Today's Treatment

Diseases of the alimentary system

Gall stones

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In the 100 years after the first operation on the gall bladder by John Stough Bobbs cholecystectomy became the accepted method of treating cholelithiasis. The recent introduction of an agent that can safely dissolve gall stones and new advances in fibreoptic instruments have added new dimensions to managing this common and economically important disease. The doctor can now offer several therapeutic options to the patient with gall stones, and while this has enhanced the scope for manoeuvre it has created new and novel difficulties in decision making.

Diagnosis

Gall stones may present in various ways. The most common and characteristic is either acute cholecystitis or obstruction of the common bile duct. Only 5% of patients with acute cholecystitis do not have coexistent gall stones. Less commonly stones may rupture into the bowel, obstruct the terminal ileum, or cause pancreatitis. Gall stones and cancer of the gall bladder may coexist. A few patients with acute cholecystitis may be icteric in the absence of choledocholithiasis but most patients with gall stones who are jaundiced will have a stone obstructing the common bile duct. Cholangitis is diagnosed when, in addition to the cholestasis, there are chills, fever, and pain and tenderness in the right upper quadrant. Flatulence, intolerance to fatty food, and vague right upper quadrant and epigastric pain are often ascribed to gall stones and chronic cholecystitis. Such complaints, however, are as often as not related to other common gastrointestinal disorders, and one of the major difficulties for the doctor is to decide what treatment to offer patients with gall stones who present with these symptoms.

Since only 15% of gall stones are radio-opaque a plain abdominal radiograph is often unhelpful. Oral cholecystography is the basic diagnostic tool, but if obstruction of the bile duct is suspected intravenous cholangiography, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, and ultrasonic scanning may all be useful.

Gall stones in the gall bladder

Gall stones and acute cholecystitis are an indication for cholecystectomy, which is the most frequent major abdominal operation performed in Britain. The gall bladder is removed via a vertical paramedian incision or a subcostal incision, which is favoured in obese patients with a wide costal angle. Because choledocholithiasis occurs in some 10-15% of patients with gall-bladder stones it is generally accepted that operative cholangiography must be undertaken as a routine in all patients undergoing operation for gall stones. With experience the procedure adds little more than five minutes to the operating time and may be performed via a cannula in the cystic duct or by direct needle puncture of the common bile duct. Thus surgeons undertaking gall-bladder surgery must be capable of using the technique, and adequate radiographic facilities must be available in all operating theatres. The routine use of operative cholangiography has the advantage of reducing unnecessary bile-duct explorations; of diagnosing gall stones that would otherwise have been overlooked by palpation, thereby reducing the number of residual gall stones in the common bile duct; and of revealing unsuspected disease. The criticism that the procedure is accompanied by an increased morbidity is not convincing when the many benefits from operative cholangiography are considered.

While debate continues over the timing of the cholecystectomy in acute calculous cholecystitis, increasingly the consensus is moving towards early operation. On admission the patient is given such medical support as is appropriate. Analgesics recommended include morphine, pethidine, and pentazocine, the latter having the theoretical advantage that it does not raise biliary pressure. Intravenous fluids are given if the patient is vomiting, and an adequate urinary flow is maintained; it is seldom necessary to use a nasogastric tube. Appropriate treatment is given for associated cardiac or pulmonary disease. There is no evidence that anticholinergic agents are useful.

The rational use of antibiotics in acute cholecystitis remains controversial. Only half the patients coming to operation have infected bile, when various aerobic and anaerobic organisms may be cultured. The positive yield of bacteria increases if there is cystic duct obstruction or cholangitis. There is a correlation between the incidence of positive bile cultures and the frequency of wound infection, intra-abdominal sepsis, and the mortality rate. The choice of antibiotic may be governed by either the degree to which it is concentrated in the bile or the probable bacterial sensitivity. Unfortunately it seems that when there is liver dysfunction or obstruction of the cystic or common bile duct therapeutic levels of the antibiotic are unlikely to be achieved in the bile. Recommended antibiotics include parenteral cephaloridine (2-4 g daily), gentamicin (2-4 mg/kg/day), ampicillin (4 g daily), and tetracycline (2-4 g daily). Recent evidence, however, suggests that most organisms isolated from the biliary tract are not susceptible to ampicillin and tetracycline. Some authorities recommend using a Gram stain on uncentrifuged bile obtained at cholecystectomy as an aid to the choice of antibiotics, thereby avoiding unnecessary antibiotic prophylaxis. Each patient will have to be considered individually, but generally the following recommendations may be made: no antibiotics are required for the average patient with acute gall-bladder inflammation; antibiotics are given if the illness is of more than four days' duration, if the clinical condition is deteriorating, or if there is any evidence of perforation, general peritonitis, or cholangitis.

