

CLINICAL APPROACH TO LIVER DISEASE AND TREATMENT OPTIONS

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DIAGNOSTIC CONSIDERATIONS

The clinician is constantly presented with patients that have abnormal liver enzymes identified on the routine biochemical profile. The question often asked is “does this patient have liver disease”. The answer is often no; not primary hepatic disease but rather secondary hepatic involvement resulting from some extrahepatic event or drugs. I generally refer to these secondary conditions as reactive hepatopathies. Management of the liver in this condition involves first treating the primary disease condition and providing optimal hepatic support to maintain normal liver function. Consequently it is important that the clinician must first evaluate the entire patient when encountering the animal with abnormal enzymes to exclude the possibility of a secondary reactive hepatopathy.

Another important principle that should be kept in mind when evaluating the patient with abnormal liver enzymes is that the liver has a great reserve capacity and clinical signs of liver disease often do not appear until the disease is quite advanced. Similarly liver function tests become abnormal only when significant liver dysfunction is present. Because the liver is involved in so many metabolic functions and there are variable hepatic responses to an insult there is no ideal liver function test to tell us the extent of liver damage. Of the test available bile acids (urine or serum) are a reflection of the efficiency and integrity of the enterohepatic circulation of these bile acids. Abnormal bile acid concentrations support the presence of portal vascular anomalies or hepatic insufficiency. When serum bile acid concentrations are greater than 25 $\mu\text{mol/L}$ for the dog and cat there is a high probability that the histological findings will define a lesion. One study found the optimal test combination of abnormal serum ALT activity and abnormal bile acid concentrations provided the best sensitivity and specificity for the diagnosis of chronic hepatitis in the dog.

An Algorithm for Liver Evaluation.

When a patient presents with abnormal liver enzymes (such as ALP, ALT or GGT) the clinician must evaluate the animal carefully to first rule out the possibility that the liver enzyme abnormalities are not secondary to a primary non-hepatic disorder (see figure below). As previously noted the most common cause for abnormal ALT and ALP values is most likely not primary hepatic disease but rather secondary hepatic changes as a result of a non-hepatic disease process. These secondary changes are generally reversible once the primary disease is treated (see reactive hepatopathies).

Asymptomatic patients having abnormal liver enzymes in which an underlying non-hepatic disease is not identified the patient should be evaluated at a later date, perhaps in 4 to 6 weeks. Continued abnormal liver enzymes would be a strong indication for further investigation of the liver. Further investigation should include evaluating hepatic function using serum bile acids. Unexplained persistent abnormal liver enzymes or animals with abnormal hepatic function determined by bile acids warrant further liver evaluation. Liver evaluation would include imaging studies and liver biopsy. Ultrasonography is very useful to evaluate the character of the liver parenchyma and the biliary system. Masses,

nodules, choleliths, obstructed biliary system and vascular abnormalities are generally detected. Frequently fine needle aspiration (FNA) for cytological evaluation is performed in conjunction with ultrasound. Although FNA is safe and easy to perform interpretation of the cytological diagnosis of disease can be variable. One must be cautious in the interpretation of the results and use those FNA findings in conjunction with other diagnostics to make a diagnosis. Although there are a number of indications for performing a liver biopsy and one must carefully evaluate each case on its own merits. If presented with a patient with abnormal liver enzymes and clinical evidence of liver disease and when the liver biopsy will offer useful information about the case a liver biopsy would be indicated. Additional reasons to perform a liver biopsy would be to explain the cause of abnormal liver enzymes or function tests such as serum bile acids. The method of liver biopsy procurement involves surgery, ultrasound needle biopsy or laparoscopy. Each method has certain advantages and disadvantages.

COMMON LIVER DISEASES

Reactive Hepatopathies

The so-called “reactive hepatopathies” occur secondary to extrahepatic disease can result in both serum hepatic test and histomorphologic abnormalities. Most of the reactive hepatopathies cause increases in laboratory tests that evaluate hepatocellular integrity (ALT, AST) and tests of hepatic cholestasis (ALP, GGT). In most cases there are little if any changes in tests that evaluate hepatic function (bilirubin, albumin, glucose and BUN). Most of the animals with secondary liver disease also have normal serum bile acid concentrations, which again support a concept that there is generally minimal hepatocellular dysfunction in most of these disease conditions.

A reactive hepatopathy is not a specific histologic diagnosis rather grouped as a number of entities that are not associated as a primary liver disease. Findings are often characterized by nonspecific hepatocellular degeneration or necrotic changes without evidence of chronic progressive inflammation. The reason the liver often undergoes these changes is that the liver is involved in many metabolic and detoxification functions and is very dependent on adequate oxygenation. Endogenous toxins, anoxia, metabolic changes, nutritional changes and endogenous stress related glucocorticoid release might be responsible for the majority of these changes. These changes are usually very reversible and no specific hepatic therapy is required short of treating the primary disease and providing adequate liver support. The liver changes resolve once the primary etiology is successfully treated.

