ANAESTHESIA AND LIVER DISEASE: WHEN TIME TO START TO WORRY?

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Marieke De Vries concludes her two-part series (first article *VT*41.38) with a look at how the liver is affected by treatments and drug-induced cases

Summary

This is the second part of two articles dedicated to anaesthesia and liver disease in dogs and cats. In the first part, interpretation of abnormalities in biochemistry which may be found on routine pre-anaesthetic blood work up was discussed. The current part will cover effects of anaesthesia on the liver, together with drug-induced liver diseases, and anaesthesia for liver disease-related procedures.

Key words

drug-induced, liver disease, anaesthesia, liver metabolism

THE healthy liver has a substantial reserve capacity due to the dual blood flow from the portal vein (70 to 75 per cent) and hepatic artery (25 to 30 per cent), as well as its regenerative capacity.

The hepatic artery supplies 45 to 50 per cent of the liver’s oxygen requirements, and the portal vein supplies the remaining 50 to 55 per cent.

Hepatocytes are susceptible to hypoxia, as only 25 per cent of the blood flow is oxygenated blood (coming from the hepatic artery). The remainder is deoxygenated blood derived from the portal vein. Hypoxia rapidly results in plasma membrane and cytosolic organelle damage secondary to adenosine triphosphate (ATP) depletion, with leakage of hepatic enzymes as a consequence.

Splanchnic blood supply may be highly variable – to compensate for this, the so-called “hepatic arterial buffer response” exists, mediated by locally active substances, such as adenosine, nitric oxide and endothelin. This response enables the hepatic artery to dilate in reaction to reduced portal venal blood flow. The portal venous system is essentially a passive vascular system – intra-operative reductions in cardiac output and systemic vascular resistance, and increases in right atrial pressure, which may result in decreased portal vein blood flow. Sympathetic activation results in vasoconstriction of the hepatic artery and mesenteric vessels, decreasing hepatic blood flow.

Patients with severe liver disease may be (relatively) volume depleted due to a decrease in total vascular resistance and splanchnic vasodilation. Hepatic blood flow may also be decreased because of an increase in portal venal vascular resistance. These patients may be functionally hypovolaemic, despite normal or elevated total blood volume. Renal blood flow (due to, for instance, increased intra-abdominal pressure [ascites]), may be altered and kidney function suboptimal – assessment of kidney function is, therefore, recommended (urea, creatinine, electrolytes and urinalysis).

As already pointed out in part one of this article, there is a difference between anaesthetising a patient with “just raised” liver enzymes and patients with liver function impairment. Raised enzymes do not necessarily mean that liver function is compromised, and these patients can be anaesthetised according to relatively “normal” protocols.

In general, the goal of intraoperative management in patients with (suspected) liver disease is maintaining adequate hepatic blood flow and oxygen delivery to the hepatic cells by ensuring adequate circulating volume and arterial oxygen tension.

Factors known to reduce hepatic blood flow (hypotension, excessive sympathetic stimulation and high mean airway pressures [IPPV]) should be avoided. In these patients, perioperative fluid therapy and measuring blood pressure during the anaesthetic period are paramount.

Drugs and liver disease

One of the important functions of the liver is drug metabolism – lipid-soluble compounds are converted to more water-soluble structures, which are then excreted in urine or bile.

Liver disease may result in impairment of the enzymes involved, resulting in a prolonged duration of action. Metabolism of certain drugs (lidocaine, morphine, verapamil, labetalol and propranolol) is highly dependent on hepatic blood flow. These drugs have very high rates of hepatic extraction

from the circulation. Decreased hepatic blood flow may result in a decrease in their metabolic clearance. In general, in patients with impaired liver function, administrating drugs that are short acting (pethidine), can be rapidly antagonised (alpha-2-adrenoceptor agonists) or (partly) rely on extra-hepatic metabolism (propofol, remifentanil and atracurium) is preferable.

Sedatives

Acepromazine is extensively metabolised by the liver, has a long duration of action and is, therefore, not recommended for use in patients with liver disease. Its use may not only result in profound, long-lasting sedation, but also in long-lasting side effects, such as hypotension and hypothermia due to vasodilation.

