

Anaesthesia for patients with liver disease

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Patients with end-stage liver disease are at significant risk of morbidity and mortality after anaesthesia and surgery. Medical or surgical interventions may exacerbate liver dysfunction and result in life-threatening hepatic failure.^{1, 2} The incidence and prevalence of liver disease (particularly alcoholic liver disease and hepatitis C) is increasing in the developed world and presents the anaesthetist with considerable challenges. In the UK, in 2006, 4450 people died from alcoholic liver disease, and deaths are increasing by 7% per year. Outside the setting of liver transplantation programmes, end-stage liver disease should constitute a relative contraindication to surgical intervention except in life-threatening situations.

Causes of liver disease

Chronic

The most common causes of chronic liver disease are viral hepatitis (hepatitis B and C), autoimmune disease, and alcoholic liver disease.³ Cryptogenic liver disease is also common; other known factors are cholestatic conditions (primary biliary cirrhosis and sclerosing cholangitis), venous outflow obstruction, drugs, toxins, and metabolic disease (e.g. Wilson's disease, haemochromatosis, α_1 -antitrypsin deficiency).

Acute

In the UK, acetaminophen overdose is the most common cause of acute hepatic failure (70%) while worldwide it is viral hepatitis. Alcohol and other drugs including methyl-dopa, isoniazid, rifampicin, acetyl salicylic acid, and other non-steroidal anti-inflammatory drugs (NSAIDs) are also implicated. Amanita phalloides, a poisonous mushroom, is a rare cause

of acute liver failure. Despite the diversity of causes of liver disease, the outcome after anaesthesia and surgery depends more on the degree of liver impairment than the actual cause.²

Extrahepatic manifestations of liver disease

Gastrointestinal

Portal hypertension (portal pressure >10 mm Hg) is associated with the development of a collateral venous circulation, ascites, and splenomegaly. The presence of gastric and oesophageal varices can result in catastrophic gastrointestinal haemorrhage. Even mild bleeding into the gut may precipitate or worsen encephalopathy, as digestion of blood grossly increases the bilirubin load presented to the liver. Splenomegaly leads to sequestration of platelets and thrombocytopenia. Massive ascites can raise intra-abdominal pressure with adverse effects on respiratory and renal function. Gastric emptying is also delayed and patients are therefore at increased risk of acid aspiration syndrome, necessitating protection with H_2 antagonists and cricoid pressure.

Portal hypertension may initially be treated with β -blockers such as propranolol.^{3, 4} Octreotide or vasopressin may be added to control gastrointestinal bleeding. Ascites is normally treated with sodium and water restriction; however, abdominal paracentesis is occasionally required. A rapid reduction of intra-abdominal pressure after drainage of a large volume of ascites causes marked reductions in central venous pressure, pulmonary capillary wedge pressure, and cardiac output. Plasma volume is reduced because of the re-accumulation of ascites and

Key points

Patients with end-stage liver disease have a high perioperative morbidity and mortality.

The pharmacokinetics and pharmacodynamics of anaesthetic drugs are significantly altered in liver disease.

Coagulopathy, intravascular volume, and the extra-hepatic effects of liver disease must be addressed before surgery.

Invasive monitoring is recommended during major surgery.

Close attention should be paid to liver blood flow, renal function, encephalopathy, and the prevention of sepsis.

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cardiovascular collapse may occur. If drainage of ascites is necessary, the simultaneous infusion of i.v. colloids or human albumin solution, and drainage of no more than 5 litres is recommended.

Cardiovascular system

The circulation in patients with advanced liver disease is characteristically hyperdynamic with a high cardiac output and low systemic vascular resistance. Alcoholic liver disease and haemosiderosis are associated with cardiomyopathy. Patients with advanced liver disease may have risk factors for coronary artery disease such as cigarette smoking and hyperlipidaemia. The reduced left ventricular workload caused by vasodilatation may mask underlying coronary artery disease and cardiomyopathy; these may become apparent during anaesthesia or surgery.

Respiratory

Diaphragmatic splinting from ascites or the presence of pleural effusions restricts alveolar ventilation, reduces FRC, and predisposes to atelectasis and hypoxia. Associated gastro-oesophageal reflux disease, acute alcohol ingestion, and massive ascites may increase the risk of aspiration of gastric contents. Intrapulmonary arteriovenous shunting may also occur. Patients may experience dyspnoea and hypoxaemia when sitting upright, which improves on lying flat (orthodeoxia).⁴ The presence of pulmonary vascular shunting is best detected on echocardiography (this incorporates the ‘saline bubble test’—where agitated saline is injected i.v. as a contrast medium) and if present can be termed the hepatopulmonary syndrome. In some patients, hypoxaemia may be severe which can be reversed by liver transplantation in suitable cases. Very occasionally, a patient with portal hypertension will be found to have pulmonary hypertension with increased pulmonary vascular resistance and normal pulmonary capillary wedge pressure, which cannot be attributed to any other cause. This is termed portopulmonary hypertension.⁵

