Gut, 1983, **24**, 599–608

Leading article

Management of stones in the biliary tree

Stones in the biliary tree may coexist with gall-bladder stones, may be found only in the common duct (in the absence of gall-bladder stones) or, more rarely, may be present in the intrahepatic biliary tree – as in the Caroli syndrome.[1] One of the most frequent causes of choledocholithiasis, however, is the retained common duct stone which has been left behind inadvertently after elective or emergency cholecystectomy. Despite the routine use of intraoperative cholangiography, exploration of the common duct (where indicated) at the time of cholecystectomy and even, on occasions, the use of fibre optic choledochoscopy, there is still a 1–4% incidence of retained common duct stones after cholecystectomy.[2] When stones are discovered in the biliary tree, there are several therapeutic options – including, in selected patients, the use of oral chenodeoxycholic (CDCA) or ursodeoxycholic (UDCA) acid, the gall-stone dissolving agents which are more commonly used in the treatment of cholesterol-rich stones in the gall bladder.[3]

Elsewhere in this issue Dr Gianfranco Salvioli and his colleagues from Modena in Italy describe the results of a random allocation, double masked trial in 28 patients with uncomplicated biliary stones, half of whom were treated with 12 mg UDCA/kg/day in three divided doses, while the other half received placebo. Seventeen of these patients had stones in the gall bladder while four had a radiologically normal gall bladder with stones only in the biliary tree. Although the end point of the study was intended to be 24 months, only four of the 28 patients actually completed the two year trial – either because the stones had disappeared completely before that time, or because the patients developed biliary colic, pain or cholangitis, underwent surgery or simply 'dropped out'. None of the 14 patients given placebo showed evidence of gall-stone dissolution, but seven of the 14 UDCA-treated patients showed complete disappearance of the stones, as judged by normal intravenous cholangiograms, after six, 12, or 18 months' treatment – while one showed partial gall stone dissolution (defined as at least a 25% reduction in stone diameter or the disappearance of one or more stones).

If one arbitrarily classifies 'drop-outs' as treatment failures, then the complication rate, whether because of the stones or of the treatment, was higher in the placebo treated patients (12 out of 14) than in the UDCA-treated group (six out of 14). The reason for the 'drop-outs' in three of the 14 patients given UDCA is not stated. These patients may simply have defaulted from treatment because they lacked motivation or they may have become disenchanted with it for good reason – because of complications for example. Of the three other UDCA-treated patients who stopped, one underwent surgery for obstructive jaundice after three months, one developed colic, and one pain (the distinction between biliary colic and abdominal pain or discomfort, was not defined).

Given the choice between ursodeoxycholic acid and chenodeoxycholic acid as oral, gall-stone dissolving treatments for either gall bladder or biliary tree stones, the evidence at present favours UDCA. It appears to be a more 'benign' treatment which causes no appreciable diarrhoea, or hepatoxicity. The only possible side-effect of UDCA recognised to date is impaired calcium solubility during treatment,[4] which might render further dissolution therapy ineffective.[5] This phenomenon also occurs spontaneously and during CDCA treatment, but we do not yet know if it develops more frequently during ursotherapy. The Modena study was not designed to compare oral CDCA and UDCA in the treatment of stones in the biliary tree, but the Salvioli *et al* results support the idea that UDCA is indeed non-toxic. In fact, they found significant reductions in serum alkaline phosphatase and transaminase concentrations during treatment. The reduction in fasting serum triglycerides noted in the Modena study, however, is a controversial finding during ursotherapy. It was first reported during chenotherapy by Bell *et al* in 1973[6] and this observation was subsequently confirmed by many observers throughout the world.[7–9] Williams *et al*[10] claimed that UDCA had a comparable effect on fasting serum triglycerides with that seen during CDCA treatment and showed that this reduction was because of a decrease in the very low density lipoprotein (VLDL) triglyceride fraction. Roda *et al*[11] also found significant reductions in fasting plasma triglycerides during ursotherapy – as did Salvioli in an earlier study of patients with gall-bladder stones given UDCA.[12] Other investigators, however, have found that ursotherapy has no significant effect on serum triglyceride concentrations.[13–15]

Although, in theory, one does not need double blind trials to assess objective end-points, such as the presence or absence of gall stones on radiographs, if one is also assessing changes in symptoms during treatment, then the inclusion of a placebo group becomes mandatory. In the Modena study there was a significant reduction in abdominal pain/discomfort and in biliary colic during UDCA treatment, when compared with placebo, although we are not told if this improvement relates to the frequency and/or the severity of the symptoms.

