Liver Support

Meri Stratton Phelps, DVM, MPVM, DACVIM (LAIM), DACVN

Liver disease is a challenging medical problem in adult horses, which requires a combination of medical and nutritional therapies. While there are several etiologies for liver disease in horses, the most commonly encountered ones are ingestion of a hepatotoxin, infiltration of the liver with excess lipid, hepatocellular damage from an infectious agent, and biliary tract disease.[1-2]

Common Causes of Liver Disease

A leading cause of liver disease is ingestion of toxins that damage liver cells (i.e., hepatotoxins). These toxins often are present in horse feeds and include mycotoxins that are found in moldy corn. The horse's liver cells also may be damaged by heavy metals and toxic chemicals that are present in the environment or by exposure to hepatotoxic drugs.[1-2] Plants that contain pyrrolizodine alkaloids are highly toxic to horses. These compounds have a cumulative toxic effect, and consumption of only 5% of the horse's body weight can result in hepatic failure.[1] Plants containing pyrrolizodine alkaloids are often avoided by horses grazing in a pasture, but may be consumed in a high concentration when these plants are mistakenly baled into hay that is later fed as the primary source of forage.

Obese horses, ponies, donkeys and Miniature horses that do not consume adequate calories may be predisposed to developing hyperlipemia and possibly hepatic lipidosis.[1-2] These animals may be consuming poorly digestible forage, have increased metabolic energy demands associated with late pregnancy or lactation, or may be experiencing environmental stress from cold and/or inclement weather.

Other causes of liver disease in horses include chronic active hepatitis, viral hepatitis, bacterial hepatitis, parasitic hepatitis, cholangiohepatitis, and abnormalities of the biliary tract. Chronic active hepatitis has an unknown etiology, although toxic and infectious causes may be implicated.[1] Affected horses present with active liver failure, elevated hepatic enzymes and clinical signs including weight loss, anorexia, depression, colic, icterus and fever.[1] Viral hepatitis can develop in association with equine infectious anemia and equine viral arteritis.[2] Bacterial hepatitis can be caused by a variety of different enteric bacteria including *Salmonella* spp. and *E. coli*.[2] Parasitic hepatic damage may develop following migration by *Parascaris equorum*, *Strongylus edentatus* or *Strongylus equinus*.[2] Biliary calculi (choleliths, choledocholiths, hepatoliths) may form at a variety of sites within the biliary tree.[1-2] Extrahepatic causes of biliary tract disease include other disease processes that obstruct the flow of bile through the cannicular system (abscesses, neoplasia, inflammation).[1]

Clinical Signs of Liver Disease

Common clinical signs of hepatic disease include anorexia, weight loss, icterus, skin abnormalities, and colic. Other clinical signs may be present depending on the etiology of the liver disease. Horses with severe hepatic disease may have abnormal findings on a neurologic examination and signs of hepatoencephalopathy, including a change in behavior and mentation, incoordination, head pressing, and yawning.[1-2]

Serum Biochemical Tests

The first indication that a horse has developed liver disease may be abnormal findings on serum biochemical tests. Elevations in hepatocellular enzymes including aspartate aminotransferase (AST), sorbitol dehydrogenase (SDH) and lactate dehydrogenase (LDH) may be early indicators of liver damage, although both AST and LDH must be

evaluated in light of any muscle damage which may have occurred in the patient.[1-2] Damage to the biliary tract results in elevations of γ-glutamyltransferase (GGT) and alkalkine phosphatase (ALP), and may provide evidence of more chronic liver damage. Additional tests (ammonia, total bile acids, serum albumin, serum triglyceride) also may provide evidence of hepatic damage.[1-2] An ultrasound examination can be a useful tool in evaluating the overall appearance and size of the liver, and to examine the liver for gross evidence of abscesses, neoplasia, fibrosis and choleliths.[1-2] Depending on the suspected severity of the liver damage, a liver biopsy can be performed to aid in the diagnosis and prognosis of the liver disease.

