Study of Hepatic Problems in livestock

S. Masoud Davoudi

Department of Animal Science, Shahin Shahr Esfahan Branch, Islamic Azad University, Shahin Shahr Esfahan, Iran

_____

ABSTRACT

Hepatic disease is usual in large animals. Increases in serum hepatic enzymes and total bile acid concentration may indicate hepatic dysfunction, insult, disease, or failure. While liver disease is particularlyusual in foals, progression to liver failure isn't.Diseases that frequently result in hepatic failure in horses include Theiler's disease, Tyzzer's disease, pyrrolizidine alkaloid toxicosis, hepatic lipidosis, suppurative cholangitis or cholangiohepatitis, cholelithiasis, and chronic active hepatitis. Obstructive disorders, aflatoxicosis, leukoencephalomalacia, pancreatic disease, kleingrass or alsike clover poisoning, portal caval shunts, hepatic abscess, and perinatal herpesvirus 1 infections sporadically result in hepatic failure. Less frequently, hepatic failure is relatedby endotoxemia, steroid administration, inhalant anesthesia, systemic granulomatous disease, and drug-induced amyloidosis, hyperammonemia in Morgan foals, parasite damage, iron toxicity, or following neonatal isoerythrolysis.

Key words: Hepatic disease, livestock
_____

INTRODUCTION

Hepatic disease is usual in large animals. Increases in serum hepatic enzymes and total bile acid concentration may indicate hepatic dysfunction, insult, disease, or failure. While liver disease is particularlyusual in foals, progression to liver failure isn't.Diseases that frequently result in hepatic failure in horses include Theiler's disease, Tyzzer's disease, pyrrolizidine alkaloid toxicosis, hepatic lipidosis, suppurative cholangitis or cholangiohepatitis, cholelithiasis, and chronic active hepatitis. Obstructive disorders, aflatoxicosis, leukoencephalomalacia, pancreatic disease, kleingrass or alsike clover poisoning, portal caval shunts, hepatic abscess, and perinatal herpesvirus 1 infections sporadically result in hepatic failure. Less frequently, hepatic failure is relatedby endotoxemia, steroid administration, inhalant anesthesia, systemic granulomatous disease, and drug-induced amyloidosis, hyperammonemia in Morgan foals, parasite damage, iron toxicity, or following neonatal isoerythrolysis[33].

In ruminant animals, hepatobiliary disease is relatedby hepatic lipidosis, hepatic abscesses, endotoxemia, pyrrolizidine alkaloid and other plant toxicoses, certain clostridial diseases, liver flukes, mycotoxicosis, and mineral toxicosis or deficiency. Vitamin E or selenium deficiency, aflatoxicosis, ascarid migration, bacterial hepatitis, and ingestion of toxic substances are relatedby hepatic damage in swine.Thus, the exact incidence of hepatic disease in camelids is unknown; it appears to be usual in North America. Hepatic lipidosis is reportedly the most usual liver disease in llamas and alpacas, occurring in crias and adults. Bacterial cholangiohepatitis, adenoviral hepatitis and pneumonia, fungal hepatitis, toxic hepatopathy, halothane-induced hepatic necrosis, hepatic neoplasia, and liver fluke infestation have also been indicating in camelids. The liver can respond to insult in only a limited many of ways. Fat droplets in the liver may be early and usual reversible divers. Biliary hyperplasia is also reversible if the insult is removed early. Necrosis of hepatocytes indicates more recent damage. The dead cells are removed with an inflammatory process and replaced by new hepatocytes or fibrosis. Unless the dysfunction is severe and hepatocellular regeneration is evident, prognosis for animals by liver failure is commonly unfavorable. Early hepatic fibrosis may be reversible by prompt recognition and intervention. Chronic disease by extensive loss of hepatic parenchyma and fibrosis, particularlyby portal bridging, warrants a poor prognosis [11, 24].

Clinical Findings

Clinical symptoms of hepatic disease may not be evident until >60–80% of the liver parenchyma is nonfunctional or when hepatic dysfunction is secondary to disease in another organ system. Clinical symptoms may vary by the course of the disease, primary site of damage and specific etiology. Onset of symptoms of hepatic encephalopathy and liver failure is commonlysevere regardless of whether the hepatic disease process is severe or chronic. Clinical symptoms and acute of hepatic pathology reflect the degree of compromise of one or more of the liver's vital functions, including blood glucose regulation; fat metabolism; production of clotting factors, albumin, fibrinogen, nonessential amino acids, and plasma proteins; bile formation and excretion; bilirubin and cholesterol metabolism; conversion of ammonia to urea; polypeptide and steroid hormone metabolism; synthesis of 25-hydroxycholecalciferol; and metabolism and detoxification of many drugs and toxins [3, 17 and 19].

Icterus, weight loss, or abnormal behavior isusual in horses by liver disease and hepatic failure. CNS symptoms are usual the initial and predominant symptom in horses bysevere hepatic failure, therefore weight loss is a prominent symptom in most but not all horses by chronic liver disease and failure.Photosensitization and, less usually, bilateral pharyngeal paralysis, causing inspiratory stridor, diarrhea, or constipation, may be present. Affected cattle commonly show inappetence, less milk production, and weight loss. Ascites are seen in cattle but aren'tusual in affected horses. Weight loss the only symptom relatedby liver abscesses. Icterus, thus most pronounced when the biliary system is diseased, is also usual in horses by acute liver failure. It's more variably present in horses by chronic liver failure or in ruminant animals. Fasting hyperbilirubinemia is a more usual cause of icterus in horses and isn'trelatedby hepatic disease. Occasionally, persistent hyperbilirubinemiamay be seen in healthy horses, without document of hemolysis or hepatic disease. In ruminant animals, icterus is more usually due to hemolysis and primarily involves increases in indirect bilirubin [25, 34]. Hyperbilirubinemia caused obstructive biliary conditions is rare in sheep [9].