MECHANISM FOR GALL STONE DISAPPEARANCE DURING UDCA TREATMENT

If, as a result of well tolerated oral treatment, the patients' stones disappear, arguably it does not matter how this is achieved. Nonetheless, the logic for prescribing oral UDCA (or indeed its sister compound, CDCA) is that it should enrich the bile with the conjugates of that bile acid, thereby reducing biliary cholesterol output and lowering the cholesterol saturation of the secreted bile. Yet, in the Modena study, although the mean percentage of UDCA conjugates in fasting duodenal bile increased predictably from just over 1% to almost 55% during UDCA treatment with a corresponding reduction in the moles percent cholesterol and in the lithogenic index, by Salvioli *et al*'s calculation the mean on treatment lithogenic index was still greater than unity. In other words, the gall stones disappeared completely in seven of the 14 UDCA-treated patients despite the persistence of supersaturated bile. This suggests either (i) that the stones dissolved in supersaturated bile, (ii) that they did not dissolve, but simply disintegrated and/or passed down the bile duct and out

through the sphincter of Oddi, or (iii) that the calculation of biliary cholesterol saturation in dilute samples of fasting bile-rich duodenal fluid may be inappropriate. (The authors assumed a total lipid concentration of 4 g/100 ml but although they gave results for relative molar composition of the three major biliary lipids, they did not indicate the absolute concentrations in their fasting duodenal bile samples).

The results of Salvioli *et al* are also unusual in that before UDCA treatment began, the lithogenic indices in fasting duodenal bile were exceptionally high. Normally there is a diurnal variation in bile lipid composition[16 17] and it is believed that the sequestration of an appreciable proportion of the bile acid pool in the gall bladder during fasting results in a physiological interruption of the enterohepatic circulation, with a secondary increase in biliary cholesterol saturation. Bile is therefore at its most supersaturated after an overnight fast. After cholecystectomy, however, the pool can no longer be seqestered in the gall bladder and even though removal of the gall bladder may result in a slightly smaller bile acid pool,[18] because that pool is cycling constantly, it tends to lower biliary cholesterol saturation and to render the bile unsaturated in cholesterol. The results of several studies have suggested that after cholecystectomy[19 20] or, indeed, when the gall bladder becomes 'non-functioning' with cystic duct obstruction, [21] the saturation, or lithogenic index, tends to fall. That being the case, as 17 of the 18 patients in Salvioli's study had previously undergone cholecystectomy, it is surprising that mean, pretreatment lithogenic indices of 2·11 and 2·25 were recorded. Whether or not these high values were the result of applying correction factors for the dilute duodenal bile samples, is unknown.

STONE DISSOLUTION BY LIQUID CRYSTALLINE MESOPHASE FORMATION?

The assumptions made by Salvioli and colleagues when calculating the lithogenic or saturation indices during ursotherapy may not be all that important. As first suggested by Corrigan *et al*[22] from their *in vitro* studies, urso-rich bile probably removes crystalline cholesterol from gall stones not by solubilising it in mixed micelles, but by inducing the formation of a lecithin-cholesterol liquid crystalline mesophase at the surface of the stone. Whether mesophase formation and liquid crystalline dissolution of stones occur in patients treated with UDCA and particularly in those with supersaturated, on-treatment, fasting duodenal bile, is unknown.

STONE PASSAGE OR STONE DISSOLUTION?

The concept that common duct stones may pass through the ampulla of Vater spontaneously is, of course, well recognised. In a much quoted study from Argentina, Acosta and Ledesma[23] found gall stones in the stools from 34 out of 36 patients who presented with acute pancreatitis associated with gall stones. Sieving stools, however, is never a popular occupation – even for gastroenterologists – and this was not done in the Italian study. The fact that serial radiographs taken at six month intervals, however, showed a sequential reduction in gall stone size in five of the eight patients who later showed partial, or complete stone disappearance suggests that the oral UDCA treatment did at least reduce stone size, which may have facilitated their subsequent passage through the sphincter of Oddi.

A CHOLERETIC/FLUSHING EFFECT OF UDCA?