Over 90% of patients improve after admission and may be operated on within five to 10 days. At this stage the predominant pathological features are oedema and congestion, which may even enhance the ease of dissection. Thereafter organisation and fibrosis become more prominent, making the procedure more difficult, so that an elective operation two to three months later may be no easier than if undertaken

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in the first 14 days. The advantage of the earlier operation is that there is a saving of time for the patient, whose illness is restricted to a single hospital admission. There is no difference in the mortality and morbidity figures when early and delayed operations are compared.

An emergency operation on the biliary tract is seldom needed because the average patient is not critically ill, but for the patient who is highly toxic or has a perforation, spreading infection, or severe cholangitis it will be necessary. In such cases a cholecystectomy may not be possible, and the wiser decision is to undertake a cholecystostomy. In this way the gall stones may be removed; but they will reform unless the gall bladder is removed later. Cholecystostomy is inadequate in the presence of acute cholangitis.

GALL-BLADDER DISEASE IN THE ELDERLY

Whereas the mortality among patients under the age of 50 undergoing cholecystectomy is less than 1%, it rises to nearly 3% in patients between 50 and 65 and approaches 8% in geriatric patients. Elderly patients tolerate emergency operations on the biliary tract poorly, and unfortunately it is in this group that most perforated or gangrenous gall bladders are found. A cholecystostomy may often be the most advantageous operation in the aged because it can be performed rapidly through a small incision and under a local anaesthetic if necessary. On recovery a cholangiogram is needed. If the biliary tree is normal there is no need for a further operation; if the gall bladder is not filled or stones are seen either in the gall bladder or in the duct system a cholecystectomy is warranted provided that the patient's general health is satisfactory.

DISSOLUTION TREATMENT

Great advances have been made in understanding the many factors concerned in the formation of gall stones. About 10% of gall stones from Western communities are composed purely of cholesterol, and 80% of the remainder contain at least 70% cholesterol. The outstanding biochemical abnormality in these patients is the secretion of hepatic bile that is saturated or supersaturated with cholesterol. At least two factors are responsible: the increased secretion of biliary cholesterol, and reduced secretion of bile acids in bile associated with a smaller than normal bile-acid pool. The initial observations by J L Thistle and L J Schoenfield, of the Mayo Clinic, that taking by mouth the primary bile acid chenodeoxycholic acid caused saturated hepatic bile to become unsaturated started an extensive study of chenodeoxycholic acid as a method of dissolving gall stones. Furthermore, it stimulated the search for other agents that might influence cholesterol output in bile.

Metabolism of chenodeoxycholic acid—Chenodeoxycholic acid (3α,7α-dihydroxy-5β-cholanic acid) is a primary bile acid derived semisynthetically from animal bile and is similar to that produced normally in the human liver. It is absorbed to some extent by passive nonionic diffusion in the jejunum but the major absorption occurs in the distal ileum, where an active transport system ensures the conservation of free and conjugated bile acids. After returning to the liver, chenodeoxycholic acid is excreted in the bile, having been conjugated to glycine and taurine. Under the influence of intestinal bacteria, free and conjugated chenodeoxycholic acid undergoes 7α-dehydroxylation to the secondary bile acid lithocholic acid, which is either excreted in the stool or reabsorbed and returns via the portal circulation to the liver. There it is conjugated and most is additionally sulphated at the 3 position. The sulphated compounds are water-soluble, and thus once excreted in the bile they have a decidedly decreased intestinal absorption compared with the free and conjugated (but not sulphated) bile acid. In this way little lithocholic acid is retained in the body, which has important implications for hepatotoxicity.

Dose and selection of patients—Chenodeoxycholic acid is given as a gelatin capsule of 250 mg of the free bile acid. The optimal dose remains to be determined but doses used have ranged from 1·5 to 4·5 g daily; 10-15 mg/kg/day is probably adequate for the average patient. Attempts are being made to define a minimal effective dose, and this may be around 300 mg/day or about 5 mg/kg/day. Available information indicates that chenodeoxycholic acid is effective only in patients who have radiolucent gall stones and functioning gall bladders; it is these patients who may be recommended for dissolution treatment. The indications for chenodeoxycholic acid treatment need defining. Some users have used the drug only for those patients who have been rejected by the surgeon as unfit for operation or for patients who have refused surgery; others have widened the scope for dissolution treatment and offered it to relatively fit patients with minimal symptoms. The current recommendation is that the agent should not be used in women of childbearing age. It usually takes between six and 24 months to dissolve gall stones, though multiple small stones respond more rapidly than a single large stone. Hence it is normally inappropriate to offer treatment to patients who have severe symptoms attributable to the gall stones or who are icteric. Chenodeoxycholic acid is currently under trial in several centres in Britain and is not yet available commercially.

