HEPATOPROTECTIVE THERAPY

Susan E. Johnson, DVM, Diplomate ACVIM (Internal Medicine)
Associate Professor, Department of Veterinary Clinical Sciences
Service Head, Small Animal Internal Medicine
College of Veterinary Medicine, The Ohio State University

Introduction

Hepatoprotective agents have recently received attention for their role in the ancillary treatment of liver disease in dogs and cats [1-4]. These products include both prescription drugs and nutraceuticals. A drug is defined as "any substance, food, or nonfood that is used to treat, cure, mitigate, or prevent a disease and any nonfood substance that is intended to affect the structure or function of man or animals"[5]. In order for a compound to become a drug, it must be shown to be safe and effective for its intended use, undergoing an extensive FDA drug approval process that is lengthy and costly.

The term nutraceutical (not a legal term) was coined in the 1980's to reflect products that have characteristics of both a nutrient and a pharmaceutical (drug). There is no federal agency that regulates the manufacture or sale of nutraceuticals. The North American Veterinary Nutraceutical Council (NAVNC) is a non-regulatory group formed in 1996 by interested persons in industry, practice, and academia. The NAVNC defines a nutraceutical as "a non-drug substance that is produced in purified or extracted form and administered orally to patients to provide agents required for normal body structure and function and administered with the intent of improving the health and well-being of animals." This is a very narrow definition, including only those substances that play a known biochemical role in the normal body such as glucosamine or vitamin C. However, the term nutraceutical is also used for a broad range of substances including herbals and other botanicals, chondroprotective agents, antioxidants, omega-fatty acids, amino acids, and probiotics. Since nutraceuticals are not drugs, they cannot be sold with a label that claims or implies a medical intent. However, the medical intent is often conveyed by other means.

Nutraceuticals are readily available to pet owners through health food stores or internet mail order sites, similar to over-the-counter drugs. Yet over-the-counter drugs have undergone an approval process to substantiate efficacy and safety. For many nutraceuticals, there is a lack of safety and efficacy data. Many users of nutraceuticals are unaware of this lack of scientific support. Furthermore, pet owners may have the misconception that these products are "natural" and therefore safer or better than drugs. In fact, many of these products are synthesized. It should be emphasized, however, that lack of a regulatory mechanism is not justification for ignoring the potential therapeutic benefits of some of these products.

The purpose of this is to review the nutraceuticals and drugs that are commonly used for hepatoprotection and explore what we know about their efficacy and safety. Unfortunately, controlled clinical trials to demonstrate effectiveness are lacking for most of these products. However, all of the products mentioned here do not appear to be toxic when used as described.

S-adenosylmethionine (SAMe)

S-adenosylmethionine (SAMe) is an endogenous molecule produced in the body from the amino acid methionine and ATP by the enzyme SAMe synthetase. It plays a central role in three major biochemical pathways: transmethylation, trans-sulfuration, and aminopropylation. SAMe is essential to all cells but is especially important in the liver because of the liver's central role in metabolism. Transmethylation is important in phospholipid synthesis and maintenance of membrane structure, fluidity, and function. The trans-sulfuration pathway generates most endogenous sulfur compounds including glutathionine, an oxidant and free radical scavenger, which is a major physiologic defense mechanism against oxidative stress in the liver. Aminopropylation pathway results in products with anti-inflammatory and analgesic effects and polyamines which are important in DNA and protein synthesis.

Conversion of methionine to SAMe can be impaired in humans with liver disease. The result is decreased hepatocyte glutathione concentrations and increased risk for oxidative injury. Evaluation of hepatic glutathione levels in dogs and cats with severe spontaneous liver disease revealed that decreased levels of glutathione were common in necro-inflammatory liver disease, extrahepatic bile duct obstruction, and feline hepatic lipidosis [6]. Oral administration of SAMe to healthy cats has been shown to increase hepatic glutathione concentrations. SAMe also prevents glutathione depletion in dogs with steroid-induced hepatopathy. SAMe has been shown to have a protective effect on the erythrocytes in cats with experimental acetaminophen toxicity [7] and in a dog with acetaminophen toxicity causing methemoglobinemia and Heinz-body anemia. ([8].