Haematological

Anaemia may be present secondary to chronic blood loss from the gastrointestinal tract, hypersplenism-induced haemolysis, chronic illness, and malnutrition. Reduced capacity to synthesize clotting factors results in coagulopathy, particularly affecting the vitamin K-dependent factors II, VII, IX, and X, with elevated prothrombin and activated partial thromboplastin times. Thrombocytopaenia and platelet dysfunction are common.⁴ Dysfibrinogenaemia and fibrinolysis may occur in alcoholic cirrhosis.

Renal and metabolic

Secondary hyperaldosteronism leads to water retention and hyponatraemia resulting in the formation of ascites and peripheral oedema. Loop diuretics used to treat the ascites and oedema can cause relative hypovolaemia and hypokalaemia. Conversely, the

aldosterone antagonist spironolactone can cause hyperkalaemia. Vasodilatation associated with general anaesthesia may result in renal hypoperfusion and the development of pre-renal renal failure. Any acute deterioration in liver function can lead to the hepatorenal syndrome,⁶ caused by renal hypoperfusion, portal hypertension, intra-abdominal hypertension, and nephrotoxins alone or in combination. The development of hepatorenal failure will necessitate postoperative haemodialysis and carries a poor prognosis. Depletion of hepatic and muscle glycogen stores may result in perioperative hypoglycaemia. Muscle wasting is common due to impaired protein synthesis and malnutrition.

Central nervous system

Patients with alcoholic liver disease with vitamin B1 (thiamine) deficiency are at risk of Wernicke’s encephalopathy. The development of hepatic encephalopathy in patients with chronic liver disease can be precipitated by infection, gastrointestinal haemorrhage, electrolyte or acid–base disturbance, sedative drugs, hypoglycaemia, hypoxia, hypotension, or excessive dietary intake of protein. Alternatively, it may be a sign of gradual progression of the liver disease. Hepatic encephalopathy is a major feature in acute liver failure and is graded according to level of consciousness (Table 1). High grades of coma reflect cerebral oedema with raised intracranial pressure and carry a grave prognosis.³

Relevant pharmacology

I.V. anaesthetic agents

The dose of thiopental should be reduced because a reduction in plasma proteins results in an increased unbound fraction of drug; the distribution half-life and consequently the duration of action are also prolonged. Sensitivity to the sedative and cardiorespiratory depressant effects of propofol is increased; hence the dose should be reduced. Etomidate may be used safely but offers little advantage over thiopental. Chronic alcohol use may increase anaesthetic requirements, but all i.v. agents should be used with great care.

Neuromuscular blocking drugs

The metabolism of succinylcholine may be slowed because of reduced pseudocholinesterase concentrations, but in practice this

Table 1 Grades of hepatic encephalopathy

Grade	Status	Neurological signs
0	Alert and orientated	None
1	Drowsy but orientated	Tremor, apraxia, incoordination
2	Drowsy and disorientated	Asterixis, dysarthria, ataxia
3	Agitated and aggressive	Asterixis, muscle rigidity, Babinski reflex, hyper-reflexia
4	Unresponsive to deep pain	Decerebration

gives few problems. There is an apparent resistance to non-depolarizing neuromuscular blockers (NMBs) in patients with liver disease, which may be due to an increased volume of distribution or to altered protein binding. Vecuronium and rocuronium, both steroid-based NMBs, have a prolonged elimination phase in severe liver disease. Atracurium and cisatracurium are suitable NMBs as they do not rely on hepatic excretion. After prolonged administration, concentrations of laudanosine (a metabolite of both atracurium and cisatracurium with potential to cause seizures) are lower with cisatracurium than atracurium due to the higher potency of cisatracurium, although this is unlikely to be of clinical significance. In all cases, it is advisable to monitor neuromuscular function.

Opioids

Elimination of morphine is delayed in cirrhotic patients due to both reduced hepatic blood flow and extraction ratio. In patients with associated renal failure, accumulation of the active metabolite morphine-6-glucuronide will occur. Morphine is perhaps best avoided in patients with decompensated liver failure as it may precipitate hepatic encephalopathy. Fentanyl, given in low doses, is suitable for intraoperative use as it does not have an active metabolite and is renally excreted.⁷ However, in repeated or large doses, fentanyl will accumulate. Elimination of alfentanil is reduced in liver disease, its volume of distribution increased, and protein binding reduced by the lack of alpha-1-acid glycoprotein. Remifentanyl is ideally suited to intraoperative use as it is metabolized by tissue and red cell esterases, which unlike plasma esterases are preserved in patients with severe liver disease.

