but other nuts and grains can be affected. Aflatoxin metabolites bind with cellular components disrupting normal cellular processes. Signs of acute toxicity include anorexia, lethargy, vomiting, bloody diarrhea, weakness, and seizures. Liver failure, oliguria, and DIC often result in death within a few days. Aflatoxins can be measured in food, urine, vomitus, or liver. There is no specific treatment for aflatoxicosis.

Acetaminophen

Acetaminophen (Tylenol®, non-aspirin pain reliever, APAP) is a synthetic non-opiate. It is available in tablets (80-650 mg) and liquid preparations. APAP's exact mechanism of action is unknown but it is believed to block production of prostaglandins from arachidonic acid by inhibiting COX-3. Acetaminophen is rapidly and almost completely absorbed from the GI tract. Peak plasma levels are seen at 10-60 minutes (60-120 min for extended release). APAP is distributed into most body tissues with the highest concentrations in the peri-portal zone of the liver and the renal medulla. Two major conjugation pathways are used to metabolize APAP by most species (P-450 metabolism followed by glucuronidation or sulfation). Acetaminophen-induced hepatoxicity and nephrotoxicity is due to the formation of the oxidative metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). Glutathione can conjugate and neutralize NAPQI, but when glutathione stores are depleted, NAPQI binds to sulfhydryl groups on the hepatic cell membrane and damages the lipid layer. Para-aminophenol causes severe oxidative stress to RBCs leading to methemoglobinemia and Heinz body formation.

Methemoglobin values increase within 2-4 hours, followed by Heinz body formation. Clinical signs include depression, weakness, hyperventilation, icterus, vomiting, methemoglobinemia, hypothermia, facial or paw edema, death, cyanosis, dyspnea, and hepatic necrosis. Liver necrosis is less common in cats than in dogs. Clinical signs of methemoglobinemia may last 3-4 days. Hepatic injury may not resolve for several weeks.

Early decontamination is most beneficial. Activated charcoal adsorbs APAP and may be repeated, due to enterohepatic recirculation. Monitor liver values and for the presence of methemoglobinemia. ALT, AST and bilirubin may rise within 24 hours after ingestion and peak within 48 to 72 hours. Symptomatic patients need initial stabilization, including oxygen if dyspneic. Treatment involves replenishing the glutathione stores and converting methemoglobin back to hemoglobin. N-acetylcysteine (Mucomyst®, NAC) is a precursor in the synthesis of glutathione and can be oxidized to organic sulfate which provides sulfhydryl groups that bind with APAP metabolites to enhance elimination. An initial loading dose of 140 mg/kg (dilute to 5% in dextrose or sterile water) is given, followed by 70 mg/kg PO QID for 7 treatments. Continue treatment until normal. Ascorbic acid helps reduce methemoglobin back to hemoglobin. For hepatic injury, s-adenosylmethionine (SAMe, Denosyl-SD4®) at 20 mg/kg/day shows a positive effect for treatment of APAP toxicosis. Prognosis is good if the animal is treated promptly. Animals with severe signs of methemoglobinemia or with hepatic damage have poor to guarded prognosis.

Aspirin

Aspirin (acetylsalicylic acid, ASA) is the salicylate ester of acetic acid and is a weak acid derived from phenol. It is available as tablets and capsules (65, 81, 325, and 500 mg), powders, effervescent tablets and oral liquid preparations. Aspirin reduces pain and inflammation by reducing prostaglandin and thromboxane synthesis through inhibition of cyclooxygenase. At very high doses, aspirin and other salicylates uncouple oxidative phosphorylation leading to decreased ATP production. Salicylates also affect platelet aggregation. Aspirin is rapidly absorbed from the stomach and proximal small intestines in monogastrics. Aspirin is metabolized in the liver and excreted through the urine. Cats are deficient in glucuronyl transferase and have prolonged excretion due to decreased metabolism. Elimination is also slower in neonates and geriatric animals.

In dogs, single doses over 150 mg/kg should be decontaminated. Signs may include vomiting (+/- blood), hyperpnea, respiratory alkalosis, metabolic acidosis, gastric hemorrhage, central lobular liver necrosis, and bleeding diathesis. Fever and seizures may be seen due to the uncoupling of oxidative phosphorylation.