Alpha-2-adrenoceptor agonists are known for their reliable sedative properties and analgesic effects that are, however, accompanied by cardiovascular side effects (hypertension, bradycardia and reduced cardiac output). These drugs are metabolised by the liver.

Although they may not be ideal sedatives because of their side effects and potential reduction in hepatic blood flow, they can be useful if sedation is required, as they are relatively short-acting and can be antagonised by the use of atipamezole if needed. Low doses are advocated in these cases, starting with 1.0µg/kg to 5µg/kg of medetomidine and 0.5µg/kg to 2.5µg/kg of dexmedetomidine IM/IV.

For termination of their effects, benzodiazepines rely on liver metabolism. Their effect may be severely prolonged in liver disease cases. Midazolam is shorter-acting than diazepam and less cumulative, so may be a better option if the use of a benzodiazepine is desired.

Induction agents

All the induction agents – propofol, ketamine, alfaxalone and thiopental – are metabolised by the liver. Out of these, propofol is perhaps the best option, as it is partly metabolised by extrahepatic tissues (lungs, kidneys), and can easily be administered to effect.

Volatile agents

All volatile agents reduce cardiac output and arterial blood pressure, and, therefore, may reduce liver blood flow. These agents may also blunt the hepatic arterial buffer response, further reducing hepatic blood flow. Halothane appears to reduce hepatic blood flow more than the “newer” agents, such as isoflurane, sevoflurane and desflurane, because of systemic vasodilation and negative inotropic effects. Isoflurane undergoes minimal metabolism (0.2 per cent) and may positively affect hepatic blood supply by direct reduction of portal vascular resistance. Although sevoflurane is metabolised to a higher extent (two to five per cent), it appears to be as safe as isoflurane,

considering its effect on hepatic blood flow. As these volatile agents will (dose-dependently) reduce arterial blood pressure, it is important to monitor blood pressure and maintain mean arterial blood pressure above 60mmHg to 70mmHg.

Opioids

Some controversy exists as to whether opioids are contraindicated in patients suffering from pancreatitis and/or cholangitis. In dogs, the common bile duct terminates in the duodenum near the opening of the minor pancreatic duct, on the major duodenal papilla.

The feline common bile duct usually joins the major pancreatic duct before entering the duodenum.

The sphincter of Oddi is located in the wall of the duodenum as the terminal part of the common bile duct. Some opioids may result in constriction of Oddi, and may theoretically result in stasis of bile and pancreatic secretions in cats. As no evidence suggests that administering opioids to these patients increases this risk, and as these patients are often full of pain and will benefit from (multimodal) analgesic therapy, opioids should not be withheld. Lower doses may be used initially, in case prolonged effects may be seen due to decreased liver metabolism. When insufficient analgesia is achieved, a top-up may be administered. If severe or prolonged side effects occur, naloxone may be used to antagonise the pure-mu opioid agonists. However, it is important to realise that its administration will also antagonise the analgesic effect of the opioids, and analgesia may have to be provided in other ways.

NSAIDs

In general, NSAIDs form the mainstay of (multimodal) analgesia protocols, and are very effective in alleviating pain.

Increased liver parameters per se should not be an indication to withhold the use of these drugs, as this does not necessarily correlate with impaired liver function. Even a one-off (reduced) dose of meloxicam or carprofen may be very effective in providing analgesia in painful conditions. However, in case of liver function impairment, use of these drugs is contraindicated.

Hartmann’s solution (lactated Ringer’s)

Lactated Ringer’s solution contains lactate as a bicarbonate precursor. Lactate is metabolised in the liver, and it has been suggested that administering this type of fluid may increase lactate concentrations in animals with severe liver disease.

However, this is controversial and the clinical importance of this effect must be determined on an individual basis. Lactate accumulation following the administration of Hartmann’s solution to

patients with liver dysfunction is not typically observed. Other organs (kidneys and heart) may increase their lactate utilisation to compensate for a reduced metabolism by the liver.

