Management of hepatopathy in horses

The liver plays a crucial role in metabolism, detoxification and nutrient storage. The liver's response to insult is often non-specific, with inflammation and subsequent fibrosis being the key pathological consequences. The treatment of liver disease is guided by clinical signs and biopsy findings. The aims of therapy are to support the recovery of the liver, treat the clinical signs (if present) and treat the cause of liver disease (if known). Corticosteroids are recommended first-line anti-inflammatory agents, and treatment is continued until biochemical evidence of improvement of hepatopathy is observed. Hepatic support supplements are commonly used but evidence of efficacy is lacking. This review outlines current treatment methods for hepatic disease and liver failure.
https://doi.org/10.12968/ukve.2023.7.?.??

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Key words: liver | hepatopathy | encephalopathy | supplements | ursodeoxycholic acid | milk thistle | S-adenosylmethionine

Submitted: 31 August 2023: accepted for publication following double-blind peer-review: 27 September 2023

The liver is the largest organ in the body and performs a range of essential metabolic, secretory, excretory and storage roles. All nutrients and toxins that are absorbed from the gastrointestinal tract pass directly to the liver through the portal vein, and therefore the liver has a vital role in detoxification of endogenous and exogenous substances, as well as maintenance of nutritional homeostasis.

The liver's response to insult is often non-specific; inflammation and subsequent fibrosis are the key pathological consequences (Durham et al, 2003). Overall hepatic function is not impaired until more than 80% of the hepatic mass is lost (Reed et al, 2018). When considering management, there are two general case presentations: those with high liver enzyme activity (liver disease), and those with biochemical, clinical and histopathological evidence of hepatic dysfunction (liver failure). Both presentations may be acute or chronic. Identifying the underlying cause of a hepatopathy can be challenging and treatment is therefore often non-specific. The liver has the ability to regenerate, as hepatocytes will proliferate in response to acute external stimulation and up-regulation of humoral factors (Reed et al, 2018). If hepatocyte loss is gradual and matches regeneration, then hepatic failure may not follow. The different aetiologies of liver disease have been discussed by *UK-Vet Equine*, and readers are directed to this article for more information (Tallon and McGovern, 2020a).

Diagnosis

For a comprehensive discussion of the approach to the liver disease case, readers are referred to a previous *UK-Vet Equine* review (Tallon and McGovern, 2020b). Once hepatic disease has been identified on biochemical parameters (liver enzyme activity), it is important to then ascertain whether the liver is failing by performing tests of liver function (bile acid concentration, conjugated bilirubin, ammonia concentration). The extent of increase in liver enzyme activity does not always correspond to functional abnormalities of the liver (Divers, 2015; Tallon and McGovern, 2020b). If liver enzyme activity is severely or persistently increased, or if there is evidence of hepatic failure, liver ultrasonography and biopsy are invaluable to identify aetiology, assess chronicity, aid formulation of treatment plans and provide a prognosis (Durham et al, 2003). Treatment of acute hepatic injury can result in a full recovery. On the other hand, chronic injury is more likely to result in irreversible changes and fibrosis which negatively impacts prognosis (Durham et al, 2003).

Treatment

Even with biopsy, the aetiology of liver disease or failure is often not identified (Durham et al, 2003). Treatment is guided by clinical signs and biopsy findings and is often non-specific. The aims of therapy are:

- To treat the clinical signs (if present)
- To treat the cause of liver disease (if known)
- To support recovery of the liver.

Treatment of clinical signs

Hepatic failure refers to the inability of the liver to perform its normal functions properly, with clinical signs of liver failure observed in conjunction with biochemical evidence of liver dysfunction. Clinical signs of hepatic failure are often not specific to aetiology; these are

commonly lethargy and weight loss. Success of treatment depends on the severity of the insult, chronicity of the disease and associated fibrosis (Durham et al, 2003).

Hepatic encephalopathy is a complex clinical syndrome associated with liver failure (Divers, 2015). It occurs irrespective of the aetiology of hepatic failure and the pathophysiology is not completely understood. The predominant hypothesis is increased circulation of enteric neurotoxins, particularly ammonia. Other components include augmented activity of gamma-aminobutyric acid (the predominant inhibitory neurotransmitter) in the brain, altered neurosteroid synthesis and release, cerebral inflammation and vascular dysfunction. Clinical signs are widely variable, from mild and non-specific depression, anorexia and yawning, or can be severe including head pressing, blindness, circling and coma (Reed et al, 2018). If the insult is acute, restoration of hepatic function may reverse the clinical signs (Gammal and Jones, 1989); treatment should therefore be instigated while further diagnostic testing is performed. Treatment is focused on maintaining organ perfusion and oxygenation, correcting electrolyte and acid–base disorders, reducing circulating neurotoxins and cerebral oedema. Referral for intensive care may be required if the horse is able to travel. If laryngeal paralysis is present, tracheostomy should be performed before referral to prevent upper respiratory obstruction and pulmonary oedema.

