ANAESTHESIA AND THE LIVER

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Anaesthesia and surgery in patients with problems related to the liver cause concern because of the central role of the liver in many of the body's metabolic and synthetic functions. The process of anaesthesia may adversely effect these functions and equally the patient's response to anaesthetic drugs and surgery may be influenced by hepatic dysfunction. It is therefore necessary for those practicing anaesthesia anywhere in the world to have an understanding of liver function in normal physiology.

Liver Functions

The liver conjugates bilirubin, produced from the degradation of the haemoglobin of red cells that are at the end of their normal life span. This now water-soluble form of bilirubin is then excreted into the bile ducts and thence into the small intestine. Also passed to the gut are the bile salts produced by the liver and necessary for the absorption of the fat-soluble vitamins A, D, E and K. Vitamin K is essential for the production of prothrombin and some other protein factors that are essential for the normal clotting of blood.

Synthesis of many proteins takes place in the liver including most clotting factors and many carrier proteins, such as albumin, which to a varying degree bind drugs used during anaesthesia. The liver is also central in lipid metabolism with cholesterol and triglycerides synthesised here. The synthesis and breakdown of glycogen in the liver is pivotal in carbohydrate metabolism. It stores glycogen and releases glucose into the blood when the blood glucose falls for any reason.

The liver is responsible for the biotransformation of drugs either by oxidation or conjugation in order to render them water-soluble and therefore more easily excreted in the urine or bile.

The Effect of Anaesthesia and Surgery on Liver Function

Inhalational anaesthetics effect carbohydrate metabolism in several ways. Ether, unlike the newer agents, enhances the breakdown of glycogen in the liver. Halothane has been shown, experimentally, to decrease the rate of glycogenesis, inhibit insulin release and inhibit the effect of insulin on the tissues. The catacholamine mediated stress response to surgery and trauma also increases glycogenolysis, so the overall effect of both surgery and inhalational anaesthesia is to elevate blood glucose**.**

Protein synthesis is reduced by halothane but this is of questionable clinical significance.

Halothane and ether both inhibit the Cytochrome P450 enzyme system, slowing the oxidative metabolism of drugs; gluconuride conjugations are not effected. The following drugs, as a result, have a prolonged half-life in the presence of halothane, fentanyl, ketamine, lignocaine, pancuronium and propranolol.

Hepatic blood flow is decreased by halothane in parallel with an overall decrease in cardiac output. Intermittent positive pressure ventilation and decreases in carbon dioxide potentiate this effect while hypoventilation and increased carbon dioxide results in an increase in hepatic blood flow. These effects are unlikely in isolation to lead to liver hypoxia or damage.

Opioids such as morphine, pethidine and fentanyl are known to be able to cause spasm of the Sphincter of Oddi and increase biliary pressure, the effect lasting about two hours in the case of morphine. This should not preclude their use to provide adequate analgesia in biliary surgery.

Halothane and Jaundice

It was discovered some years ago that some adult patients can,very rarely, become jaundiced from severe hepatic damage after a second halothane anaesthetic. The incidence of this *halothane hepatitis* in adults is thought to be 1:7000-30,000 halothane anaesthetics. It is even rarer in paediatric patients and with the newer volatile agents. The risk is thought to be higher in women, the middle aged and the obese.

The cause of so-called halothane hepatitis is not fully established and may be multifactorial. The effect seems to be related to the degree of metabolism of the volatile agent, so toxic metabolites may be involved. The onset time of the jaundice is shorter with increasing numbers of exposures to halothane and there have been suggestions of a possible immunological cause. It has also been suggested that reduced hepatic blood flow and hypoxia are to blame. In most cases of post operative jaundice halothane is unlikely to be the cause so given the rarity of the condition, and the limited choice of agents in the developing world, anaesthetists under these circumstances should not hesitate to use halothane whenever it is appropriate.

Interestingly there is no evidence that halothane will precipitate hepatic deterioration in patients with jaundice of a different origin. Ether may cause a transient depression of liver function but does not cause significant damage.