SAMe has been formulated as a patented stabilized salt for pharmaceutical purposes (Denosyl SD4®; Nutramax Laboratories) and most veterinary experience has been with this formulation. It should be noted that there is considerable variation in product purity, and lack of bioavailability may be an issue in some over-the-counter SAMe products. SAMe is absorbed in the small intestine but enteric coating is necessary to maximize absorption. The enteric-coated tablets should not be broken or crushed. Giving the drug on an empty stomach will also improve absorption. SAMe is dispensed as a foil-wrapped product because it is easily oxidized when exposed to air.

SAMe is administered orally at a dose of 20 mg/kg/day in both dogs and cats. There is a low incidence of side effects [3]. Nausea or refusal of food may occur in the post-pill interval (hours); this problem may resolve with time. Some cats may develop post-pill vomiting [3]. Anxiety may also be seen. Although further clinical studies need to be performed, the use of SAMe for hepatoprotection seems reasonable because it has been shown in dogs and cats that SAMe (Denosyl®) is absorbed; it can influence hepatic glutathione concentrations; it is nontoxic in healthy and sick animals, and liver glutathione is decreased in spontaneous hepatobiliary disease in dogs and cats [3]. Specific indications for use of SAMe include treatment of dogs and cats with necroinflammatory and cholestatic disorders and treatment of hepatic lipidosis in cats.

N-acetylcysteine

N-acetylcysteine, the acetylated form of the amino acid L-cysteine, is rapidly hydrolyzed to cysteine, which is subsequently available for glutathione synthesis. N-acetylcysteine is the treatment of choice for acetaminophen toxicity in dogs and cats. It provides a ready source of glutathione to detoxify toxic intermediates. N-acetylcysteine should also be considered for the treatment of any severe toxin-related hepatic injury (including carprofen or potentiated sulfonamide toxicity in dogs and diazepam toxicity in cats), hepatic lipidosis in cats, or severe Heinz body hemolysis [3].

N-acetylcysteine (10% solution) is diluted 1:2 or more with saline and given IV through a nonpyrogenic 0.25um filter at an initial dose of 140 mg/kg over a 20-30 minute period. A maintenance dose of 70 mg/kg is given IV or orally every 6 hours for 7 treatments. N-acetylcysteine is rapidly absorbed from the gastrointestinal tract but may cause nausea and vomiting.

Vitamin E

Vitamin E (α-tocopherol) is a nutritional antioxidant found in all cell membranes. It is an essential nutrient derived from food and nutritional supplements. Mammalian cells cannot synthesize it. Vitamin E is an important defense mechanism against peroxidation membrane damage but also has other non-antioxidant functions that may be beneficial in the liver disease [3]. Increased production of free radicals has been implicated in a variety of experimentally-induced hepatic diseases, including hepatic copper and iron accumulation, alcohol consumption, cholestasis, ischemia-reperfusion injury, and drug-induced hepatic injury (such as phenobarbital and CCl_4). Free radicals may contribute to oxidative hepatocellular injury, if not counteracted by cytoprotective mechanisms. Antioxidants, such as vitamin E, are important to scavenge free radicals and prevent oxidative injury. In experimental studies (in vitro and in vivo), vitamin E can protect against this type of injury [3].

Little information is available on Vitamin E supplementation in dogs and cats with liver disease. However, Bedlington terriers with copper-associated hepatitis have reduced mitochondrial vitamin E, which correlates with markers of oxidative damage [9]. Dogs with chronic hepatitis treated for 3 months with a vitamin E supplemented diet had increased serum and liver vitamin E concentrations and evidence of protection against oxidative injury based on an increase in hepatic glutathione (GSH):GSSH ratio compared to untreated dogs [10]. However, there was no significant difference in clinical, laboratory, or histologic features in this time period.

Vitamin E is recommended for dogs and cats with necro-inflammatory or cholestatic hepatic disorders at a dose of 10 IU/kg per day (50 – 400 IU/day)[3,4]. It is safe and inexpensive. The natural form, d-α tocopherol, is recommended over the synthetic dl-α-tocopherol because it has greater uptake, dispersion, and bioactivity [4]. If severe cholestasis is present, a water soluble form is recommended [4].

Vitamin C

Vitamin C (ascorbic acid) is an important intracellular antioxidant and cofactor for many metabolic pathways. As part of the antioxidant network, it also functions to convert oxidized vitamin E back to its active form. However, in the presence of increased metal concentrations, especially copper and iron, it can act as a pro-oxidant. Vitamin C should be avoided in animals with necroinflammatory liver disease (which can be associated with increased hepatic iron) and copper-associated hepatitis [3].

