Essential Strategies for Treating Hepatic Disease in Dogs and Cats

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The use of "hepatoprotectants" in canine and feline liver disease

Nutraceuticals and other hepatoprotectants are often used in the management of dogs and cats with liver disease. Unfortunately there are very few clinical trials in dogs and cats that assess their efficacy. This can make it difficult for clinicians to know when their use is justified. By understanding how these agents work it is easier to make rational treatment decisions.

Because of its role in metabolism the liver is very susceptible to oxidative damage. Oxidative damage is important in the pathogenesis of a range of hepatic diseases. Reduced hepatic concentrations of the antioxidant glutathione have been found in dogs and cats with variety of severe hepatic diseases. S-adenosyl methionine (SAMe) is a precursor of glutathione. The main rationale for using this agent is that it helps prevent oxidative damage by preventing depletion of hepatic glutathione. It has also been purported that SAMe may have anti-inflammatory properties, modulate apoptosis, and be anticarcinogenic. However, these effects have not been documented in dogs or cats. At the recommended dose of 20 mg/kg PO q12 hours SAMe has rarely been reported to have side effects in dogs or cats other than occasional vomiting and decreased appetite after dosing. Potential indications for SAMe include liver disease where there is oxidative stress i.e. necroinflammatory, cholestatic, and metabolic liver disease. However, it is important to note that there currently is little evidence that SAMe is efficacious in dogs and cats. Oral administration of SAMe has been shown to increase hepatic glutathione concentrations when given to healthy dogs and cats and to reduce oxidative stress but not histological changes consistent with vacuolar hepatopathy in dogs receiving prednisone.

Silymarin is extracted from the milk thistle plant. Silibinin is the most biologically active component of silymarin. Silymarin is believed to have antioxidant effects by scavenging free radicals and reducing lipid peroxidation. It is also believed to have anti-inflammatory and antifibrotic properties. Additionally, silymarin may be a choleretic agent. At commonly used doses silymarin does not appear to cause side effects although its bioavailability is low. Potential indications for silymarin include necroinflammmtory, cholestatic, and metabolic liver disease of dogs and cats. Again there is very limited evidence to support its efficacy in the veterinary literature. In one study of Beagles administered Amanita phalloides toxin, 11 dogs treated with intravenous silibinin survived whereas four out of twelve control dogs died. Although, statistical analysis was not reported in this manuscript, this difference was not statistically significant, possibly due the small number of dogs enrolled. Additionally the dogs treated with silibinin had smaller increases in serum liver enzyme activities, bilirubin, and prothrombin time than those that were not, again statistical analysis was not reported. Another study did not find strong evidence that silymarin has a protective effect after carbon tetrachloride ingestion in dogs. In a study of dogs being treated with the chemotherapy agent CCNU, dogs treat with a product containing silymarin, SAMe, and phosphatidylcholine (Denamarin) were shown to have smaller increases in serum ALT and ALP activities than those that were not, suggesting a hepatoprotective effect.

Ursodeoxycholic acid (UCDA) was found to be the active compound in the traditional Chinese remedy of dried black bear bile. Ursodeoxycholic acid is a hydrophilic bile acid that is believed to have multiple beneficial properties including: choloretic effects, displacement of other more toxic bile acids from the circulating pool, an anti-apoptotic effect, and immunomodulatory effects. When used at a dose of 15 mg/kg/day PO this drug has few side effects other than causing occasional diarrhea. Because of its choleretic effect and the displacement of more toxic hydrophobic bile acids it makes sense to use this drug in dogs and cats with cholestasis. This drug is often used in cats with cholangitis. The use of UCDA in dogs and cats with complete bile duct obstruction is controversial as some clinicians are concerned about the possibility of gall bladder rupture. Other clinicians feel comfortable using UCDA in this situation and studies in rats where bile duct ligation has been performed indicate that it has a beneficial effect. Additionally, UCDA is sometimes used in the medical management of canine gall bladder mucoceles. Due to its claimed immunomodulatory and anti-apoptotic there is a theoretical reason to use UCDA in dogs with chronic hepatitis. However, evidence supporting the use of UCDA in dogs is limited to case reports and to the author's knowledge there have been no clinical studies in cats.

Vitamin E is actually a family of eight lipid soluble vitamins. The main role of vitamin E is is as an antioxidant, protecting phospholipids from oxidative injury by scavenging free radicals. Generally vitamin E is well tolerated and side effects are not observed. Because of these properties consider using this supplement in dogs and cats with liver diseases that can lead to oxidative damage, such as, cholestatic disease, feline hepatic lipidosis, copper associated chronic hepatitis, and certain hepatotoxins. However, it is important there is no clinical evidence supporting the efficacy of vitamin E in dogs or cats with hepatobiliary disease.

Treatment of hepatic encephalopathy

Supportive care is very important when treating dogs and cats with hepatic encephalopathy (HE). It is important to identify and manage factors that potentially precipitate HE such as, gastrointestinal bleeding, infection, dehydration, dehydration, electrolyte abnormalities, and alkalosis. Patients who have had or are having seizures should be treated with anticonvulsant drugs.

