

Liver Toxins

(Hepatotoxins)

Basics

OVERVIEW

- A “toxin” is a poisonous substance; “hepato-” refers to the liver
- Liver toxins are substances (such as drugs or toxins) that cause liver injury or damage
- Direct liver toxin—cause predictable injury to liver cells and the liver
- Individual pet may be more likely to develop ill effects to a particular medication than other pets and the reaction is unexpected (known as “idiosyncratic reactions”)—unpredictable injury unrelated to amount of medication
- The liver is the largest gland in the body; it has many functions, including production of bile (a fluid substance involved in digestion of fats); production of albumin (a protein in the plasma of the blood); and detoxification of drugs and other chemicals (such as ammonia) in the body
- Whether the pet has had a prior exposure to the liver toxin, is currently exposed (such as being treated with a medication that can cause liver injury or damage), or has a new exposure does not eliminate the drug or toxin as a cause of liver toxicity



GENETICS

- Some breeds of dogs may be susceptible to certain drug-associated liver toxicities

SIGNALMENT/DESCRIPTION OF PET

Species

- Dogs
- Cats
- Dogs may be more susceptible to certain liver toxins (such as acetaminophen and aflatoxins) than other mammals
- Cats have higher risk than dogs to some liver toxins due to reduced enzyme systems to detoxify some agents (such as acetaminophen, aflatoxins)

Breed Predispositions

- Some dog breeds have high risk for selected drug toxicities—examples include Doberman pinschers, Dalmatians, Samoyeds: trimethoprim-sulfa (an antibiotic) in Doberman pinschers: oxibendazole (medication used to kill intestinal parasites) in Labrador retrievers: possibly nonsteroidal anti-inflammatory drugs (NSAIDs); cocker spaniels and German shepherd dogs: phenobarbital; herding breeds: related to multidrug resistance gene *MDR1*, includes various drugs
- Siamese cats—some families or lines have high risk

Mean Age and Range

- Any age
- Young pets (less than 16 weeks of age)—immature liver and less ability to detoxify drugs and other chemicals; more likely to eat substances that are potentially toxic

SIGNS/OBSERVED CHANGES IN THE PET

- Signs may reflect long-term (chronic) exposure or single, sudden (acute) exposure to a liver toxin
- Signs variable, ranging from simple general signs of discomfort and “not feeling well” (known as “malaise”) to near death (known as the “moribund state”)
- Gastrointestinal signs: lack of appetite (known as “anorexia”) or reduced appetite (known as “hyporexia”), vomiting, diarrhea
- Yellowish discoloration to the gums and other tissues of the body (known as “jaundice” or “icterus”)
- Variable body temperature, from below normal temperature (known as “hypothermia”) to above normal temperature (known as “hyperthermia” or “fever”)
- Weakness
- Fluid buildup in the abdomen (known as “ascites”)—rare (grave sign)
- Brain disorder caused by accumulation of ammonia in the system due to inability of the liver to rid the body of ammonia (known as “hepatic encephalopathy”) or coma
- Blood-clotting disorder (known as “disseminated intravascular coagulopathy” or DIC) secondary to the death of liver tissue (known as “liver necrosis”)—bleeding; small, pinpoint areas of bleeding (known as “petechia”); bruises or purplish patches under the skin, due to bleeding (known as “ecchymoses”)