Dietary Therapy for Liver Disease

Horses with liver disease should be fed a ration containing a highly digestible forage to meet their energy, protein and other essential nutrient requirements. The protein requirement established by the 2007 Horse NRC should be met with forage that contains 10% crude protein.[3] Dietary protein intake should not be lower than requirements to prevent protein malnutrition and catabolism of body stores of protein. A forage analysis is extremely useful to help design a ration with an appropriate amount of protein and other essential nutrients; poorly digestible forage should be avoided.

Horses with liver disease should be fed in multiple small meals throughout the day to help maintain blood glucose concentrations. A slow feeder device like a NibbleNet® is a useful tool to help provide the horse with continuous access to hay, provided the device can be safely placed in the horse's environment. Supplemental calories can be added to the ration using other highly digestible feeds including soaked beet pulp, oil (if the patient does not have hepatic lipidosis or hypertriglyceridemia), and cracked corn (if the patient can tolerate some non-structural carbohydrates).

Supplemental nutrients that provide antioxidant, anti-inflammatory and anti-fibrotic activities in hepatocytes may be beneficial in the management of liver disease. ***Silybum marianum***, which is commonly called milk thistle, is frequently used to manage liver disease in humans and in other animals.[4-5] Silibinin, the primary active ingredient in milk thistle, has limited solubility in water and is not very bioavailable following oral consumption.[4-5] When silibinin is complexed with a more bioavailable compound like a phospholipid to form a phytosome complex, its bioavailability is greatly increased, allowing silibinin to be easily absorbed and transported across cell membranes.[4] A recent study evaluating the safety of oral therapy using a silymarin phospholipid complex in healthy adult horses showed that the silibinin was both safe and non-toxic in doses up to 26 mg/kg body weight, although a mild increase in serum GGT was measured in the treated horses.[6]

Although the oral bioavailability of the silymarin phospholipid complex in horses is low like in other species, the silibinin in horses follows a non-linear pharmacokinetic pattern and plasma values may be higher than expected based on the reported low bioavailability.[6] In horses, the antioxidant activity of silibinin is measured as an increase in plasma ORAC (oxygen radical absorbance capacity), and a decrease in the red blood cell enzyme NQO1 (nicotinamide adenine dinucleotide phosphate:quinone oxidoreductase 1), that provides some protection against oxidative damage.[7] Silymarin also has anti-inflammatory properties and decreases the expression of proinflammatory cytokines (IL-1, IL-2, TNF-α) when there is hepatocyte damage.[8-10] An additional benefit of silibinin is a reduction in hepatic fibrosis and collagen production.[4-5] Finally, silibinin may improve protein synthesis in hepatocytes to promote regeneration and repair of liver tissues.[4]

N-aceteylcysteine is a drug that provides L-cysteine for the synthesis of glutathione, a protein that has an important role protecting hepatocytes from oxidative damage.[11] N-aceteylcysteine reduces fibrosis in humans with non-alcoholic steatohepatitis and has a variety of other hepatocellular effects including

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reducing the expression of pro-inflammatory genes, reducing nitric oxide production, and inhibiting NF-kB transcription activity.[12-14] The anti-inflammatory actions of N-aceteylcysteine may also be helpful in the management of hepatoencephalopathy.[15] In horses, N-aceteylcysteine is well tolerated when administered orally, and has an anti-inflammatory effect on endometrial tissues.[16]

Taurine, a sulfur-containing amino acid used in the conjugation of bile acids in horses, also has antioxidant and detoxification properties. Experimentally, dietary supplementation with taurine offers protection to hepatocytes affected by toxic, oxidative and neoplastic disease processes.[17] Supplemental taurine helps prevent hepatic fibrosis that typically occurs after oxidative damage to hepatocytes, and reduces the accumulation of fat in the liver thereby limiting hepatic injury, inflammation and plasma triglycerides.[18-19]

