

CHRONIC HEPATIC DISEASE OF DOGS – COMMON AND CUREABLE IF YOU DIAGNOSE IT IN TIME

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Chronic Inflammatory/Necrotic Diseases

Adverse drug reactions may cause mild to fatal hepatic disease. They can be due to almost any drug (e.g., cimetidine, amoxicillin, clindamycin, etc, etc, etc); however, some drugs are clearly more likely to cause hepatic disease than others. Whenever there is any doubt as to whether a particular drug might be responsible for hepatic disease in a patient, stop administering it and observe the results. Again, as for cats, the healthier the patient is, the more inclined we are to wait and see what happens after stopping the drugs. The sicker the patient is, the quicker we are to biopsy, just in case there is something more significant that we need to eliminate now.

Doxycycline occasionally causes increased ALT and even icterus. Although this is not a commonly recognized problem, we use so much doxycycline for suspected rickettsial diseases that it is very important to recognize the possibility. I have seen a few dogs that appeared to have substantial hepatic side effects (including icterus) from doxycycline administration.

Sulfa drugs are famous for causing severe hepatic disease (as well as bone marrow, cutaneous, joint, ocular and renal problems). Furthermore, the hepatic disease caused by sulfa drugs may not occur for 1-2 weeks after starting the drug, even if the patient has not received the drug for over a week. The hepatic lesions caused by sulfa drugs can look a lot like idiopathic chronic hepatitis. Doberman pincers and Rottweilers appear to be especially sensitive to sulfa drugs.

Carprofen (i.e., Rimadyl) causes hepatotoxicity in dogs, especially Labrador retrievers. The histologic changes seen in carprofen hepatotoxicity can resemble chronic hepatitis, so be sure that you have an adequate history. Also, be aware that hepatotoxicity may not be seen until 1-2 weeks after starting a drug; in fact, the patient may have stopped taking the medication several days before clinical signs of toxicity occur.

Lomustine is a chemotherapeutic used as rescue therapy when treating lymphoma. It will reliably cause severe hepatic disease if used inappropriately.

Amiodarone is an anti-arrhythmic drug that can cause substantial hepatotoxicity, and patients receiving this drug should be monitored closely. Some breeds appear to be excessively prone to adverse effects from specific drugs.

Itraconazole can cause icterus, but the signs usually regress quickly after withdrawing the drug.

Anticonvulsants (i.e., phenobarbital and Primidone) are famous for causing severe hepatic disease, eventually resulting in cirrhosis. This is why it is so important to perform therapeutic blood monitoring and measure the serum phenobarbital levels in patients receiving these drugs.

Azathioprine can cause severe, acute hepatocellular necrosis in some patients. This may be due to different rates of metabolism of the drug in different patients. I have not seen this problem when the patient was receiving azathioprine on an every-other-day basis as opposed to receiving it daily.

Acetaminophen is toxic and fatal when overdosed. You need to be very careful if you decide to use this drug in a dog.

Vacuolar hepatopathy (hydropic change) is probably the most common histologic change seen in hepatic biopsy of canine livers. In general, this lesion seldom causes any clinical signs. I did not say it never caused clinical disease; rather, it very seldom causes clinical disease itself. There are some suggestions that severe change is sometimes responsible for hepatic failure. Vacuolar hepatopathy is best known for being associated with steroids. Both exogenous or endogenous steroids can be involved. Furthermore, it appears that vacuolar hepatopathy can be due to hyperadrenocorticism or to dogs with excessive steroid release associated with significant illnesses (e.g., tumors, infections). Classically, these dogs have a high SAP with a relatively minor (or no) increase in ALT. The GGT may be increased.

Chronic hepatitis is probably one of the main reasons it is a good idea to biopsy dogs' livers. It is a reasonably common disease, and a lot can often be done for the dog if you diagnose it before the hepatitis causes cirrhosis. Chronic hepatitis can be found in almost any breed of dog, although Doberman pinchers (especially young to middle-aged females) seem to have a very high incidence of the disease. There are several clinical presentations of this disease. First, one may see a chronically ill dog with high ALT and SAP. Second, one may be presented with a dog that was normal until it was stressed (e.g., underwent surgery or anesthesia). Third, one may see a dog that was normal until a few days ago but that now suddenly presents with signs of hepatic failure and is found to have an absolutely end stage cirrhotic liver (see discussion under cirrhosis) even though the clinical signs have only been present for 1-3 days. Finally, one may see a clinically normal dog that has an increased ALT that was fortuitously found during routine health screening or during a preanesthetic work up for a dental. The ALT typically remains increased despite the dog acting and appearing fine. Chronic hepatitis is more common than many people realize and is one reason why it is better to biopsy clinically normal dogs with persistent increases in ALT rather than wait until clinical signs occur.

