Metabolism of orally administered tauroursodeoxycholic acid in patients with primary biliary cirrhosis

K D R Setchell, C M P Rodrigues, M Podda, A Crosignani

Abstract

The metabolism of tauroursodeoxycholic acid orally administered and its effects on the bile acid pool of patients with asymptomatic/mildly symptomatic primary biliary cirrhosis is described. Patients were randomly assigned 500, 1000, or 1500 mg/day of tauroursodeoxycholate for six months. Biliary and serum bile acids were measured before and during treatment by gas chromatography-mass spectrometry and by high performance liquid chromatography. During tauroursodeoxycholate administration, the proportion of total ursodeoxycholate in bile reached mean (SEM) 34·4 (4·5)%, 32·8 (2·8)%, and 41·6 (3·0)% with doses of 500, 1000, and 1500 mg/day, respectively. Significant decreases in the proportions of chenodeoxycholate and cholate resulted. The glycine/taurine ratio of the biliary bile acid pool decreased from 1·9 at baseline, to 1·1 with the highest dose. Ursodeoxycholate in bile was conjugated with glycine and taurine, indicating that tauroursodeoxycholate undergoes significant deconjugation and reconjugation during its enterohepatic recycling. The proportion of lithocholate in bile remained unchanged. Fasting serum conjugated ursodeoxycholate concentration positively correlated with the tauroursodeoxycholate dose, and the increased proportion of ursodeoxycholate was accompanied by substantial decreases in the endogenous bile acids. Compared with previously published data for ursodeoxycholic acid therapy, these findings indicate that the shift toward a more hydrophilic bile acid pool is greater and potentially more favourable with tauroursodeoxycholate, and this is because of the reduced intestinal biotransformation of tauroursodeoxycholate.

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Over the past two decades, several clinical studies have established ursodeoxycholic acid (UDCA) to be a useful drug for the treatment of a variety of chronic liver diseases.[1–8] Improvements in clinical and biochemical markers of liver function consistently occur after UDCA administration,[1 2 7 8] a trend toward histological improvement[2 7] and a reduction in aberrant hepatic expression of human leucocyte antigen class I molecules[9] have been shown in patients with primary biliary cirrhosis (PBC). Furthermore, recent data emerging from longer term clinical trials indicate a significant delay in the time to transplantation in patients with PBC undergoing UDCA therapy,[10] while it has been concluded that patients with early stage PBC seem to benefit the most (B Combes *et al*, XIII international meeting on bile acids, 1994).

In PBC, the accumulation of endogenous hydrophobic bile acids, following the disappearance of bile ductules is thought to play an important part in the progression of liver cell injury,[2 11 12] and the beneficial effect of UDCA therapy has in part been attributed to the resulting increase in the hydrophilicity of the biliary bile acid pool.[11–13] When given orally, UDCA is absorbed, transported to the liver, and undergoes rapid and extensive biotransformation, predominantly involving conjugation with glycine and taurine. However, UDCA is also converted to the more hydrophobic bile acids, chenodeoxycholic and lithocholic acids, and while little is known about the extent of this conversion, it may be a limiting factor in its therapeutic effectiveness. As the cytotoxicity of a bile acid decreases with increasing hydrophilicity,[14] the conjugated bile acid tauroursodeoxycholic acid (TUDCA), which is considerably more polar than UDCA, should in principle be a more effective therapeutic agent. This contention is supported by in vivo and in vitro studies that show the taurine conjugate of UDCA to have a stronger cytoprotective effect than UDCA against the liver cell injury induced by hydrophobic bile acids.[15–19] Interestingly, it has been proposed that the hepatoprotective effect of UDCA may indeed be the consequence of its metabolism to its more polar conjugated species.[17 18]

TUDCA is now commercially available in Europe, and based upon the above rationale it is being evaluated as a second generation drug to UDCA for treating cholestatic liver disease. We describe for the first time the metabolic fate of TUDCA, given orally and at different doses, in patients with asymptomatic or mildly symptomatic PBC. When our data were compared with published studies of UDCA metabolism,[20] they show that the biliary UDCA enrichment, and shift in the hydrophobic/hydrophilic composition of the bile acid pool is greater during TUDCA administration, and that this is because of its reduced biotransformation.

Methods

Patients

Twenty four patients (age range 33–75 years) with asymptomatic or mildly symptomatic PBC (12 patients with stage I or II and 12 patients with stage III or IV disease) were randomly assigned to receive a daily dose of 500, 1000 or 1500 mg of TUDCA for six months. No differences were found among the three dosage groups in the most relevant clinical and biochemical data, and the clinical responses to treatment were reported elsewhere.[21] Fasting blood samples were obtained at entry (n=21) and after six months of treatment (n=21) for the determination of individual serum bile acid concentrations and liver function tests. In three patients, paired serum samples were not available for analysis. In patients who consented, duodenal bile was sampled at baseline and during TUDCA by means of a string test (Enterotest; PBI International, Milan, Italy),[22] after inducing gall bladder contraction with intramuscular caerulein (0·3 mg/kg body weight). Bile acid analysis was performed in seven bile samples obtained in basal conditions and in 10 samples collected during TUDCA administration. Informed consent was obtained from each patient, and study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Bile acid analysis by gas chromatography-mass spectrometry

Bile acids were measured by gas chromatography-mass spectrometry after liquid-solid extraction, hydrolysis, isolation by lipophilic anion exchange chromatography, and conversion to methyl ester-trimethylsilyl (Me-TMS) ether derivatives.