Vitamins E and **C** are natural antioxidants that prevent cellular oxidative damage. Vitamin E helps to protect hepatocytes against toxic damage, and also helps to prevent hepatic fibrosis by limiting collagen deposition.[12,20] Vitamin C helps to prevent inflammatory damage to hepatocytes after toxic injury through its actions as an antioxidant, and by reducing the induction of a variety of inflammatory mediators.[21-24] These beneficial effects of vitamins C and E are increased when vitamin C supplementation is combined with vitamin E, and when vitamin C supplementation is combined with silymarin.[25-27]

In a clinical trial, feeding a dietary supplement designed to support liver health* for 30 days to horses with clinical signs of hepatic disease and elevated hepatic enzymes resulted in improvements in patient body weight, body condition score, and 73% of horses (8/11) had a decrease in their hepatic enzymes (Chart 1).

Conclusion

Dietary therapy for horses with hepatic disease can be complemented with silibinin, N-acetylcysteine, taurine, vitamin E, and vitamin C because these nutrients help to provide anti-inflammatory, antioxidant and anti-fibrotic support to hepatocytes.

Chart 1. **Liver Enzyme Concentrations in Horses Before and After Supplementation with a Dietary Supplement Designed to Support Liver Health***

Horse	GGT† (IU/L) Pre-Supplement	GGT† (IU/L) Post-Supplement	AST† (IU/L) Pre-Supplement	AST† (IU/L) Post-Supplement
A	32	*19*	*326*	*253*
B	38	36	*313*	*308*
C	31	*23*	411	*245*
D	173	240		
E	148	70	884	*242*
F	*24*	*17*	386	*262*
G	57	88	377	385
H	36	66	142	*291*
I	32	*17*	*288*	*255*
J	498	220	*226*	*262*
K	116	34	547	142

†GGT = γ-glutamyltransferase; AST = aspartate aminotransferase
Numbers in italic font are within normal limits

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Literature Cited

1. Smith GW, Davis JL.Diseases of the hepatobiliary system, 843-872. In Smith BP (ed), Large animal internal medicine, ed 5. Elsevier Mosby, St. Louis, MO.
2. Barton MH. Disorders of the liver, 951-994. In Reed SM, Bayly WM and Sellon DC (eds), Equine internal medicine, ed 2. Saunders, St. Louis, MO.
3. National Research Council 2007 Nutrient requirements of horses, ed 6 revised National Academies Press: Washington, DC p 54–68, 294–303.
4. Hackett ES, Twedt DC, Gustafson DL. (2013) Milk thistle and its derivative compounds: A review of opportunities for treatment of liver disease. *J Vet Intern* Med 27:10-16.
5. Vargas-Mendoza N, Madrigal-Santillan E, Morales-Gonzalez A, et al. (2014) Hepatoprotective effect of silymarin. *World J Hepatol* 6(3):144-149.
6. Hackett ES, Mama KR, Twedt DC, et al. (2013) Pharmacokinetics and safety of silibinin in horses. *Am J Vet Res* 74(10):1327-1332.
7. Hackett ES, Mama KR, Twedt DC, et al. (2013) Evaluation of antioxidant capacity and inflammatory cytokine gene expression in horses fed silbinin complexed with phospholipid. *Am J Vet Res* 74(10):1333-1339.
8. Toklu HZ, Tunali Akbay T, Velioglu-Ogunc A, et al. (2008) Silymarin, the antioxidant component of Silybum marianum, prevents sepsis-induced acute lung and brain injury. *J Surg Res* 145:214-222.
9. Haddad Y, Vallerand D, Brault A, et al. (2011) Antioxidant and hepatoprotective effects of silibinin in a rat model of nonalcoholic steatohepatitis. *Evid Based Complement Alternat Med* 2011:nep164.
10. Hovarth ME, Gonzalez-Cabello R, Blazovics A, et al. (2001) Effect of silibinin and vitamin E on restoration of cellular immune response after partial hepatectomy. *J Ethnopharmacol* 77(2-3):227-32.
11. Rushworth GF, Megson IL. (2014) Existing and potential therapeutic uses for N-acetylcysteine: The need for conversion to intracellular glutathione for antioxidant benefits. *Pharm Thera* 141, 150-159.
12. Czaja AJ. (2014) Hepatic inflammation and progressive liver fibrosis in chronic liver disease. *World J Gastroenterol* 20(10):2515-2532.