Treatment of chronic hepatitis usually centers around a) removing the cause, if possible, b) administration of anti-inflammatory therapy (i.e., steroids, azathioprine), and c) administration of supportive therapy (i.e., ursodeoxycholic acid and anti-oxidants). Two causes of chronic hepatitis that you might be able to remove are drugs and copper. Copper is a bit confusing in that it can be the cause of chronic hepatitis, it can be secondary to chronic hepatitis but not causing a clinical problem, and we think that it can sometimes be secondary to chronic hepatitis and yet be severe enough to cause disease in and of itself. There has been one report that seemed to show that removing copper from the liver of dogs with chronic hepatitis in which the copper accumulation clearly appeared to be secondary to the hepatic disease was clinically beneficial to the dogs. You can measure copper levels in biopsies, or you can do special stains on hepatic biopsies. If you are in doubt as to how significant the hepatocellular copper is, it is probably best to just remove it. If the decision is made to remove copper, then one may elect oral zinc therapy before meals or copper chelation with D-Penicillamine. Feeding a copper restricted diet is

reasonable; but, feeding a copper restricted diet by itself often will not lower hepatic copper concentrations sufficiently. D-Penicillamine (10-15 mg/kg bid) is the drug typically used to lower hepatic copper concentrations. This drug occasionally causes vomiting, and administering it with food seems to lessen that problem. Trientine is another copper chelator (Cuprimine) that is also effective (10-15 mg/kg bid) and seems to have fewer side effects than d-penicillamine. If the dog is clearly being intoxicated by very large concentrations of hepatic copper, chelators should be used.

Zinc can be used to prevent copper accumulation, but it can also act as an antifibrotic agent. Various forms can be given, but the idea is to administer approximately 100 mg of elemental zinc daily for 3-6 months and then decrease it to about 50 mg daily. Zinc should be administered on an empty stomach, and generally should not be given with copper chelators. Be aware that zinc administration can rarely cause hemolytic anemia, and periodic blood zinc measurements are not a bad idea in patients receiving zinc therapy.

Dogs with chronic hepatitis not due to copper accumulation or drugs often need anti-inflammatories, and this usually includes glucocorticoids. However, it seems important to use the lowest effective dose of the corticosteroid. If you give too much corticosteroid to a dog with steroid-resistant hepatic disease, you may create a vacuolar hepatopathy in addition to the preexisting hepatic disease. When corticosteroids are used for this disorder, they should typically be used at an anti-inflammatory dose (1 mg prednisolone/kg/day) and then tapered quickly. The steroid treatment should be for relatively short periods of time (i.e., until a week or two after clinical signs substantially diminish or disappear). Severely affected patients and patients that require excessive amounts of corticosteroids may benefit from azathioprine or cyclosporine therapy. Azathioprine may cause severe hepatic disease, but this appears to be an idiosyncratic reaction, possibly due to differences in the rate of metabolism of the drug in different dogs. I do not hesitate to use azathioprine when it seems like it may be helpful. Indications seem to be when steroids are insufficient to control signs, when excessive doses of steroids are required to control signs but cause substantial side effects, and when very severe hepatic disease is found on the initial biopsy. While 1 mg/lb daily is a commonly quoted dose, I typically give azathioprine at the same dose but only every other day, which seems to be much safer.

Patients with hepatic disease may also benefit from supportive therapy, especially those drugs and neuroceuticals that are antioxidants. Antioxidants (i.e., s-adenosyl-L-methionine, silymarin, phosphatidylcholine, N-acetylcystine) and ursodeoxycholic acid are what should be called “hepatosupportive” therapy. These drugs will generally not cure severe disease all by themselves, but they can substantially help the patient if appropriate therapy is being directed at the primary cause. In general, antioxidants are poorly effective if used as single drugs. Rather, antioxidant therapy is best accomplished if multiple drugs are used simultaneously.