In most animal species, including man, there is a linear relationship between bile flow and bile acid output.[24] Bile acids, therefore, are choleretics and UDCA in particular is a potent choleretic – at least in the rat.[25] Indeed, in their paper Salvioli *et al* discuss the possibility that changes in bile flow induced by UDCA treatment, when coupled with relaxation of the sphincter of Oddi (the effect of bile acid treatment on sphicter function has yet to be studied), might lead to stone migration into the duodenum. Whether or not oral UDCA treatment in patients who have gall stones (either in the gall bladder or in the biliary tree), consistently increases the total bile acid pool size, bile acid secretion rate and/or bile flow, has yet to be established. But even if it did, it seems doubtful that the increment in bile flow would, of itself, have a flushing effect sufficient to displace common duct stones into the duodenum. Certainly in postcholecystectomy patients, when trials of gall-stone dissolving infusions have included control periods during which saline was infused through the t-tube, induced migration of stones rarely, if ever, occurred.[26]

OPTIMAL DOSE OF UDCA FOR THE TREATMENT OF STONES IN THE BILIARY TREE

Before considering alternative approaches to the management of stones in the biliary tree, several other points raised by the Modena study merit comment. First, the dose of UDCA which these authors used was relatively large. For the treatment of radiolucent, presumed cholesterol-rich stones in the gall bladder, most investigators now recommend a dose of 8–10 mg UDCA/kg/day which produces a comparable degree of enrichment of bile with UDCA conjugates[27] to that found by Salvioli and colleagues. It seems that one cannot enhance the percentage of UDCA conjugates in bile beyond a certain point. Certainly, the results of the large Franco-Belgian multicentre trial[28] suggest that this plateau is reached at about 8 mg UDCA/kg/day. Doubling the UDCA dose had no further effect, either on bile composition, or on gall-stone dissolution efficacy.[28]

COMPLIANCE IN TAKING THE PRESCRIBED TREATMENT

Secondly, the percentage of UDCA conjugates in bile was used as an index of patients' compliance in taking the prescribed bile acid dose. If the speed of change in bile acid and bile lipid composition after stopping or starting UDCA is comparable with that after CDCA,[29] we know that it takes three to four weeks before bile composition reaches a new steady-state. Even if a patient failed to take UDCA for several days, therefore, one would not necessarily expect this to be evident from studies of biliary bile acid composition. As emphasised in the Modena study, it does mean, however, that despite 45–58% UDCA conjugates in bile, the lithogenic index was greater than unity.

DIAGNOSTIC METHODS FOR DETECTING COMPLETE GALL STONE DISSOLUTION/DISAPPEARANCE

Thirdly, the efficacy of treatment in the Modena report was apparently assessed by a single intravenous cholangiographic study. The results of several recent investigations comparing ultrasonagraphy and radiology

have questioned the reliability of not one, but two, consecutive oral cholecystograms during continued bile acid treatment, to detect complete dissolution of stones in the gall bladder.[30–32] Unfortunately, ultrasound is less efficient in the diagnosis of choledocholithiasis than it is in the detection of stones within the gall bladder. Furthermore, delineation of the biliary tree during intravenous cholangiography is sometimes inferior to the definition of the gall bladder seen during oral cholecystography, where the storage and concentration of the contrast material often provides a better radiographic image.[33] In the context of treating gall-bladder stones medically we badly need validation studies of both the cholecystographic and ultrasonographic diagnoses of complete gall-stone dissolution.[34] We need this information even more for the treatment of choledocholithiasis.

TREATMENT OPTIONS FOR STONES IN THE BILIARY TREE

Logically, decision making about the management of choledocholithiasis in the individual patient should depend upon a knowledge of the natural history of the untreated stone, the composition of the stone and the risks and benefits of the different treatment options.

It is beyond the scope of this leading article to argue the pros and cons of medicine (oral dissolution therapy) *versus* surgery (elective cholecystectomy ± common duct exploration), or of a 'watch-and-wait' policy in the treatment of radiolucent gall stones in the gall bladder and the biliary tree. Furthermore, at present we have too little information to comment usefully on the treatment of stones confined to the intrahepatic biliary tree. Let us restrict our further discussion, therefore, to patients with retained radiolucent common duct stones which have been detected after cholecystectomy. The treatment options in such a patient have been reviewed several time before[35 36] and these are summarised schematically in the form of a flow diagram in Fig. 1.