Total and individual bile acids – bile acids were quantitatively extracted from duodenal bile (0·10–0·50 ml) and serum (0·25–0·50 ml) using reverse phase octadecylsilane bonded silica cartridges (Bond-Elut C_{18}, Analytichem, Harbor City, CA) as described by Setchell and Worthington,[23] after addition of nordeoxycholic acid (0·5 μg), which was used as internal standard for quantifying the unconjugated bile acids. Following liquid-solid extraction, bile acids were separated according to conjugation state on diethylaminohydroxypropyl Sephadex LH-20 (Lipidex-DEAP, Packard Instruments, Groningen, Holland).[24] After further addition of nordeoxycholic acid (2 μg or 5 μg, respectively for serum and bile) to the conjugated bile acid fraction, the buffer was removed by passage of the sample through a Bond-Elut C_{18} cartridge. Bile acid conjugates were solvolysed[25] and enzymically hydrolysed[26] and the unconjugated bile acids released were extracted by liquid-solid extraction[23] and isolated by liquid-gel chromatography on Lipidex-DEAP.[24]

Bile acid conjugates – six of the duodenal bile samples collected during treatment with TUDCA (two patients from each dose regimen) were analysed to evaluate the extent of bile acid conjugation, following lipophilic ion exchange chromatography on Lipidex-DEAP.[24]

Gas chromatography-mass spectrometry – bile acids were converted to the Me-TMS ether derivatives and qualitatively and quantitatively analysed by gas chromatography-mass spectrometry; as previously described.[27] Identification of individual bile acids was made on the basis of the gas chromatography retention index relative to a homologous series of *n*-alkanes, referred to as a methylene unit (MU) value, and the mass spectra were compared with authentic standards.[27] Bile acids were quantified by comparing the peak height response with the peak height of the internal standard and assuming a unity response factor.

Bile acid analysis by high performance liquid chromatography

The principal amidated biliary bile acids were determined by reverse phase high performance liquid chromatography, after liquid-solid extraction, essentially as described by Rossi *et al.*[28]

Statistical analysis

Data are given as mean (SEM). Baseline and during treatment results were compared using paired two tailed Student's *t* test. The relation between dose, expressed as mg/kg body weight/day, and serum or biliary per cent of UDCA was examined by linear and polynominal regression analysis. Regression analysis was performed on all available data and also after having excluded data obtained in basal conditions. Two tailed significance values were used.

Results

BILIARY BILE ACID COMPOSITION DURING TUDCA ADMINISTRATION

Unconjugated and total conjugated biliary bile acids

After separation by lipophilic anion exchange chromatography, the unconjugated fraction was found to contain only small proportions (baseline value, 0·9 (0·2)%; with 1500 mg TUDCA, 0·6 (0·3)%) of the total bile acids, irrespective of whether TUDCA was given. Within the unconjugated bile acid fraction, UDCA accounted for 9·1 (2·2)% of the total bile acids identified in the bile at baseline and 19·4 (4·1)%, 24·6 (7·4)%, and 19·6 (1·1)% respectively, for doses of 500, 1000, and 1500 mg/day TUDCA. Despite this proportional increase in unconjugated UDCA during TUDCA administration, there was no overall increase in the proportion of total unconjugated biliary bile acids.

During TUDCA administration the proportion of total conjugated UDCA in bile significantly increased ($p<0·001$), from 2·5 (0·7)% at baseline, to 34·4 (4·5)%, 32·8 (2·8)%, and 41·6 (3·0)% with doses of 500, 1000, and 1500 mg/day, respectively (Fig 1). There were no