Emesis can be performed in the asymptomatic animal, unless contraindicated. Activated charcoal adsorbs aspirin and repeated doses may be used with large ingestions. Liver values, glucose, acid base status and electrolytes should be monitored. Maintain hydration and start GI protectants. Gastric protectants should be continued for 5-7 days, longer in the symptomatic patient. Alkalinization of the urine results in ion trapping of salicylate in the kidney tubule and increases its secretion. Ion trapping should only be used in cases where the acid base balance can be monitored. Assisted ventilation and supplemental oxygen may be required if the animal is comatose. Seizures should be treated with diazepam. Fluids and whole blood may be needed to control hypotension and

hemorrhage. Hyperpyrexia can be treated conservatively. Prognosis is good if the animal is treated promptly and appropriately. The development of hepatic necrosis is considered to have a poor prognosis. With hepatic damage, treatment may need to be continued for weeks.

NSAIDs
Hepatotoxicity can be seen with any NSAID and is thought to be an immune mediated reaction. Most cases are reversible with supportive care.

Ketoconazole
Ketoconazole is a broad-spectrum imidazole antifungal agent that alters the permeability of the cell membrane and inhibits intracellular enzymes of susceptible fungi. Adverse events following therapeutic doses may include hypertension, nausea and vomiting, liver toxicity, skin eruptions, and adrenal suppression. Antacids, H2 blockers and sucralfate have all been shown to reduce the absorption of ketoconazole. Activated charcoal may also be given. Discontinue the drug and support the liver.

Sago palms
Sago palms (Cycas and Macrozamia sp.) are ornamental plants found in tropical to subtropical climates, but they can also be grown as houseplants. There are three toxins in cycads: cycasin (hepatic necrosis, GI hemorrhage), B-methlamino-L-alanine (neurotoxin) and another unidentified neurotoxin. The seeds contain the highest amount of cycasin, but the entire plant is toxic. GI signs begin within a day and laboratory values (ALT, bilirubin, Alk Phos) become abnormal in 24-48 hrs. The most common signs are vomiting (+/- blood), depression, diarrhea, anorexia, and seizures. Decontamination is emesis, followed by activated charcoal. Monitor liver enzymes for 48 hours, or until levels return to normal. Blood or plasma transfusions may be necessary if coagulopathies develop. Prognosis is good if caught early, but guarded in cases where the animal is already showing signs. Mortality rate is about 30%.

Amatoxins
Amatoxins are found in some of the Amanita, Galerina and Lepiota sp. of mushrooms. These mushrooms have a wide distribution throughout the U.S.. Amanitins inhibit nuclear RNA polymerase II, interfering with DNA and RNA transcription, thus inhibiting ribosomal protein synthesis. Cells with high metabolic rates (hepatocytes, intestinal crypt cells) are most sensitive. There are three phases in amatoxicosis. A latent phase of approximately 6-24 hours is followed by a GI phase with abdominal pain, vomiting and diarrhea (lasts 2-3 days). The hepatic phase begins 36-48 hours after ingestion. Jaundice progresses to coma, coagulopathies and anuria. Many humans require liver transplantation.

Emesis and activated charcoal is recommended in witnessed exposures. Monitor serum glucose, liver and renal values, acid/base, electrolytes, PCV/TS, and coagulation parameters. Fluid diuresis has been shown to enhance amatoxin elimination via the urine and recent evidence shows that acetylcysteine is also useful (APAP treatment dosages). Penicillin G interferes with enterohepatic recirculation of amatoxins and cimetidine also improves the outcome. Silymarin (milk thistle) is used extensively in Europe, but is not available in the injectable form in the U.S.. Prognosis is guarded and hepatic injury may be permanent.

Blue green algae
Accumulation of large amounts of blue-green algae (cyanobacteria) can be found in many lakes, ponds and rivers. Macroscopically they appear as a “scum” on top of the water. Toxic blooms occur following warm, sunny weather and are seen more frequently in ponds that get runoff from heavily fertilized fields or from feed lots or pastures bearing significant numbers of animals. The most important toxin-producing genera of fresh and brackish water blue-green algae include Microcystis, Anabaena, Oscillatoria, Aphanizomenon, Nodularia, and Nostoc. The primary toxic effects of blue-green algae in animals include acute hepatotoxicoses, peracute neurotoxicoses, and gastrointestinal disturbances.