Mode of action—Several mechanisms have been proposed to explain the action of chenodeoxycholic acid. The most favoured one is that it may reduce the output of cholesterol secreted into the bile. The hepatic synthesis of cholesterol is regulated by the microsomal enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, while the rate-limiting enzyme for bile acid synthesis from cholesterol is 7α-hydroxylase. Chenodeoxycholic acid is believed to inhibit HMG-CoA reductase to a greater extent than it inhibits bile-acid synthesis, hence the reduction in biliary cholesterol secretion by the liver. Probably of secondary importance is the expansion in the bile-acid pool accompanying taking exogenous chenodeoxycholic acid.

Evaluation of treatment—Treatment may be evaluated in two ways. A cholecystogram may be taken at about six-monthly intervals until the stones have dissolved. Additionally, samples of bile obtained by duodenal drainage may be measured for the degree of cholesterol saturation. It has been argued that the effective dose of chenodeoxycholic acid is one that causes the bile to become unsaturated with cholesterol; but some users have reported that the measurement of cholesterol saturation in bile does not always predict effective response to the bile acid.

Response to treatment—Opinions differ on how effective chenodeoxycholic acid is when given to apparently suitable patients. Most users find that successful dissolution can be achieved in over half the patients, and at least one group has suggested that the success rate will approach 100% if bile can be maintained unsaturated with cholesterol. The bile acid should be continued for at least three to six months after stones are no longer identified on the cholecystogram. Unfortunately some patients return to excreting saturated bile after chenodeoxycholic acid is discontinued and the gall stones recur. It is still uncertain what should be the long-term management of patients who have responded to dissolution treatment: should the drug be discontinued or should the patient continue to take a smaller dose that is just enough to maintain the bile in an unsaturated state?

Side effects—Chenodeoxycholic acid has proved to be remarkably safe in clinical practice. Minor diarrhoea, which is caused by the colonic secretion of water and electrolytes induced by the free bile acid, is readily reversed by reducing the dose. A transient mild (less than twice normal) increase in hepatic transaminases or alkaline phosphatase or both may occur in the initial months of treatment but resolves spontaneously and is not an indication to stop treatment. So far no meaningful changes have been reported in the cholesterol pool size. Extensive liver biopsy studies with comparison before and after chenodeoxycholic acid treatment have failed to show any appreciable morphological changes. Electron microscopical studies have shown a slight increase in Ito cells, the significance of which is not apparent. These observations are both interesting and reassuring because of the recognised hepatotoxic effects of lithocholic acid and the severe liver damage that has been seen under certain conditions in animals fed chenodeoxycholic acid. The probable reason for the difference between the human and animal results is the sulphation of lithocholates, thereby preventing the accumulation of this bile acid in the enterohepatic circulation.

Other agents used to dissolve gall stones—No other drug is as effective as chenodeoxycholic acid in dissolving gall stones. Cholic acid has been evaluated and is ineffective, probably because it has a different effect on the rate-limiting enzymes of cholesterol and bile-acid synthesis. The use of lecithin remains controversial. Phenobarbitone has been tried but it appears to be ineffective when used on its own, and there is no advantage in combining it with chenodeoxycholic acid. Ursodeoxycholic acid, the 7β epimer of chenodeoxycholic acid, increases in the bile of patients given chenodeoxycholic acid. It has been suggested that this metabolite might dissolve gall stones but there are insufficient supportive data.

INFLUENCE OF DIET

There is no acceptable evidence that any particular diet influences gall-bladder or gall-stone disease. A low-fat diet is often prescribed but has not been evaluated satisfactorily. It remains to be determined how much beneficial effect such a diet has either on symptoms or on the

underlying disorder of hepatic metabolism or the gall-bladder function and, if any effect is present, whether it is due to the low fat content of the diet, a reduction in calories, or a concomitant increase in the dietary fibre content.

THE SILENT STONE

The management of the silent gall stone remains one of the most vexed and controversial issues in biliary tract disease. Should silent stones be removed? The answer is often Yes, and in support the excellent study of A Wenckert and B Robertson is quoted, which showed that 35% of patients with gall stones followed up for 11 years developed complications. It must be emphasised, however, that the patients under study did not have silent stones: they had all presented with some feature of gall-stone disease. By definition a silent stone should be completely asymptomatic, and it is impossible to see how these might be diagnosed during life. Evidence from necropsy data suggests that truly silent gall stones are not uncommon. The treatment of the silent stone is uncertain, with arguments favouring cholecystectomy contrasting with the attitude that the stones should be left alone. My personal prejudice is for the latter approach. It would be comforting to think that chenodeoxycholic acid might be used for these patients and, indeed, it may, except that so many silent stones are radio-opaque that have been discovered by chance on plain radiographs of the abdomen, and these stones are unsuitable for dissolution treatment.