Vacuolar Hepatopathies

The histological reports of a vacuolar hepatopathy are often very frustrating in determining the underlying etiology. Hepatocellular vacuoles distending the cytosolic compartment may contain, fat, glycogen, intracellular water (edema) or other metabolic wastes or intermediates.

Hepatic lipidosis is a distinct clinical condition in common in cats but uncommon in dogs. Hepatic lipidosis occurs either as a primary idiopathic disease syndrome or secondary to a number of primary disease conditions. Lipid accumulation in the liver is simply the result of nutritional, metabolic or toxic insults to the liver and the degree of lipid accumulation can be quite variable. **Feline idiopathic hepatic lipidosis** however appears to be a distinct syndrome observed in obese older cats that have undergone a stressful episode associated with anorexia. Cats will present with an acute history of rapid weight loss, depression and icterus. A liver

biopsy confirms diffuse hepatic lipidosis. Treatment involves aggressive tube feeding and general liver support.

Glucocorticoid (steroid) hepathpathies occur in the dog (but not in cats) secondary to exogenous or endogenous glucocorticoids. On histology the vacuolar lesions contain glycogen. The development of a steroid hepatopathies is linked with marked increases in ALP. The diagnosis of canine Cushing's disease requires specific testing.

Idiopathic vacuolar hepatopathy is a frustrating diagnosis frequently observed in older dog. In all intense purposes they appear typical of steroid hepatopathies based on histology and abnormal ALP but without clinical or laboratory evidence of Cushing's disease or steroid therapy. One recent retrospective review of 336 cases if vacuolar hepatopathy in dogs based on histology found 65% had a steroid history however 45% did not. Many of these dogs had some other chronic illness or disease and it was postulated that endogenous steroid release in these sick dogs caused the histological changes. Of the later group of dogs approximately 5% were not ill or had concurrent disease. These dogs typify the classification of idiopathic vacuolar hepatopathy. The liver of these dogs contains excess glycogen identical to the typical steroid hepatopathy. We also identify many dogs having vacuolar hepatopathy and increased ALP without overt Cushing's disease or concurrent disease to have abnormal concentrations in other adrenal steroids (i.e. sex hormones such as progesterone, estradiol, DHEAS-S or 17 OH-progesterone). There is now speculation that increases in some of these steroid hormones may result in the hepatic changes and the ALP increase. Recently we have identified a disproportionate number of Scottish terriers with this condition suggesting a breed predisposition for this condition.

Nodular Hyperplasia

Although nodular hyperplasia is an intrahepatic event, it is included because this relatively benign process may cause an increase hepatic tests and histomorphologic changes that include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes observed most often in older dogs. Nodular hyperplasia is usually associated with increases in ALP and ALT at variable levels. Ultrasound may be normal or may demonstrate nodules (many can be only microscopic and not observed). Biopsy confirms the diagnosis however a wedge section is preferred, as a needle biopsy may not demonstrate the nodules. No specific therapy is indicated.

Chronic Hepatitis / Cirrhosis

Chronic hepatitis is the most common and most important liver disease to diagnose in the dog. The etiology includes copper toxicity from abnormal metabolism, certain drugs (NSAIDs and anticonvulsants), infectious agents, and possibly autoimmune mechanisms. There are also certain breeds that are overrepresented as well. It is observed most often in female middle-aged dogs (mean age of 7 years).

There are a number of breeds that have an increased incidence of chronic hepatitis, which suggests a genetic basis. Chronic hepatitis in Doberman Pinschers and Cocker Spaniels is considered to be an inherited liver disease. Other breeds that appear to have increased incidence include Labrador retrievers, Standard poodles and Scottish terriers.

Hepatic copper toxicity was first identified in Bedlington terriers as a genetic defect in copper metabolism. Liver disease with concurrent Cu accumulation is also reported in the Doberman pinscher, Dalmatians, West Highland White terrier, Labrador

retriever, Keeshond and Skye terrier. Other breeds are sometimes also observed to have elevations in copper concentrations consequently all cases of hepatitis in dogs should be evaluated for abnormal copper. The diagnosis of abnormal Cu accumulation requires a liver biopsy as serum copper levels do not reflect liver concentrations. Excess Cu within the liver can be demonstrated by histochemical staining for hepatic Cu. Definitive determination of excess hepatic Cu requires a quantitative analysis of tissue Cu determined on the biopsy sample. If requested most diagnostic labs can determine both.

The clinical signs parallel the extent of hepatic damage. Early in the disease there are usually no or only minimal clinical signs. Only after the disease progresses do the clinical signs of liver disease become evident. Ascites, jaundice and hepatic encephalopathy may then occur in the latter stages of the disease. With development of these late signs the long-term prognosis is generally poor. With cirrhosis the mean survival is often 1-3 months.

