Liver disease and anaesthesia

Patients with liver dysfunction are especially liable to ill effects from anaesthesia, and yet the consequences of their disease increase the likelihood of major surgery. Full assessment and careful management are as important for them as for patients with the more familiar problems of respiratory or cardiovascular disease, and their preoperative assessment has been reviewed in a recent symposium.1

Testing for hepatitis B virus surface antigen and e-antigen is essential for assessing the risk of infecting others.2 For the anaesthetist, however, the liver's metabolic activity is the central issue, and tests designed to find the cause of the liver dysfunction, while helping the overall management of the patient, are less important for his preoperative assessment than are investigations to determine metabolic activity. Increased concentrations of liver enzymes reflect continuing disease activity, but not metabolic function. The available investigations of metabolic function are non-specific and show up abnormalities only when considerable damage has already occurred. Unless these investigations give abnormal results, however, major problems during anaesthesia are unlikely. A reasonable estimate of operative risk may be based on measurements of serum bilirubin and albumin concentrations and prothrombin time, with a clinical assessment of encephalopathy, ascites, and nutritional state.3 4 Other factors that may affect the risk of operation include anaemia, often associated with blood loss into the gastrointestinal tract, and electrolyte abnormalities, sodium retention and potassium depletion being exacerbated by diuretics.5 If time permits, the risk can be reduced by active preoperative management—reducing protein intake, emptying the bowel, giving lactulose and non-absorbable antibiotics such as neomycin, and restricting sodium intake. Defects of haemostasis may be reduced by vitamin K treatment or, when this is ineffective, infusion of fresh-frozen plasma.6

Attention to renal function is an integral part of management. In patients with obstructive jaundice the fall in post-operative creatinine clearance, which otherwise correlates well with preoperative bilirubin concentrations, can be prevented by diuresis with mannitol from the time of premedication until two or three days after the operation.7 Endotoxin absorbed from the bowel because of reduced bile salt excretion8 is probably the main cause of renal impairment rather than retained bilirubin.9 Renal failure often develops in patients with chronic liver dysfunction10 and may be precipitated by hypovolaemia,11 though this is clearly not the only cause.12 The value of a diuresis in these patients has not been established and maintaining their circulating fluid volume may be more important. Desalination is preferable to saline for infusion, both to protect against hypoglycaemia and to prevent additional sodium loading.

The response of these patients to some drugs may be gauged from the vitamin-K1-corrected prothrombin time and the serum albumin concentration,13 but this does not

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A1c are also increased in uncontrolled diabetics, but to a smaller extent.3 6 Increased amounts of glycolysed haemoglobin reflect hyperglycaemia and are not genetically determined, being normal in the non-diabetic member of identical twins discordant for diabetes.8

The amount of haemoglobin A1c reflects blood glucose concentration over some weeks, so that its measurement provides an assessment of long-term diabetic control. Several studies have shown that this measurement may be correlated with almost any assessment of long-term control whether by the physician's clinical judgment; the results of mean fasting or daily blood glucose determinations; eight weeks of urine tests; or 24-hour urine glucose excretion, especially when determined about two months before measuring HbA1c.5 6 10 There is no correlation with random blood glucose readings.

In man the time needed for HbA1c to increase after development of hyperglycaemia is uncertain, but in mice it is about four weeks.11 After controlling diabetes there is no immediate decrease. No change was detectable in one study for even 10 days after ketoacidosis,7 and in others there has been a time lag of up to 25 days before the proportion of HbA1c started to fall.14 12 Recently Ditzel and Kjaergaard8 have shown that after starting insulin treatment in newly diagnosed diabetics the decrease continues for 25 to 80 days and even then in apparently well-controlled diabetics the amounts may still be raised. Thus, a raised HbA1c concentration reflects hyperglycaemia for between four weeks and two months or more previously. It is difficult to be more exact than this, because the yardstick for comparison—several weeks of fluctuating blood glucose control—is itself so imprecise.

The relation of microangiopathy to diabetic control assessed by haemoglobin A1c can be observed only prospectively, and its measurement may yield results that will at last settle the argument whether the two are linked or not. Single measurements of HbA1c have not so far shown any correlation with the presence of retinopathy—nor would they be expected to do so.15 There is some correlation between HbA1c and blood lipid concentrations, especially of triglycerides,16 which is not surprising since both depend on the maintenance of good glucose control; indeed, measuring the blood lipid concentration has been suggested as one way of evaluating long-term control.

We have no evidence that HbA1c is itself harmful, though it alters haemoglobin function by increasing the blood's affinity for oxygen; any suggestion, however, that this might cause harmful tissue hypoxia is speculative.17 Possibly HbA1c might make the red cell less distortable, but again this theory is unproved.18 Perhaps hyperglycaemia alters the composition and therefore function of other proteins after synthesis as it does with haemoglobin A. In practical terms, however, the discovery of the relation between HbA1c and diabetes seems likely to lie in its potential in monitoring diabetic control by providing an objective measure of the effectiveness of management.