Stones in common bile duct

The presence of stones in the common bile duct is generally an indication for laparotomy, cholecystectomy, and exploration of the common bile duct. Preoperative preparation includes giving parenteral vitamin K if jaundice is present (5-10 mg daily for three days) and antibiotic cover. The intravenous administration of 500 ml of a 10% solution of mannitol one hour before the operation helps to reduce the risk of the patient with deep jaundice developing acute renal failure. An operative cholangiogram is always recommended. The usual procedure is a supraduodenal choledochotomy with T-tube drainage. The T tube is left for seven to 10 days, and before removal a cholangiogram is usually obtained. A transduodenal sphincterotomy may be attempted if the gall stones are impacted at the lower end of the common bile duct, and in such cases T-tube drainage may be unnecessary.

About 2% of patients who have undergone choledochotomy subsequently have residual bile-duct stones. Many of these patients are unsuitable for further surgery, and other methods have been proposed for dealing with the stones. If the T tube is still present it may be possible to pass, under radiological control, a urethral stone basket. Another method that has received encouraging reports is the infusion, via the T tube, of 100 M sodium cholate at a rate of 30 ml hourly for 10 days. It is usually necessary to take cholestyramine by mouth (6-12 g daily) to reduce any diarrhoea. An infusion of heparin (25 000 units eight-hourly) via the tube has also been recommended. None of these methods has been subjected to an adequate clinical trial, and present information indicates that irrigation of the common bile duct with a simple saline washout might be just as effective.

A method of great interest is the removal of gall stones by means of a fibreoptic duodenoscope suitably modified and equipped to perform a papillotomy. At a later date the endoscope is passed again and the stone may be removed using a Dormia catheter. This technique calls for great skill and at present is suitable for only relatively small stones.

If the gall stone is discovered after the T tube has been removed oral chenodeoxycholic acid treatment may be attempted; there is no point in using this agent to infuse down a T tube because cholic acid is as effective. Favourable results have been reported in some patients, who have had fewer episodes of cholangitis and ultimate stone dissolution; but many patients have not responded.

It needs to be emphasised that the accepted treatment for choledocholithiasis is surgical removal. All other methods are to some extent under trial and are mainly relevant to those patients who are unsuitable for further surgery.

The Future

The future must lie with the development and better understanding of dissolution treatment. It is necessary to predict more accurately which patients will respond to treatment. The correct dose of chenodeoxycholic acid requires definition, and clear indications are needed for deciding when to stop treatment both in responders and in non-responders. Of great importance is the development of a rational programme for the management of those patients whose gall stones have dissolved. For this the suggestion that a high intake of dietary fibre might favourably influence cholesterol solubility in bile is relevant. Perhaps the most important lesson to be learnt from chenodeoxycholic acid treatment is that bile composition can be manipulated to render it unsaturated with cholesterol. This has important implications for preventing gall stones. Although saturated bile is only one aspect of the complicated mechanism for gall-stone formation, gall stones might possibly be prevented by influencing bile composition. Probably drug treatment will not be the solution. The promising work with fibre-rich diets points the way, and it may well be that the ultimate solution to gall-stone disease will be the rational use of specific diets.

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Further reading

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What should be the dose of rifampicin in leprosy and for how long? What precautions should a patient with erythema nodosum leprosum reaction take?

The optimum dose of rifampicin for adult patients with lepromatous leprosy is 600 mg daily. Much smaller doses are probably as rapidly bactericidal as this high dose. The maximum effect is probably achieved in two to three weeks since after this viable bacilli can no longer be found in nasal mucus, skin, or circulating blood. Nevertheless, viable organisms may persist in bone marrow and at other deep sites. Much longer treatment does not materially improve the bacteriological (or clinical) state, and the drug's cost is an important consideration. Because of the possible presence of persistent organisms and the absence of cell-mediated immunity potential in patients with lepromatous leprosy, dapsone at standard doses should be given together with rifampicin and continued for as long as is recommended generally. Thus, while rifampicin will considerably reduce the period of infectiousness, it will not shorten the total duration of treatment until clinical quiescence has been achieved. Thereafter dapsone should be continued for life. A patient who presents while in the throes of an attack of erythema nodosum leprosum should be treated by anti-inflammatory agents (corticosteroids are best) until the acute episode is controlled. Rifampicin should then be introduced under corticosteroid cover, after which the dose of the latter should be progressively reduced as rapidly as is consistent with continued control of the episode. The general principles of treating the patient in this condition—rest, sedation, attention to the eyes and peripheral nerves, etc—must of course be observed, and all necessary supportive treatment started.

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