CAUSES

- Many substances (such as drugs or toxins) may cause liver toxicity, including some drugs that are used routinely in the treatment of dogs and cats. Examples include the following:
- Commonly reported drugs
 - ♦ Acetaminophen (pain reliever and fever reducer)—dogs and cats (note: acetaminophen should never be administered to cats as it is extremely toxic; if a cat accidentally ingests acetaminophen, seek immediate veterinary care)
 - ♦ Azole antifungals—dogs and cats
 - ♦ Amiodarone
 - ♦ Amoxicillin (an antibiotic)
 - ♦ Azathioprine (a chemotherapeutic drug, frequently used to decrease the immune response)
 - ♦ Nonsteroidal anti-inflammatory drugs (NSAIDs)—dogs
 - ♦ CCNU—dogs
 - ♦ Cyclosporine (used to decrease the immune response)
 - ♦ Diazepam (used to decrease anxiety, to control seizures, and as an appetite stimulant)—cats
 - ♦ Doxycycline—cats and dogs
 - ♦ Steroids—dogs
 - ♦ Griseofulvin (used to treat ringworm [known as “dermatophytosis”])—cats
 - ♦ Mebendazole, oxbendazole—dogs
 - ♦ Methimazole (used in the treatment of increased levels of thyroid hormone [known as “hyperthyroidism”])—cats
 - ♦ Mitotane (Lysodren®, op'-DDD; used in the treatment of increased levels of steroids produced by the adrenal glands [known as “hyperadrenocorticism” or “Cushing's syndrome”])—dogs
 - ♦ Medications to control seizures, such as phenytoin, primidone, and phenobarbital—dogs
 - ♦ Medication to improve appetite and weight gain (stanozolol)—cats
 - ♦ Sulfa antibiotics—dogs (including trimethoprim-sulfadiazine)
 - ♦ Tetracycline (an antibiotic)—cats and dogs
 - ♦ Thiacetarsamide (medication to kill adult heartworms)—dogs and cats (no longer available in the United States)
- Common environmental toxins
 - ♦ *Amanita* mushrooms
 - ♦ Aflatoxins/mycotoxins
 - ♦ Blue-green algae (Cyanobacteria)
 - ♦ Chlorinated compounds

- ◆ Cycad (sago palm nuts), cottonseed (gossypol)
- ◆ Heavy metals (such as lead, zinc, copper, Mn, Ar, Fe)
- ◆ Phenolic chemicals (especially cats)
- Bacterial toxins (known as “endotoxins”)
 - ◆ Intestinal bacteria—*Clostridium perfringens*; *Clostridium difficile*; gram-negative bacteria
 - ◆ Food poisoning—*Staphylococcus*; *E. coli*; *Salmonella*
- Nutritional/herbal products (products linked to liver toxicity in people and animals)
 - ◆ *Atractylis gummifera*
 - ◆ Black cohosh
 - ◆ *Callilepis laureola*
 - ◆ Chaparral
 - ◆ Comfrey extracts (pyrrolizidine alkaloids)
 - ◆ Chinese herbal medicines (certain ingredients, particular one difficult to identify)
 - ◆ Germander
 - ◆ Greater celandine
 - ◆ Green tea extract (not all products)
 - ◆ Lipoic acid—cats, glucosamine-based joint supplements (dogs)
 - ◆ Kava Kava—dogs
 - ◆ Licorice
 - ◆ Mistletoe
 - ◆ Pennyroyal
 - ◆ Senna
 - ◆ Usnic acid
 - ◆ Valerian
 - ◆ Xylitol (sugar substitute found in many products, such as candy and chewing gum)—dogs

RISK FACTORS

- Medications influencing liver function (current or prior)
- Previous liver disease (such as copper storage disease)
- Susceptibility and severity influenced by age, species, nutritional status, concurrent drug administration, hereditary factors

Treatment

HEALTH CARE

- Inpatient—critical care setting
- Prevention or correction of shock is essential
- Fluid therapy—maintain liver blood flow, improve oxygen delivery and waste removal
- Colloid administration—colloids are fluids that contain larger molecules that stay within the circulating blood to help maintain circulating blood volume; plasma initially preferred for delivery of clotting substances
- Bleeding tendencies—the veterinarian will provide vitamin K₁; fresh whole blood or fresh frozen plasma as needed (stored blood products may deliver high ammonia concentrations causing hepatic encephalopathy [brain disorder caused by accumulation of ammonia in the system due to inability of the liver to rid the body of ammonia])
- Nasal oxygen—if the pet has low blood pressure (known as “hypotension”) or fluid buildup in the lungs (known as “pulmonary edema”); may improve oxygen delivery to liver tissue
- Monitor urine output—initiate medications to remove excess fluids from the body (known as “diuretics”), as necessary
- Treat low blood sugar (hypoglycemia), if present—administer dextrose to maintain normal blood glucose levels

