Lack of response to chenodeoxycholic acid in obese and non-obese patients

Role of cholesterol synthesis and possible response to ursodeoxycholic acid

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SUMMARY This paper describes seven patients with radiolucent gallstones in functioning gallbladders who did not respond to chenodeoxycholic acid (CDCA). Despite large doses (>19 mg CDCA/kg/day), CDCA-rich bile (CDCA conjugates 70–97% of total biliary bile acids) and > one year’s treatment, their fasting duodenal bile remained supersaturated with cholesterol and their gallstones did not dissolve. Five patients came to cholecystectomy, gallstone analysis and liver biopsy for measurement of hepatic cholesterogenesis (HMGCoAR activity). In three who stopped CDCA before surgery, the mean HMGCoAR (pmol/mg microsomal protein/min) of 50.2 was higher than in our untreated gallstone controls (32.2±SEM 2.0; p < 0.05). Two patients who took CDCA until surgery had a mean HMGCoAR of 33.5—more than twice that in CDCA-treated gallstone controls. These findings suggest that non-response to CDCA may be related to high or unsuppressed hepatic cholesterogenesis. In one patient who did not respond to CDCA, treatment with 19 mg ursodeoxycholic acid/kg/day did desaturate his bile.

We have previously shown that treatment of non-obese gallstone patients with 13–15 mg chenodeoxycholic acid (CDCA)/kg/day almost always produces unsaturated bile and dissolves gallstones,1 while, in the obese, 18–22 mg/kg/day of CDCA are needed to produce the same effect.2

From a total of 125 patients with radiolucent gallstones in functioning gallbladders treated with CDCA, we have identified seven who, despite being given 19–22 mg/kg/day, never developed unsaturated bile nor did their gallstones dissolve. In this paper we describe the clinical details in this 'resistant' group and, in an attempt to define the mechanism for the non-response, we measured hepatic cholesterol synthesis as judged by the activity of the rate limiting enzyme in cholesterogenesis, HMGCoA reductase (E.C.1.1.1.34).

Methods

Patients and Study Design
Clinical details in the seven ‘resistant’ patients studied are given in Table 1. There were four men and three women whose ages ranged from 29 to 68 years. Four were non-obese—arbitrarily defined as less than 120% of ideal body weight (range 102 to 119% IBW), and three were obese—137 to 168% IBW. All the patients started treatment with an initial dose of 13–15 mg CDCA/kg/day, but were subsequently given larger amounts of CDCA—the doses shown in Table 1 together with the corresponding data for bile lipid and biliary acid composition. None of the patients was diabetic or hyperlipidaemic—factors known to influence bile lipid composition,3,4 none was taking medications other than CDCA, and the women were all post-menopausal, which therefore excluded the possibility of changes in bile lipid composition known to occur during the menstrual cycle.5

The criteria for non-response to CDCA treatment were: (1) radiolucent stones in ‘functioning’ gallbladders, (2) supersaturated fasting duodenal ‘bile’ on at least two occasions despite 19 mg or more CDCA/kg/day for a minimum of six weeks, (3) 70% or more CDCA conjugates in biliary bile acids,
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Table 1  Clinical details (age, weight, percentage of ideal body weight), biliary cholesterol saturation index before and during CDCA treatment, dose of CDCA and percentage of CDCA conjugates in total biliary bile acids during therapy in non-responsive patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>IBW (%)</th>
<th>SI</th>
<th>Dose (mg/kg/day)</th>
<th>CDCA in bile (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>58</td>
<td>79-1</td>
<td>168</td>
<td>2-56</td>
<td>1-20</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>62</td>
<td>72-6</td>
<td>140</td>
<td>1-64</td>
<td>1-18</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>29</td>
<td>86-8</td>
<td>137</td>
<td>1-66</td>
<td>1-32</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>35</td>
<td>81-5</td>
<td>111</td>
<td>1-81</td>
<td>1-03</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>60</td>
<td>47-4</td>
<td>102</td>
<td>2-19</td>
<td>1-90</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>68</td>
<td>84-4</td>
<td>115</td>
<td>1-24</td>
<td>1-27</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>33</td>
<td>65-0</td>
<td>107</td>
<td>2-03</td>
<td>1-24</td>
<td>22</td>
</tr>
</tbody>
</table>

* Pretreatment. † During CDCA treatment

Table 2  Results of HMGCoA reductase, total hepatic, and microsomal cholesterol content and gallstone cholesterol content