Volatile anaesthetics

All volatile anaesthetics reduce cardiac output and mean arterial pressure and thereby reduce liver blood flow. Isoflurane, sevoflurane, and desflurane undergo minimal hepatic metabolism and can be regarded as safe.⁸ Desflurane is probably the ideal volatile agent, being the least metabolized and providing the quickest emergence from anaesthesia. It also relatively preserves hepatic blood flow (it has minimal effects on the hepatic arterial buffer response) and cardiac output.

Preoperative evaluation and optimization

Preoperative evaluation of patients with liver disease should focus on the extent of liver dysfunction and effects on other organ systems. Viral hepatitis presents a risk to operating theatre personnel and a diagnosis of hepatitis B or C should be ascertained. Patients with hepatitis of unknown aetiology should be considered infectious.

History and examination

Patients with compensated liver disease may be asymptomatic or have only vague symptoms such as malaise, weight loss, or dyspepsia.³ Physical signs may be absent or non-specific. A full physical examination should be performed with particular reference to the presence of muscle wasting, spider naevi, pleural effusions, ascites, splenomegaly, and level of encephalopathy (all signs of advanced liver disease).

Investigations

A full blood count will detect anaemia, thrombocytopaenia, or raised white cell count if infection is present. Prothrombin time (PT) is a useful indicator of hepatocellular function and is used as a prognostic indicator in acute liver failure and after surgery in patients with chronic liver disease. However, PT may be elevated independent of liver function in patients with vitamin K deficiency, disseminated intravascular coagulation, or warfarin therapy. Where possible, vitamin K should be administered for several days before operation.

Baseline renal function should be determined and severe hyponatraemia or potassium abnormality corrected before surgery. Severe hyponatraemia associated with advanced liver disease may be the cause of abnormal conscious state. Rapid correction of hyponatraemia should be avoided because of the significant risk of potentially fatal central pontine myelinolysis and correction of hyponatraemia at a rate of <10 mmol litre⁻¹ in 24 h is recommended. Synthetic liver function is best assessed by PT, but albumin levels are also useful. Elevated bilirubin is common and the pattern of enzyme rises varies with the aetiology.

Cardiac investigations should include ECG and also echocardiography if risk factors for left ventricular dysfunction, cardiomyopathy, valvular lesions, or pulmonary vascular pathology are present. If significant coronary artery disease is suspected, an exercise ECG, dynamic assessment of left ventricular function, or both may be helpful. Chest X-ray or ultrasound may be useful for demonstrating pleural effusions in need of drainage before operation. Lung function tests can be helpful to delineate any restrictive or obstructive pulmonary disease.

The Pugh modification of Child's classification is used to estimate the risk of mortality in patients with liver disease undergoing surgery (Table 2).⁹ Points from each variable are added to make the total

Table 2 Pugh's modification of Child's criteria

Clinical or biochemical variable	Points scored for increasing abnormality		
	1	2	3
Encephalopathy (grade)	None	Minimal (1 and 2)	Advanced (3 and 4)
Ascites	None	Easily controlled	Poorly controlled
Serum bilirubin (mg dl ⁻¹)	<2.0	2.0–3.0	>3.0
Serum albumin (g dl ⁻¹)	>3.5	2.8–3.5	<2.8
Prothrombin time (s >control)	1–4	4–6	>6

score. A total score of 5 or 6 is considered Child's class A and is associated with a low operative mortality risk (<5%); a total score of 7–9 (Child's class B) carries a moderate risk (25%) and total score of 10–15 (Child's class C) carries a high risk (>50%). Although this classification was originally used in patients undergoing portosystemic shunts, the variables included have been shown to be predictive of outcome for all types of abdominal surgery in patients with liver disease.⁴ Other predictors of poor outcome include malnutrition, emergency surgery, sepsis, and blood loss.

Conduct of anaesthesia

Elective surgery should only be considered in patients who have well-compensated chronic liver disease.² For patients needing emergency surgery, urgent optimization of the patient is mandatory and should include attention to intra-vascular volume status, coagulation function, and also neurological assessment and screening for infection.