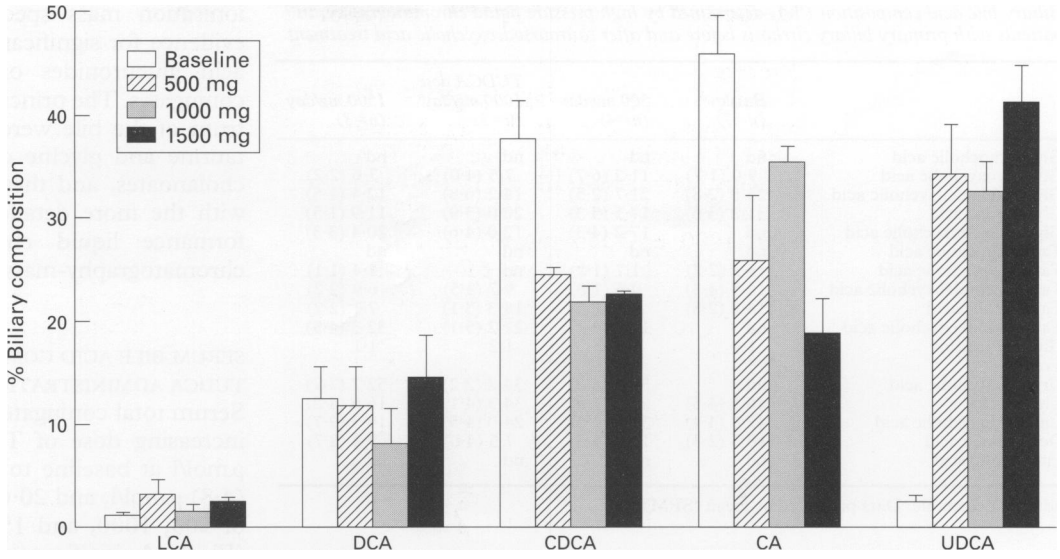

Figure 1: Per cent composition of the principal conjugated bile acids in bile from patients with PBC, determined by gas chromatography-mass spectrometry, at baseline (n=7) and during increasing doses of TUDCA (n=4, 500 mg/day; n=3, 1000 mg/day; n=3, 1500 mg/day). LCA, lithocholic acid; DCA, deoxycholic acid; CDCA, chenodeoxycholic acid; CA, cholic acid; UDCA, ursoedeoxycholic acid.

statistically significant differences in the proportions of total UDCA in the bile among the individual doses of TUDCA given. Enrichment of bile with UDCA occurred with a concomitant and significant decrease in the proportion of chenodeoxycholic and cholic acids. The proportion of the secondary bile acids, lithocholic and deoxycholic acids in bile remained comparatively unchanged after TUDCA treatment. In two patients unusually high proportions (22–24%) of deoxycholic acid were found at baseline and during treatment, which suggests these patients may have had undiagnosed bacterial overgrowth. There was minimal further change in biliary bile acid composition with increased doses of TUDCA. With the highest dose, chenodeoxycholic and cholic acids accounted for 22·6 (0·3)% and 18·9 (4·0)% of the biliary pool, compared with 37·8 (3·8)% and 46·0 (4·6)% respectively, at baseline ($p<0·001$).

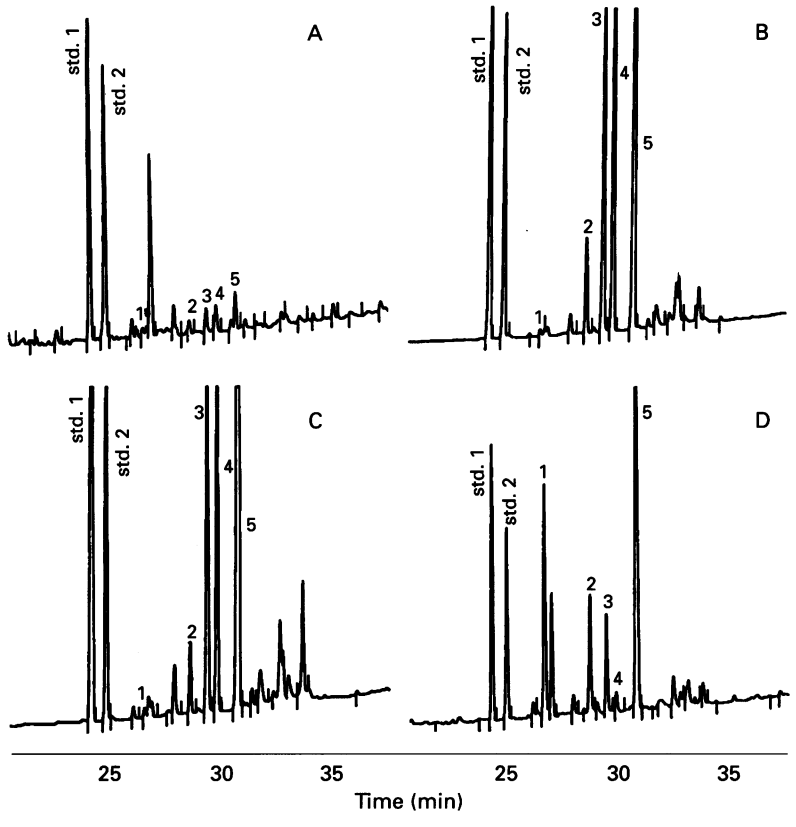

Figure 2: Typical gas chromatography profiles of the (A) unconjuated, (B) glycine conjugated, (C) taurine conjugated, and (D) sulphate conjugated bile acids in bile from one patient with PBC, during TUDCA (1500 mg/day) administration. The Me-TMS ether derivatives were separated on a 30 m×0·25 mm DB-1 fused silica capillary column using a temperature programme from 225 to 295°C in increments of 2°C/min, with initial and final isothermal periods of 2 min and 30 min, respectively. Std. 1, coprostanol; std. 2, nordeoxycholic acid; 1 lithocholic acid; 2, deoxycholic acid; 3, chenodeoxycholic acid; 4, cholic acid; 5, ursodeoxycholic acid.