S-adenosyl-L-methionine (20 mg/kg sid) is a neuroceutical that appears to have benefit in some patients with hepatic disease. It increases hepatic glutathione concentrations as well as enabling a variety of important, intermediary metabolism reactions. The drug appears to have no adverse effects, and there is good evidence that it helps protect against alcoholic hepatitis in people. It should be given on an empty stomach, and the patient should not be feed for 30 minutes. It

comes in foil-wrapped, enteric coated tablets. Milk thistle (silymarin) (4-8 mg/kg/day OR 50-250 mg/day) is a herbal treatment that has proven efficacy in some diseases (e.g. Amanita mushroom poisoning). There are different active fractions, and silybin seems to be the most active. There is one preparation in which silymarin is complexed with phosphatidylcholine complex (i.e., Marin by Nutramax) which seems to have increased uptake and bioavailability. N-acetylcysteine can be obtained from the health food store. It is an anti-oxidant, and has been given to dogs and cats at a dose of 70 mg/kg tid. It seems to be safe, but should be given on an empty stomach. It seems that s-adenosyl-L-methionine is probably effective in promoting intracellular glutathione concentrations. It is important to note that administering glutathione orally is ineffective; the orally administered drug will not increase intracellular glutathione concentrations. Ursodeoxycholic acid (15 mg/kg/day) is beneficial because of its ability to displace more toxic hydrophobic bile acids from the hepatocyte membrane. Like the antioxidants, it generally should not be used as sole supportive therapy. It seems to work best if combined with anti-oxidants.

Copper storage is reported in Bedlington terriers, where it commonly causes chronic hepatitis that progresses to cirrhosis. West Highland White terriers often have excessive hepatic copper accumulation, but it is different than what is found in Bedlington terriers and seldom causes clinically significant hepatic disease. Dalmatians, Labrador retrievers and Skye terriers have recently been reported to have a copper-associated hepatic disease in which accumulation of copper by the liver may be the cause of the clinical disease. Recently, there is increased concern that many dog foods have increased amounts copper that is more bioavailable than before, making it easier for some breeds (e.g., Labrador retrievers) to accumulate toxic amounts and develop chronic hepatitis. Biopsy with special stains or preferably quantitated copper analysis performed on frozen hepatic tissue is required for diagnosis.

Cirrhosis is an end-stage hepatic disease that may be caused by various problems, especially chronic hepatitis. In particular, Cocker spaniels seem to have a distinct genetic predisposition to having cirrhosis at inordinately young ages (i.e., < 5 years of age). This may be due to an inherited problem in which they accumulate alpha-1 protease inhibitor in their hepatocytes, which eventually results in cellular death. In general, these dogs are clinically normal until they have completely exhausted all of their hepatic compensatory mechanisms. This means that there is usually little or nothing that can be done when they start showing clinical signs.

Unfortunately, many of these dogs have normal serum ALT and SAP activities when they are approaching end stage. Serum albumin and BUN are often decreased, and serum bile acids, if measured, are typically markedly increased (e.g., > 90 umol/L). However serum bile acids are not as sensitive or specific as desired. If blood ammonia is increased, that is very specific for hepatic insufficiency, but we are not sure how sensitive it is. Chronic hepatitis may cause the identical scenario in other breeds (especially but in no way limited to the Doberman pincher). There may be ascites due to portal hypertension and salt accumulation in cirrhotic animals. In such animals there is usually acquired hepatic portal shunting with many tortuous shunts seen in the abdomen, especially around the kidneys. Hypoalbuminemia can make the ascites more likely and more severe if it occurs.

Although controversial, I believe it is usually appropriate to biopsy dogs that you strongly suspect of having cirrhosis, unless the anesthesia risks are too great. I say this because I hope to

find other disease in the liver (e.g., inflammation that caused the cirrhosis in the first place) that can be treated. By treating the apparent primary hepatic disease, you may a) prevent further cirrhosis, and b) allow the remaining hepatocytes to heal and recompensate the patient. However, remember that a dog with cirrhosis may have exhausted all of its compensatory mechanisms, and even minimal anesthesia may result in acute decompensation and death. This is not common or likely, but it is devastating when it happens. Most patients with hepatic cirrhosis die shortly after diagnosis. However, some can live for months or even over a year with aggressive supportive therapy. It is hard to know which dogs will respond in which way. All you can do is treat and hope.

You must be very careful about diagnosing cirrhosis based upon clinical appearance. There are several diseases that look like cirrhosis but that are not cirrhosis.