Equine liver disease; nutritional causes and nutritional management

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The liver has numerous key metabolic functions

The numerous and diverse key metabolic functions of the liver include metabolism of proteins, carbohydrates and lipids, gluconeogenesis, synthesis of most of the plasma proteins, storage of glycogen, fat-soluble vitamins (A, D, E, K) and other key nutrients (iron, copper, selenium, molybdenum) and detoxification of dietary xenobiotics such as mycotoxins. Consequently nutritional support is an important consideration when managing horses with hepatic disease.

Nutritional causes of equine liver disease

Determining the aetiology of liver disease can be frustrating. Reported dietary causes include plant toxicity (particularly those containing pyrrolizidine alkaloids), iron overload, mycotoxins, macrofungi (eg Amanita spp.), heavy metals, agrochemicals, cyanobacteria and hyperlipaemia. In the author’s experience, the aetiology of many outbreaks unfortunately remains undetermined, despite extensive and costly investigation, including specialist laboratory testing. This suggests that many other, as yet unidentified, causes of equine liver disease exist. Herein nutritional causes of equine liver disease are reviewed.

Hepatotoxic plants

Hepatotoxic plant species include; Senecio spp., Lupinus, Heliotropium, Echium, Symphytum, Crotalaria, Trichodesma, Amsinckia, Cynoglossum, Panicum and Trifolium hybridum and T. pratense. Many of these contain pyrrolizidine alkaloids (PA), with Senecio spp. being the most commonly implicated in equine hepatic disease in Europe. Senecio spp. are generally unpalatable and are typically only consumed when other food is unavailable, or when palatability increases following droughts or frost. As PA retain their toxicity in dried forages, toxicity may occur when horses ingest plants within conserved forages, or when the plants are cut and left on pasture. All parts of the Senecio plant contain PA, with levels being highest at the onset of flowering. PA are prootoxins which are converted by hepatic CYP450 enzymes into highly reactive derivatives which react with macromolecules (eg proteins, nucleic acids and lipid) in hepatocytes and hepatic endothelial cells. This inhibits protein synthesis and induces oxidative stress and lipid peroxidation. DNA damage inhibits hepatocyte mitosis, preventing hepatocyte regeneration, leading to megalocytosis and fibrosis. Comparative toxicity indices for PA are; pigs 1, chickens 5, cattle and horses 14, rats 50, mice 150, sheep and goats 200
The lethal intake of *S. jacobaea* approximates 5-15% of body mass on a DM basis (Mattocks 1986; Cheeke 1988; Craig et al 1991). PA have a cumulative effect, with chronic, cumulative toxicity being the most common scenario, although there is typically an acute onset and rapid deterioration in clinical signs as hepatic failure ensues. Experimental challenge with *Senecio vulgaris* at 10% of diet resulted in failure around 5-7 months (Mendel et al 1998). Early clinical signs of reduced appetite and weight loss were considered difficult to recognise, while the onset of more definitive clinical abnormalities was acute and typically rapidly fatal. Experimental challenge with *S. jacobaea* at 5% of diet resulted in 2 clinical patterns; a chronic disease with death in 1.5-5 months and a chronic delayed form with death in 9-15 months (Craig et al 1991). Pathologic sequelae include karyomegaly, progressive fibrosis, nodular regeneration, bile duct proliferation, veno-occlusion and cirrhosis. The extensive and progressive fibrosis carries a poor prognosis. Since megalocytes are typically present only after 30 days of PA toxicity, acute PA toxicity may present only with centrilobular necrosis. Furthermore megalocytes were not identified in all experimental horses receiving PA, despite all having chronic disease (Craig et al 1991). PA toxicity may be suspected/confirmed by current or historical evidence of PA exposure, histopathology, and, if available, laboratory detection of pyrrolic metabolites in plasma or tissues (Moore et al 2008). Identification of PA toxicity should prompt attempts to prevent further PA exposure and testing of in-contact horses to detect those with sub-clinical liver disease.