Sedation may be necessary to facilitate the safe examination of the horse and instigation of treatment. Alpha-2-agonists are appropriate. Care should be taken not to over-sedate, as a low head carriage may exacerbate cerebral oedema and worsen neurological status. Benzodiazepines are contraindicated as they enhance the effect of gamma-aminobutyric acid on inhibitory neurons and may worsen neurological signs (Mullen et al, 1990).

Intravenous fluid therapy is a crucial component to correct fluid deficit; volume expansion aids ammonia excretion, and horses with hepatic encephalopathy frequently have acid–base and electrolyte abnormalities (Divers, 2015). If the horse is anorexic, an intravenous infusion of 5% dextrose and electrolytes is beneficial (Divers, 2015). Hypertonic saline or mannitol can improve mentation by reducing cerebral oedema. In addition to supportive care, attempts should be made to reduce production and absorption of enteric neurotoxins, particularly ammonia. Oral antimicrobials (metronidazole, neomycin) may reduce the amount of ammonia-producing bacteria in the gastrointestinal tract, and therefore intestinal uptake of ammonia (Rose, 2012). Oral lactulose (0.3–0.5 ml/kg every 8 hours) is metabolised by ileal and colonic bacteria to organic acids, decreasing luminal pH and increasing ammonia 'trapping' as poorly absorbed ammonium in the intestine. Rarely reported complications include diarrhoea and laminitis (Scarratt and Warnick, 1998; Reed et al, 2018).

If the horse is eating, ideally a low protein and high carbohydrate diet should be offered in several small meals until the neurological disease is controlled. However, in reality, these patients are often inappetent, and encouraging food intake regardless of composition is essential. Extensive periods of anorexia may lead to negative energy balance and hyperlipaemia, which can further contribute to liver failure and other organ dysfunction (Durham and Thiemann, 2015).

Treating specific causes of liver disease

Cholangiohepatitis

Cholangiohepatitis is an infrequent cause of liver disease in adult horses in the UK, and may be acute or chronic. The aetiopathogenesis is uncertain but retrograde bacterial flow from the gastrointestinal tract through the bile ducts is probable. Clinical signs are consistent with non-specific liver disease, and include weight loss and dullness. Some may have intermittent pyrexia and, in cases with concurrent cholelithiasis, colic may be seen (Reed et al, 2018). Haematological parameters are often normal and hyperfibrinogenaemia may or may not be present (Peek and Divers, 2000). Therefore, the decision to treat with antimicrobial therapy may be difficult, and should be based on a combination of clinical signs, laboratory parameters and biopsy results.

Antimicrobial therapy is indicated if clinical signs, laboratory parameters and biopsy results show clinical evidence of cholangiohepatitis or evidence of neutrophilic infiltrates on histopathology. In these cases, long-term therapy may be warranted (Peek and Divers, 2000). One study reported a median treatment period of 51 days (17–124 days), with clinical improvement preceding biochemical recovery (Peek and Divers, 2000). Cessation of therapy should be based on normalisation of biochemical parameters and resolution of clinical signs. Antimicrobial selection should ideally be made based on culture and sensitivity of liver biopsy material; however, Peek and Divers (2000) found that 77% of cholangiohepatitis cases had negative culture results. The isolation of predominantly Gram negative and mixed anaerobes from horses with cholangiohepatitis supports the use of antimicrobials with efficacy against these organisms and antimicrobial stewardship should be exercised. Good empirical antimicrobial choices include trimethoprim sulphonamides or a combination of a B-lactam and aminoglycoside. Protected antimicrobials should not be prescribed unless supported by culture and sensitivity data.

Viral hepatitis

Commercial screening for viral hepatopathy is now available in the UK. Although there are no specific antiviral treatments available, diagnostic testing is valuable to provide prognosis, prevent horizontal spread of infection and avoid unecessary treatment (for example, with antimicrobials). With the exception of equine parvovirus, the clinical relevance of other identified hepatotropic viruses (equine pegivirus, Theiler's disease-associated virus and non-primate hepavirus) is the subject of current research (Tomlinson et al, 2019).

Fasciola hepatica

Fasciola hepatica (liver fluke) has an estimated seroprevalence of approximately 10% in the UK, with 2% of horses found to have adult fluke in the liver at post-mortem (Howell et al, 2020). Although they are more resistant to infection, horses can be infected with the same species as ruminants, and horses with liver disease were more likely to be seropositive than those without (Howell et al, 2020). Therefore, liver flukes should be considered in horses with liver disease which co-graze with ruminants or on wet pasture. Serology is commercially available in the UK and is superior to faecal analysis for diagnosis (Charlier et al, 2008). There is no licensed treatment for horses, but triclabendazole (15 mg/kg

orally) or closantel (10 mg/kg orally) may be administered according to the cascade. Resistance to these medications is prevalent in ruminants, and therefore this is likely to be the case when treating horses.