Benzodiazepines should be avoided as they are thought to precipitate HE in humans. Phenobarbital has been used to control seizures in dogs and cats with HE but the liver metabolizes this drug. Levetiracetam (20 mg/kg PO q8 hours) acts rapidly and has few side effects. Fluid therapy may also be required in some patients. When raised intracranial pressure is suspected, mannitol should be administered (0.5−1 g/kg IV).

Severe protein restriction is no longer recommended for dogs with hepatic encephalopathy (HE) as this can lead to protein malnutrition. It is important to also note that dogs with liver disease that do not have signs of HE likely do not benefit from dietary protein restriction. Diets formulated for dogs with liver disease are moderately protein-restricted and often have other characteristics such as reduced copper and sodium contents, and are supplemented with zinc and antioxidants. Non-meat protein based diets are often recommended for dogs with HE. Once the signs of HE are controlled with a commercial hepatic support diet, it is recommended to add non-meat protein to the patient's diet to help prevent protein malnutrition. Severe protein restriction is inappropriate for cats. Commercial hepatic support diets with moderate levels of high quality protein have been recommended for cats with HE due to congenital portosystemic shunts. Cats with feline hepatic lipidosis (FHL) should be fed a high quality protein diet that contains adequate arginine and taurine.

Lactulose is commonly used to treat HE in dogs and cats. Lactulose can be given orally to patients with chronic HE. It is usually started at a dose of 1−3 mL per 10 kg of body weight every 6−8 hours for dogs and cats. The dose is then adjusted until the patient passes three to four soft stools per day. In patients that are stuporous or comatosed, lactulose can be given per rectum after a cleansing warm water enema. Neomycin is a poorly absorbed aminoglycoside antibiotic that is sometimes used to treat HE in dogs and cats. The gastrointestinal absorption of neomycin is very low, but can be increased in patients with decreased gastrointestinal motility or bowel wall damage. Substantial systemic absorption can cause ototoxicity and nephrotoxicity. In humans, neomycin is no longer used in the treatment of HE for these reasons. Metronidazole is another antimicrobial that is sometimes used for the treatment of HE in dogs and cats. Metronidazole is usually given at a dose of 7.5 mg/kg PO q8−12 hours in dogs and cats with HE. Metronidazole is hepatically metabolized and can have neurological side effects that mimic those of HE. However, these are more likely to occur at the higher dosages used for other purposes.

Treatment of canine chronic hepatitis

Although the hepatoprotectant agents described above are often used and may be beneficial in treating used in dogs with chronic hepatitis they are not a substitute for treating the underlying causes of the liver disease when this is possible and hepatic biopsy is required to diagnose chronic hepatitis.

Hepatic accumulation of copper can lead to hepatocellular injury due to oxidative stress and therefore chronic hepatitis in dogs. Sometimes copper accumulates in the liver secondary to cholestasis, in which case its distribution tends to be periportal. Even when copper accumulation occurs secondary to cholestasis it can potentially contribute to hepatocelullar injury. Copper accumulation can also be the primary cause of chronic hepatitis in which cause it tends to be centrolobular in distribution. A genetic defect of the COMMD1 gene has been identified as the cause of copper associated chronic hepatitis in Bedlington Terriers. Other breeds such as Dalmatians, Skye Terriers, West Highland White Terriers, and Labradors may also be at increased risk. Hepatic copper concentrations between 120−400 ppm are considered normal and concentrations >1,500 ppm are considered diagnostic for hepatic copper retention. However, I consider treating dogs with concentrations >1,000 ppm with copper chelating agents, especially when there is centrolobular copper accumulation or when there is necrosis associated with copper containing macrophages. The dogs should also be started on a copper restricted diet such as one of the commercial liver support diet. D-penicillamine is my first choice of chelating agent for dogs (10−15 mg/kg q12 hours before feeding). This drug may cause side effects such as vomiting. The exact time for which chelation should occur is not known as prolonged therapy can result in copper deficiency. Monitoring the dog's clinical signs and liver enzymes can provide some indirect information regarding the efficacy of treatment. A study in Labradors suggested that 6−10 months of chelation is adequate. Ideally at this point hepatic biopsy and copper quantification is performed. Trientine (10−15 mg/kg q12 hours) may be used is penicillamine is not tolerated. At this point, if hepatic copper concentrations, when measured, have returned to normal, treatment, with zinc acetate at a dose of 5−10 mg/kg of bodyweight is initiated. The dog should be continued on a copper restricted diet. A copper causes oxidative damage antioxidants such as SAMe and possibly vitamin E may also be beneficial.