A presumptive diagnosis is made based on the clinical features and persistent increases of ALT values with variable ALP concentrations. The diagnosis is supported by abnormal bile acid concentrations, radiographic or ultrasound findings. A definitive diagnosis however requires a hepatic biopsy showing characteristic morphological patterns. Antiinflammatory therapy, copper reduction and general liver support are included in the therapy.

Acute Hepatic Necrosis

Hepatocytes will die due to various insults including hypoxia, toxins, drugs, microorganisms, immunological events and severe metabolic disturbances. When hepatic death is severe clinical signs of liver disease occur. The best example of drug associated liver toxicities result from NSAIDs, diazepam, anticonvulsants and certain antibiotics. The clinical course is often acute, characterized by massive increases in leakage liver enzymes (ALT, AST). When the damage is severe liver function declines and clinical evidence of liver failure occurs. The prognosis for recovery depends on the degree of hepatic damage, ability of hepatic regeneration and development of secondary complications. General liver support is the mainstay of the therapy.

Feline Inflammatory Liver Disease

Chronic inflammatory liver disease in the cat is different from the dog in that the inflammatory disease in cats is centered on the bile ducts and not the hepatic parenchyma. Although the nomenclature is confusing most agree the inflammation is bile duct associated and is referred to as cholangitis. The disease can be either acute suppurative (neutrophilic) cholangitis secondary to a biliary tract infection or as a chronic (nonsuppurative or chronic neutrophilic) cholangitis with a mixed inflammatory infiltrate. The acute form is observed in younger cats and is most always antibiotic responsive while the chronic form is observed in older cats, often is progressive and is treated with corticosteroids and ursodeoxycholic acid.

A second liver disorder is referred to as lymphocytic cholangitis. Lymphocytic infiltration confined only to the portal areas (lymphocytic portal hepatitis) is common in old cats and does not progress and may be a nonspecific liver reaction. Chronic lymphocytic cholangitis on the other hand is a slowly progressive disease spreading through the liver and may have an immune-mediated component. This later condition appears to be poorly responsive to therapy and ascites, hepatic encephalopathy and liver failure often results.

THERAPEUTIC CONSIDERATIONS

The treatment of liver disease should be first directed at identifying the inciting etiology and removing the cause of the disease. For example, primary copper associated toxicities should be treated using **copper chelators** (penicillamine or trientine, 15 mg/kg bid) and infectious causes such as leptospirosis should be treated with appropriate antibiotics. Idiopathic chronic inflammatory liver disease is often treated with **anti-inflammatory therapy** (prednisolone, 1 to 2 mg/kg/day tapered eventually to a dose of 0.5 mg/kg/day or every other day and/or azathioprine, 0.5 mg/kg/day) when suspected immune mediated mechanisms are involved in chronic hepatitis. Other accepted pharmacologic agents include colchicine for hepatic fibrosis and ursodeoxycholic acid to protect against the toxic effects of bile acids. The benefit of **colchicine** (0.03 mg/kg/day) in liver disease in small animals is unproven and questionable. **Ursodeoxycholic acid** (Ursodiol, 10-15 mg/kg daily) however is shown to have hepatoprotective, antioxidant and anti-inflammatory properties. Additional mechanisms include choleresis by increasing bile flow in cholestatic liver disease. Evidence supports the beneficial effects of ursodeoxycholic acid in many types of cholestatic liver disease being especially important in cats with chronic cholangitis.

If an etiology can't be identified then the clinician is then left with providing general liver support and treating any complications from liver dysfunction as they occur. Complications associated with liver dysfunction include such conditions as ascites, hepatic encephalopathy, coagulopathies and gastrointestinal ulceration.

Basic Liver Support

General liver support is a vague definition that involves promoting an environment conducive for ideal hepatocellular function and regeneration. Liver support should first include appropriate dietary management. Maintaining adequate energy intake with proper protein supplementation is essential for hepatic regeneration. There is a major misconception about diet and liver disease that states all patients should be placed on a protein-restricted diet. The goal of dietary therapy should be to adjust the quantities and types of nutrients to provide needed nutrient requirements but to avoid the production of excess nitrogen by-products associated with liver disease. Diet is important to provide factors that support liver function and regeneration.

There has also been recent interest in the management of certain types of liver disease with antioxidants. There is considerable evidence showing that free radicals are generated in liver disease and participate in the pathogenesis of oxidative liver injury in dogs and cats. Normally there is an extensive system of cytosolic and membrane bound enzymatic and non-enzymatic antioxidants which function to prevent oxidative damage by "scavenging" or "quenching" free radicals that are formed. Though the pathogenesis of most types of liver disease is unknown there is considerable evidence showing that free radicals are generated in all types of liver disease and participate in the pathogenesis of liver injury.