Mycotoxins

Specific forage mycotoxins have been associated with outbreaks of liver disease, but evidence for a causal association has not yet been found (Bates et al, 2022; Durham, 2022). Commercial mycotoxin binders are available and appear safe but there is no evidence of efficacy.

Support of liver recovery

Inflammation

Hepatic inflammation is a non-specific response to hepatic insult and is usually lymphoplasmacytic unless bacterial infection is present (Durham et al, 2003). Chronic inflammation (chronic active hepatitis) may lead to fibrosis, as hepatic stellate cells proliferate and produce collagen in response to inflammatory cytokines (Durham et al, 2003). Fibrosis is theoretically reversible, but in practice this is rarely seen, and therefore early control of inflammation is recommended to prevent development or progression of fibrosis. Surprisingly, there are currently no clinically approved effective anti-fibrotic therapies for humans. Agents with some evidence for use include glucocorticoids, pentoxifylline and vitamin E (Du et al, 2014; Shipley et al, 2019; Abdel-Maboud et al, 2020).

Dexamethasone (0.05–0.1 mg/kg every 24 hours) or prednisolone (0.5–1 mg/kg orally every 24 hours) are recommended first-line anti-inflammatory agents (Divers, 2015). Treatment should be continued until biochemical evidence of improvement (ie the levels of liver enzymes are reducing instead of increasing) of hepatopathy is observed, and then tapered. In humans with chronic active hepatitis, corticosteroids improved clinical signs, reduced inflammation and delayed fibrosis (Czaja, 2014). Azothioprine has been used in humans to control cases refractory to corticosteroids, but the oral bioavailability of this drug in horses is low (1–7%) (White et al, 2005). Corticosteroids and azathioprine can induce hepatopathy in humans, but this is rarely reported in horses, with a single case report of the former (Cohen and Carter, 1992). Pentoxyfylline, a phosphodiesterase inhibitor, has been shown to reduce hepatic fibrosis in humans (Windmeier and Gressner, 1997). Its oral bioavailability in horses is questionable and efficacy in liver disease unproven, but it does not have reported adverse effects and may be used in horses at a dose of 8–10 mg/kg orally every 12 hours (Liska et al, 2006). Colchicine is an anti-fibrotic, anti-inflammatory and immunomodulatory agent that has been used in inflammatory hepatopathies in humans. It has been used in horses (0.03 mg/kg orally once daily) but does not have evidence supporting its use. It is contraindicated in cases of pyrrolizidine alkaloid toxicity because of its anti-mitotic effect, and suspected toxicity causing bone marrow suppression and pancytopaenia has been reported (Peek et al, 2007).

Ursodiol (ursodeoxycholic acid) is the first-line treatment for humans with non-specific cholestatic liver disease (Camilleri and Gores, 2015). It is a secondary bile acid and a choleretic agent. It is cytoprotective of both hepatocytes and biliary epithelium against toxic changes and has immunomodulatory properties to reduce the harmful intra-hepatic immune response to toxic injury. It has been used anecdotally in horses in the USA (15 mg/kg orally every 24 hours) with cholangiohepatitis and chronic active hepatitis with evidence of cholestasis (Divers, 2015). There are no studies to assess bioavailability, efficacy or adverse side effects.

Hepatic support supplements

Critical appraisal of the human, small animal and equine data produces little evidence to support or refute the use of common hepatic supplements. Their use is based on extrapolated likely beneficial effects given the known pathophysiological pathways and mechanisms of action of the compounds.

The liver is responsible for storage of various vitamins (particularly A, D, E and K), and therefore storage, and possibly gastrointestinal absorption, of these vitamins may be reduced in horses with hepatic failure. National Research Council (2007) guidelines on daily requirements are available. There is evidence for antioxidant effects of vitamin E (Finno and Valberg, 2012), and therefore its supplementation to horses with hepatopathy is logical (5000 IU every 24 hours). In humans, vitamin E has been shown to reduce biochemical and histopathological liver scores in cases of non-alcoholic fatty liver disease (Rau et al, 2015; Amanullah et al, 2019; Abdel-Maboud et al, 2020) and is recommended in National Institute for Health and Care Excellence guidelines (2016) for this condition. There are two commercial sources of alpha-tocopherol: synthetic alpha-tocopherol (all-rac-alpha-tocopherol) has equal amounts of the 8 stereoisomers, whereas natural alpha-tocopherol (RRR-alpha-tocopherol) contains just the single isomer. RRR-alpha-tocopherol is the most biologically active isoform, preferentially taken up by the liver and has the most potent antioxidant properties (Finno and Valberg, 2012). Bioavailability of RRR-alpha-tocopherol is significantly higher than the synthetic form, and water-dispersible formulation is more bioavailable than powdered or pelleted forms (Brown et al, 2017).