Conjugation of biliary bile acids

Figure 2 compares typical gas chromatographic profiles of the unconjugated, glycine, taurine, and sulphate conjugated bile acids of the bile from patients with PBC, during TUDCA treatment. The relative proportion of unconjugated UDCA was small compared with total conjugated UDCA, for all doses (0·3%, 0·2%, 0·1%, respectively for doses of 500, 1000, and 1500 mg/day). UDCA was a major bile acid in all fractions. Lithocholic acid was present in only trace amounts in the glycine and taurine fractions, and although the proportion of sulphated bile acids (amidated and non-amidated) was small (3·6 (0·6)%), within this fraction, lithocholic acid was quantitatively the second most important bile acid sulphate, accounting for 24·3 (2·4)%. UDCA sulphate accounted for 3·6 (0·1)% of the total UDCA in bile. With regard to amidation the bile contained 59·5 (9·4)% TUDCA and 36·8 (9·3)% glycoursodeoxycholic acid, during administration of the highest dose of TUDCA.

High performance liquid chromatography analysis of the principal conjugated bile acids in the same bile samples provided data (Table) that was in close agreement with the more detailed analysis by gas chromatography. It was not possible to reliably quantify UDCA by high performance liquid chromatography in the basal bile samples because of the low concentrations. After TUDCA treatment, total

Biliary bile acid composition (%), determined by high pressure liquid chromatography, in patients with primary biliary cirrhosis before and after tauroursodeoxycholic acid treatment

	Baseline (n=7)	TUDCA dose 500 mg/day (n=4)	1000 mg/day (n=3)	1500 mg/day (n=3)
Glycolithocholic acid	nd	nd	nd	nd
Glycodeoxycholic acid	9·9 (1·7)	11·2 (6·7)	7·5 (4·0)	7·6 (2·2)
Glycochenodeoxycholic acid	25·8 (2·8)	21·7 (2·5)	14·2 (6·8)	12·4 (1·5)
Glycocholic acid	31·2 (3·6)	17·5 (5·3)	20·0 (3·9)	11·9 (1·5)
Glycoursodeoxycholic acid	nd	17·2 (4·3)	12·0 (4·6)	20·4 (3·3)
Taurolithocholic acid	nd	nd	nd	nd
Taurodeoxycholic acid	5·3 (2·2)	1·7 (1·2)	nd	2·4 (1·1)
Taurochenodeoxycholic acid	16·5 (4·3)	9·6 (1·8)	9·7 (3·5)	6·9 (2·2)
Taurocholic acid	14·8 (2·8)	8·1 (1·4)	14·3 (5·1)	7·1 (2·2)
Tauroursodeoxycholic acid	nd	17·0 (4·1)	22·2 (5·1)	32·3 (4·5)
Glycine/Taurine	1·9	1·8	1·2	1·1
Total				
Ursodeoxycholic acid	nd	34·3 (5·2)	34·2 (2·2)	52·7 (7·7)
Cholic acid	46·1 (4·5)	25·6 (7·8)	34·3 (4·1)	16·6 (4·2)
Chenodeoxycholic acid	42·3 (4·4)	31·3 (1·5)	24·0 (4·5)	19·3 (2·7)
Deoxycholic acid	13·5 (2·3)	11·8 (6·5)	7·5 (4·0)	9·2 (2·7)
Lithocholic acid	nd	nd	nd	nd

nd=not detectable. Data presented as mean (SEM).

UDCA accounted for 34·3%, 34·2%, and 52·7% of the total biliary bile acids with doses of 500, 1000, 1500 mg/day of TUDCA, respectively. Lithocholic acid conjugates were not detected in any of the bile samples using high performance liquid chromatography. The enrichment of the bile in UDCA was accompanied by a substantial decrease in the proportions of the two primary bile acids and a slight reduction in deoxycholic acid. The ratio of glycine/taurine conjugates in the basal bile samples was 1·9 and this ratio decreased to 1·1 with the highest dose of TUDCA (Table). A more complete study of a larger number of duodenal bile samples analysed by high performance liquid chromatography is presented elsewhere with the clinical correlates.[21]

Direct analysis of the bile by liquid secondary ionisation mass spectrometry failed to find evidence for significant amounts of either bile acid glucuronides or *N*-acetylglucosaminide conjugates. The principal ions in the mass spectrum of the bile were due to the presence of taurine and glycine conjugates of dihydroxycholanoates, and these findings are in accord with the more detailed analysis by high performance liquid chromatography and gas chromatography-mass spectrometry.