Hepatic encephalopathy is relatedby behavioral diverse in horses and ruminant animals. The acute of hepatic encephalopathy often reflects the degree of hepatic failure but doesn't differentiate between severityand chronic liver failure. symptoms of hepatic encephalopathy from nonspecific depression and lethargy to head pressing, circling, aimless walking, dysphagia, ataxia, dysmetria, persistent yawning, pica, increased friendliness, aggressiveness, stupor, seizures, or coma. Pharyngeal or laryngeal collapse by loud, stertorous inspiratory noises and dyspnea occurs in some cases of hepatic failure, particularly in ponies [1, 30]. The pathogenesis of hepatic encephalopathy is unknown, but proposed theories include ammonia as a neurotoxin, alterations in monoamine neurotransmission or catecholamine neurotransmitters, imbalance between aromatic and short branch chain amino acids resulting in increased inhibitory neurotransmitters, neuroinhibition due to increased cerebral levels of endogenous benzodiazepine-like substances, increased permeability of the blood-brain barrier, and impaired CNS energy metabolism. Thus, the symptoms can be dramatic, hepatic encephalopathy is reversible if the underlying hepatic disease can be resolved.

Photosensitization may be seen bysevere or chronic liver failure must be differentiated from primary photosensitization. Hepatogenous photosensitization develops when compromised hepatic function results in phylloerythrin, a photodynamic metabolite of chlorophyll, entering the skin. Phylloerythrin in the skin reacts by ultraviolet light and releases energy, causing inflammation and skin injury. Symptoms of photosensitization are varied but include uneasiness, pain, and pruritus, mild to acutedermatitis by erythema, extensive subcutaneous edema, and skin ulceration, sloughing of skin by lacrimation, photophobia, and corneal cloudiness. Dermatitis and edema are speciallydocument on non-pigmented, light-colored or hairless zoon of the body and surface exposed to sun. Mucocutaneous junctions and patches of by hair are the most usuallocations of photosensitization in cattle. Occasionally, the underside of the tongue may be affected. Blindness, pyoderma, loss of condition, and occasionally death are possible sequelae. Pruritus may result from photosensitization or from deposition of bile salts in the skin secondary to alterations in hepatic excretion [12].

Diarrhea may be seen in animals with hepatic disease. Diarrhea is more usually seen in cattle than in horses by chronic liver disease or in ruminant animals by chronic fascioliasis and hepatotoxic plant poisonings. Ponies and horses by hyperlipemia and hepatic failure may develop diarrhea, laminitis, and ventral edema. Some ruminant animals by liver disease have alternating diarrhea and constipation. Horses by liver failure and hepatic encephalopathy frequently develop colonic impaction due to decreased water intake [22].

Recurrent colic, intermittent fever, icterus, weight loss, and hepatic encephalopathy may be seen in horses bycholeliths that obstruct the usual bile duct. Infectious or inflammatory hepatic disease or failure of the liver to prevent endotoxin from gaining access to the systemic circulation may also result in intermittent fever and colic. Abdominal pain, due to pressure on the liver capsule from parenchymal swelling, often is seen in ruminant animals by acute diffuse hepatitis or trauma to the capsule itself. Affected ruminant animals stand by an arched back, are

reluctant to move, or show symptoms of colic. In ruminant animals, pain may be localized to the liver by palpation over the anterior ventrolateralsides of the abdomen or the last few ribs on the right side. Tenesmus followed with rectal prolapse is seen in some ruminant animals by liver disease. It may be relatedby diarrhea, hepatic encephalopathy, or edema of the bowel from portal hypertension [5].

Hypoalbuminemia isn't as frequently relatedby liver disease in horses as previously thought. Due to the long half-life and liver acute for albumin production, hypoalbuminemia is commonly a very late event in the disease process. Serum total protein concentrations may be normal or increased because of an increase in β-globulins in horses by liver disease. Hypoalbuminemia and hypoproteinemia most usually develop in chronic liver disease, and they are usual findings in llamas by liver disease. Generalized ascites or dependent edema may result. Ascites is related to portal hypertension caused with venous blockage and increased hydrostatic pressure and to protein leakage into the peritoneal cavity. The abdominal fluid present by liver disease commonly is a improve transudate. Hypoalbuminemia can aggravate the ascites, but if it is seen alone, it more likely will cause intermandibular, brisket, or ventral edema. Ascites is difficult to appreciate in horses and adult cattle unless it is extensive. Ascites is a usual finding in calves by liver cirrhosis [18, 20].

Anemia may be seen in ruminant animals by liver dysfunction due to parasitic diseases, chronic copper toxicity, some plant poisonings, and chronic inflammatory disease. Anemia in severefasciolosis results from severe hemorrhage into the peritoneal cavity as the larvae penetrate the liver capsule. Trauma and feeding activity of adult flukes into the bile tube cause anemia and hypoproteinemia in ruminant animals by chronic fasciolosis. Chronic inflammatory disease may cause anemia without accompanying hypoproteinemia [2].