**Mycotoxins**

Recent developments in our understanding of the aetiology of equine liver disease include association of liver disease with mycotoxins, particularly fumonisin B1 in stored forage (Durham et al 2018; Verdruscolo et al 2017). More than 30 fumonisins have been described, being produced by *Fusarium verticillioides*, *F. proliferatum*, *other Fusarium* spp. and *Aspergillus niger*. Horses are reported to be the most sensitive species (Voss et al 2007), with more than 5,000 horses dying in 1934-1935 in US after consuming corn infected with *F. verticillioides* and *F. proliferatum*. Occasional deaths have occurred following ingestion of barley contaminated with *F. graminearum* and ingestion of contaminated hay. The possibility of fumonisin induced liver disease affecting pastured horses was raised following the report of hepatic disease in deer grazing pastures in New Zealand where fumonisins were detected in grass samples (Mirocha et al 1992). High doses of fumonisins cause liver pathology and mild cerebral lesions, while chronic, lower-level exposure causes predominantly leukoencephalomalacia. Hepatic disease is characterised by hepatic lobular necrosis, hepatocyte vacuolation, centrilobular fatty change, periportal fibrosis, periportal vacuolation, bile duct proliferation and mild mononuclear infiltrate.

Aflatoxins may cause equine liver disease (Bortell et al 1983; Divers 2015). Experimental administration of aflatoxin B1 (AFB1) identified the liver as the major target organ, with effects ranging from sub-clinical to rapid-onset fatal hepatopathy. AFB1 causes centrilobular necrosis, biliary proliferation, fibrosis, megalocytosis, coagulopathy, ascites, encephalopathy, pleural fluid accumulation, tracheal exudates and hepatocellular carcinomas (Angsubhakorn et al 1981). As with many mycotoxins, hepatic metabolism of AFB1 is augmented by previous exposure to this toxin. Subclinical hepatopathy is a well-recognised syndrome in grazing horses in Northern France, which tends to occur in particular fields and following particular weather
conditions. While it appears to be associated with ingestion of a mycotoxin produced by endophytes on *Fescue* spp., extensive investigation has not identified the causal toxin.

The author has identified a potential association of acute fulminant hepatopathy in grazing horses with ingestion of the hepatotoxic mycotoxin sterigmatocystin (STC) in wilted grass colonised by *Aspergillus* spp. STC is the precursor of aflatoxin B1, and is similarly hepatotoxic, mutagenic, nephrotoxic, and teratogenic (EFSA 2013). Experimental challenge induces acute hepatocellular necrosis in rats, mice, monkeys, poultry, pigs and guinea pigs, with LD50 values in the range of 120 to 166 mg/kg body weight (Versilovskis et al 2009; EFSA 2013). Clinical consequences of natural exposure are rarely reported. Ingestion of feed contaminated with 7.75 mg/kg STC was associated with bloody diarrhoea and death in dairy cattle (Vesonder and Horn 1985). Fatal, acute centrilobar hepatic necrosis in a southern white rhinoceros (*Ceratotherium simum*) was associated with ingestion of *Aspergillus nidulans* contaminated lucerne hay which contained 1.56 µg/kg STC (Bryant et al 2016).

Interpreting the clinical significance of mycotoxin data for feeds in relation to equine liver disease is challenging, given a) the inhomogeneous distribution of mycotoxins in feed, b) the degradation of some mycotoxins in feed, c) the presence of masked mycotoxins, d) the synergistic effect of other mycotoxins, e) the marked individual susceptibility in quantity of mycotoxins required to cause disease/death, f) the influence of genetics, diet, substrates, rate and duration of ingestion, and g) inter-species differences in susceptibility. Horses are typically more sensitive to ingested mycotoxins than ruminants because of the limited microbial detoxification in the proximal gastrointestinal tract.

### Iron overload

Animals lack an efficient mechanism to eliminate iron from the body, with only small quantities of iron being eliminated via loss of blood, sweat, intestinal epithelial cells, skin and urinary cells. Consequently, abnormalities in iron homeostasis can cause significant iron overload. Hepatic and systemic iron overload is a common finding in many advanced liver disorders in man and horses (McGorum et al 1999; Dunkel et al 2015; Kowdley 2016). In most cases this is a secondary consequence of underlying liver disease attributable to abnormal iron homeostasis, in part because of reduced hepatic synthesis of hepcidin which leads to uncontrolled intestinal iron absorption. Less commonly, iron accumulation is due to primary iron overload, with the hepatic iron accumulation leading to secondary hepatic disease. Primary iron overload may occur with excess dietary iron intake, parenteral administration of excess quantities of iron, and possibly with haemolytic disorders and repeated blood transfusions. Oral administration of a probiotic/nutritional supplement containing 64 mg of ferrous fumarate caused fatal liver failure in many neonatal foals (Divers et al 1983). Theelen et al (2015) reported haemochromatosis and liver disease/failure in a group of horses due to chronic excessive intake of iron in ditch water. Horses had elevated serum Fe, Fe saturation and total iron binding capacity. Water iron concentration was markedly elevated (72.5 mg/l; acceptable threshold <0.5 mg/l), while iron levels in soil were feeds not increased.