Drug-induced liver disease

• Volatile agents

Sometimes, a mild hepatic reaction may be seen post-anaesthesia, with small (transient) increases in liver enzymes associated with low morbidity and mortality. This is likely to be due to alterations in hepatic oxygen delivery relative to demand, resulting in inadequate oxygenation of the hepatocytes.

In humans, halothane is also associated with a risk of autoimmune-mediated hepatitis following (repeated) exposure, resulting in severe liver failure with high mortality. Halothane is, compared to the other volatile agents, extensively metabolised by the liver (up to 25 to 40 per cent). One of its metabolites (trifluoroacetate, TFA) may act as a hapten: specific circulating IgG antibodies react with TFA bound to microsomal proteins on the surface of hepatocytes, resulting in cell-mediated toxicity. Although, theoretically, isoflurane and desflurane metabolism may also result in the formation of TFA, the amount produced is very small, as these agents are metabolised to a much lesser extent and, therefore, the risk of hepatic damage is reduced. Sevoflurane metabolism does not result in formation of TFA due to the difference in its chemical structure.

• Anticonvulsants

Phenobarbital and phenytoin may result in increased liver enzymes, but patients are often asymptomatic and tests of liver function are often normal.

These drugs may also cause microsomal enzyme induction, leading to a (theoretically) increased anaesthetic drug requirement and a shorter duration of action. However, this does not seem to have a clinically noticeable effect. Most dogs in which clinical signs of liver impairment occur have been on treatment for more than one year. Improvement may be seen after drug therapy cessation.

• NSAIDs/carprofen

Hepatic toxicity has been described with the use of NSAIDs. However, the exact mechanism is not known, but it is not related to prostaglandin inhibition. An acute, idiosyncratic reaction to carprofen has been described in dogs.

Twenty-one dogs, of which 13 were Labrador retrievers, receiving carprofen developed hepatocellular toxicosis.

Clinical signs (anorexia, vomiting, lethargy, polyuria/polydipsia and icterus) were noted five to 30

days after initiation of therapy. Treatment consisted of immediate cessation of carprofen administration, supportive care (fluid therapy, gastrointestinalprotectants) and administrating antibiotics. Four dogs died or were euthanised, and all Labrador retrievers survived. In all surviving dogs, biochemistry repeated three to four weeks after the onset of clinical signs showed marked improvement of liver parameters.

In a number of dogs, renal function was compromised as well. It is noteworthy that, at the time the study was p e r f o rmed, already more than 500,000 dogs in the US had been administered carprofen. Pfizer (Pfizer Animal Health Technical Bulletin) has published a result in which the incidence of adverse reactions involving the liver was reported to be 0.052 per cent in dogs. At that time, more than four million dogs had received carprofen in the US.

It is recommended to assess liver and renal function before initiating carprofen therapy, and have these parameters measured again after approximately two to three weeks to detect patients with developing hepatic or renal disease. Clients should be informed of the clinical signs of drug intolerance and instructed to immediately discontinue the drug if these signs develop. As this idiosyncratic reaction to carprofen is often acute in dogs, repeat biochemistry is not necessarily needed on a yearly basis.

• Diazepam

Hepatotoxicosis in humans is uncommon, and serious adverse effects of diazepam administration in veterinary patients are rare. Most common reported side effects are sedation and a temporal increase in appetite. However, in cats, an idiosyncratic reaction has been described, resulting in hepatotoxicity with a high mortality rate. Affected cats received oral diazepam repeatedly for treating inappropriate urination, urethral spasm or aggression. Signs occurred within the first week of treatment included anorexia, vomiting, lethargy, jaundice with increased levels of alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transpeptidase (?GT) and bilirubin.

Other symptoms included hypoglycaemia, coagulopathies and acute renal failure. Care should be taken with the repeated oral administration of diazepam to cats. It is prudent to assess liver function in these patients prior and during treatment, if treatment is indeed instigated. Owners should be informed to monitor closely for (the first) signs of liver compromise to stop treatment immediately.

• Corticosteroids

Steroid hepatopathy can result from either excessive endogenous (hyperadrenocorticism) or exogenous glucocorticosteroids, and represents one of the most common causes of increased liver enzymes in canine patients.