<table>
<thead>
<tr>
<th>Patient</th>
<th>On CDCA at time of biopsy</th>
<th>HMGCoAR activity (pmol mevalonate formed mg microsomal protein/min)</th>
<th>Total hepatic cholesterol (mg/g)</th>
<th>Microsomal cholesterol (mg/g)</th>
<th>Gallstone cholesterol content (% by weight)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>35-4</td>
<td>3-20</td>
<td>41-9</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>31-5</td>
<td>2-98</td>
<td>36-8</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>63-0</td>
<td>3-02</td>
<td>—</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>47-1</td>
<td>3-40</td>
<td>44-7</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>40-5</td>
<td>2-51</td>
<td>31-4</td>
<td>100</td>
</tr>
</tbody>
</table>

Hepatic HMGCoA reductase
HMGCoA reductase activities were measured in operative wedge liver biopsies using an isotopic substrate method. The present results were then compared with our previous data in untreated gallstone patients and in those taking CDCA.

Hepatic cholesterol content
The cholesterol contents of both the total liver homogenates and their microsomal fractions were determined using the gas chromatographic method of Ishikawa et al. Again these findings were compared with our previous results for untreated and for CDCA-treated gallstone patients.

Gallstone analyses
Gallstones obtained at cholecystectomy were dried to constant weight, crushed, extracted into isopropanol, and their cholesterol content measured using the cholesterol oxidase method.

Statistical methods
The statistical significance of the differences between HMGCoA reductase activity in the different groups of patients was assessed using Lord's test.

Results
The bile lipid and biliary bile acid results are given together with the clinical data in Table 1; the results

(4) no radiological evidence of gallstone dissolution after a minimum of 12 months' CDCA therapy and at least six months on the highest CDCA dose.

In one of the patients fulfilling the above criteria (Table 3), therapy was changed from 19 mg CDCA/kg/day to 19 mg ursodeoxycholic acid (UDCA)/kg/day. After another six weeks, bile lipid and biliary bile acid composition were again measured.

Five of the original seven patients came to cholecystectomy: the remaining two stopped treatment but declined surgery. At laparotomy, a wedge biopsy of liver was obtained for determination of HMGCoA reductase activity and the levels of cholesterol both in whole liver homogenate and in the microsomal fraction.

PROCEDURES
Fasting bile-rich duodenal fluid was obtained and analysed for its cholesterol, phospholipid, and bile acid content as previously described. The biliary cholesterol saturation indices (SIs) were then calculated according to the criteria of Hegardt and Dams and Holzbach et al., using the equations of Thomas and Hofmann.

Biliary bile acid composition
To ensure that the small quantities of sulphate esters normally present in bile were included, the samples were first solvolyzed and individual bile acids measured by gas chromatography.
of the gallstone analyses and of HMGCoAR and hepatic cholesterol content are given in Table 2.

Bile lipid and biliary bile acid composition
Before treatment all patients had supersaturated bile, the mean saturation index being $1.88 \pm 0.16$. During therapy, although CDCA reduced the saturation index in five of the seven patients, even with the highest CDCA doses the mean post-treatment SI was still $1.37 (\pm 0.13$).

Biliary bile acid analyses showed that in all seven patients, the bile had become 'cheno-rich', the CDCA conjugates accounting for 70–97% of the bile acid total. The patient who took 19 mg UDCA/kg/day developed 'urso-rich' bile, his UDCA conjugates making up $67\%$ of his biliary bile acid total. At this stage he developed unsaturated bile (SI = 0.82).

HMGCoA reductase activity
The Figure shows the present results for hepatic HMGCoA reductase activity together with our previous data for untreated cholesterolithic gallstone patients and for those given standard doses (13–15 mg/kg/day) of CDCA.

In the three patients who had discontinued treatment before surgery (Table 2, nos. 3, 4, and 5) the mean HMGCoAR level of 50.2 pmol/mg microsomal protein/min was considerably higher than that in our corresponding group of untreated gallstone patients ($32.2 \pm 2.0; P < 0.05$). In the two remaining patients (nos. 1 and 2 in Table 2), who had taken high doses of CDCA until the eve of cholecystectomy, the mean enzyme activity of 33.5 units was more than twice that found previously in gallstone patients given smaller doses of CDCA ($15.7 \pm 1.5; P < 0.01$).

**Hepatic cholesterol content**
The mean whole liver homogenate cholesterol content was comparable in the three patients who had stopped treatment before surgery (2.94 mg/g wet weight of liver) and in the two patients who continued CDCA until the time of operation (3.20 and 2.98 mg/g wet weight of liver). A similar pattern of results was found for microsomal cholesterol (Table 2).

On the basis of these results, it seems that the tissue cholesterol content in patients who are resistant to CDCA is not related to HMGCoA reductase activity.

