Combination therapy with oral ursodeoxycholic and chenodeoxycholic acids: pretreatment computed tomography of the gall bladder improves gall stone dissolution efficacy

J R F Walters, K A Hood, D Gleeson, J P M Ellul, A Keightley, G M Murphy, R H Dowling

Abstract
In a five year study, 55 patients with radiolucent gall stones were treated with the combination of 7.5 mg chenodeoxycholic acid (CDCA) and 5.0 mg ursodeoxycholic acid (UDCA)/kg/day—that is, half the monotherapeutic doses. Side effects were few but four patients could not tolerate the prescribed bile acids because of diarrhoea or nausea. Analysis of fasting duodenal bile confirmed that CDCA+UDCA converted supersaturated into unsaturated bile but the saturation indices did not predict the dissolution response. By actuarial analysis, the confirmed (by ultrasound ×2) complete gall stone dissolution rates in all 55 patients were mean (SEM) 29 (7)% at 12 and 44 (8)% at 24 months. The advent of routine computed tomography before treatment enabled comparison of dissolution efficacy in those screened by computed tomography (n=24), whose maximum gall stone attenuation was <100 Hounsfield units, with that in those not screened (n=29). Although stone size and number were comparable, patients screened by computed tomography had significantly better dissolution rates (p<0.025) than those not screened in this way. At 12 months, partial or complete gall stone dissolution rates were 93 (7)% in the screened and 55 (11)% in the non-screened patients. At 18 months, complete dissolution rates were 64 (12)% and 20 (9)% respectively. Computed tomography before treatment is cost effective in selecting those patients likely to achieve gall stone dissolution on treatment with UDCA+CDCA.

Monotherapy with oral chenodeoxycholic acid (CDCA) or ursodeoxycholic acid (UDCA) is moderately effective in dissolving cholesterol rich gall stones.1-4 The dose related side effects of diarrhoea, hypertransaminasemia,5 and hypercholesterolaemia,4 however, have limited the acceptability of CDCA as a gall stone dissolving agent. UDCA causes minimal side effects but in our experience its efficacy in dissolving gall stones completely is less than that of CDCA, partly because of secondary gall stone calcification.4 Furthermore, although less UDCA than CDCA is required to desaturate bile4 and dissolve gall stones, the cost of monotherapy with UDCA is somewhat greater than that of CDCA. For these reasons, several groups5-8 have advocated the combination of CDCA and UDCA, each at half their monotherapeutic doses, with the aim of maintaining dissolution efficacy while minimising side effects. We began using CDCA plus UDCA for gall stone dissolution in 1984 and report here the results of a five year study with this combination in 55 patients.

We,9 and others,10-13 have recently shown that no less than 50% of gall bladder stones which are lucent by conventional radiology (plain x ray with or without oral cholecystography), look dense on computed tomography. These stones have high Hounsfield unit (HU) attenuation values and contain calcium in amounts that render complete dissolution with oral therapy unlikely. Indeed, over the past three years we have routinely screened all patients being considered for non-surgical management of their gall bladder stones by localised scanning of the gall bladder, and have accepted patients for treatment with oral CDCA + UDCA only if their stones had a maximum computed tomographic attenuation of <100 HU. We show here that patients selected in this way have significantly higher partial and complete gall stone dissolution rates than those not so screened and suggest that routine computed tomography of the gall bladder before treatment is cost effective in predicting the dissolution response to oral bile acid therapy.

Methods

PATIENT SELECTION

Admission criteria
Fifty five patients were entered into the study between June 1984 and June 1989: their clinical details and gall stone characteristics are given in Table 1. Eight patients had previously been treated with oral bile acids and were given the combination of CDCA plus UDCA for management of either recurrent (n=2) or incompletely dissolved (n=6) stones.

All 55 patients had specific, gall stone related symptoms (biliary colic) and all chose oral bile acids in preference to surgery or other non-surgical management options.14 The presence of gall bladder stones was usually diagnosed first by ultrasonography. In addition, however, all patients underwent oral cholecystography which included a preliminary plain abdominal x ray and, during the contrast study, erect and after fatty meal films. Liver function tests (serum albumin, bilirubin, alkaline phosphatase, and transaminase), serum lipids, and a full blood count were all normal before treatment.