Specific blood component therapy should be considered, depending on the results of thromboelastography and coagulation studies. Fresh-frozen plasma may be required if the PT is >1.5 times the control and platelets should be administered if the platelet count is <50 000 mm⁻³. Cryoprecipitate is usually only indicated if the fibrinogen concentrations are <1.0 g litre⁻¹. Recombinant factor VIIa is increasingly being used for both prophylaxis and therapeutic management of perioperative bleeding;¹⁰ other pharmacological options include tranexamic acid and desmopressin.¹⁰

Sedative premedication should be avoided as it may precipitate encephalopathy; however, premedication with an H₂ receptor antagonist such as ranitidine is advisable. The goals of intraoperative management should be maintenance of adequate hepatic blood flow and oxygen delivery. Relative hypoperfusion or hypoxaemia may produce further hepatocellular injury and result in de-compensation. In the presence of portal hypertension, hepatic blood supply is dependent on hepatic arterial blood flow. All forms of anaesthesia can reduce mean arterial pressure and thereby reduce hepatic blood flow. Other intraoperative factors which can reduce hepatic blood flow include surgical traction on the liver, positive pressure ventilation, hypocapnia, alpha-adrenoceptor agonists, and laparoscopic surgery.

All patients should receive standard monitoring (as recommended by the AAGBI), but for major surgery, invasive monitoring of both arterial and central venous pressure is recommended, although central venous catheterization is not without risk. Oesophageal Doppler or transoesophageal echocardiography may be helpful in certain patients, but probe placement is contraindicated in patients with oesophageal varices, as are the insertion of nasogastric tubes and oesophageal temperature probes. Patients with varices may therefore require a pulmonary artery catheter. An intra-arterial catheter allows regular monitoring of arterial blood gases, lactate, glucose, electrolytes, and coagulation status. Monitoring of core body temperature, neuromuscular block, and urine output is also recommended.

The choice of drugs for anaesthesia induction and maintenance is less important than the care with which they are used. A suggested technique is i.v. induction of anaesthesia using propofol and remifentanyl, in most cases using a modified rapid sequence induction with cricoid pressure and rocuronium 1 mg kg⁻¹, followed by maintenance with oxygen/air/desflurane and remifentanyl infusion. Target-controlled infusion of propofol is an alternative to inhalation anaesthesia and is useful for gastrointestinal endoscopic and radiological procedures; propofol clearance is not significantly impaired by liver disease. Atracurium is preferred for maintenance of neuromuscular block. Ventilation is controlled to maintain arterial P_{CO}₂ between 4.5 and 5.3 kPa. Appropriate antibiotic prophylaxis is required before surgery.

Large-bore i.v. access is mandatory. All fluids should be administered via a fluid warming device and access to a rapid infusion device is important for all major surgery. Fluid replacement should be guided by cardiovascular variables, blood loss, and urine output; only when cardiac filling pressures are optimized should vasopressors such as metaraminol, phenylephrine, or norepinephrine be considered for the treatment of hypotension. Maintenance of intravascular fluid volume and appropriate cardiovascular management are critical to achieve an adequate urine output; however, loop diuretics or mannitol are occasionally used.^{2, 3} The administration of antioxidants to reduce free radicals and preserve renal function is still experimental. Crystalloid solutions may be less effective than colloids in the presence of ascites, but a background infusion of 5–10% dextrose at 50–100 ml h⁻¹ helps to avoid hypoglycaemia and protect against inadvertent increases in plasma sodium concentration.

Postoperative pain management

I.V. patient-controlled analgesia using fentanyl (or occasionally morphine) is well tolerated in patients with compensated liver disease. A regimen of a fentanyl bolus of 10 µg with a lockout time of 10 min and no background infusion is effective. Regional analgesia may be very useful in reducing the need for systemic analgesia, but attention to coagulation status is essential. The use of TAP blocks or local infiltration is recommended. Epidural analgesia should be considered with extreme caution and only if INR is <1.5 and platelet count is >100 000 mm⁻³. These authors do not routinely practice correction of coagulopathy with clotting factors to facilitate the siting of an epidural catheter. I.M. or s.c. injections risk formation of haematoma. NSAIDs are not recommended because of the risk of gastrointestinal haemorrhage, platelet dysfunction, and nephrotoxicity. Acetaminophen is not contraindicated but should be used with care and liver function monitored carefully.

Postoperative care

Postoperative ICU admission should be anticipated for patients with advanced liver disease. In some circumstances, postoperative

artificial ventilation may be appropriate, but in general, sedative drugs should be discontinued early and patients allowed to recover from anaesthesia so that neurological assessment can be performed. Worsening encephalopathy, jaundice, and ascites are very important clinical markers of decompensation of liver function. Invasive cardiovascular monitoring and careful fluid management is continued to avoid the development of postoperative renal failure. Monitoring of coagulation and also maintaining vigilance for signs of postoperative bleeding should be continued. Intravascular catheters should be removed as soon as they are no longer needed because of the increased risk of catheter-related sepsis.

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Please see multiple choice questions 11–14