Optimum bile acid treatment for rapid gall stone dissolution

R P Jazrawi, M G Pigozzi, G Galatola, A Lanzini, T C Northfield

Abstract

To determine the optimum bile acid regimen for rapid gall stone dissolution, 48 gall stone patients were divided into four groups of 12 according to stone diameter and were randomly allocated to receive one of four treatment regimens: bedtime or mealtime chenodeoxycholic acid (CDCA, 12 mg/kg/day) and bedtime or mealtime ursodeoxycholic acid (UDCA, 12 mg/kg/day). An additional 10 patients treated with a combination of CDCA plus UDCA (each 6 mg/kg/day) at bedtime were matched with the 10 patients on bedtime CDCA and the 10 on bedtime UDCA. The gall stone dissolution rates at six and 12 months were determined by standardised oral cholecystography and expressed as the percentage reduction in the gall stone volume after treatment. The gall stone dissolution rate at six months was higher for UDCA than CDCA treatment (median 78% ± 48%, p<0.01), and for bedtime than mealtime administration (69% ± 39%, p<0.02). Both differences were greater for stones <8 mm diameter. The dissolution rate was faster for combination therapy than for CDCA alone at both six (82% ± 36%, p<0.05) and 12 months (100% ± 54%, p<0.05), but was not different from UDCA alone. We conclude that bile acid treatment should be confined to patients with small gall stones and that bedtime administration of combined UDCA and CDCA is likely to provide the most effective and safe combination.

Since the introduction of chenodeoxycholic acid (CDCA) in the early 70s and ursodeoxycholic acid (UDCA) in the late 70s, many controlled and uncontrolled trials have been carried out to assess the efficacy of the two bile acids in terms of the proportion of gall stones for which complete or partial dissolution is achieved over a defined time interval. Available data suggest that the overall efficacy is similar; both bile acids achieve complete dissolution in 10-60% of patients and partial dissolution in another 10-45% of patients. The wide variation in the response rate can be attributed to differences in the dose of bile acid used, in treatment length, and in patient's weight in relation to ideal body weight and to different approaches to the inclusion of 'dropouts' in the final analysis. Only three controlled studies have directly compared CDCA with UDCA, and each reported that UDCA had a slight though not significant advantage over CDCA. A recent study has reported that a combination of CDCA plus UDCA is more effective than UDCA alone. We have also shown that bedtime administration of CDCA is more effective than mealtime administration in improving the gall stone dissolution rate.

Subjects

Fifty eight of a total of 72 consecutive patients with radiolucent gall stones in functioning gall bladders were entered in the study on the grounds of matching of initial gall stone size. This matching was carried out before measuring the gall stone dissolution rate. All patients gave informed consent, and the studies were approved by the local hospital ethical committee.

EXPERIMENT I

Forty eight of the first 59 consecutive patients were prospectively matched in four groups of 12 to within 2 mm according to the diameter of their largest stone and were randomly allocated to one of four treatment regimens: CDCA at bedtime or at mealtimes and UDCA at bedtime or at mealtimes. Each patient grouped had a representative patient with diameter matched gall stones.
in each of the other three groups. In eight patients with large stones (two in each of the above groups) the matching was not to within 2 mm of stone diameter. The diameters of the largest stones in these patients were 18 mm, 19 mm, 28 mm, and 30 mm in the first matched quartet, and 18 mm, 20 mm, and 26 mm in the second quartet of patients on mealtime CDCA, bedtime CDCA, mealtime UDCA, and bedtime UDCA respectively. The bile acids were given in a mean total daily dose of 12 mg/kg/day either at bedtime or in three equal divided doses at mealtimes.

EXPERIMENT II

Ten of a total of 13 consecutive patients receiving bedtime combination therapy were matched for initial gall stone diameter with 20 patients already studied — 10 taking CDCA and 10 taking UDCA at bedtime. The patients on combination therapy received CDCA and UDCA, both in a dose of 6 mg/kg/day, giving a total daily dose of 12 mg/kg administered at bedtime. Clinical details of the patient groups are shown in Table I. There were no significant differences in terms of age and percentage ideal body weight between the groups in either of the experiments.

For all patients, we used a dose of approximately 12 mg/kg/day, as this dose maintains an unsaturated gall bladder bile for CDCA as well as for UDCA. For the combination treatment, we used the same total dose of 12 mg/kg/day, because we wished to study an equimolar dose of the two bile acids.