Anaesthesia and Surgery in Patients with Liver or Biliary Dysfunction Before the anaesthetist can assess the implications of a patient's hepatic disease for the conduct of an anaesthetic, it is necessary to understand the various causes of jaundice - the cardinal sign of liver disease.

Jaundice can be prehepatic (haemolytic), hepatic (hepatocellular) or posthepatic (obstructive) in origin. An example of prehepatic jaundice is in the haemolysis that accompanies the breakdown of a large haematoma, or the jaundice that can occur when there is a massive intravascular haemolysis - as in some forms of malaria or in sickle cell anaemia. In these situations the hepatocellular function is normal but overwhelmed and so the increased bilirubin is for the most part unconjugated. Protein and carbohydrate metabolism is intact and there is no reduction in the absorption of Vitamin K or production of clotting factors.

Where there is actual hepatocellular dysfunction, as in hepatitis or cirrhosis, there may be evidence of decreased protein synthesis, with oedema and ascites, signs of delayed clotting only partly reversed by vitamin K administration, and even encephalopathy. Hepatic encephalopathy is a condition of progressive deterioration of cerebral function from drowsiness to coma, in patients with liver disease, probably caused by toxic metabolites of proteins in the large intestine not adequately detoxified by the liver. These patients may show other signs of chronic liver disease as listed in Table 1.

Patients with active liver disease, such as hepatitis, are at high risk of deterioration during surgery and this should be avoided or delayed where possible. The poorest outcome is predicted by the combination of deranged clotting, oedema and encephalopathy.

Obstructive Jaundice Biliary obstruction is the most likely cause of jaundice to be encountered by the anaesthetist in the developing world. It can result from a stone in the common bile duct, pancreatic tumour or ascending cholangitis where the bile and biliary tree are infected. Hepatocellular function is normal (although it may deteriorate in prolonged obstruction) so the excess plasma bilirubin is chiefly conjugated. As conjugated bilirubin is water-soluble it will be excreted in the urine which becomes dark. Stools are pale as a result of poor lipid absorption. Although protein synthesis is normal, the production of vitamin K dependant clotting factors will be reduced, as the absorption of vitamin K is dependent on the excretion of bile salts into the small intestine. The clotting time can, therefore, be prolonged but this can be readily reversed by parenteral administration of vitamin K. Surgery in these cases is to remove or bypass the obstruction or to drain infected obstructed bile.

Liver Function Tests

Where laboratory investigations are available these should be part of any preoperative assessment of patients with probable liver or biliary dysfunction. As well as providing an indication of severity, they may help differentiate between prehepatic, hepatocellular and obstructive jaundice.

Jaundice is the outward sign of an elevation of serum bilirubin. As already discussed a predominantly conjugated bilirubin suggests an obstructive cause, while unconjugated bilirubin points to a prehepatic problem. Hepatic disease may result in a predominantly unconjugated or a mixed pattern. Dark urine containing bilirubin suggests biliary obstruction.

Protein and albumin levels are usually normal in prehepatic or obstructive jaundice, whereas low values may indicate impaired synthetic activity in the liver resulting from hepatocellular damage.

Table 1 Some Signs of Liver Disease

Jaundice	Hepatomegaly	Spider Naevi	Splenomegaly
Scratch Marks	Ascites	Palmer Erythema	Dilated Abdominal Veins
Peripheral Oedema	Finger Clubbing	Testicular Atrophy	Bruising
Gynaecomastia	Confusion/Coma		

A measure of clotting impairment is the Prothrombin Time, given as an absolute value or compared to a control. The WHO recommends the use of the International Normalized Ratio (INR) which is the Prothrombin Time ratio obtained when using a WHO International Reference Thromboplastin. An elevated INR may indicate impaired synthesis of clotting factors due to hepatocellular damage or malabsorption of vitamin K due to biliary obstruction. The INR is also used to monitor therapy with the anticoagulant warfarin.

Plasma glucose should be measured because of the pivotal position the liver plays in carbohydrate metabolism discussed earlier.