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apply to many drugs used in anaesthesia. Sedatives and analgesics may produce disproportionate changes in consciousness, even when they are metabolised fairly normally. The patient's response to premedication with pethidine and promazine or diazepam and atropine may be a useful guide to his postoperative requirements, but when liver function is severely impaired these drugs should be omitted. Of the intravenous anaesthetic induction agents, thiopentone has proved safe, but in incremental doses its effects are cumulative and its excretion depends ultimately on the liver. Althesin (alphaxalone and alphadone acetate) may be preferable, but, though usually it is rapidly metabolised by the liver, patients with liver disease may have a delayed recovery from its effects. Suxamethonium has a prolonged action when liver disease is associated with low plasma cholinesterase concentrations, but this has not been a problem in clinical practice.

Maintaining anaesthesia presents greater problems, because all anaesthetic techniques reduce liver blood flow, with the risk of increasing liver damage. This risk can be minimised by preventing hypotension, hypoxaemia, and hypercarbia or hypocapnia. This is most easily achieved with light anaesthesia combined with a muscle relaxant and controlled ventilation. Larger than normal doses of muscle relaxants are widely thought to be required, perhaps because they become bound to serum protein to a greater extent or because they are redistributed to an enlarged liver and spleen or have an increased volume of distribution. It is also held that reversing the neuromuscular blockade at the end of the operation may be difficult, whether pancuronium or tubocurarine has been used. These beliefs have not been substantiated, however, by controlled trials or nerve stimulator monitoring. Pancuronium is the neuromuscular blocking agent of choice because of the hypotensive action of tubocurarine. The volatile anaesthetic agents reduce hepatic oxygenation to varying degrees; methoxyflurane has the greatest and halothane the least effect. Fluoroxyene, halothane, and trichloroethylene have been used during liver transplantation, but pethidine and its synthetic derivatives fentanyl and phentanyl are now preferred for patients with impaired liver function. Dopamine used prophylactically to dilate the superior mesenteric and coeliac vascular beds, so increasing hepatic blood flow, might be the next to counteract the effect of the anaesthetic agent—but its use has not been studied.

After operation sedatives and analgesics must be given with great care, the dose and frequency being tailored to the patient's response. But for some patients with severe decompensated liver disease no drug is satisfactory.

Kidney failure in liver disease

The blood urea concentration rises in up to 80% of patients with terminal cirrhosis or fulminating hepatic failure. Two forms of renal dysfunction are recognised. In functional renal failure the glomerular filtration rate falls, the ability to excrete a water load is reduced, and the blood urea and creatinine concentrations rise. The urine volume is reduced and it is concentrated (with a urine:plasma osmolality ratio of over 1:1:10) with a low sodium concentration, indicating that tubular function is preserved. The view that the renal impairment is "functional" is supported by the relatively normal glomerular appearances in renal biopsy specimens and by the return of renal function when the kidney is transplanted into a recipient with a normal liver. Furthermore, renal function has improved in patients with terminal cirrhosis after orthotopic liver transplantation.

The second form of renal failure is characterised by evidence of tubular damage, with low urine osmolality; urinary sodium concentrations above 12 mmol/l; increased renal clearance of lysozyme; and histological changes such as tubular casts, tubular dilatation with epithelial flattening, and interstitial oedema. This picture of acute tubular necrosis may be present initially or may follow a period of functional renal failure, especially if the glomerular filtration rate falls below 3 ml/min. Either variety of renal impairment may be precipitated by gastrointestinal haemorrhage, abdominal paracentesis, or the overvorous use of diuretics; often, however, there is no obvious explanation. Typically, both the cardiac output and extracellular fluid volume are normal or increased, and since expansion of the plasma volume does not benefit most of these patients a prerenal cause seems unlikely. Renal blood flow is reduced, and angiographic studies have shown reversible constriction of the intrarenal blood vessels; studies using the xenon-133 washout technique or para-aminomhippuric acid excretion ratio suggest that the blood flow is diverted from the outer cortical to juxtamедullary and medullary nephrons.

What causes this vasocostriction? The sympathetic nervous system, renin, and false neurotransmitters such as octopamine have been suggested as possible mediators, but more recently interest has centred on the role of endotoxin in modifying renal haemodynamics. Endotoxin derived from the cell walls of Gram-negative bacteria is a normal constituent of portal venous blood and may be detected in the peripheral circulation in patients with liver disease. In cirrhosis endotoxaemia is associated not only with functional renal failure and acute tubular necrosis but also with erosive gastritis, ascites, and a poor short-term prognosis. **Wilkinson et al** detected