SERUM BILE ACID COMPOSITION DURING TUDCA ADMINISTRATION

Serum total conjugated UDCA increased with increasing dose of TUDCA, from 1·0 (0·2) μmol/l at baseline to 11·2 (1·3) μmol/l, 17·6 (4·8) μmol/l, and 20·6 (5·7) μmol/l with doses of 500, 1000, and 1500 mg/day, respectively (Fig 3). A significant and pronounced decrease in the serum concentration of cholic acid occurred with TUDCA treatment ($p<0·001$). Expressed as relative per cent composition, TUDCA treatment resulted in considerable decreases in the proportions of both primary and secondary bile acids in serum (Fig 3).

Unconjugated UDCA was not detected in the baseline samples (<0·05 μmol/l), but significant concentrations of serum unconjugated UDCA were found after TUDCA treatment (1·3 (0·1) μmol/l, 4·2 (2·5) μmol/l, and 3·3 (0·4) μmol/l, respectively, for doses of 500, 1000, and 1500 mg/day), which accounted for approximately 10–20% of the total UDCA in serum (Fig 4). A significant quadratic relation between the per cent composition of conjugated UDCA and the dose of TUDCA administered expressed on a body

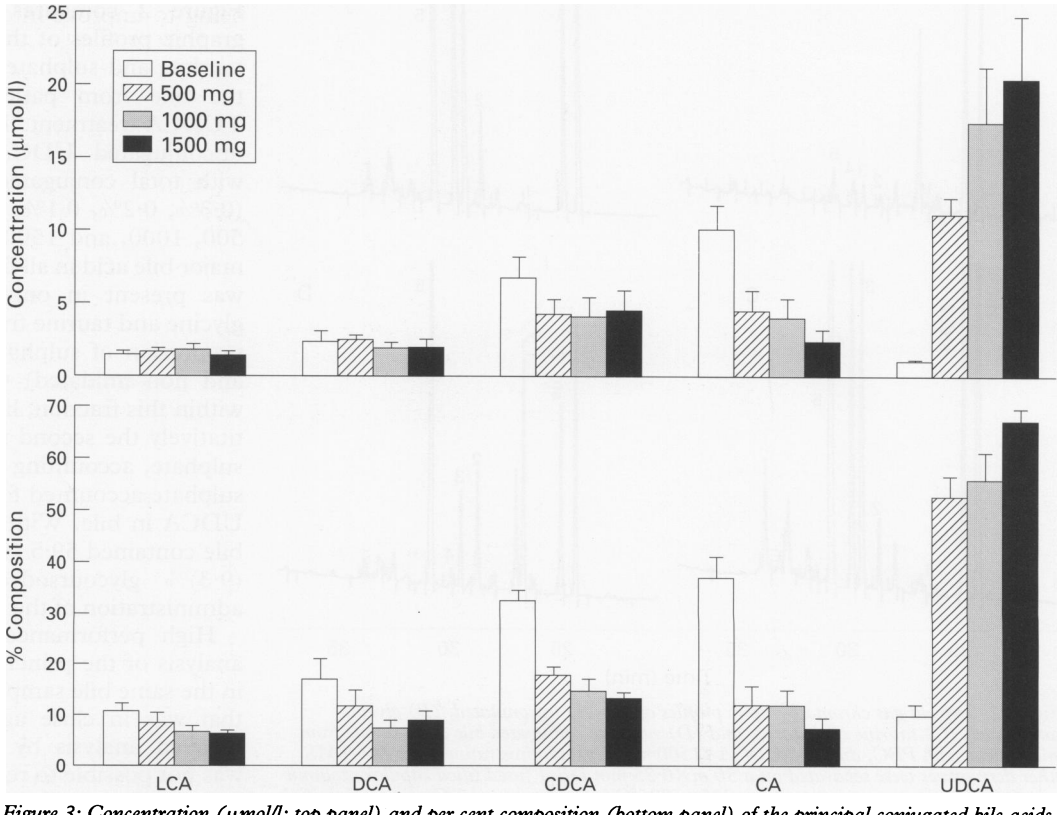

Figure 3: Concentration (μmol/l; top panel) and per cent composition (bottom panel) of the principal conjugated bile acids in serum from patients with PBC, determined by gas chromatography-mass spectrometry, at baseline and during increasing doses of TUDCA. Abbreviations as Fig 1.