Microcystis, Oscillatoria, Nodularia, and less often Anabaena may produce hepatotoxins called microcystins. Microcystins cause disorganization of the actin filaments of the hepatic cytoskeleton, leading to cellular collapse. Clinical signs in animals include weakness, stupor, prolonged capillary refill time, pallor of mucous membranes, bloody diarrhea, and cardiovascular collapse. Clinical signs are usually observed within 12 hours after exposure. Death may occur within a few hours to a few days. Death often is preceded by coma, muscle tremors, and seizures. Death usually results from intrahepatic hemorrhage and hypovolemic shock. For recent exposures, decontamination measures such as emesis and activated charcoal may be useful. Monitor liver function for 48 hours. Treat symptomatically with fluids, anticonvulsants, and blood transfusions as needed. Many animals will die before receiving any treatment.

Copper
Copper is an essential dietary mineral in mammals. In Bedlington terriers, an autosomal recessive genetic defect is responsible for the sequestration of copper within the liver. The result is chronic-active hepatocellular necrosis, ultimately resulting in fibrosis and

macronodular regeneration. Young dogs may show episodic lethargy, anorexia, and vomiting indicative of active liver disease. Older dogs (> 6 y) may show icterus, weight loss, anorexia, vomiting/diarrhea, hepatoencephalopathy, ascites, and coagulopathy. Penicillamine, trientine (2,3,2-tetramine tetrahydrochloride) or zinc supplementation is used long term in affected Bedlington terriers to attempt to reduce hepatic copper levels.

West Highland white terriers, Skye terriers, Doberman pinschers, and keeshonds are breeds in which high hepatic copper levels have been found in both animals with normal livers and those with significant hepatic injury. It is not unknown whether the sequestration of copper is the cause of hepatic injury, or whether the copper levels are a consequence of some other disease process.

Iron

Iron is an essential mineral that is important in oxygen delivery to tissues, enzymatic processes, and oxidative metabolism within the body. Accidental overdosing of iron supplements may cause corrosive gastroenteritis and hepatic injury. Iron absorption from the gastrointestinal tract is highly regulated by the body. Iron is carried in the blood by a protein called transferrin, which conveys the iron to the liver where it is transferred to ferritin. In the liver, iron is either utilized or stored in small amounts as ferritin or as in larger amounts as hemosiderin. When the level of iron exceeds the amount of protein available to bind it, free iron causes oxidative injury to hepatocytes.

Clinical signs of acute iron toxicosis include bloody vomiting and/or diarrhea, abdominal pain, weakness, shock, collapse and death. Animals that survive may subsequently develop signs of acute hepatic failure. Dyspnea and exercise intolerance may be seen if cardiac injury is present. Elevated liver enzymes occur within 24-48 hours. A high serum iron, can aid in determining whether iron toxicosis is likely. Treatment of acute iron toxicosis entails stabilizing the animal (oxygen, blood replacement as needed) and possible chelation with desferoxamine.

Xylitol

Xylitol is a sugar alcohol. It is used in sugar-free products such as gums and candies as well as for baking. In dogs, xylitol causes rapid, dose-dependent insulin release hypoglycemia. Signs can include vomiting, weakness, ataxia, depression, hypokalemia, seizures, and coma. Some dogs have developed liver failure following ingestion of xylitol although the mechanism has not been established. Hyperphosphatemia is associated with a poor prognosis.

Treatment of xylitol ingestion by dogs should include emesis if asymptomatic. Dogs can show signs of hypoglycemia in as few as 30 minutes or it may be delayed for several hours. Activated charcoal is not efficacious for decontamination. If clinical signs of hypoglycemia develop, dextrose should be given (bolus +/- CRI). Hypokalemia, likely secondary to insulin-induced movement of potassium into cells, should be treated if significant. Treatment should continue until blood glucose normalizes.

References available upon request