Similarly, vitamin C has antioxidant effects and supplementation has been demonstrated to be beneficial in humans with non-alcoholic fatty liver disease, with less evidence than for vitamin E (Wei et al, 2016; He et al, 2021). Ascorbic acid is poorly absorbed in horses, therefore supplementation with ascorbyl monophosphate is advised (20 mg/kg every 24 hours) (Deaton et al, 2003). Supplementation with vitamins E and C is considered relatively safe.

In humans with chronic liver disease, zinc deficiency is common, and supplementation has been shown to reduce fibrosis and aid in ammonia detoxification (Hosui et al, 2018). In horses, zinc modulates the immune system and has antioxidant properties, therefore supplementation in the face of liver disease could be considered (van Bömmel-Wegmann et al, 2023). Supplementation with iron, copper or manganese is not advised as these have potential for toxicity in excess (Auer et al, 1989; Theelen et al, 2019).

Milk thistle (*Silybum marianum*) and its active derivatives (flavonolignans) are reported to have hepatoprotective properties (Saller et al, 2007), with the group silybin considered to have the most hepatoprotective properties. Experimental studies have identified antifibrotic, anti-inflammatory and metabolic effects

of *silybin*, but a meta-analysis of the use of milk thistle for treatment of liver disease in humans did not identify a positive effect of the compound on liver enzyme activity, liver histopathology or mortality (Jacobs et al, 2002). Pharmacokinetic data identified oral bioavailability to be as low as 0.6% (Jaramillo et al, 2020). However, as silybin undergoes primarily biliary excretion with high concentrations in the enterohepatic circulation, antioxidant effects may not directly relate to serum levels. Weak antioxidant effects were identified in horses when high oral doses were administered (26 mg/kg) (Hackett et al, 2013). Milk thistle is common in commercial equine supplements, but most commercial formulations provide between 1–7 mg/kg at recommended feeding rates, lower than doses used in clinical studies, and therefore these supplements are unlikely to have a significant clinical effect. No adverse effects of supplementation have been recorded.

S-adenosylmethionine is a bioactive form of methionine which is converted to glutathione peroxidase, an important antioxidant in the liver. In chronic liver disease, conversion of methionine to glutathione peroxidase is suppressed, therefore supplementation with S-adenosylmethionine may bypass hepatic synthesis and increase systemic glutathione peroxidase. Human and small animal data show some benefit in cholestatic disease, but studies have shown that it only has a minimal effect in hepatotoxicity or alcoholic cirrhosis (Center et al, 2005; Guo et al, 2015; Kilanczyk et al, 2020). There are no clinical trials investigating the pharmacokinetics, oral bioavailability or clinical efficacy of S-adenosylmethionine in equine liver disease. Recently, S-adenosylmethionine has been removed from the UK equine feed register, meaning that it cannot be marketed for use in equine supplements in the UK. Therefore, recent UK liver supplements are more likely to contain methionine, but as this requires hepatic metabolism to convert to glutathione peroxidase, the logic behind supplementation with this compound is flawed. Similar to milk thistle, where S-adenosylmethionine has been included in supplements, the doses used are considerably lower (2–10 mg/kg) than those used in human medicine therefore it is likely that it is under-dosed. S-adenosylmethionine is also destroyed by gastric acid unless it is enteric coated (Cameron et al, 2020) and therefore commercial, non-enteric coated formulations are unlikely to be successfully absorbed.

Dietary alterations for horses with hepatic disease but adequate liver function are not required. Protein should not be restricted, as it is important to maintain muscle mass and prevent ammoniagenesis associated with catabolism (Divers, 2015).

Conclusions

Management of both acute and chronic hepatopathy is based on reducing inflammation and subsequent fibrosis to allow the liver to recover. Antimicrobials should be administered if there is evidence of infection clinically or on histopathology. Beyond this, although they appear safe, there is no evidence for the clinical efficacy of hepatic support supplements. Liver failure may require intensive management especially if the patient is inappetent or displaying signs of hepatic encephalopathy. The prognosis is dependent on the severity of clinical signs, liver enzyme activity and bile acid concentration, histopathology results and response to initial therapy. EQ

KEY POINTS

- The aetiology of hepatopathy is often unknown; therefore, management is often based on clinical signs and histopathology and focused on reducing inflammation and fibrosis.
- Cholangiohepatitis is uncommon in the UK. Antimicrobials should only be used if there is evidence of bacterial hepatopathy.
- Liver failure can result in hepatic encephalopathy, which may require intensive management.
- There is no evidence to support or refute the efficacy of liver support supplements in horses.

Conflicts of interest

The authors have no conflicts of interest to declare.

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