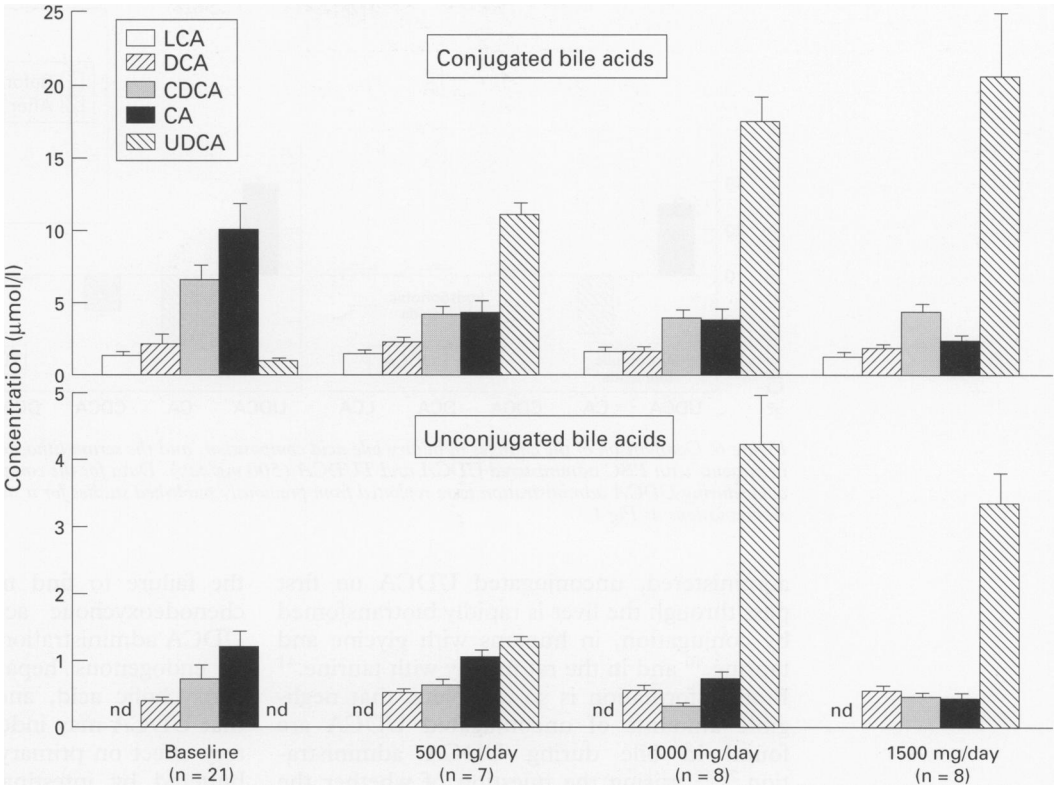

Figure 4: Concentration (μmol/l) of the principal conjugated (top panel) and unconjugated (bottom panel) bile acids in the serum from patients with PBC, determined by gas chromatography-mass spectrometry, at baseline and during increasing doses of TUDCA. nd=not detectable, other abbreviations as Fig 1.

weight basis, was seen for serum ($p<0{\cdot}0001$) and bile ($p<0{\cdot}001$) (Fig 5). When the baseline values were excluded from the statistical analysis, a linear relation was found between the proportion of UDCA in bile and the administered dose, only for serum ($y=0{\cdot}93\times+44{\cdot}60$, $r=0{\cdot}54$, $p<0{\cdot}05$).

Discussion

Oral UDCA treatment is increasingly an accepted treatment modality for a number of chronic liver diseases, and the versatility of this hydrophilic bile acid is becoming appreciated from preliminary studies of its potential application to diseases unrelated to the liver.[29 30] (U Glük, XIII international bile acid meeting, 1994). Irrespective of its mechanism of action,[31] an improvement in biochemical markers of liver function is a consistent finding in patients with liver disease given UDCA, but these are not maintained if treatment is interrupted.[32 33] With few exceptions,[34] the beneficial effect is in general associated with an ability to enrich the biliary bile acid pool with this hydrophilic bile acid, and presumably to induce a choleresis.[13 35 36] Inevitably, the search for better analogues to UDCA will continue, with some of the main objectives being to improve intestinal absorption, which for UDCA is relatively poor,[37 38] and to attain greater enrichment of the bile acid pool, which should presumably result in improved efficacy. Based upon the rationale that it is the relative hydrophilicity of UDCA that determines its effectiveness, bile acids more polar than UDCA, if absorbed, should in principle be potentially better therapeutic agents. In most in vivo and in vitro systems, the cytotoxicity or membrane damaging effect of a bile acid is proportional to the hydrophobicity of the molecule.[11 12 39] While UDCA is comparatively hydrophilic, it is not as polar as its amidated or sulphated metabolites. When

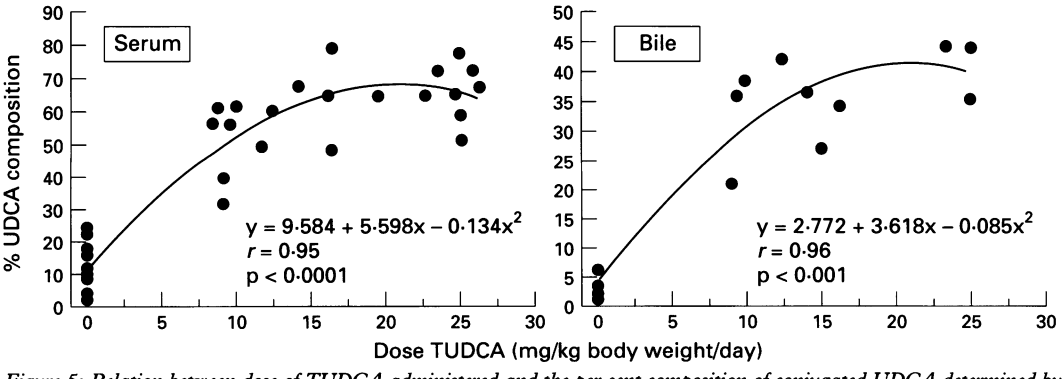

Figure 5: Relation between dose of TUDCA administered and the per cent composition of conjugated UDCA determined by gas chromatography-mass spectrometry in the serum (left panel) and bile (right panel) from patients with PBC.