Milk Thistle (Silymarin)

Silymarin comes from the milk thistle plant (*Silybum marianum*) which grows worldwide. The active derivative, silymarin, is highest in concentration in the fruit and seeds, but is present throughout the plant. A standard milk thistle extract contains 60-70% silymarin, which actually consists of a complex of flavonolignans including silybin (silibinin), isosilibin, silidianin, and silicristin. The most biologically active isomer is silybin. Milk thistle has been used in Europe for over 2000 years as a home remedy for liver disease. In the last 30 years, it has become the most researched plant extract used for treatment of liver disease [3].

Silymarin has antioxidant, hepatoprotective, antifibrotic, and anti-inflammatory effects [1,3,11]. Although somewhat controversial, silymarin may have a therapeutic benefit in humans with acute viral hepatitis, alcoholic liver disease, and toxin or drug-induced hepatitis. Silymarin is best known for its protective role in the treatment of Amanita mushroom hepatotoxicity [3]. Silymarin inhibits phalloidin and amanitin transporters, preventing hepatic uptake of these mushroom toxins. Silymarin was protective in beagles with experimental mushroom toxicity, showing less hepatic damage and improved survival compared to the control group [12]. Clinical studies documenting the effectiveness of silymarin treatment in dogs and cats with spontaneous hepatobiliary disease have not been published.

Commercially available preparations vary in content and bioavailability and there is no assurance of extract purity [11]. The therapeutic dose for dogs and cats is unknown. A dose of 50-250 mg q 24 hours has been suggested [4]. Silymarin appears to have very low toxicity and there are no known contraindications. Diarrhea may occur at high doses [11]. Silymarin can suppress certain P450 enzymes, which may be an important consideration for drug interactions in patients taking multiple drugs [3]. Silymarin is poorly absorbed from the gastrointestinal tract [11]. Intestinal absorption and bioavailability are improved by combining the active isomer, silybin, with phosphatidylcholine [4]. A commercially available silybin-phosphatidylcholine complex (Sil-phos®, Indea Labs) has been evaluated in a preliminary pharmacologic study in healthy cats at a dose of 5 mg/kg [4]. No evidence of toxicity was noted.

Ursodiol

Ursodiol or ursodeoxycholic acid (Actigall; Ciba Geneva) is a synthetic, hydrophilic bile acid, that is used in the treatment of cholestatic hepatobiliary disorders and chronic hepatitis in humans [1,2]. Ursodiol is the major bile acid in black bear's bile and has long been used in Chinese traditional medicine.

Ursodeoxycholic acid is believed to be beneficial by expanding the bile acid pool and displacing potentially hepatotoxic hydrophobic bile acids, which may accumulate in cholestasis. It is hepatoprotective (anti-inflammatory, immunomodulatory, and antifibrotic effects) and it is a choleretic, promoting increased fluidity of biliary secretions.

Although no controlled clinical studies have been performed, ursodiol is believed to be useful in dogs and cats as adjunctive therapy in cholestatic and necroinflammatory hepatic disorders (for example cholangitis in cats; chronic hepatitis in dogs) or those associated with high bile acids [2]. One clinical report describes the use of ursodiol in the treatment of a dog with chronic hepatitis and cholestasis [13]. Clinical and biochemical improvement were noted over a 6-month period. Evaluation of individual bile acid profiles revealed a decrease in potentially hepatotoxic endogenous bile acids.

Ursodiol appears to be safe when used at a dose of 15 mg/kg PO q24 in both dogs and cats. Actigall® comes as a 300 mg. capsule which can be compounded into 30 mg. capsules to aid in dosing cats and small dogs. It is contraindicated in biliary obstruction because of its choleretic action. It can be expensive to use in large breed dogs on a long-term basis.