There is limited information supporting the use of the anti-inflammatory drugs in the treatment of chronic hepatitis. One study of dogs with chronic liver disease showed prednisone had a positive effect on survival and another more recent retrospective study showed that prednisolone reduced hepatic inflammation, hepatic fibrosis, and abnormalities of coagulation in a subset of dogs with chronic idiopathic hepatitis. Where there is histological evidence suggesting a major component of inflammation the use of anti-inflammatory drugs such a prednisolone should be considered. Typically a dose of 1−2 mg/kg day is started initially and is then gradually tapered. It should be noted that high dosages of prednisolone/prednisone often cause vacuolar hepatopathy, which can be detrimental to these dogs. Other anti-inflammatory drugs that are sometime in place of prednisolone include azathioprine (2 mg/kg q48 hours) and cyclosporine (5−10 mg/kg/day).

Supportive care is also important for these dogs. Dogs with hepatic disease, especially those with portal hypertension are at increased risk of gastroduodenal ulceration. Consequently, treatment with omeprazole (1 mg/kg q12-24 hours) should be considered. The development of ascites in dogs with chronic hepatitis is a poor prognostic indicator. Furosemide can lead to hypokalemia and metabolic acidosis both of which can precipitate HE in humans. The aldosterone receptor antagonist spironolactone (2−4 mg/kg q12hours) is a better choice. If this is ineffective furosemide can be added started at a low dose (1 mg/kg PO q12 hours).

Treatment of feline hepatic lipidosis

Most cats with FHL have some kind of underlying disease such a pancreatitis, inflammatory bowel disease, diabetes, or upper respiratory tract infections. In order to optimize the patient's treatment it is essential to identify and if possible manage these concurrent disorders. Cats with feline hepatic lipidosis should initially be stabilized before feeding can be started and fluid therapy often plays a big part of this. Balanced electrolyte solutions are a good choice. Some clinicians avoid using lactate-containing fluids because they are concerned that the hepatic metabolism of lactate is compromised in these cats. I use lactated Ringer's solution in patients with hepatic disease without apparent adverse effects. Hypokalemia is common and can causes severe muscle weakness. Therefore, intravenous fluids should be supplemented with potassium chloride as needed. Hypophosphatemia is also common, especially when the cats are initially fed. Therefore, supplementation with potassium phosphate is often required. Occasionally intravenous supplementation of magnesium is needed. Cats with FHL have intrahepatic cholestasis and so may be vitamin K deficient. Treatment with vitamin K (0.5−1.5 mg/kg subcutaneously every 12 hours for 3 doses) is recommended. This is important to start before invasive procedures such as hepatic biopsy or esophageal feeding tube placement are performed. Cats with FHL are often nauseous so antiemetics are indicated. Ondansetron (0.2 mg/kg IV q8−12 hours) and maropitant (1 mg/kg SQ q24 hours) are my preferences. Mirtazipine (3.75 mg per cat PO q72 hours) is an appetite stimulant that is sometimes used in cats. This drug is not a substitute for placing a feeding tube in most cats. Cyproheptadine (1−4 mg per cat q12−24 hours) is also an option but diazepam should be avoided as it can lead to acute hepatic injury in some cats. Oxidative injury is part of the pathogenesis of FHL and so antioxidant drugs are indicated. Initially, N-acetylcysteine (an initial dose of 140 mg/kg IV, followed by subsequent doses of 70 mg/kg IV q6−8 hours) is used as it can be given IV to anorexic cats. When oral medications can be given, the cat should be switched to an oral SAMe supplement. Some clinicians also treat with vitamin E. L-carnitine has been shown to increase the beta-oxidation of fatty acids in cats during weight loss. Therefore, it is reasonable to supplement cats suffering from FHL with L-carnitine (250 mg per cat PO q24 hours). Cobalamin deficiency is not uncommon and cats with serum cobalamin concentrations <400 ng/L should be supplemented with cyanocobalamin (250 μg SQ q7 days for 6 weeks the once monthly).

It is essential to ensure the adequate nutritional for cats with feline hepatic lipidosis. As previously mentioned these cats should be fed a high quality protein diet that contains adequate arginine and taurine. Of the macronutrients, protein is the most important in resolving FHL. Once the cat has been stabilized, unless it is eating an adequate caloric intake voluntarily, a feeding tube should be placed. If the cat is not stable enough for anesthesia a nasoesophageal feeding tube can be placed. However, these tubes necessitate feeding a liquid diet. Commercial liquid recovery diets that are suitable to feed cats with FHL are available. My preference is to briefly anesthetize the cat and place an esophageal feeding tube. I prefer esophageal tubes to gastrostomy tubes as they can be removed as soon as the cat is eating well and have a reduced rate of serious complications. Commercial canned recovery diets contain adequate protein and can be fed via esophageal/gastric feeding tubes as they can be liquidized and have an adequate calorie density. In order to avoid refeeding syndrome and because these patients cannot tolerate large volumes of food in their stomach, it is important to feed small amounts of food initially. The cat's resting energy requirement should be estimated using the formula: RER (kilacalories) = 70 × lean body weight (kg) $^{0.75}$. Typically 25% of resting energy requirement is fed on the first day then if tolerated this amount is increased by 25% of RER each day. The food should be divided into 4−6 meals and these should be fed slowly over 10−20 minutes or given as a continuous rate infusion. If feeding are not tolerated the meal size/rate of infusion should be decreased.