Cholic acid and ursodeoxycholic acid therapy in primary biliary cirrhosis

Changes in bile acid patterns and their correlation with liver function

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Summary. We treated 6 patients with Stage II primary biliary cirrhosis with cholic acid (CA) 10 mg·kg⁻¹ per day for 3 months and then with the same dose of ursodeoxycholic acid (UDCA). A matching group of 6 patients was observed for 3 months without any therapy. Liver function tests and serum and stool bile acids were investigated before, during and at the end of CA and UDCA therapy.

The results of liver function tests deteriorated after 6-8 weeks of CA therapy and the changes were correlated (r = 0.92) with an increase in α-dihydroxy-bile acids (chenodeoxycholic acid and deoxycholic acid) in the serum. The 24 h excretion of DCA in 24 h faeces was markedly increased.

Ursodeoxycholic acid treatment improved liver function tests; after 4 weeks glutamate dehydrogenase (GLDH) had decreased. After 8-12 weeks of therapy ursodeoxycholic acid had increased to 50-60 % of the total serum bile acids whereas the more apolar bile acids were significantly decreased. No changes in liver function tests or bile acid metabolism were found in the untreated group.

Since CA and UDCA are non-toxic in man, this trial indicates that the apolar bile acids chenodeoxycholic acid and deoxycholic acid may be responsible for the deterioration of liver function in primary biliary cirrhosis. However, the therapeutic effect of UDCA cannot be explained merely by the decrease in α-dihydroxy-bile acids in the serum, since the laboratory results had improved prior to the decrease in the serum apolar bile acids.

Key words: Primary biliary cirrhosis – Ursodeoxycholic acid therapy; cholic acid, α-dihydroxy bile salts

Ursodeoxycholic acid (UDCA) and chenodeoxycholic acid (CDCA) have been used for the dissolution of gallstones since the early seventies [1-3]. In 1985 we introduced UDCA into the therapy of liver diseases, since when it has mainly been used in the treatment of primary biliary cirrhosis (PBC) [4]. The mode of action of UDCA is unknown. During therapy, UDCA becomes the predominant bile acid both in serum and bile [5-10], but controversy remains as to whether its beneficial effect lies in the replacement of the more apolar toxic bile acids CDCA, deoxycholic acid (DCA) and lithocholic acid (LCA) [5, 7-9], or whether it exerts a directly protective effect on cell structures [10-12]. In animal experiments, UDCA prevented the cholestasis induced by CDCA and LCA [13-15], and a similar effect was seen with trihydroxylated cholic acid (CA) [16].

From these observations several questions arise: does UDCA exert its effect by inducing choleresis, thus increasing the excretion of the apolar bile salts? Does UDCA replace toxic bile salts? Does UDCA have a direct influence on the structure or function of the hepatocytes or bile duct epithelia? And, does CA, which possesses similar physico-chemical properties, have a similar therapeutic effect?

In patients with chronic liver disease, there is normally little or no conversion of CA to the toxic bile acid DCA [17-20]. CA is included in many of the so-called liver protective drugs and is cheaper than UDCA. Moreover, CA has previously been administered to humans in doses up to 1 g per day [21, 22, 23] and has been infused into patients with biliary drainage [24] without any adverse effects. For these reasons we believed a therapeutic trial with CA in PBC patients would not be hazardous.