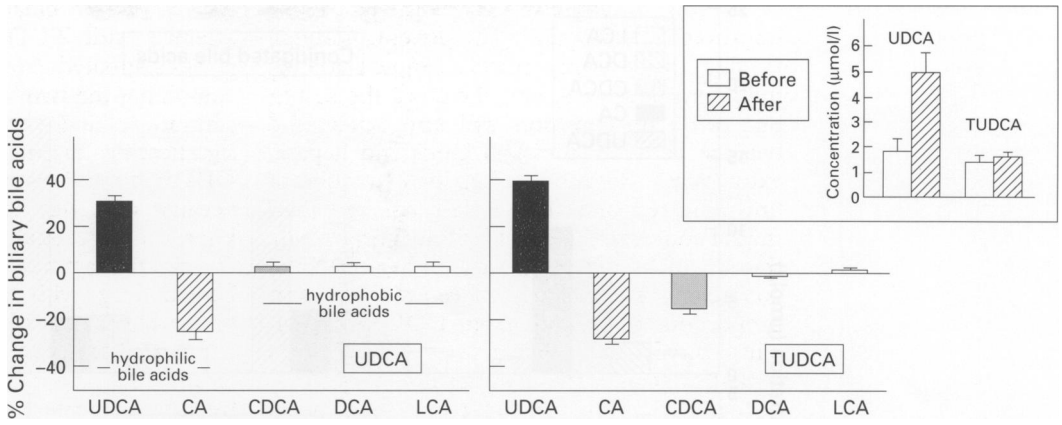

Figure 6: Comparison of the changes in biliary bile acid composition, and the serum lithocholic acid concentrations (inset), in patients with PBC administered UDCA and TUDCA (500 mg/day). Data for the compositional change in biliay bile acids during UDCA administration were replotted from previously published studies for a similar patient population.[20] Abbreviations as Fig 1.

administered, unconjugated UDCA on first pass through the liver is rapidly biotransfomed by conjugation, in humans with glycine and taurine,[40] and in the rat mainly with taurine.[41] Biotransformation is so complete, that negligible amounts of unconjugated UDCA are found in bile during UDCA administration,[20 42] raising the question of whether the mechanism of action may be the result of its conversion to more polar conjugated species. This has been suggested from animal studies, which show TUDCA to be more effective than UDCA in protecting against cholestasis induced by the more hydrophobic bile acid, taurochenodeoxycholic acid.[18]

TUDCA was recently introduced in Europe for the treatment of cholelithiasis and cholestatic liver disease, yet few data are available regarding its pharmacology or clinical effectiveness.[21 43 44] A dose response study of TUDCA in patients with PBC established 9 mg/kg body weight/day to be the optimal dose for lowering serum liver enzymes,[21] and that the magnitude of response was similar to that seen for therapeutic doses (10–15 mg/kg body weight/day) of UDCA,[1 2 7 8] but on a molar basis is lower than the recommended dose of UDCA. Serum alanine aminotransferase, aspartate aminotransferase, γ-glutamyltranspeptidase, and alkaline phosphatase values decreased by 45–64% compared with baseline values, and there was no significant difference in the per cent change among the different doses.[21] We describe here, and for the first time, the metabolic fate of TUDCA and its effect on the endogenous bile acid pool of patients with PBC. It is apparent that there are significant and important differences between the metabolism of TUDCA and UDCA, which may have relevance to the longterm therapeutic effects. As the consensus view is that the main mechanism by which UDCA improves cholestatic liver disease is by replacing or displacing hydrophobic bile acids from the bile acid pool,[13] then our findings show that TUDCA is significantly better at accomplishing this goal.

UDCA is extensively biotransformed to the more hydrophobic bile acids, chenodeoxycholic and lithocholic acids,[45–47] which explains the failure to find major changes in biliary chenodeoxycholic acid concentrations after UDCA administration.[20 42 48 49] Any reduction in endogenous hepatic synthesis of chenodeoxycholic acid, and the evidence suggests that UDCA may indeed have a mild stimulatory effect on primary bile acid synthesis,[50] is buffered by intestinal bacterial synthesis of chenodeoxycholic acid from exogenously administered UDCA. Furthermore, UDCA inhibits the intestinal uptake of cholic acid[51 52] and leads to increased loss of cholic acid into the colon, with the consequence of increased formation of the secondary bile acid, deoxycholic acid. The extent of biotransformation of UDCA may well be a significant factor in limiting its overall effectiveness.