Alanine Transaminase (ALT) and Aspartate Transaminase (AST) are enzymes that are released into the circulation by damaged hepatocytes. Raised levels of these enzymes tend, therefore, to indicate hepatocellular damage. AST can also be elevated in other circumstances such as myocardial infarction so other indicators of liver disease must be sought.

Alkaline Phosphatase (ALP) is an enzyme localized near the bile cannaliculi and is elevated in biliary obstruction. Again this enzyme is not specific to hepatobiliary disease, it is, for example, raised in malignant bone disease. An accompanying rise in Gammaglutamyl Transferase (Gamma GT) suggests that the ALP is from the liver.

Other laboratory investigations of use in the preoperative assessment of these patients are the haemoglobin, a blood film (for evidence of haemolysis), plasma urea and creatinine.

Hepatorenal failure

One of the main concerns in surgery for biliary obstruction is the development of renal failure. This serious condition has been recognized since the 1950's although the cause is not completely understood. It may be related to pre and peroperative dehydration and hypovolaemia, falls in renal blood flow during surgery, a direct effect of the excess conjugated bilirubin on the renal tubules or possibly an increased absorption of endotoxin from the gut.

The key to managing this condition is to avoid it developing by ensuring adequate hydration and a urine flow of at least 50mls/hr in the average adult patient. In most patients with moderately elevated bilirubin this can be achieved with simple fluid loading for 12 hours before surgery using 0.9% NaCl and during the operation. If the urine output is not maintained in this way mannitol 10% should be administered until an adequate diuresis is achieved.

Where the bilirubin is greatly elevated (>140 micromols/litre), patients should be given intravenous fluids during the 24 hours before surgery and for 36 hours postoperatively. In these cases mannitol 10% 0.5-1g/kg should be administered prior to surgery, although the patient must not be allowed to become dehydrated as a result of an over-zealous diuresis.

Hepatorenal failure does not appear to be a major risk in patients with prehepatic jaundice.

Drug Elimination

In biliary obstruction there is no significant alteration in drug handling and normal doses of thiopentone, opiates, benzodiazepines and muscle relaxants are given. Although the nondepolarising muscle relaxant vecuronium is partly cleared through the bile, the normal rapid uptake by the liver cells is unchanged and there is no effect on the half-life.

In contrast, where there is significant hepatocellular dysfunction as in advanced cirrhosis or acute hepatitis, drug handling can be disturbed. Decreased synthesis leads to lowered levels of carrier proteins in the blood. This means that for the same dose of a highly protein bound drug, such as thiopentone, there will be a greater level of unbound and therefore active drug. Smaller doses are required. The liver produces serum cholinesterase, responsible for the breakdown of suxamethonium, but a reduction of 50% is required for any clinically significant prolongation of the effect of this drug, which is uncommon.

Drugs that are metabolised in the liver may have prolonged half-lives when hepatocellular function is poor. This may lead to accumulation of drugs given by infusion and where drugs given in repeat or top up doses, such as muscle relaxants, the interval between doses should be prolonged. Ideally drugs such as induction agents should be titrated to effect and neuromuscular blockade should be monitored with a peripheral nerve stimulator.

Regional Anaesthesia

Spinal and epidural anaesthesia carries the risk of epidural haematoma and paralysis if there is abnormal clotting but there are otherwise no special precautions. The half-life of lignocaine is prolonged in liver failure but this is not significant when used in regional anaesthesia.

Conclusions

It is important to assess each patient with disease of the liver or bile ducts for signs of liver dysfunction, bearing in mind that conditions involving the liver do not necessarily disturb normal hepatic physiology – eg amoeboma and schistosomiasis. Patients with severe liver failure are unlikely to present for surgery in the developing world unless they suffer unrelated trauma. These patients would be at high risk of deterioration or death during surgery; the combination of clotting abnormality, oedema and encephalopathy predicts a poor outcome. If these patients must have surgery vitamin K should be administered preoperatively and care taken with drug dosage. The more likely indication for surgery is biliary obstruction. Here drug dosing is less problematic, the more important issues being correction of impaired clotting and avoidance of the hepatorenal syndrome.