**Gallstone analyses**
As the results of Table 2 show, the five patients with radiolucent stones who came to surgery all proved to have cholesterol-rich stones containing 82–100% cholesterol by weight.

**Discussion**
The present results suggest that there is a small number of cholesterolithic gallstone patients, both obese and non-obese, who do not respond predictably to CDCA. Despite taking 19–22 mg CDCA/kg/day, they failed to achieve unsaturated bile and their gallstones did not dissolve. This lack of response may be related to the fact that they had high or unsuppressed hepatic cholesterol synthesis.

**Differences between patients in present study and 'resistance' to CDCA treatment in obesity**
The present group of patients were both obese and non-obese—unlike the previous group of 'resistant' patients who were all obese. And, although in both groups the bile remained supersaturated during
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with the standard dose of 13–15 mg CDCA/kg/day, in the previous group the bile ultimately became unsaturated with 18–22 mg CDCA/kg/day. With the higher CDCA doses, the gallstones in four of the eight obese 'resistant' patients subsequently dissolved; in the present group, there was no evidence of gallstone dissolution with comparably high doses, even though the radiolucent stones proved to be cholesterol-rich in the five patients who came to cholecystectomy.

**DEFINITION OF 'LACK OF RESPONSE'**
With duodenal intubation, one can decide within the first few weeks of starting treatment whether or not criteria (2) and (3)—as described in 'Patients and study design' to define non-response to CDCA—have been fulfilled. Ultimately, however, before one can accept that the patients are truly 'resistant' to CDCA, one must ensure that they are taking the doses of CDCA prescribed. The fact that all seven had at least 70% CDCA conjugates in bile means that there was little room for further enrichment of their bile with CDCA.

There were several other differences between the patients in the present study and those described previously. From our earlier reports, the mean pretreatment SI in much larger numbers of patients was 1.44±0.07 compared with 1.88±0.16 in the present group. This greater degree of supersaturation in the present study was not simply a function of obesity—a factor known to further increase biliary cholesterol saturation in patients with or without gallstones—as the pretreatment SIs were comparable in the obese and non-obese patients who failed to respond. However, the lack of response described here was probably not due to the high pretreatment SIs alone. We have previously shown that, in non-resistant gallstone patients, the greater the initial supersaturation, the greater is the fall in saturation index during treatment. In the present patients, the bile was not totally resistant to treatment, as chenotherapy reduced the SI in most cases but the degree of change was inadequate.

**MECHANISM FOR LACK OF RESPONSE**
Although the results of this paper suggest that the lack of response to CDCA was due to high or unsuppressed hepatic cholesterol synthesis, this hypothesis remains unproven. The high HMGCoAR activity in the two treated non-responsive patients was comparable to that found normally in untreated cholelithiasis. It may well be that the on-treatment results in these two patients had indeed been reduced by chenotherapy from an excessively high pretreatment value. Alternatively, the enzyme levels may have failed totally to respond to CDCA.

Furthermore, we do not know if the very high levels seen in the three non-responsive patients who had discontinued treatment before the time of biopsy had been lowered during the period of chenotherapy. This uncertainty could have been resolved only with repeated liver biopsies.

While the contribution of newly synthesised hepatic cholesterol to biliary cholesterol secretion is debated, the fact remains that chenotherapy usually reduces both hepatic HMGCoAR activity and biliary cholesterol output. In the present study, no secretion-perfusion studies were performed.

**UDCA TREATMENT IN LACK OF RESPONSE**
In one patient, treatment with UDCA caused the bile to become unsaturated in cholesterol, whereas a similar dose of CDCA failed to produce such a change. The UDCA dose given to this individual was large (19 mg/kg/day) when compared with the usually recommended UDCA dose of 8–10 mg/kg/day. When given in the same doses, UDCA lowers biliary cholesterol saturation and secretion to a greater extent than CDCA; alternatively, lower doses of UDCA are required to produce the same effect. If the response to high-dose UDCA in this patient is confirmed in others, UDCA-therapy may offer a means of overcoming the lack of response to CDCA.

We are grateful to Weddell Pharmaceuticals for supplies of CDCA, to the Giuliani Company for UDCA, to Professor I McColl for his help in supplying surgical specimens, to Miss Julia Ellis, Mr Younis Qureshi and Miss L Matthews for technical help, and to Miss Lorraine Byrne who typed the manuscript. PNM was a Weddell Research Fellow.

**References**


5. This ignores a correction factor for equilibrium cholesterol solubility in UDCA-rich bile which, in our experience, is less useful clinically than the uncorrected SI as a predictor of gallstone dissolution.


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