Clinical symptoms of acute or terminal hepatic failure include coagulopathies and hemorrhage due to decreased production of clotting factors with the liver and possibly increased using in septic or inflammatory processes. A prolonged prothrombin time is commonly seen first because factor VII has the shortest plasma half-life. Horses may develop a terminal hemolytic crisis caused with increased RBC fragility. This hasn't been indicated in ruminant animals [13].

Fecal color rarely divers in mature herbivores by liver disease. In young ruminants and monogastric, cholestasis may result in lighter color feces being passed because of loss of stercobilin, a metabolite of bilirubin.Liver disease should almost be considered when nonspecific clinical symptoms, such as depression, weight loss, intermittent fever, and recurrent colic, are present without an apparent cause [10]. Differentiation between severe and chronic hepatitis and failure based on the duration of clinical symptoms before presentation may be misleading, because the disease process is often advanced before clinical symptoms are evident. Early vague symptoms of depression and decreased appetite may be overlooked. Liver biopsy to determine the type of pathology, degree of hepatic fibrosis present, and the regenerative capabilities of the liver parenchyma is mandatory for developing a treatment plan and giving an accurate prognosis.

Laboratory Analyses

Laboratory tests often detect liver disease or dysfunction before hepatic failure occurs. Routine biochemical tests as serum enzyme concentrations are sensitive indicators of liver disease, but they don't assess hepatic function. Dynamic biochemical tests that assess hepatic clearance provide quantitative information regarding hepatic function. Experiments of hepatic function is useful diagnostic and prognostic devise and provide a guide for the modification of drug-dosing regimens [7, 15 and 37].

Serum Enzyme Concentrations

Serum concentrations of liver-specific enzymes are generally higher in severe liver disease than in chronic liver disease. They may be within normal limits in the later stages of sub-acute or chronic hepatic disease. The magnitude of increases in hepatic enzymes shouldn't be utilized to determine prognosis. Hepatic enzymes are used to determine the presence of disease not degree of hepatic dysfunction. Careful interpretation of laboratory values in conjunction by clinical findings is mandatory [4].

Sequential measurements of serum γ-glutamyltranspeptidase or transferase, sorbitol dehydrogenase, AST, bilirubin, and bile acids are usually used to assess hepatic dysfunction and disease in large animals. Serum GGT, bilirubin and total bile acid concentrations, and sulfobromophthalein clearance aren't sensitive indicators of liver disease in calves. Therefore GGT is primarily relatedby microsomal membranes in the biliary epithelium, its present in the canalicular surfaces of the hepatocytes, pancreas, kidneys, and udder. Due to urinary and milk excretion of GGT and rarity of pancreatitis in large animals, increased serum GGT concentrations most usually indicate bile tube or liver disease. Some consider GGT to be the symptoms test of highest sensitivity for liver disease in mature large animals. Increase of GGT is most pronounced byobstructive biliary disease. In acute hepatic disease in horses, GGT may continue to

126

increase for 7–14 days despite clinicalimprovement and return toward normal of other laboratory tests. Reportedly, serum GGT concentrations become elevated within a few days of liver injured and remain elevated until the terminal phase. Chronic hepatic fibrosis is the only liver disease in which an abnormal increase in GGT mightn't be seen. Neonatal young horses, particularly those in training, may show a nonspecific increase in GGT that isn'trelatedby liver disease or other increases in liver enzymes or serum bile acid concentration. GGT is of little value in diagnosing liver disease in neonatal calves or lambs because it's present in colostrum and milk. GGT activity may also be increased by colonic displacement or administration of drugs. Some liver-derived enzymes are higher in young calves and foals because they are transiently elevated or come from sources other than the liver. Serum levels of hepatic enzymes vary in goats by age, breed, and sex. Reference ranges must be almost for the species and age group being evaluated.SDH, arginase, ornithine carbamoyltransferase (OCT), AST, isoenzyme 5 lactate dehydrogenase (LDH-5), glutamate dehydrogenase (GLDH), and AP are also used to assess hepatic dysfunction and disease. Arginase, SDH, and OCT are liver-specific enzymes in horses, most ruminant animals. SDH is most predictive for active hepatocellular disease, by marked increases in enzyme activity after hepatocellular injured. Mild increases in SDH can also occur by obstructive GI lesions, endotoxemia, and anoxia from shock, acute anemia, hyperthermia, and anesthesia. Because of their short half-lives, SDH and LDH-5 are useful in assessing resolution or progression of liver insult. Both enzymes commonly return to near-normal values 4 days after liver insult, and neither is usually increased in chronic liver disease. Rarely, in severe cases of hepatic failure, SDH may return to normal in spite of a fatal outcome. Arginase and GLDH are considered specific for severe liver disease, because both have high tissue concentrations in the liver and short half-lives in the blood. AST is highly acutefor liver disease but lacks specificity because high concentrations come from liver and skeletal muscle. Other AST sources include cardiac muscle, erythrocytes, intestinal cells, and the kidneys. When CK is simultaneously measured to rule out muscle disease and the serum isn'themolyzed, increases in AST and LDH-5 are caused with hepatocellular disease. AST may remain increased 10–14 days or more after an acute, transient insult to the liver. AST values are often normal in chronic hepatic disease. SDH and AST may be markedly increased by intrahepatic cholestasis and mildly increased by extrahepatic cholestasis. Increases in AP and GGT are relatedby irritation or destruction of biliary epithelium and biliary obstruction. AP comes from the placenta, bone, macrophages, intestinal epithelium, and liver. AP is increased in very young calves, because of the placental or bone source. In calves, AP levels up to 1,000 IU/L at birth and 500 IU/L at several weeks of age are considered normal. In calves (<6 wk old), none of the usual tests (bilirubin, GGT, GLDH, AP, LDH, AST, or alanine transaminase) for liver injured or function are clinically useful for detection of hepatic disease when used alone. AST and GLDH are the most sensitive of the enzymes for hepatic damage, but AST also increases by muscle injured. AST levels in foals may be elevated compared by values of acute for many months. This elevation is also likely associated to muscle development. Transient and mild increases in SDH activity may be noted in some foals <2mo old [13, 32].