Accumulation of iron within the liver, whether primary or secondary to liver disease, can exacerbate liver disease and fibrosis *via* production of reactive oxygen species through...
the Fenton and Haber–Weiss reaction (Zou and Sun 2017). Consequently, severe hepatic
haemosiderosis is associated with increased risk of short and long-term non-survival in
horses with liver disease (Durham et al 2003; Dunkel et al 2015). Iron overload may also
lead to insulin insensitivity in horses (Nielsen et al 2012). Iron toxicity may be treated
by feeding a diet low in iron, administration of oral deferoxamine and repeated
phlebotomy.

**Hyperlipaemia**

Hyperlipaemia is a very common cause of liver failure, particularly amongst insulin
resistant native breed ponies, miniature breeds and donkeys, and those with pituitary pars
intermedia dysfunction. Negative energy balance and increased levels of stress hormones
triglyceride lipolysis in adipose tissue, with resultant increases in circulating
free fatty acids, triglycerides and lipoproteins. Upregulation in the activity of lipoprotein
lipase, which converts triglycerides to free fatty acids to be used as energy substrates or
to be stored in adipose tissue, fails to clear circulating triglycerides. Deposition of lipid
within organs leads to multi-organ failure. Ketonaemia, due to incomplete oxidation of
free fatty acids, rarely occurs in equine hyperlipaemia.

**Nutritional management of equine liver disease**

The mainstay of nutritional support for equine liver disease is prevention of further
exposure to hepatotoxins and provision of a high-energy and adequate-protein diet. For
horses that are appetent, this may simply involve offering frequent (q 4-6 h) small meals
of palatable, readily digestible carbohydrate and protein rich feeds such as grass, cereals
and sugar beet pulp. Individual meals should comprise of only small quantities (< 1g/kg
bw) of high glycaemic feeds, to avoid dramatic and detrimental fluctuations in blood
glucose and insulin levels, and passage of undigested carbohydrate into the large
intestine.

Numerous ancillary treatments are commonly administered to horses with liver disease,
in an attempt to counteract the detrimental effects of hepatotoxins and promote
hepatocyte regeneration, but this is largely done without any evidence of efficacy. Various forms of dietary vitamin E, S-adenosyl methionine (SAMe) and silymarin are
commonly administered. In some natural and experimental hepatic diseases, silymarin
in milk thistle extract exerts membrane-stabilizing and antioxidant activity, promotes
hepatocyte regeneration, reduces hepatic inflammatory reaction, and inhibits hepatic
fibrogenesis (Feher and Lengyel 2012), however there is no clear clinical benefit in
human chronic hepatopathy (Loguerico and Festi 2011). There are no efficacy data for
silymarin in equine liver disease, and any potential benefit may be limited by the poor
(<1%) oral bioavailability of silymarin flavonoids in horses (Hackett et al 2013). Similarly, there is no evidence of efficacy for SAMe, a precursor of the antioxidant
glutathione, in human liver disease (Anstee and Day 2012), although SAMe and vitamin
E attenuated the hepatic oxidative stress induced by monocrotoline pyrrole in rats (Amin
et al 2014). Dietary supplementation with cysteine, butylated hydroxyanisole, 200 ug
vitamin B12/kg of feed, and 5 mg/kg of folic acid/kg of feed did not alter toxicity in
ponies with experimental *S. jacobaea* hepatotoxicosis (Garrett et al 1984). While oral
mycotoxin binding agents such as charcoal and rock powders (eg selective calcium
montmorillonites), which provide a large surface area to adsorb mycotoxins, have some
efficacy in farm animals, data are lacking for horses. Given the potential to interfere with absorption of essential nutrients, chronic prophylactic administration of these agents is currently not recommended.

Lactulose, metronidazole, neomycin, prebiotics and probiotics may be fed to horses at risk of developing hepatic encephalopathy, to decrease intestinal bacterial-derived ammonia production. Administration of the branched chain amino acids (BCAA) valine, leucine, and isoleucine to horses with hepatic encephalopathy is controversial. In other species, BCAA may improve glucose metabolism, decrease protein and muscle catabolism, and provide an alternative pathway for ammonia detoxification, however they may increase glutamine synthesis and potentially worsen encephalopathy.

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