13. Zafarullah M, Li WQ, Sylvesster J, et al. (2003) Molecular mechanisms of N-acetylcysteine actions. *Cell Mol Life Sci* 60(1):6-20.

14. Majano PL, Medina J, Zubia I, et al. (2004) N-Acetyl-cysteine modulates inducible nitric oxide synthase gene expression in human hepatocytes. *J Hepatol* 40(4):632-7.

15. Bemeur C, Butterworth RF. (2013) Liver-brain proinflammatory signaling in acute liver failure: role in the pathogenesis of hepatic encephalopathy and brain edema. *Metabol Brain Dis* 28(2):145-50.

16. Witte TS, Melkus E, Walter I, et al. (2012) Effects of oral treatment with N-acetylcysteine on the viscosity of intrauterine mucus and endometrial function in estrous mares. *Theriogenology* 78(6), 1199-208.

17. Miyazaki T, Matsuzaki Y. (2014) Taurine and liver diseases: a focus on the heterogenous protective properties of taurine. *Amino Acids* 46, 101-110.

18. Miyazaki T, Bouscarel B, Ikegami T, et al. (2009) The protective effect of taurine against hepatic damage in a model of liver disease and hepatic stellate cells. *Adv Exp Med Biol* 643, 293-303.

19. Gentile CL, Nivala AM, Gonzales JC, et al. (2011) Experimental evidence for therapeutic potential of taurine in the treatment of nonalcoholic fatty liver disease. *Am J Physiol Regul Integr Comp Physiol.* 301(6), R1710-22.

20. Parola M, Leonarduzzi G, Biasi F, et al. (1992) Vitamin E dietary supplementation protects against carbon tetrachloride-induced chronic liver damage and cirrhosis. *Hepatology* 16:1014-1021.

21. Abhilash PA, Harikrishnan R, Indira M. (2014) Ascorbic acid suppresses endotoxemia and NF-ÐB signaling cascade in alcoholic liver fibrosis in guinea pigs: a mechanistic approach. *Toxicol Appl Pharmacol* 274(2):215-24.

22. El-Meghawry El-Kenawy A, Osman HE, Daghestani MH. (2014) The effect of vitamin C administration on monosodium glutamate induced liver injury. An experimental study. *Exp Toxicol Pathol* 65(5):513-21.

23. Liang T, Chen X, Su M, et al. (2014) Vitamin C beneficial hepatoprotection against Concanavalin A-induced immunological hepatic injury in mice through inhibition of NF-κB signal pathway. *Food Funct* 5(9):2175-82.

24. Su M, Chen H, Wei C, et al. (2014) Potential protection of vitamin C against liver-lesioned mice. *Int Immunopharmacol* 22(2), 492-7.

25. Prathibha P, Rejitha S, Harikrishnan R, et al. (2013) Additive effect of alpha-tocopherol and ascorbic acid in combating ethanol-induced hepatic fibrosis. Redox Rep 18(1):36-46.

26. Karakilcik AZ, Zerin M, Arslan O, et al. (2004) Effects of vitamin C and E on liver enzymes and biochemical parameters of rabbits exposed to aflatoxin B1. *Vet Hum Toxiol* 46(4):910-2.

27. Shalan MG, Mostafa MS, Hassouna MM, et al. (2005) Amelioration of lead toxicity on rat liver with vitamin C and silymarin supplements. *Toxicology* 206(1):1-15.

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