Once the diagnosis of radiolucent common duct stones has been made,

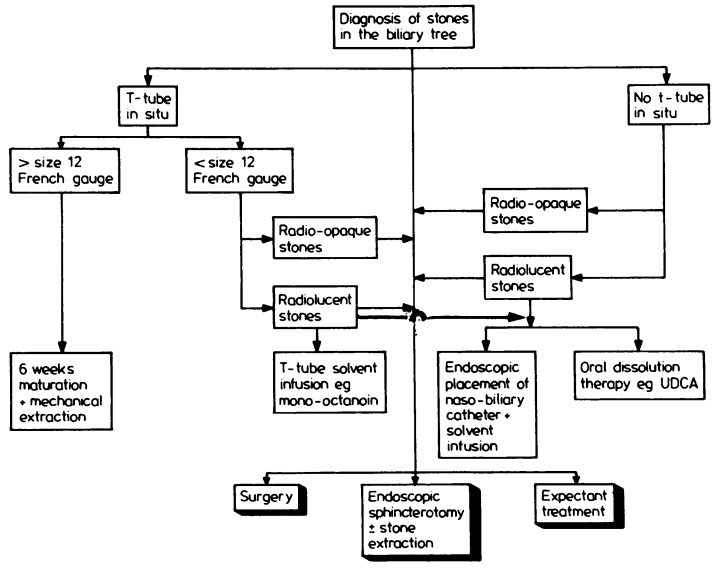

Fig. 1 *Flow diagram indicating treatment options in patients with choledocholithiasis.*

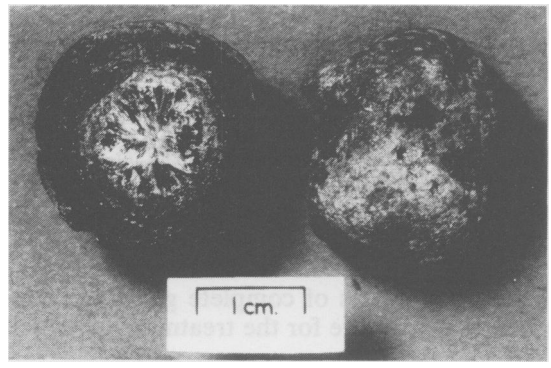

Fig. 2 *Common duct gall stone showing crystalline of cholesterol interior with spoke-like radiations of crystals and laminated outer surface of amorphous insoluble non-cholesterol debris which renders dissolution therapy ineffective.*

irrespective of whether or not the common duct has been explored and a t-tube inserted at the time of the elective cholecystectomy, the option of (i) a second operation, (ii) endoscopic sphincterotomy with or without the use of mechanical extraction techniques, or even endoscopic placement of naso-biliary catheters for direct infusion of gall-stone dissolving agents, or (iii) an expectant approach – treating symptoms if and when they arise – may be considered. (iv) If oral dissolution therapy such as that described by Salvioli *et al* is to be considered, the common duct gall stones should be radiolucent and it is helpful to confirm that the stones removed from the gall bladder during cholecystectomy are indeed cholesterol-rich. This assumes, of course, that (a) the stones present in the common duct originated in the gall bladder, (b) they are, therefore, of the same generation and composition as the gall-bladder stones, and (c) during their residence in the biliary tree, the stones have not become appreciably modified – for example, by the deposition of amorphous non-cholesterol material which would render them unsuitable for dissolution therapy (Fig. 2).

Surgery – the second laparotomy

Despite the fact that the morbidity and mortality for a second operation on the biliary tree is appreciably greater than that of an elective cholecystectomy and despite the fact that a second operation is often technically more difficult – many still feel that a direct surgical approach is the treatment of choice for common duct stones.

Edoscopic sphincterotomy

In experienced hands, endoscopic sphincterotomy carries only a small risk – comparable with, or smaller than surgical exploration of the duct. Sphincterotomy may be contra-indicated for larger stones measuring more than 12 mm in diameter, which are likely to be impacted in the biliary tree. The cost, benefit and risks of endoscopic sphincterotomy, with or without mechanical extraction using such devices as Fogarty balloons or Dormia baskets, has also been reviewed extensively[37–39] and need not be considered further here. The endoscopic placement of naso-biliary catheters and even the use of sonic disintegration of stones by

endoscopically guided sonic probes are interesting new approaches which are presently under evaluation.