Non-Pharmacologic Hepatic Support

The non-pharmacologic options for liver support are many. Included in this category are vitamins, minerals, nutrient supplements and herbals. Most of these options are directed at preventing oxidative damage and maintaining hepatic membrane structure and function. Unfortunately many of these compounds have no scientific evidence based support for their use. In many there is limited knowledge of potential toxicity, adequate dosage and therapeutic benefit for small animal liver disease. Recently there is increasing scientific evidence of

benefit of several non-pharmacologic compounds for liver support. Included below here are compounds with minimal or no toxicity having evidence of therapeutic benefit in liver support

Vitamin E (alpha tocopherol) is a membrane bound antioxidant that functions in preventing lipid membrane peroxidation in liver disease. Vitamin E has protection against copper, iron, bile acids and certain hepatic toxins. One study we found vitamin E improved the GSH:GSSG ratio (glutathione concentrations as a measure of oxidatitive damage) in dogs with chronic hepatitis. Doses of 10-15 IU/kg/day are recommended.

Zinc is an essential trace element and often deficient in chronic liver disease. We have found it is not unusual to have patients with chronic hepatitis to have subnormal hepatic zinc concentrations. Zinc functions in intermediary metabolism but also has antioxidant function. In a canine study of copper associated liver toxicity zinc given orally at high concentrations for a prolonged course prevented intestinal copper intake and depleted excessive hepatic copper concentrations. There are no studies evaluating zinc as an antioxidant in liver disease in small animals. Doses of 2-3 mg/kg of zinc per day have been suggested with much higher doses to block copper absorption (approximately 50 mg bid).

Silymarin is an extract from the plant milk thistle and has been shown to act as a free radical scavenger in liver disease. *InVitro* studies suggest it will protect against lipid peroxidation and increase GSH concentrations in the liver. In one canine mushroom hepatotoxicity study dogs given silybin had a beneficial protective effect against the toxin. Unfortunately, the purity of commercial products, and therapeutic dosage is unknown. Dosage of milk thistle ranges from 50 to 250 mg bid. Milk thistle is also reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects. Silybin is the active stereoisomer of silymarin and is shown to be this compound that exerts the main biological hepatoprotective effects. Because of silymarin and silybin's poor GI absorption characteristics a silybin-phosphatidylcholine complex (Marin™) is now available for use. The phosphatidylcholine increases GI absorption. In our preliminary pharmacokinetic studies using normal cats we found no clinical outward signs of toxicity giving a dose of 5 mg/kg. For dogs Marin™ also contains vitamin E and zinc and for cats contains vitamin E.

S-adenosylmethionine

The naturally occurring molecule, S-adenosylmethionine (SAME), is synthesized in all living cells and is essential in intermediary metabolism having both hepatoprotective and antioxidant properties. Some of the highest concentrations of SAME occur in the liver. SAME is derived from the amino acid methionine and ATP driven by the enzyme SAME synthetase. The liver normally produces abundant SAME but there is also evidence to suggest conversion from methionine to SAME by SAME synthetase mediated is hindered in liver disease. Once SAME is formed it then is used in three major biochemical pathways of metabolism: transmethylation, transsulfuration and aminopropylation. The products of SAME have an influence on modulating inflammation, promotion of cell replication, and protein synthesis. SAME also plays a major role in membrane function and is an essential precursor for the essential intracellular antioxidant GSH.

SAME pharmacology has been studied in both dogs and cats. Oral SAME is bound to a stable salt and should be enteric coated. Without enteric coating the product can be oxidized readily and broken down. Tablets should be foil wrapped and should not be divided to prevent breakdown. When given on an empty stomach there is also better bioavailability. SAME is

rapidly absorbed and peak plasma levels can be detected for up to 6-8 hours. Studies in normal dogs and cats given SAME for 12 and 16 weeks respectively found it was well tolerated without adverse side effects. Doses used were 20 mg/kg/day. Studies have also found that all SAME products are not similar in bioavailability and the concentration of SAME in the product. SAME is available as Denosyl™. Recently a combination product, Denamarin™, containing both SAME and Silybin has become available.

Clinical experience with SAME is considerable both with experimental studies and through management of clinical cases in dogs and cats. We performed a placebo-controlled feline model of oxidant injury from acetaminophen and found SAME treated cats had reduced Heinz body formation and erythrocyte destruction and evidence of protection in hepatic GSH in the treated cats as well.

SUMMARY

It is important to systematically evaluate patients with abnormal liver enzymes. When liver disease is identified then appropriate therapy can be instituted. Because there are very limited studies evaluating therapy for specific liver diseases it is important to monitor each individual case and adjust the treatment protocol as dictated by response or repeat liver biopsy.

Abnormal Liver Enzymes