The exact aetiology of these glucocorticosteroid-induced liver changes is unknown. The degree of

rise in liver enzymes depends on the individual patient, and on the type, route and duration of administration. Changes may persist for months after a single injection of a long-acting glucocorticosteroid or after long-term administration of oral preparations. Changes may also occur after topical, aural and ocular administration.

Clinical signs (polyuria/polydipsia, polyphagia and lethargy) are often related to the glucocorticosteroid excess, rather than to liver impairment. Development of severe hepatic disease is rare. In dogs, AP and ?GT are markedly increased, while ALT and AST are mild to moderately. These changes are completely reversible when the source of excess glucocorticosteroids is removed. Albumin and bilirubin are often normal; in case of abnormal values, other causes should be looked for.

Anaesthesia for liver-disease related procedures

• Liver biopsy

Fine-needle aspirates may be acquired under sedation. Ultrasound-guided biopsies are taken under general anaesthesia.

As part of the pre-anaesthetic work up, the coagulation profile should be assessed. Fresh frozen plasma may be required to increase circulating coagulation factors. Vitamin K may be administered 24 hours before liver biopsy in case of biliary obstruction and absence of bile salts, which are needed to facilitate gastrointestinal absorption of this vitamin.

Ideally, liver biopsies are scheduled as morning procedures, so that during the day the patient can be monitored for potential haemorrhage.

Pulse rate and quality, respiratory rate, colour of mucous membranes and capillary refill time are regularly assessed in the post-biopsy period. After two to three hours, the patient is rescanned for the presence of free abdominal fluid (haemorrhage).

An IV catheter is maintained for ongoing IV fluid therapy if needed, and otherwise kept patent for rapid IV access in case of an emergency. Often, these patients are hospitalised overnight to ensure that adequate monitoring and, if needed, treatment, can be provided.

• Portosystemic shunt work up/ligation

Patients with portosystemic shunts are prone to hepatoencephalopathy, which may manifest itself from mild clinical signs (anorexia, depression and lethargy) to head pressing, circling, behavioural changes, seizures and coma.

Prior to anaesthesia/surgery, medical treatment with lactulose, antibiotics and a low-protein diet

– with an increased ratio of branched chain to aromatic amino acids – should be instigated to optimise the patient's condition. Routine haematology and biochemistry are often relatively unremarkable – total bilirubin is typically normal, liver enzymes (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) may be increased to two to three times the normal values, consistent with a lesion of hepatic atrophy and minimal hepatocellular injury. Bile acids, especially after stimulation, and fasting ammonia concentrations are increased.

Urea, glucose, total proteins and albumin are often typically decreased. A mild, non-regenerative microcytic anaemia and hypokalaemia (due to vomiting, diarrhoea and urinary loss due to diuresis) may also be present. Although uncommon, increased clotting times may be seen, but clinical evidence of impaired coagulation is rare.

In one retrospective study, activated partial thromboplastin time was prolonged by 25 per cent or more in 51 per cent of the patients with congenital portosystemic shunts, but this was not associated with bleeding tendencies.

In the same study, prothrombin time (PT) was only above normal upper limits in eight per cent of the patients. If clinical haemorrhage because of abnormalities in coagulation does occur, it is mainly seen in the immediate postoperative period and rarely during surgery itself.

Often, these patients are young and small (puppies), and may require sedation for imaging or IV catheterisation (Figure 2).

The use of acepromazine should be avoided, as it is extensively metabolised by the liver, has a long duration of action (which will be longer in case of liver impairment), and may result in hypotension and hypothermia due to its peripheral vasodilatory effects. Sometimes an opioid may be sufficient to sedate these patients (methadone or pethidine when analgesia and sedation are needed, or butorphanol for sedation purposes only). If not sufficient, a small dose of an alpha-2-adrenergic receptor agonist may be used, as these drugs can be antagonised if needed, but be aware of their cardiovascular depressant effects (bradycardia, increase in systemic vascular resistance and reduction in cardiac output). Recommended doses vary from as low as 1.0ìg/kg to 2ìg/kg of medetomidine or dexmedetomidine IM/IV.