Conservative approach

The natural history of untreated choledocholithiasis has been poorly studied – as indeed has the natural history of untreated stones in the gall bladder. The fate of untreated gall-bladder stones has been the subject of intense recent interest as a result of an article by Gracie and Ransohoff,[40] three associated editorials[41–43] and related correspondence in the medical press,[44–47] suggesting that 'innocent' or silent gall stones are not a myth. While this may be true early in the evolution of gall-stone disease when the stones are confined to the gall bladder, it is widely believed that the frequency of complications – such as biliary colic, obstructive jaundice, and gall-stone associated pancreatitis – are considerably greater in patients with choledocholithiasis, than in those with stones in the gall bladder. Indeed, it is for this reason that many investigators with a special interest in the medical dissolution of gall stones have abandoned attempts to dissolve common duct stones with cheno- or urso-deoxycholic acids.[48] Although most centres report successful cases where gall stones have disappeared from the biliary tree during bile acid therapy,[49 50] the efficacy of treating common duct stones seems lower, and the complication rate higher, than in the treatment of stones within the gall bladder. Furthermore, examination of stones removed from the biliary tree which have been present for some time frequently shows layers of pigment-rich amorphous debris and/or calcium salts (Fig. 2) which are likely to compound the problem of radiolucent non-cholesterol stones found in 10–20% of patients with stones in the gall bladder.[51–53]

T-tube infusion of gall-stone solvents

When common duct stones are detected in patients who have t-tubes *in situ*, two other approaches may be considered – infusion of solvents and mechanical extraction. Where the t-tubes are small (<12 French gauge), the option of infusion therapy through the t-tube may be considered. A variety of agents including saline, heparin,[54] sodium cholate[55] and other bile acids alone, or in combination with ethylenediaminetetra-acetate (EDTA)[56] have been tried, but at present, mono-octanoin, the monoglyceride of the medium-chain fat, trioctanoin, is probably the infusion treatment of choice,[57] even though it carries a small incidence of side-effects, such as nausea, vomiting, and diarrhoea.

T-tube extraction (Burhenne technique)

In patients who have a larger (>12 French gauge) t-tube *in situ*, the option of mechanical extraction of the stones under fluoroscopic control exists. This technique was pioneered and perfected by Burhenne,[58] but it has now been mastered by many radiologists, physicians, and surgeons throughout the world. Further discussion of this topic is beyond the scope of this article, and the subject has been reviewed elsewhere.[59]

Conclusions

The study by Salvioli and his colleagues is important in that it establishes

the feasibility of oral dissolution therapy for stones in the biliary tree. In a reasonable number of patients the authors have confirmed that bile acid treatment can lead to dissolution/disintegration/disappearance of common duct and biliary tree stones.[49 50] The inclusion of a placebo group and the use of a double blind study design are valuable, not so much for establishing the efficacy of treatment as a means of ridding the biliary tree of stones, but more for the collateral information which such a study provides – the effect of UDCA on symptoms and compliance, withdrawals and drop-outs and on serum lipids and liver function tests. Nevertheless, 6–24 months ursotherapy is expensive and in the hierarchy of treatment options, many would consider other forms of management preferable.

In patients who have accessible small or medium sized common duct stones of any type (radiolucent or radio-opaque; cholesterol-rich, calcium-rich or pigment-rich), endoscopic sphincterotomy ± mechanical extraction is probably the treatment of choice. It is quick (often instantaneous or, at most, requiring one to two weeks) and, in experienced hands highly effective, although it does carry a small risk of morbidity and mortality. Infusion/dissolution therapy through t-tubes [55–57] or down endoscopically placed nasobiliary catheters[60–62] also has a place in the treatment of retained radiolucent cholesterol-rich common duct stones. It too is relatively quick (one to four weeks) and reasonably effective, but can be tiring for the patient and side-effects limit its acceptability. In specialist units, mechanical extraction of retained common duct stones through mature t-tube tracts (the Burhenne technique[58]), may sometimes be helpful in avoiding surgery – particularly in the older age groups who tolerate second operations on the biliary tree rather poorly.

Perhaps the time has come, therefore, for surgeons, endoscopists, radiologists, and physicians to pool their resources and to plan a prospective random-allocation trial in an attempt to find the 'best buy' for the management of patients with choledocholithiasis.

R HERMON DOWLING

Gastroenterology Unit
Guy's Hospital and Medical School
London

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