Serum Total Bile Acid Concentration

Serum concentration of bile acids is highly specific for liver dysfunction but doesn't define the type of insult or disease present. Serum bile acid concentrations increase by hepatocellular injured, cholestasis, or shunts from the portal system to the vena cava. Elevations are highest by biliary obstruction and portosystemic shunts. Serum bile acid concentrations increase early in liver disease and often remain elevated through the later stages.Total bile acid concentration remains increased in horses by chronic liver disease. In horses, there is no diurnal variation, no postprandial rise, and no significant hour-to-hour variation in bile acid concentrations. Serum total bile acid concentration in most healthy horses is <10 µmol/L. Concentrations of serum or plasma bile acids >20 µmol/L have a high sensitivity and positive predictive value for determining liver disease in horses but not in ruminant animals. While bile acid concentrations >30 µmol/L can be an early predictor of liver failure, caution must be used in interpretation of mild elevations because bile acid concentrations up to 20 µmol/L may be seen in horses by anorexia. Prolonged, but not short-term, fasting may cause increased serum bile acid concentrations in horses.Interpretation of total bile acid concentrations is difficult in foals <1 wk old. Compared by those in healthy mature horses, serum bile acid concentrations in healthy foals are considerably greater during the first 6 wk of life. When measuring serum bile acid concentrations in sick foals, it'sespecially important to have healthy age-matched controls or age-dependent clinical pathology values for reference.In dairycattle, serum bile acid measurement is of little value in recognizing fatty liver or liver disease or failure because of significant hour-to-hour variations. In recently freshened cows, serum total bile acid concentrations are significantly higher than in cows in mid-lactation or in 6-mo-old heifers.Total bile acid concentration may be the best single test for hepatic disease in calves. In calves, concentrations >35 µmol/L may indicate liver disease, bile obstruction, or a portosystemic shunt.Reported reference intervals for serum concentration of bile acids are 1.1–22.9 µmol/L for llamas >1 yr old and 1.8–49.8 µmol/L for llamas <1 yr old. Bile acid concentrations in individual llamas may vary with feeding or sampling time of day, remaining within the reference interval [31, 35].

Serum Bile Pigments

Evaluation of serum bilirubin concentration is useful for determining hepatic dysfunction in horses and ruminant animals. Increases in bilirubin result from hemolysis, hepatocellular disease, cholestasis, or physiologic causes. Anorexia in horses causes a physiologic increase in total serum bilirubin to usually <6–8 mg/dL and rarely as high as 10.5–12 mg/dL. The indirect bilirubin increases 2- to 3-fold, thus the direct bilirubin remains into the reference range. In foals, indirect more than direct bilirubin may be increased by prematurity, neonatal isoerythrolysis, septicemia, or a portocaval shunt. Enteritis, umbilical infection, intestinal obstruction, and certain drugs may also cause hyperbilirubinemia. Mild, transient physiologic hyperbilirubinemia and icterus may be seen in newborn foals and calves. Although the mechanism(s) isn't fully known, proposed causes include pre-birth "loading of hepatocytes," naturally high RBC destruction at or around birth, inefficiency in bilirubinexcretion, or lower hepatocellular ligandin concentrations in neonatal foals compared to mature horses. In healthy calves <72 hr old, total bilirubin may be as high as 1.5 mg/dL and up to 0.8 mg/dL in 1-wk-old calves. Direct bilirubin is commonly<0.3 mg/dL in calves. In healthy foals (<2 days old), total bilirubin concentrations may range from 0.9–4.5 mg/dL, by most beingunconjugated bilirubin (0.8–3.8 mg/dL). Prematurity or illness may increase unconjugated bilirubin fraction in foals. Bilirubin concentrations in healthy foals should be intomature reference ranges with the time they are 2 wk of age. Normal values for total bilirubin in goats are 0–0.1 mg/dL.Horses by hepatic disease and failure most often have significant increases in indirect and direct bilirubin. With liver injure in horses or ruminant animals, most of the retained bilirubin is indirect, and the direct-to-total ratio commonly is <0.3. Acute liver failure caused with hepatic necrosis results in increases in indirect and direct bilirubin fractions. In horses bysevere liver failure, the increase in bilirubin is primarily because of an increase in the indirect fraction. Hepatocellular disease should be considered when the indirect bilirubin fraction is >25% of the total bilirubin value. Direct-reacting bilirubin rarely exceeds 25–35% of the total bilirubin in horses. Increases of this magnitude suggest predominant biliary disease or obstruction. With bile blockage or intrahepatic cholestasis, the direct-to-total ratio may be >0.3 in horses or 0.5 in cows. Elevations in direct bilirubin may be seen in septic foals by intestinal ileus and minimal evidence of hepatocellular dysfunction.In chronic liver disease, bilirubin concentrations are often into normal limits. Mature cattle and calves may have acute liver disease without any increase in serum bilirubin. In cattle, and sheep, circulating bilirubin levels increase only modestly byacute, generalized hepatic disease. The most dramatic increases in serum or plasma bilirubin concentrations are due to hemolytic crises rather than to liver dysfunction. In the absence of hemolysis, total serum bilirubin concentrations >2 mg/dL indicate impaired hepatic function in ruminants [10, 26].