It is important to realise that reversal of an alpha-2-adrenergic receptor agonist also reverses its analgesic effects. These patients may exert exacerbated responses to centrally acting drugs, especially benzodiazepines. This is the result of an increase in the number of central gamma-aminobutyric acid (GABA) receptors, and a decrease in clearance by the liver of endogenous benzodiazepinelike substances derived from the gastrointestinal tract. Induction of anaesthesia in these patients can best be achieved by use of propofol, as this can be easily titrated to effect by slow injection and undergoes some extrahepatic metabolism as well.

Prior to anaesthesia, measurement of packed cell volume, total protein, albumin and electrolytes

are minimal requirements to assess hydration state and liver function. Perioperative monitoring of glucose is very important, as these patients are prone to hypoglycaemia; glucose concentrations below 3.5mmol/L should be treated promptly with the IV administration of dextrose/ glucose solutions if oral supplementation is not possible.

Fasting time should be kept to a minimum – for instance, to four hours. As these patients are often small, they may develop hypothermia rapidly, as their body surface area to volume ratio is large. Measuring body temperature and preventive actions should be undertaken to minimise heat loss. These patients often experience hypotension during anaesthesia – it is, therefore, important to measure blood pressure, ideally via direct arterial cannulation. IV fluids, reduction of vaporiser settings as much as possible and the administration of colloids or (fresh) frozen plasma may all help in the prevention and treatment of hypotension.

For shunt ligation, blood substitutes should be available, as these procedures carry an increased risk of haemorrhage, especially when ligation of an intra-hepatic shunt is performed.

Postoperatively after shunt ligation, patients are monitored closely for signs of portal hypertension – abdominal distension and discomfort, haemorrhagic diarrhoea, ileus, shock and cardiovascular collapse.

Abdominal haemorrhage must be distinguished from portal hypertension as both conditions may result in shock and cardiovascular collapse. Seizures may occur as a postoperative complication and should be treated with anticonvulsants (keppra or phenobarbital) or propofol, after having ruled out other causes (hypoglycaemia).

The exact pathogenesis of these seizures is unknown, but sudden withdrawal of the anticonvulsant effects of endogenous benzodiazepines has been hypothesised, together with changes in brain amino acid and neurotransmitter profiles.

Analgesia can be provided by the multimodal approach. Opioids, guided by regular pain checks and given as needed, epidural administration of morphine and (a one-off dose of) NSAIDs may all be beneficial.

Feline hepatic lipidosis

This condition is essentially a consequence of catabolism from anorexia due to any cause. Most common signs are chronic vomiting and anorexia, weight loss, icterus, hypersalivation and previous obese body condition.

These patients may suffer from concurrent diabetes mellitus or pancreatitis. Increased AP can be seen, with smaller or often no increases in ?GT (different from most other liver diseases in cats).

Mild-to-moderate increased alanine transaminase and aspartate aminotransferase, bilirubin and cholesterol may also occur. Acid-base and electrolyte disorders may be profound and need to be addressed with appropriate fluid therapy. These cats may require anaesthesia for placing feeding tubes (Figure 3). In general, the use of short-acting, reversible agents is advocated for these procedures, after stabilisation of the patient first.

Liver lobectomy/ tumour resection

These patients are at risk for haemorrhage during the procedure, not only because of the potential coagulation impairment, but also because of the invasiveness of the procedure itself.

The clotting profile should be assessed prior to surgery, and fresh frozen plasma and blood should be available if haemorrhage is of concern.

Placing two IV catheters is advisable in case various IV drugs and fluids have to be administered (rapidly). It is paramount to monitor arterial blood pressure in these patients, ideally by the direct, invasive way.

Conclusion

Although the liver is an organ with an enormous reserve capacity, hepatocytes are prone to hypoxia and consequent cell damage. Main goals during anaesthesia of patients with (suspected) liver function impairment are adequate liver perfusion and oxygen delivery.

Measurement of arterial blood pressure during anaesthesia, and undertaking actions to maintain blood pressure within normal limits, are paramount. To avoid long-lasting effects of drugs heavily metabolised by the liver, use of short-acting and potentially reversible agents are highly recommended in these patients.

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