L-carnitine

L-carnitine, an amino acid derivative, is an essential cofactor that mediates transfer of long-chain fatty acids across the mitochondrial membrane for β-oxidation [1,2]. L-carnitine is synthesize in the liver and is found primarily in skeletal and cardiac muscle. Carnitine therapy has been recommended for treatment of cats with hepatic lipidosis, although plasma and liver carnitine concentrations are not decreased [14]. A relative deficiency of carnitine compared to an increased oxidative demand or carnitine deficiency at the mitochondrial level are theorized. In healthy cats undergoing weight loss, carnitine supplementation appears to increase fatty acid oxidation [15]. A dose of 250 mg/cat/day has been suggested [2]. Tablets, capsules, and oral solutions are available. L-carnitine appears to be well-tolerated but can be expensive. D-carnitine should be avoided.

Zinc

Zinc, an essential element that functions in many metabolic processes, is absorbed in the small intestine and metabolized by the liver. Zinc salt therapy has been evaluated as an alternative to copper chelators, because zinc decreases intestinal copper absorption. Zinc has also been shown to decrease hepatic copper content in Bedlington and West Highland white terriers with hepatic copper accumulation and chronic hepatitis when used as the sole therapeutic agent for 2 years [16]. Zinc acetate (Galzin® Gate Pharmaceuticals) has been recommended at a dose of 15 mg/kg body weight of elemental zinc twice a day for 2 months [4]. The dose is then cut in half for maintenance therapy. Zinc administration should be separated from meals by at least 1 hour. Serum zinc concentrations should be monitored to achieve a level of 200-400 ug/dl. Zinc concentrations greater than 500 ug/dl may be toxic (hemolytic anemia).

Zinc administration has also been recommended for other canine hepatobiliary disorders. Antioxidant and antifibrotic effects have been suggested [1]. Decreased hepatic zinc levels have been reported in dogs with chronic hepatitis or cirrhosis [4]. A lower dose of 2-4 mg/kg q24 hours is recommended when used for hepatoprotective therapy.

References

1. Flatland B: Botanicals, vitamins, and minerals and the liver: Therapeutic applications and potential toxicities. Comp Cont Educ **25**:514-524, 2003.
2. Sartor LL and Trepanier LA: Rational pharmacologic therapy of hepatobiliary disease in dogs and cats. Comp Cont Educ **25**:432-447, 2003.
3. Center SA: Metabolic, antioxidant, nutraceutical, probiotic, and herbal therapies relating to the management of hepatobiliary disorders. Vet Clin North Am **34**:67-172, 2004.
4. Twedt DC: The use of nutraceuticals in liver disease. Proceedings of the 28th Annual Royal Canin/OSU Symposium. Columbus, OH Oct 16-17, 2004. p.63-66.
5. Boothe DM: Nutraceuticals in veterinary medicine. Part I. Definitions and regulations. Comp of Cont Educ Nov 1997; p 1248-1252.
6. Center SA et al: Liver glutathione concentrations in dogs and cats with naturally occurring liver disease **63**:1187-1197, 2002.
7. Webb CB et al: S-adenosylmethionine (SAMe) in a feline acetaminophen model of oxidative injury. J Fel Med Surg **5**:69-75, 2003.
8. Wallace KP et al; S-adenosyl-L-methionine (SAMe) for the treatment of acetaminophen toxicity in a dog. JAAHA **38**:246-254, 2002.
9. Sokol RJ et al: Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis. Gastroenterology **107**:1788-1798, 1994.
10. Twedt DC et al: The effect of dietary vitamin E on the clinical and laboratory and oxidant status of dogs with chronic hepatitis. JVIM **17**:403, 2003.
11. Minton J: Milk Thistle. Comp Cont Educ: Aug 2004:631-632.
12. Vogel G et al: Protection by silibinin against Amanita phalloides intoxication in beagles. Toxicol Appl Pharmacol **73**:355-362, 1984.
13. Meyer DJ et al: Use of ursodeoxycholic acids in a dog with chronic hepatitis: Effects on serum hepatic tests and endogenous bile acid composition. JVIM **11**:195-197, 1997.
14. Jacobs G et al: Comparison of plasma, liver, and skeletal muscle carnitine concentrations in cats with idiopathic hepatic lipidosis and in healthy cats. Am J Vet Res **51**:1349-1351, 1990.
15. Center SA et al: The clinical and metabolic effects of rapid weight loss in obese pet cats and the influence of supplemental oral L-carnitine. JVIM **14**:598-608, 2000.
16. Brewer GJ et al: Use of zinc acetate to treat copper toxicosis in dogs. JAVMA **201**:564-568, 1992.