ACTIVITY

- Quiet and rest

DIET

- Protein—normal, unless overt hepatic encephalopathy (brain disorder caused by accumulation of ammonia in the system due to inability of the liver to rid the body of ammonia)
- Nutrition via the gastrointestinal tract (as with a nasoesophageal feeding tube) if not eating after more than 2 days—small volume, frequent meals to optimize digestion and absorption of nutrients and to minimize formation of intestinal toxins that may contribute to hepatic encephalopathy (brain disorder caused by accumulation of ammonia in the system due to inability of the liver to rid the body of ammonia)
- Nutrition through intravenous route (known as “parenteral nutrition”)—may be used as a partial means of providing nutrition (recommended for short-term lack of appetite) to minimize breakdown of muscle (catabolism) or as a total means of providing nutrition (known as “total parenteral nutrition” or TPN), which is recommended if the pet has lack of appetite of more than 5 days and providing nutrition via the gastrointestinal tract is not possible

Medications

Medications presented in this section are intended to provide general information about possible treatment. The treatment for a particular condition may evolve as medical advances are made; therefore, the medications should not be considered as all inclusive

- Fluid therapy with judicious supplementation of potassium
- Short-acting steroids—for endotoxic shock (steroid such as prednisolone sodium succinate) may or may not be elected by the veterinarian; controversial
- Antibiotics—ampicillin, metronidazole—to protect against infections derived from migration of intestinal bacteria into the body
- Antioxidant therapy—crisis intervention: *N*-acetylcysteine for sudden (acute) or very sudden, very severe (known as “fulminant”) death of liver tissue (hepatic necrosis); when the pet can accept oral medications and condition stabilizes will change to *S*-adenosylmethionine (SAME), which is a liver protectant against various hepatotoxins; vitamin E (d-alpha-tocopherol acetate)
- B-complex vitamins—necessary co-factors for liver metabolism
- Vitamin K₁—necessary for blood clotting
- Silibinin (milk thistle extract silybin is active component); may improve liver regeneration; provides a variety of effects, such as antioxidant and liver protection
- Ursodeoxycholic acid—for long-term (chronic) liver disease (known as “hepatopathy”)
- Provide taurine supplementation to cats, especially in cats that are not eating; taurine is an amino acid (protein) that is an important component of the diet of cats; cats cannot produce enough taurine in their bodies and so, must obtain taurine from their food to maintain the health of several organs, including the heart and retina (back of the eye)

Follow-Up Care

PATIENT MONITORING

- Prevent low body temperature (hypothermia)
- Monitor bloodwork (such as blood glucose, electrolytes, and packed cell volume [PCV, a means of measuring the percentage volume of red-blood cells as compared to the fluid volume of blood])—monitor frequently; fluctuations may occur rapidly
- Complete blood count (CBC), serum biochemical analysis, blood-clotting test(s)—typically repeated every 48 hours, as warranted
- Monitor urine output

PREVENTIONS AND AVOIDANCE

- Close scrutiny of environment and future medications

POSSIBLE COMPLICATIONS

- Blood-clotting disorder (disseminated intravascular coagulopathy)
- Bleeding

- Brain disorder caused by accumulation of ammonia in the system due to inability of the liver to rid the body of ammonia (hepatic encephalopathy)
- Progressive liver failure
- Damage and scarring of the liver (known as “cirrhosis”) with ascites (fluid in the abdomen)

EXPECTED COURSE AND PROGNOSIS

- Three to five days of treatment and observation are needed to estimate prognosis
- Progressive worsening of status: vomiting that does not respond to treatment and vomiting of blood (known as “hematemesis”), intolerance to supportive treatments, production of only small amounts of urine (known as “oliguria”), blood-clotting disorder (disseminated intravascular coagulopathy), and the brain disorder caused by accumulation of ammonia in the system due to inability of the liver to rid the body of ammonia (hepatic encephalopathy)—negative prognostic indicators
- Damage and scarring of the liver (cirrhosis)—possible in 3–6 months

Key Points

- Potential for the need for 3–10 days in intensive care (ICU)
- Many pets recover completely
- Damage and scarring of the liver (cirrhosis) develops in some pets after widespread liver injury; some pets develop long-term (chronic) inflammation of the liver (known as “chronic hepatitis”)