### METHODS AND MEASUREMENTS

A standardised cholecystogram was used to visualise the gall stones within the gall bladder. This technique involved placing a 45° wooden block under the left side of the patient as he or she lay in the supine position. Hence views taken were in the right supine oblique position. In five patients in whom abdominal gas prevented complete visualisation of the gall bladder in this position, right prone oblique views were obtained and used for subsequent studies on the same patients. The distance between patient and x ray tube was always kept constant at 100 cm. In all patients except four, the diameter of the largest stone was measured and used for calculating the gall stone dissolution rates achieved by the different bile acids by comparing gall stone volume before and after treatment. In the four exceptions (randomised to the four different treatment regimens), there were multiple small stones of similar diameter (3–5 mm). In these patients the number of stones was calculated and the percentage reduction in number was used as an estimate of the gall stone dissolution rate during treatment. The standardised oral cholecystograms were repeated in each patient after six and 12 months of treatment. Standardisation of the procedure in this manner allows valid quantitative determination of the relative change in size or number of gall stones.

### CALCULATION AND ANALYSIS OF RESULTS

From the standardised oral cholecystogram, the initial gall stone diameter and the diameters at six and 12 months were measured. We also measured the volume of gall stones at the same time intervals by the method of multiple cylinders. Although this method was developed to measure gall bladder volume, we have previously validated it for measurement of gall stone volume by comparison with the water displacement method. Gall stone dissolution rates at six and 12 months were calculated by comparing the percentage reduction in gall stone volume at these times with the volume before treatment. Complete gall stone dissolution was confirmed by ultrasonography carried out at the time of negative oral cholecystogram and repeated after three months, during which time the patient continued on treatment. Partial gall stone dissolution was defined as a reduction in gall stone volume of more than 50%. This is thus a semiquantitative measurement, by contrast with the quantitative measurement of gall stone dissolution rate (above).

### STATISTICAL ANALYSIS

Results are described as medians. The paired Wilcoxon test was used for comparison between regimens, comparisons being made between gall stone patients matched for gall stone size. The y2 test and simple regression analysis were also used where appropriate. P values of <0.05 were considered significant in the present study.

### RESULTS

The dissolution rate (percentage reduction in gall

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**TABLE I. Clinical details of patients treated with chenodeoxycholic acid (CDCA), ursodeoxycholic acid (UDCA), or a combination of both**

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>No</th>
<th>M/F</th>
<th>Age* (yr)</th>
<th>% IBW*</th>
<th>Stone diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDCA (MT)</td>
<td>12</td>
<td>2/10</td>
<td>55 (6)</td>
<td>109 (5)</td>
<td>10-9 (2)</td>
</tr>
<tr>
<td>CDCA (BT)</td>
<td>12</td>
<td>3/9</td>
<td>47 (8)</td>
<td>114 (4)</td>
<td>10-9 (2)</td>
</tr>
<tr>
<td>UDCA (MT)</td>
<td>12</td>
<td>2/10</td>
<td>55 (6)</td>
<td>107 (5)</td>
<td>11-8 (3)</td>
</tr>
<tr>
<td>UDCA (BT)</td>
<td>12</td>
<td>4/8</td>
<td>55 (9)</td>
<td>120 (2)</td>
<td>12-2 (2)</td>
</tr>
<tr>
<td>Combination (BT)</td>
<td>10</td>
<td>2/8</td>
<td>50 (6)</td>
<td>118 (5)</td>
<td>12-2 (2)</td>
</tr>
</tbody>
</table>

**MT**=mealtime; **BT**=bedtime; **IBW**=ideal body weight

* Results expressed as mean (SEM)

**TABLE II. Gall stone dissolution rates (% reduction in pretreatment stone volumes) in 48 patients in experiment I. Each patient in the first column is matched for initial gall stone diameter with the corresponding patient in the other three columns.**

<table>
<thead>
<tr>
<th>Chenoxycholic acid</th>
<th>Mealttime</th>
<th>Bedtime</th>
<th></th>
<th>Mealttime</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DIA</td>
<td>DR6</td>
<td>DR12</td>
<td></td>
<td>DIA</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>20</td>
<td>30</td>
<td>19</td>
<td>23</td>
<td>52</td>
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<tr>
<td>18</td>
<td>48</td>
<td>80</td>
<td>18</td>
<td>8</td>
<td>8</td>
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<td>11</td>
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<td>0</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>80</td>
<td>7</td>
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<td>78</td>
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<tr>
<td>4*</td>
<td>60</td>
<td>100</td>
<td>5*</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

DIA = initial gallstone diameter; DR6 and DR12 = dissolution rate at 6 and 12 months respectively; **= DR in this matched quartet of patients is calculated from % reduction in pretreatment gall stone numbers.
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Figure 2: Effect of different bile acids on the gall stone dissolution rate (expressed as the percentage reduction in gall stone volume over six and 12 months). Chenodeoxycholic acid and ursodeoxycholic acid are compared for small stones and for large stones.