Urobilinogen

Urobilinogen may be detected with dipstick analysis in normal horses. Increased levels of urobilinogen in urine without hemolysis are suggestive of a hepatic dysfunction, portosystemic shunting, or increased production with intestinal bacteria. Urobilinogen in the urine indicates the presence of a patent bile tube. Absence of urobilinogen may indicate complete biliary blockage, liver disease, or failure to excrete bilirubin into the intestine, reduce it by intestinal bacteria, or absorb it from the ileum. The correlation between urobilinogen and hepatocellular disease in animals is poor. Urobilinogen is unstable in urine; therefore, analysis must be done into 1–2 hr, or the amount will be decreased or undetectable [2, 6].

Serum and Plasma Proteins

Serum albumin and protein concentrations are variable in horses and cattle by hepatic disease. Hypoproteinemia isn't common in horses with acute liver disease. Serum albumin is most likely to be reduced in chronic liver disease due to decreased functional hepatic parenchyma. In one study of 84 horses, 13% were hypoalbuminemic. Albumin concentrations were below minimum reference values in 18% of horses by chronic liver disease and 6% bysevere liver disease. Globulin concentrations were elevated in 64% ofthe horses. Hyperproteinemia due to hyperglobulinemia may develop in horses by severe acute or chronic liver disease. Total plasma protein concentration is often normal, but the albumin to globulin ratio may be decreased.Plasma fibrinogen concentration may not be a sensitive test in horses by hepatic insufficiency. Low fibrinogen concentrations may result from parenchymal insufficiency or disseminated intravascular coagulopathy. A high fibrinogen concentration is relatedby an inflammatory response in horses bycholangiohepatitis [12].

Prothrombin Time

Abnormalities in pro-thrombin time (PT) are often the first detected because factor VII, a liver-synthesized vitamin K-dependent factor, has the shortest half-life. Serum PT may be rapidly prolonged with hepatic failure and is one of the first function tests to return to normal by recovery from severe hepatic disease. A normal PT determination, however, doesn't rule out coagulopathy due to vitamin K deficiency. Prolonged activated partial thromboplastin time (APTT) or other indications of coagulopathy may be noted in animals byacute hepatic disease. Because a number of factors may influence PT or APTT values in horses, the ratio of clotting time of the horse by suspected hepatic disease to that of a normal horse's value should be >1.3 for the test to be interpreted as abnormal [29].

Urea, Glucose, Ammonia, and Other Alterations

Serum concentration of urea may be decreased in severe and chronic liver failure. Hypoglycemia is usual in foals by hepatic failure. Blood glucose concentrations in mature horses by hepatic dysfunction are frequently normal or increased. Hypoglycemia, while less usual in mature horses and ruminant animals by hepatic dysfunction, is more in chronic liver disease. Plasma triglyceride concentrations are markedly increased in ponies, miniature horses, donkeys, and mature horses by hepatic lipidosis. The magnitude of increase in serum triglycerides may correlate by prognosis in horses. Alterations in triglycerides, very-low-density lipoproteins, and esterified cholesterol levels are more usual in ruminant animals than in horses by hepatic insufficiency. Neonatal foals have higher blood cholesterol and triglyceride concentrations than mature horses.Plasma ammonia levels may be increased by hepatic insufficiency but don't correlate well by severity of hepatic encephalopathy except during portocaval shunts. Increased levels of blood ammonia and symptoms of hepatic encephalopathy without hepatic failure are reported in Morgan weanlings by hyperornithinemia, hyperammonemia, and normocitrullinuria syndrome and in mature horses by primary or idiopathic hyperammonemia. Ingestion of urea or ammonium salts is more likely to cause increases of blood ammonia and encephalopathy in cattle than in horses.PCV and serum iron are often high in horses byacute liver disease. Increased hematocrit may persist in the face of fluid therapy and normal hydration status until the underlying liver disease is resolved. Secondary erythrocytosis has been noted in some horses by hepatic neoplasia. Increased serum iron concentration is usually seen in horses by both hepatic and hemolytic disease [21].

Dye Excretion and Clearance Tests

Sulfobromophthalein or indocyanine green dyes can be used to assess hepatobiliary transport. The BSP half-life is prolonged when >50% of hepatic function is lost. The normal clearance half-life of BSP is <3.7 min in horses, 2.13 ± 0.19 min in goats, and ≤4.0 min in sheep. BSP clearance is longer in calves (5–15 min) than in mature cattle (≤5 min). Although dye excretion tests are commonly prolonged by hepatic dysfunction, they may still be into the normal range. Hyperbilirubinemia, decreased hepatic blood flow, and significant cholestasis may falsely prolong and hypoalbuminemia may falsely shorten BSP clearance. BSP clearance in goats is most often prolonged by generalized hepatic lipidosis secondary to pregnancy toxemia. Estimation of BSP clearance time, rather than half-life, reportedly is more useful in detection of liver disease. BSP clearance time in healthy fed and 3-day fasted horses is 10 mL/min/kg and 6 mL/min/kg, respectively. These tests, however, are of limited use in clinical practice because of the lack of commercially available pharmaceutical-grade BSP. Expense, procedural limitations, and equipment requirements for quantitation of indocyanine green clearance have limited its use as a diagnostic test [28].