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Accepted for publication 13 May 1991
Table 1: Characteristics of patients treated with chenodeoxycholic acid plus ursodeoxycholic acid

<table>
<thead>
<tr>
<th>Year of entry to trial</th>
<th>Overall group</th>
<th>Not screened</th>
<th>Screened by CT (&lt;100 HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-5</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>1985-6</td>
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<td>12</td>
<td>0</td>
</tr>
<tr>
<td>1986-7</td>
<td>12</td>
<td>7</td>
<td>3*</td>
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<tr>
<td>1987-8</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>1988-9</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>29</td>
<td>24*</td>
</tr>
</tbody>
</table>

Patient characteristics:
- Age (yrs) mean (SEM): 50.2 (23-91)
- Sex ratio (M:F): 11:44
- Previous bile acid therapy: 8
- Stone characteristics:
  - Single: 13
  - Multiple: 42
  - Median number: 5
  - Maximum diameter of largest stone (mean (SEM)): 8.1 (0.6), 8.0 (0.9), 8.3 (0.8)

CT=computed tomography.
*Two further patients are not included in either subgroup. They were screened with pretreatment CT but were treated despite having CT values greater than 100 HU.

Exclusion criteria
In both subgroups (see below), patients were excluded from the study if calcification of the gall stones was seen by conventional radiology, if the gall bladder failed to opacify during oral cholecystography (two consecutive studies, the second with a double dose of contrast), or if the maximum diameter of the largest stone exceeded 20 mm. Women of child bearing age were excluded from treatment unless they were taking effective contraceptive measures.

LOCALISED COMPUTED TOMOGRAPHY OF THE GALL BLADDER
Computed tomography of the gall bladder region was performed routinely in all gall stone patients being considered for non-surgical treatment from the end of 1986 onwards. Imaging was performed on a Philips Tomoscan 350 at a setting of 120 kV and 200 mA with a scan time of five seconds, and usually comprised five to seven 6 mm contiguous ‘cuts’ to scan the gall bladder region completely. Based on our previous findings, we excluded from treatment any patient whose stones had a maximum computed tomogram density in excess of 100 HU.

Figure 1: Gall stone dissolution rates (mean (SEM)) in the entire group of 55 patients calculated by life table analysis at six monthly intervals, showing complete gall stone dissolution and partial plus complete dissolution.

Bile Lipid Analysis
Fasting, bile rich duodenal fluid was obtained by aspiration from 31 patients before treatment and from 22 after approximately six weeks of therapy. Total bile acid, phospholipid, and cholesterol concentrations were measured, and the biliary cholesterol saturation index (SI) determined, as previously described.

Treatment and Follow Up
Patients were given the combination of approximately 7-5 mg CDCA/kg/day and 5-0 mg UDCA/kg/day, which was taken as a single bedtime dose.

The patients were seen for follow up every two to three months, at which time compliance in taking the prescribed medication was checked, symptoms were assessed, and side effects were noted. Fasting serum lipids and liver function tests were also measured at each visit.

Assessment of Gall Stone Dissolution Response
Gall stone dissolution was assessed every six months by ultrasonography. Partial gall stone dissolution was defined as a 50% decrease in gall stone number or volume, or both. Complete dissolution was confirmed by two consecutive ultrasonographic examinations, at least one month apart, during continued bile acid treatment. In this study, oral cholecystography was used to exclude acquired gall stone calcification or blockage of the cystic duct in patients who had not shown ultrasonographic evidence of gall stone dissolution after one year of therapy.

Treatment was withdrawn at different times for the following reasons: (i) at one year in compliant patients who had shown no radiological evidence of gall stone dissolution; (ii) after a total of two years treatment in those who had shown partial gall stone dissolution after one year but had not progressed to complete dissolution; (iii) at any time after confirmation of complete gall stone dissolution; or (iv) because of unacceptable side effects.

Gall stone dissolution rates were assessed by actuarial or life table analysis (LTA). The results in patients whose treatment was withdrawn at one year because of non-response, were retained in the number ‘at risk’ for subsequent analysis. The results in patients who defaulted or withdrew from the trial because of complications of treatment, however, were censored from subsequent analysis. Except where otherwise indicated, the results are expressed as mean (SEM). Dissolution rates are compared by the log rank test or by the Student’s t test as appropriate.

Results
Patient characteristics and details of their gall stones are shown in Table I. Of the 55 patients who joined the study, 29 were accepted before computed tomography of the gall bladder was performed routinely and constituted one subgroup. The other subgroup was formed by 24
patients, all of whom had undergone computed tomography of their gall bladder and had stones with a maximum density of <100 HU. Not included in either subgroup were two other patients who underwent computed tomography and had HU values greater than 100, but who began treatment before our computed tomography selection criteria became firmly established.