Stone volume after treatment) for all patients is given in Table II.

Gallstone Dissolution Rate: Experiment I

Effect of individual bile acids

UDCA treatment resulted in a significantly greater gall stone dissolution rate than CDCA at six months (n=24, median 78% v 48%, p<0.01), but the difference between the two bile acids was smaller and no longer significant at 12 months (90% v 74%, NS). For small stones (Fig 1), the gall stone dissolution rate was significantly faster during UDCA than CDCA treatment at six months (90% v 55%, p<0.001, n=12), and also at 12 months (95% v 90%, p<0.01). By contrast, for large stones there was no difference between the two bile acids at six or 12 months (52% v 25%, NS, n=12; and 69% v 51%, NS, n=12 respectively).

Effect of dose timing

Pooling the results for both bile acids, the gall stone dissolution rate was higher for bedtime than mealtime administration at six months (69% v 49%, p<0.02, n=24). The difference between the two dose times was no longer significant at 12 months (91% v 77%, NS, n=24). The gall stone dissolution rate for small stones was significantly higher for bedtime than mealtime administration both at six months (90% v 55% p<0.005, n=12) and 12 months (100% v 85%, p<0.005, n=12; Fig 2). By contrast, there was no difference between six and 12 month gall stone dissolution rate for mealtime and bedtime administration in patients with large stones (35% v 37%, NS (n=12) and 51% v 58%, NS (n=12) respectively (Fig 2).

When the two bile acids are compared in terms of dose timing, UDCA was found to be more effective than CDCA for both mealtime and bedtime administration (83% v 47%, p<0.01

![Figure 2: Effect of dose timing on the gallstone dissolution rate (expressed as in Figure 1). Mealtime and bedtime administration are compared for small stones and for large stones; the results for both individual bile acids being grouped together.](http://gut.bmj.com/)

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continued during the second six months at almost the same rate as during the first six months for CDCA, it decreased considerably for UDCA.

However, when the cumulative decrease in diameter during CDCA treatment was plotted against that for matched stones on UDCA, most of the data points were above the identity line at both six and 12 months (Figs 3A and 3B) indicating that although the gall stone dissolution rate during UDCA decreased during the second six-month period compared with the first, it remained quantitatively higher than for CDCA during both periods.

**EXPERIMENT II**

**Effect of combination treatment (Fig 4)**

Combination treatment given at bedtime was more effective than bedtime CDCA after six months (82% vs 36%, p<0.05) and 12 months of treatment (100% vs 54%, p<0.05). However, there was no difference between combination therapy and UDCA at six months (82% vs 85%, NS) or at 12 months (100% vs 93%, NS, Fig 4).

**Patients achieving partial and complete gall stone dissolution**

Both UDCA and combination treatment showed a trend towards higher total (partial and complete) dissolution rates than CDCA at six months (70% and 60% on combination therapy and UDCA respectively, compared with 45% on CDCA). This trend was mainly due to a higher complete gall stone dissolution rate, with similar partial dissolution rates for all three regimens. There was no difference between the regimens at 12 months.

Dissolution failure at six months (0% dissolution), and arrested dissolution (no change in dissolution rate between six and 12 months) were found in 5/24 patients on CDCA, 7/24 patients on UDCA, and 3/10 patients on combination therapy. There was no significant difference between the three groups in this respect.

**Discussion**

In this study, we have combined two approaches in order to determine, in a controlled manner, the most effective oral treatment regimen for cholesterol gall stone dissolution. Firstly, we used a standardised cholecystographic technique to produce a quantitative measurement of gall stone dissolution rate. Secondly, we matched our gall stone patients according to the initial gall stone diameter when comparing differing treatment regimens, because gall stone size is the most important factor determining the gall stone dissolution rate. These two elements in technique have enabled us to compare several different treatment regimens and to detect significant differences between them.