Scintigraphy

Biliary patency and hepatocyte function, structure, and blood flow may be evaluated by hepatobiliaryscintigraphy. Radionucleotide liver scans and biliary scans can detect alterations in blood flow or hepatic masses and biliary obstruction, respectively. Scintigraphy has been used infoals, and lambs to differentiate biliary obstruction from other causes of hyperbilirubinemia [5, 38].

Ultrasonography

Ultrasonography can be used to evaluate liver size, appearance and location in horses and ruminant animals for diagnosis of hepatomegaly, hepatolithiasis, biliary dilatation, cholelithiasis, or focal lesions. Tumors, cysts, abscesses, and granulomas may be observed. Diffuse diseases are harder to detect than focal processes because the former cause less distortion of normal hepatic architecture. Diagnosis of diffuse liver disease should be substantiated by biopsy and histopathology. Ultrasound can be used to guide collection of liver biopsy specimens and to perform cholecystocentesis and aspiration of abscesses, masses, or bile samples. It's also an accurate, noninvasive means for monitoring the progression or resolution of disease. In horses, the liver should be imaged from the right and left sides of the animal [14].

Liver Biopsy

Percutaneous liver biopsy is the definitive means of diagnosing hepatic disease. Histologic evaluation of the liver provides valuable information regarding etiology and severity of the disease process. Most cases of liver disease are diffuse, so the sample will be representative of the disease. Samples can be obtained blindly, but ultrasonographic guidance decreases the risk of complications. Liver biopsies can also be obtained during laparoscopy that offers the additional advantage of being able to visualize the area of the liver and other abdominal organs for evidence of disease.Samples should be placed in media for bacterial culture and sensitivity and in formalin for histologic evaluation. Coagulation profiles may be performed before liver biopsy to reduce the risk of hemorrhage. Liver biopsy maynot be advised in an animal by clinical or clinicopathologic evidence of a coagulopathy or a hepatic abscess because hemorrhage or contamination of the peritoneal cavity may result [8, 27].

Radiography

Contrast abdominal radiography in foals may be beneficial in diagnosing gastroduodenal obstructions and secondary cholangiohepatitis. Portosystemic shunts in foal'scalves can be identified by mesenteric portovenography with injecting radiopaque contrast solution within a jejunal mesenteric vein, followed by fluoroscopy or sequential survey radiographs to monitor the hepatic blood flow [23].

Treatment and Management

Initial treatment of ruminant animals bysymptoms of hepatic disease or insufficiency is often supportive and started before the underlying cause and extent of hepatic injure is known. History, clinical symptoms, and laboratory data may give some clue as to the nature of the hepatic disease process, but liver biopsy is commonly required to make a definitive diagnosis and to determine the degree of hepatic damage. Specific therapies for hepatic disease depend on etiology, presence of liver failure, chronicity, degree of hepatic fibrosis or biliary obstruction, and species affected. Increases in hepatic enzymes without hepatic disease may not require specific therapy for the liver but rather for the primary disease.Therapy is successful when intervention is early, hepatic fibrosis is minimal, and there is evidence of regeneration in the liver. Horses byacute or bridging fibrosis respond poorly because of inadequate potential for liver regeneration. The goals for treatment of large animals by hepatic disease or insufficiency are to control hepatic encephalopathy, to treat the underlying disease process, to provide supportive care to allow time for liver regeneration, and most importantly, to prevent damage to the animal and persons working by the animal. Domesticby hepatic encephalopathy often show aggressive and unpredictable behavior that can result in damage to self or handlers [16, 36].