As Table I shows, the clinical and gall stone characteristics were comparable in both subgroups of patients. Of the eight who had been treated with oral bile acids previously, two (one in each subgroup) had recurrent stones after complete stone dissolution with CDCA or UDCA alone, three had had partial stone dissolution on UDCA, and three had failed to respond to ursodeoxycholic acid.

**CLINICAL RESPONSE**

**Default/withdrawal**

Table II summarises the outcome of treatment in all 55 patients. A total of 19 patients did not complete the study—10 were withdrawn and a further nine defaulted from follow up. Three withdrew because of recurrent biliary pain and underwent elective cholecystectomy. Two others who defaulted are also known to have undergone surgery. Forty two (76%) reported no further symptoms from their gall stones during bile acid therapy.

**Side effects and complications**

Four patients were withdrawn because they could not tolerate the oral bile acid treatment—two because of diarrhoea (one of whom had colonic diverticular disease) and two because they claimed that the treatment increased their pre-existing nausea. Of the three other patients withdrawn from the study, one developed a spinal artery thrombosis and another had failing eyesight; neither complication was thought to be related to therapy. The third elected to have lithotripsy for his 18 mm stone when this treatment became available.

Diarrhoea or loose stools occurred in 14 patients (25%). This was transient in seven (whose bile acid dose remained unchanged), resolved on reducing the dose of CDCA in five but, as indicated above, persisted in the remaining two. No patient developed raised serum transaminase values or hyperlipidaemia and none was found to have developed secondary gall stone calcification.

**Gall stone dissolution**

The gall stone dissolution rates, calculated by LTA, are shown for all 55 patients (those screened and those not screened by computed tomography) in Figure I. At six months, the pooled complete gall stone dissolution rate was 19 (6%) and the partial plus complete dissolution rate was 51 (8%). The corresponding figures at 12 months were 29 (7%) and 71 (7%) respectively. Because of the trial design, there are no data for partial dissolution rates beyond 12 months but the complete dissolution rates rose to 38 (8%) and 44 (8%) at 18 and 24 months respectively.

**Effect of computed tomography on outcome of therapy**

In the subgroup of 24 patients screened by computed tomography who had a maximum stone attenuation of <100 HU, the partial plus complete gall stone dissolution rates were significantly better (log rank test for all time periods; p<0.025) than those in the subgroup of 29 patients who had not been screened (Fig 2). By one year, the partial plus complete rate in screened patients with HU scores of <100 was 93 (7%) compared with 55 (11%) in those who had not been screened.

Over all time points, complete gall stone dissolution rates were significantly better in the screened group (p<0.025). At 12 months, the complete dissolution rates were 50 (12%) in the screened and 14 (8%) in the non-screened patients (Fig 3). After eighteen months’ therapy, 64 (12%) of the screened patients showed complete dissolution compared with only 20 (9%) of the unscreened patients (p<0.01). As shown in Table I, this improved dissolution rate was not due to any difference in the characteristics of the patients or their stones.

**Bile lipid analysis**

Analysis of duodenal bile showed that before treatment the biliary cholesterol saturation index was 1-32 (0-11). During treatment, the mean saturation index fell significantly to 0-74 (0-06) (p<0.001). To assess whether a pretreatment
stones in selected patients. Furthermore, they show that routine computed tomography before treatment, to exclude patients with calcified gall stones on the basis of a maximum stone attenuation value >100 HU, significantly increases the probability complete stone dissolution.

The combination of CDCA and UDCA has been used in recent years by several groups\(^{14-16}\) in order to reduce the side effects of CDCA and the cost of UDCA while maintaining the efficacy of gall stone dissolution. Podda et al\(^{11}\) have clearly shown in a prospective randomised trial that the combination of CDCA and UDCA results in better dissolution rates than UDCA alone.

UDCA and CDCA act somewhat differently to reduce biliary cholesterol saturation but, as our study shows, when combined at a dose of 5-0 mg UDCA/kg/day and 7-5 mg CDCA/kg/day the two bile acids produce a highly significant reduction in the mean biliary cholesterol saturation index from 1.32 to 0.74. This change in the saturation index is similar to that shown in another study with the combination of the two bile acids\(^{10,15,16}\) but does not take into account cholestrol present in biliary vesicles or in other non-micellar forms.