We defined two categories of gall stone size, small (<8 mm) and large (>8 mm). We chose 8 mm as the cut off point because it enabled us to divide all four treatment groups in experiment I.
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Figure 4: Effect of combination therapy given at bedtime on the gall stone dissolution rate (expressed as in Figure 1). This is compared with bedtime chenodeoxycholic acid and with bedtime ursodeoxycholic acid alone.

(each containing 12 patients), into two equal groups of six with large or small stones. The issue of gall stone size has become of great importance in recent years since the establishment of extra-corporeal shockwave lithotripsy (ESWL) as a non-surgical treatment option for cholesterol gall stones. ESWL converts large stones into small fragments which then have to be dissolved by oral bile acid therapy. This, coupled with the fact that very large stones are unsuitable for bile acid therapy, has modified the role of bile acid therapy for gall stone treatment. Our comparisons for small stones should apply also for small stone fragments after ESWL.

Our results show that UDCA was more effective than CDCA at six months but that the difference disappeared at 12 months (Fig 1). This comparison was based on all patients (24 matched pairs) encompassing a wide range of gall stone diameters (3–30 mm). Similar results have been reported for the proportion of patients achieving complete gall stone dissolution.

There are two possible reasons for the reduction in efficacy of UDCA over time. Firstly, subradiological calcification during UDCA could arrest further dissolution. Alternatively, small stones that dissolve completely with UDCA at six months are excluded from the analysis of results at 12 months, giving the impression of CDCA catching up with UDCA when the results are expressed as the proportion achieving complete dissolution. Our experimental design allowed us to differentiate between these two explanations. By separating small and large stones (Fig 1), we found that for small stones UDCA had a higher efficacy than CDCA at six months (90% v 55%) and that this was still present at 12 months, whereas for large stones there was no difference between the two bile acids even at six months. However, when the reduction in diameter for CDCA was compared with that for UDCA (Fig 3), we found a larger reduction in diameter for UDCA than CDCA both at six and 12 months.

The finding that a similar proportion of patients on CDCA and UDCA showed no dissolution (0% dissolution rate) or arrested dissolution suggests that acquired calcification does not play a major role. Since computed tomography was not performed before treatment, we cannot state whether failure of dissolution was due to subradiological calcification or to radiolucent non-cholesterol stones. However, 7/8 patients with radiolucent stones on oral cholecystography who had failed or arrested dissolution had calcification on computed tomography. This suggests that computed tomographic scanning may be an important factor in selecting patients for bile acid treatment.

In assessing the effect of dose timing, regardless of the type of bile acid, we found a higher gall stone dissolution rate for bedtime than mealtime administration at six but not 12 months. The effect of bedtime administration was more pronounced for small stones with the difference persisting at 12 months (Fig 2). When the effect of dose timing was assessed for the two different bile acids, bedtime was more efficacious than mealtime for CDCA but not for UDCA. However, we have shown in a separate study a higher efficacy of bedtime over mealtime UDCA when the bile acid is given in a lower dose of 4 mg/kg/day. The inability to show a difference at the higher dose is probably because this dose achieves an optimal effect that cannot be improved upon by further increasing the dose, as reported by Erlinger et al, or by giving it at bedtime. Looking at all the different variables together, we found that mealtime CDCA is the least and bedtime UDCA the most effective treatment, especially for small stones (95% disso-
lution at six months and 100% at 12 months).

For combination therapy, the reason for using equal doses (6 mg/kg/day) of CDCA and UDCA was to determine whether combination treatment has an additive effect (in which case its efficacy should lie between that of CDCA and UDCA in the full monotherapeutic dose) or whether it has a synergistic effect (in which case it should have a higher efficacy than either of the other two bile acids given alone). Our results suggest the latter. A comparison of three groups of patients with matched gall stones showed that combination treatment at bedtime achieved a dissolution rate at six months that was significantly higher than for bedtime CDCA, but not higher than for bedtime UDCA. These results do not confirm those of Podda et al., who reported, in a much larger group of patients, that combination treatment was significantly better than UDCA in achieving complete gall stone dissolution, but extend Podda’s study by showing that combination therapy is significantly better than CDCA (Fig 4).

We conclude that bile acid treatment should be confined to patients with small gall stones (or small fragments after ESWL). Bedtime administration is more effective than that at mealtime for CDCA, but UDCA is more effective than CDCA. Combination treatment is more effective than CDCA alone, although we could not confirm its superiority over UDCA alone.

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