Hepatic Encephalopathy and Hepatic Failure

Horses by hepatic encephalopathy may be aggressive or demonstrate repetitive behaviors that make restraint difficult. To ensure safety of the animal and handlers, sedation is required. Because most sedatives and tranquilizers are metabolized with the liver, their elimination half-life may be prolonged in ruminant animals by hepatic failure; thus, dosages should be minimized. A reduced drug dose's given to assess its effect. Xylazine or detomidine given in small doses to effect can be used to control horses exhibiting abnormal behavior. Diazepam should be avoided in animals by hepatic encephalopathy because it may enhance the effect of γ-aminobutyric acid on inhibitory neurons and worsen neurologic symptoms. Acepromazine should also be avoided because it may lower the seizure threshold.Dehydration, acid-base and electrolyte imbalances, and hypoglycemia should be corrected by appropriate IV fluids. Initially, a balanced polyionic solution is administered for rehydration. Potassium supplementation is added if the animal is hypokalemic or hypophagic. If IV infusion isn't possible in ruminant animals, rehydration may be attempted with oral administration of fluids if rumen motility is normal. Some horses by hepatic disease have polycythemia, making evaluation of hydration status with PCV difficult. Acute acidosis may be present. Because rapid correction of the acidosis may exacerbate neurologic symptoms, acidosis should be corrected gradually with IV administration of fluids by a high concentration of electrolytes. If this fails or if blood pH is <7.1, bicarbonate may be administered cautiously. Supplemental vitamins are optional. Adequate fresh water should be available if the animal can swallow normally.Factors that may contribute to the hepatic encephalopathy should be eliminated. Glucose as a 5–10% solution is given to correct hypoglycemia if present. In addition, glucose supplementation helps decrease blood ammonia concentrations and reduces catabolic gluconeogenesis, protein catabolism, and need for hepatic gluconeogenesis. Unless the animal is hyperglycemic, a continuous IV infusion of glucose should be given even to animals which aren't hypoglycemic. The infusion rate should be adjusted so that euglycemia is maintained. Induction of moderate to acute hyperglycemia, rapid diverse in glucose level, and glucosuria should be avoided. IV glucose should be used in combination by balanced electrolyte fluids and not as the sole fluid source.Therapies directed toward decreasing either ammonia production in or absorption from the bowel includes administration of mineral oil, neomycin, lactulose, and metronidazole. Administration of mineral oil decreases absorption and facilitates removal of ammonia. Passing a nasogastric tube in an animal by hepatic encephalopathy must be done cautiously because nasal bleeding caused with decreased clotting factors may be difficult to control. In addition, blood swallowed may exacerbate the neurologic symptoms. Oral administration of neomycin is used to decrease ammonia-producing bacteria in the intestine. Lactulose is metabolized to organic acids with bacteria in the ileum and colon. Reduction in colonic pH reportedly fosters an increased bacterial assimilation of ammonia, decreased ammonia production, ammonia trapping in the bowel, intestinal microflora divers, and osmotic catharsis. Reportedly, oral administration of vinegar (acetic acid) has the same effect on colonic pH and ammonia concentration in the gut. Metronidazole decreases ammonia-producing organisms in horses but shouldn't be used in food animals. If the animal can swallow, oral drugs can be mixed byKaro syrup or molasses and given via dose syringe to avoid trauma and risk of inducing hemorrhage during inert of a nasogastric tube. Neomycin, lactulose, and metronidazole may all potentially induce mild to acute diarrhea because of disruption of GI flora. Use of the drugs in combination is more to induce diarrhea than any one of the drugs given alone. Because metronidazole is metabolized with the liver, caution must be used when administering the drug to horses by hepatic failure. Neurologic symptoms due to metronidazole toxicosis may mimic hepatoencephalopathy.Until the nature of the

underlying hepatic disease is known, treatment by broad-spectrum antimicrobials is warranted if infectious hepatitis is suspected. A trimethoprim-sulfa combination is a good empiric choice because of its activity against gram-negative bacteria and its high concentration in bile. Penicillin in combination by an aminoglycoside has a broad spectrum of action and may be of useful if a Streptococcus.sp or an anaerobic or gram-negative coliform is suspected. Enrofloxacin has also been recommended. First- and second-generation cephalosporins have been used in foals and in other species. Metronidazole may be administered when anaerobic infection is suspected in horses. Specific antimicrobial therapy based on culture and sensitivity of a liver biopsy is ideal.Pain may be controlled by low doses of NSAID. In foals, butorphanol may be preferred. Vitamin K_1 and plasma transfusions may be given when coagulopathies develop or hypoalbuminemia is present. In some horses bysevere hepatic disease and failure, antioxidant and anti-inflammatory therapy may be benefit. Mannitol has been recommended for treatment of suspected brain edema in fulminant hepatoencephalopathy. Horses by hepatic disease should be protected from sunlight [4, 10, 23 and 35].

Dietary Management

Dietary management is mandatory for management of animals by hepatic encephalopathy or severe or chronic hepatopathy. Affected animals should be fed because dysphagia may be a problem. Relatively small amounts should be fed frequently. The diet should meet energy needs by readily digestible carbohydrates, provide adequate but not excessive protein, have a high ratio of branched-chain amino acids to aromatic amino acids, and be moderate to high in starch to decrease need for hepatic glucose synthesis. Fat and salt shouldn't be added to the diet. Feeds used successfully in horses include grass or oat hay and corn. Small amounts of molasses may be added to improve palatability and to add energy. Large amounts of molasses can make the feed less palatable and induce diarrhea. Linseed meal and soybean meal have an excellent branched-chain to aromatic amino acid ratio and may be used as a protein supplement in small quantities. Beet pulp may be substituted for oat or grass hay. Beet pulp should be soaked first to allow full expansion before being fed. Choke may be a problem in some animals eating beet pulp.The feeding of alfalfa hay, alfalfa-containing feeds, or other legume hays to horses by hepatic disease is controversial. Although alfalfa hay has a better branched-chain to aromatic amino acid ratio than grass hay, it may have too high a protein content. Feeding grass hay is preferred for animals by hyperammonemia or symptoms of hepatic encephalopathy. Mixed grass/alfalfa hay can be fed to horses without central neurologic symptoms if weight loss is a problem and the added protein is tolerated. Grazing grass pastures is allowable as long as symptoms of hepatic encephalopathy are controlled and exposure to sunlight is avoided.Other feeds high in branched-chain amino acids include sorghum, bran, or milo. Paren-teral or enteral supplement with branched-chain amino acids helps restore the normal ratio of branched-chain to aromatic amino acids. Supplement of vitamins A, D, and B_1 and folic acid, possibly by vitamins C and E, might be indicated. Vitamin K_1 may be indicated in animals with a coagulopathy. Large amounts of fat should not be fed to meet energy requirements; excessive fat may lead to fatty liver.Transfaunationby rumen fluid from a healthy cow may help reestablish normal ruminal flora and increase the appetite of affected cattle. Animals which will not eat voluntarily must be force fed. Gruel may be given with nasogastric tube in horses and swine or by orogastric tube or rumen fistula in ruminants. In ruminant animals, forced feeding of alfalfa meal and dried brewer's grain or beet pulp by potassium chloride and normal rumen fluid has been recommended. Alfalfa hay and alfalfa-containing feeds may be better tolerated with cattle than by horses with hepatic disease. IV polyionic fluids by 5% dextrose, potassium chloride, and B vitamins may also be needed in animals whicharen't consuming adequate amounts [5, 28].