Patients and methods

Twelve patients, 9 women and 3 men with histologically [25, 26] proven PBC (Stage II), were randomised into 2 groups, each with 6 patients. The two groups were well matched with respect to age, sex and duration of the disease. Selection criteria for enrolling patients with primary biliary cirrhosis in the study included the following: alkaline phosphatase (AP) at least 1.7-fold elevated, γ-glutamyl transpeptidase (γGT) at least 5-fold elevated, immunoglobulin M (IgM) fraction at least 2-fold elevated, and the demonstration of antimitochondrial antibodies. Endoscopic retrograde cholangiopancreatography and ultrasonic tomography were required to exclude any disorders other than PBC. At least three months prior to treatment all other medication was discontinued.
Table 1. Liver function test results in patients with primary biliary cirrhosis in Groups 1 (n = 6) and 2 (n = 6). CA 10 mg·kg⁻¹ per day; UDCA 10 mg·kg⁻¹ per day.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>GLDH (mean SD)</th>
<th>ALT (mean SD)</th>
<th>AST (mean SD)</th>
<th>gGT (mean SD)</th>
<th>AP (mean SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. Before</td>
<td>13.3 (1.5)</td>
<td>30.5 (6.3)</td>
<td>51.9 (23.6)</td>
<td>262 (155)</td>
<td>597 (132)</td>
</tr>
<tr>
<td></td>
<td>2. CA (3 mo)</td>
<td>24.0 (7.2)**</td>
<td>57.5 (21.8)**</td>
<td>84.5 (35.7)</td>
<td>341 (271)**</td>
<td>853 (511)**</td>
</tr>
<tr>
<td></td>
<td>3. UDCA (3 mo)</td>
<td>6.3 (0.7)*</td>
<td>23.5 (4.0)*</td>
<td>33.0 (6.4)*</td>
<td>197 (92)**</td>
<td>543 (188)**</td>
</tr>
<tr>
<td>2</td>
<td>4. Before</td>
<td>17.1 (9.2)</td>
<td>43.0 (18.5)</td>
<td>66.0 (30.6)</td>
<td>236 (155)</td>
<td>1030 (1050)</td>
</tr>
<tr>
<td></td>
<td>5. Without therapy</td>
<td>13.6 (7.9)</td>
<td>38.1 (10.5)</td>
<td>50.3 (17.1)</td>
<td>298 (243)</td>
<td>1260 (1410)</td>
</tr>
<tr>
<td></td>
<td>Normal and range</td>
<td>&lt; 6.0</td>
<td>&lt; 18</td>
<td>&lt; 22</td>
<td>&lt; 27</td>
<td>68–195</td>
</tr>
</tbody>
</table>

* P < 0.01; ** P < 0.05; For set 2 versus 1, 3 versus 2, and 5 versus 4

**Group 1.** 6 patients (4 f, 2 m) were treated with CA 10 mg·kg⁻¹·d⁻¹ (Falk GmbH, Freiburg i. Br., Germany) for 3 months. Subsequently, all 6 patients were treated with UDCA (10 mg·kg⁻¹·d⁻¹; Falk GmbH, Freiburg i. Br., Germany) for further 3 months.

**Group 2.** 6 patients (5 f, 1 m) received no therapy and were observed for 3 months.

In addition to the usual laboratory parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST), AP, gGT, glutamate dehydrogenase (GLDH), immune globulins (IgG, IgA, IgM), prothrombin time, antithrombin III (AT III)), we also determined bile acids in fasting serum and 24 h faeces. Specimens were collected before, during and at the end of CA and UDCA therapy, and were stored at – 70°C until analysed by HPLC [27].

Statistical analysis used the Wilcoxon-Rank test. Correlations were calculated according to Pearson.

Bile acid therapy conforms to the 1975 Declaration of Helsinki and informed consent was obtained from all patients.

**Results**

**Group 1**

**Cholic acid therapy.** In our first patient on CA therapy, AST and ALT decreased by 25% and gGT and AP by approximately 30%. There was a marked fall in mitochondrial GLDH by 60% during the 6th week of CA therapy. Pruritus only decreased slightly. The patient did not experience any detrimental effects, did not suffer from diarrhoea or constipation, and did not become icteric. At the end of the second month of CA therapy, liver enzyme values started to rise considerably above their initial levels. In the other 5 patients, gGT and AP decreased somewhat after 2–3 weeks, but in the 5–7th week of CA therapy, AST, ALT, gGT and AP rose. At the end of CA treatment, liver enzyme values had risen significantly (GLDH 1.8-fold, transaminases 1.75-fold, gGT 1.3-fold and AP 1.4-fold) above the initial values (Table 1; Fig. 1).

**UDCA therapy.** Since CA therapy caused a deterioration in all 6 patients, therapy was discontinued after 3 months and the patients were treated with UDCA. Under UDCA there was a rapid improvement both in such symptoms as fatigue, general malaise and pruritus, and in liver enzyme values (Table 1, Fig. 2). After 4–10 weeks the laboratory results had fallen to levels below those prior to CA therapy.

Bile acid metabolism. Serum and faecal bile acids are shown in Table 2. After 4 weeks of therapy, serum CA had