By contrast, our findings show that after TUDCA administration, significant reductions in the biliary composition of the hydrophobic bile acids occur, and this is particularly the case for chenodeoxycholic acid, while there is no significant change in the proportions of the principal secondary bile acids (Fig 1). These changes were seen with the lowest dose (500 mg/day) of TUDCA, and no differences were found with higher doses. Figure 6 compares the relative changes in biliary composition from baseline for TUDCA with previously published data for UDCA administration in PBC patients (comprising mainly stage III and IV disease, but noncholestatic), and clearly shows the greater reduction in the more hydrophobic bile acids, particularly chenodeoxycholic acid.

In serum, the concentration of the primary bile acids decreased significantly during TUDCA treatment, while secondary bile acids remained unchanged. When expressed as relative per cent composition, all of the endogenous bile acids decreased with increasing dose of TUDCA (Fig 3). This trend was particularly apparent for the dihydroxy bile acids, and contrasts previous findings using the same analytical methodology for PBC patients treated with UDCA.[20] In cholestatic liver disease, the serum bile acid concentration reflects the spill-over of bile acids from the hepatocyte to the peripheral circulation[53] and the pronounced decrease in endogenous serum

bile acids is consequently consistent with improved liver function. The patients enrolled in this study were either asymptomatic or mildly symptomatic, and therefore the serum bile acid concentration will also reflect the balance between intestinal input and hepatic extraction.[54] Because the hepatic extraction of unconjugated bile acids is less efficient than that of conjugated bile acids,[54] not surprisingly the serum of these patients, unlike the bile, contained significant concentrations and proportions of unconjugated UDCA (Fig 4). This serves to indicate that TUDCA is partially deconjugated by intestinal microflora. Individual serum unconjugated bile acids paralleled the changes seen in the corresponding conjugated fraction during TUDCA administration (Fig 4).

Although stable-labelled and radioactive analogues of TUDCA are presently unavailable for metabolic studies, an indication of the extent of biotransformation of TUDCA can be obtained by comparing the composition of biological fluids before and during treatment. Data from these studies show that, in contrast with previously published data for UDCA metabolism, there is little biotransformation of TUDCA, and this may be considered favourable. Interestingly, the major biotransformation seems to be deconjugation followed by reconjugation with glycine, because glycoursodeoxycholic acid, which was present in only traces in the bile at baseline, accounted for comparable proportions to that of TUDCA at the lowest dose (17·2 (4·3)% and 17·0 (4·1)% of the total conjugates, respectively), although at higher doses the taurine conjugate was predominant. As the glycine conjugates of most bile acids are more hydrophobic than the corresponding taurine conjugates, the decrease in the glycine/taurine conjugate ratio with increasing dose of TUDCA reflects a further increase in hydrophilicity of the pool.

Particularly significant is the lack of conversion of TUDCA to lithocholic acid, even with high doses of TUDCA. Lithocholic acid was not detected in bile by high performance liquid chromatography, and when measured by gas chromatography-mass spectrometry accounted for only small proportions of the total bile acids. These values were no different from baseline (Fig 1). In serum, the concentration of lithocholic acid did not change, irrespective of the dose of TUDCA given, but the relative proportion of lithocholic acid decreased with increasing doses (Fig 3). This is in contrast with data from our previous studies of UDCA metabolism in patients with PBC,[20] where lithocholic acid concentrations increased significantly following UDCA treatment (see Fig 6, inset), and is substantiated from recent studies in rats, where the biotransformation of UDCA and TUDCA were compared directly.[41] Conjugation of UDCA by amidation, therefore seems to limit the extent of biotransformation of the steroid nucleus.

Although we have yet to conduct a controlled study of UDCA and TUDCA treatment in the same patients, comparing our earlier data for UDCA treatment in PBC patients, it seems that a greater biliary UDCA enrichment is attained with TUDCA administration. This is substantiated from recent animal studies comparing the two bile acids; liver tissue concentrations and enrichment of UDCA were significantly higher for TUDCA than for UDCA administration in rats,[41] and this is because of better hepatic extraction and not improved intestinal absorption of TUDCA. Despite the fact that UDCA is a comparatively benign drug, with few side effects, concerns have nevertheless been raised regarding lithocholic acid toxicity.[55] While lithocholate toxicity may not be a clinical problem with UDCA treatment, increased formation of lithocholic acid may be a limiting factor in the overall effectiveness of UDCA. As lithocholic acid concentrations are not increased during TUDCA administration, and because it seems more effective at displacing hydrophobic bile acids from the bile acid pool of patients with PBC, our findings would suggest that TUDCA may be a preferable therapeutic option to UDCA. Longer term clinical trials, however, are required to directly compare UDCA with TUDCA and to fully evaluate the therapeutic effectiveness of TUDCA.

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