REFERENCES

[1] Bonner,C.M., DeBrie,K.L.,Hug,G.,Landrigan, E.,andTaylor, B.J.**1995**. *J. Pediatr.*126, 28.
[2] Bonomi,A.,Quantarelli,   A.,Sabbioni,A.,Mazzali,I.,Cabassi, E.,Corradi, A., andCantoni, A.M.**1991**. *Riv.Soc.Ital.Sci.Alim.* 20,401.
[3] Borum,P.R.**1981**. *Nutr.Rev.*39,385.
[4] Borum,P.R.**1985**. *Can.J.Physiol. Pharmacol.*63,571.
[5] Borum,P.R.**1991**. InHandbook ofVitamins(L.J.Machlin,ed.),p.557.MarcelDekker,NewYork.
[6] Bremer,J.**1990**. *J.Clin.Chem.Clin.Biochem.*28,297.
[7] Cantrell, C.R.,andBorum,P.R.**1982**. *J.Biol.Chem.* 257,10599.
[8] Carter, A.L.,andFrenkel, R.**1978**. *J.Nutr.* 108,1748.
[9] Chan,M.M. **1984**.InHandbook ofVitamins(L.J.Machlin, ed.),p.549.MarcelDekker, NewYork.
[10] Chapa, A.M.,Fernandez, J.M,White,T.W., Bunting,L.D.,Gentry, L.R.,Ward, T.L.,andBlum,S.A.**1998**. *J.Anim. Sci.*76,2930.
[11] Goa,K.L.,andBrogden,R.N. **1987**. *Drugs*,34,1.
[12] Golper, T.A.,andAhmad, S.**1992**. *Semin.Dialysis*,5,94.
[13] Grandjean, D., Valette, J.P.,Jougln, M., Gabillard, C., Barque, H., Bene,M., andGuillaud, J.P.**1993**. *RecueildeMedecineVeterinaire,*169,543.

131

[14] Ha,T.Y.,Otsuka, M.,andArakawa, N.**1991**.*J.Nutr. Sci.Vitaminol.*37,371.

[15] Ha,T.Y.,Otsuka, M.,andArakawa, N.**1994**. *J.Nutr.* 124,732.

[16] Helms, R.A., Mauer, E.C., Hay, W.W., Christensen, M.L., and Storm, M.C. **1990**. JPEN14,448.

[17] McDowell, L. R.**2001**.

[18] Rebouche, C.J.**1991**. *Am.J.Clin.Nutr.*54(6Suppl.),1147S.

[19] Rebouche, C.J.**1992**. *FASEBJ.*6,3379.

[20] Rebouche, C.J.,andChenard, C.A.**1991**. *J.Nutr.* 121,539.

[21] Rebouche, C.J.,andEngel,A.G.**1983**. Arch.Biochem. Biophys.220,60.Rebouche, C.J.,andPaulson, D.J. *Ann.Rev.Nutr.* 6,41.

[22] Rebouche, C.J.,Panagides,D.D.,andNelson,S.E.**1990**.*Am.J.Clin.Nutr.*52, 820.

[23] Reznic, A.Z., Kagan, V.E.,Ramsey, R., Tsuchiya, M., Khwaja, S.,Serbinova, E.A.,andPacker,L.**1992**. *Arch.Biochem. Biophys.*296,394.

[24] Roe,C.R.,andBohan,T.P.**1982**. *Lancet* 1,1411.

[25] Rossle,C.,Kohse,K.P.,Franz,H.E.,andFurst,P.**1985**. *ClinicaChimicaActa*, 149,263.

[26] Sakemi,K.,Hayasaka,K.,Tahara, M.,Sanada, Y.,andTakada, G.**1992**. *To- hoku J.Exp.Med.*167,89.

[27] Santulli,A.,andD'Amelio,V.**1986**. *Aquaculture* 59,177.

[28] Santulli, A.,Modica, A.,Curatolo, A.,and D'Amelio, V.**1988**. *Aquaculture* 68,345.

[29] Spagnoli, A.,Lucca, U.,Menasce, G.,and Bandera. L.**1991**. *Neurology* 41, 1726.

[30] Stumpf,D.A.,Parker, W.D.,andAngelini,C.**1985**. *Neurology* 35,1041.

[31] Sugiyama,N.,Suzuki,K.,andWada, Y.**1984**. *Jpn.Pediatr.Soc.*88,1968.

[32] Tanphaichitr, V.,andLeelahagul, P.**1993**. *Nutrition* 9,246.

[33] Torreele, E.,VanDerSluisgen,A.,andVerreth, J.**1993**. *Br.J.Nutr.* 69,289.

[34] Tuan, S.,andChou, C.C.**1995**. *J.Chi.Nutr. Soc.*20,73.

[35] VanKempen,T.,andOdle,J.**1993**.*J.Nutr.* 123,1531.

[36] VanKempen,T.,andOdle,J.**1995**.*J.Nutr.* 125,238.

[37] Waber, I.J.,Valle,D., Neill, C., Dimauro, S.,and Shug,A.**1982**. *J.Pediatr.* 191(5), 700.

[38] Weaver,L.T.,Rosenthal, S.R.,Gladstone, W.,andwinter, H.S.**1992**. *ActaPediatr.*81,79.