In the pooled group (computed tomography screened plus those not screened) of 55 patients, the complete dissolution rate after two years of UDCA plus CDCA treatment was only 44 (8%)%. However, this figure is biased by the outcome in the subgroup of patients screened by computed tomography. Had they been excluded, the two year complete dissolution rate in the patients without computed tomography would have been only 33 (11%)%. This is a lower figure than that obtained by others with the combination of UDCA and CDCA. For example, Podda et al\(^{11}\) reported a complete dissolution rate of 60 (6%)% at 24 months. However, their patients were highly selected in that almost half (29 of 60) had small floating stones. Other investigators have shown lower mean dissolution rates of 25%\(^{15}\) and 27%\(^{16}\) after 24 months' treatment.

In our study, complete dissolution was defined rigorously by two normal ultrasound examinations. This approach is likely to result in lower but more accurate dissolution rates than those obtained using less stringent criteria. Thus, in another study from our unit in which UDCA alone was given in a dose of 8–10 mg/kg/day, complete dissolution occurred in 25–30% of patients when defined by oral cholecystography but in only 17–19% when defined by ultrasonography.\(^{1}\) This compares with an overall complete dissolution rate of 38% diagnosed by oral cholecystography in a third group of comparably selected patients from our unit who were treated with CDCA alone.\(^{2}\)

In the present study, the combination of UDCA and CDCA was generally well tolerated. Although 25% of the patients reported some diarrhea, it was usually mild and transient. This compares with an incidence of about 50% in patients given CDCA alone.\(^{3,7}\) Indeed, in CDCA treated patients, diarrhea is a dose dependent side effect.\(^{1,7}\) Despite the fact that one quarter of the patients in the present study complained of diarrhea, it necessitated withdrawal of treat-
UDCA + CDCA for gall stones: value of CT scanning

We believe that the observed improvement in dissolution efficacy as a result of routine computed tomographic screening before treatment, is due solely to the exclusion of patients with calcium containing stones. Thus, the patient and gall stone characteristics were comparable in patients screened and not screened by computed tomography. Furthermore, there was no bias as a result of including previously treated patients in the two treatment groups. In the present study, there were too few patients with recurrent stones to extend the results of previous studies from our own unit2 and elsewhere8 which suggest that most, but not all, recurrent stones are small, cholesterol rich, and easily dissolvable.

The present report is important not only because it extends the results of previous studies in which the combination of oral UDCA and CDCA has been used as the sole treatment for gall bladder stones, but also because we30 and others31-33 routinely use this combination of oral bile acids as adjuvant treatment after extracorporeal shock wave lithotripsy (ESWL). Although the aim of ESWL is to convert large stones into as small fragments as possible,32,33 in only a minority of patients (<20%) do the fragments pass spontaneously through the cystic duct: in the majority, the fragments must be dissolved. Thus, in a large multicentre double-blind trial, patients treated with ESWL plus oral bile acids cleared their gall stones significantly better than those given ESWL plus placebo.33

It is possible to fragment calcium containing gall stones with ESWL. Since most of the resultant fragments remain within the gall bladder and must be dissolved, however, the results of lithotripsy plus oral bile acids in patients with calcified stones are appreciably worse than those in patients with radiolucent, cholesterol rich gall stones.33 For this reason, we have adopted a policy of screening with computed tomography all gall stone patients being considered for non-surgical treatment, and exclude from lithotripsy plus oral bile acids those who have maximum HU scores in excess of 100.

However, we have yet to establish that this approach is as effective in patients treated with the combination of ESWL plus oral bile acids as in those given UDCA plus CDCA alone. With both these treatments, the value of pretreatment computed tomography scanning could now be confirmed more rigorously in a prospective randomised trial.

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We conclude that in appropriately selected
patients gall stone dissolution with a combination of UDCA and CDCA can be remarkably successful and routine pretreatment computed tomography of the gall bladder seems to have an important role in improving this selection process by detecting, and thereby excluding from treatment, patients with non-cholesterol stones.

We thank Mr Younos Qureshi for technical assistance and Mrs Ann Hollington for preparation of the typescript. Thanks are also due to the St. Martin’s Group of Hospitals for partial financial support (JRFW and KAH). Parts of this study were presented at the British Society of Gastroenterology at the Autumn meetings in 1987 and 1989, and published as abstracts (Gut 1987; 28: A1360 and Gut 1989; 30: A1459).


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