Transpl Int (1998) 11 [Suppl 1]: S231–S238

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Ursodeoxycholic acid increased bile flow and affects bile composition in the early postoperative phase following liver transplantation

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Abstract Orally given ursodeoxycholic acid (UDCA) has beneficial effects on laboratory parameters in different cholestatic conditions. In order to investigate the effect on early graft function after liver transplantation, 33 patients were randomized to receive either UDCA 15 mg/kg per day or placebo from the 1st postoperative day until 3 months after transplantation. All liver grafts produced bile within 24 h after revascularization. In both groups there was an increasing bile flow each day until day 5 after transplantation. This increase was more pronounced in the UDCA group where the flow on day 2 reached a mean value of 183 ± 28 ml/day compared to 106 ± 17 ml/day in the placebo group ($P < 0.05$). The average daily volume of bile produced during the first 10 days was also found to be higher in the UDCA group compared to the placebo group (242 ± 20 ml vs 176 ± 18 ml, $P < 0.02$). In the UDCA group a significant decrease in total bile acid output between the 5th and 10th postoperative days was found, while in the placebo group the amount of bile acids excreted remained stable over time. The composition of bile differed between the two groups with an increase in the portion of UDCA in the UDCA group from the 2nd postoperative day (25% vs 4.6%, $P < 0.0003$). The fraction of UDCA then remained high during the whole study period with a peak at day 3 when 38.1 ± 6.6% of the bile acids consisted of UDCA. In the placebo group, the fraction of UDCA was low from the beginning and diminished further over time. Prophylactic UDCA treatment was found to have a significant positive impact on the ALT level during the 4th and 5th postoperative days, but had no effect on bilirubin or GGT in the early postoperative phase (days 1–10). No differences in cyclosporine requirement were found between the two groups.

Key words Bile flow · Bile acids · Ursodeoxycholic acid · Liver transplantation

Introduction

Ursodeoxycholic acid (UDCA) has been observed to reduce bile acid-induced liver damage in animal experiments [1]. Moreover, treatment with UDCA has been shown to have beneficial effects in a variety of different cholestatic liver diseases such as primary biliary cirrhosis [2–4] and primary sclerosing cholangitis [5–7]. Several prospective controlled studies have revealed improvement of liver function tests and in some studies also improvement of liver histology [3–5, 8–15]. The mechanisms of action by UDCA in these conditions are not fully understood, but a direct protective effect of the hepatocytes against hydrophobic bile salts has

Table 1 Pre- and intraoperative variables in the two groups. Results are expressed as mean ± SEM. (*M* Male, *F* female, *CIT* cold ischemia time, *UDCA* ursodeoxycholic acid)

Variable	Placebo ($n = 16$)	UDCA ($n = 17$)	*P*
Recipient age (years)	49.5 ± 2.1	46.3 ± 3.2	0.42
Gender (M/F)	10/6	10/7	0.63
Preoperative bilirubin (μmol/l)	41 ± 17	140 ± 18	0.10
CIT (h)	10.9 ± 0.6	10.8 ± 0.7	0.94
Duration of operation (h)	7.85 ± 0.43	9.06 ± 0.66	0.17
Intraoperative blood loss (l)[a]	5.78 ± 1.50	5.57 ± 1.29	0.92
Donor age (years)	41.3 ± 4.4	38.9 ± 3.3	0.66

[a] Estimated bleeding regardless of number of blood units transfused

been proposed [16–19]. It has been shown that orally given UDCA inhibits the absorption of endogenous bile acids in the intestine [20], thus changing the balance between hydrophobic, toxic bile acids and hydrophilic non-toxic bile acids [13, 21–25]. Furthermore, UDCA has been shown to exert choleretic functions which could contribute to an enhanced excretion of potentially toxic cholephilic substances [26, 27].

The role of UDCA treatment after liver transplantation is of particluar interest since an immune modulatory effect by UDCA has been suggested [28]. Such an effect has been demonstrated in vitro [29] and also in some animal [30] and clinical studies [31]. The mechanism is unclear but UDCA treatment of patients with PBC is followed by a reduction of HLA class I antigen expression on hepatocytes [32]. Furthermore, UDCA may affect cytokine production by human monocytes [28]. In liver transplantation, hepatocytes and bile duct epithelium regularly suffer from transplant-associated ischemic injury in the early postoperative phase, sometimes resulting in poor initial liver function or intrahepatic bile duct strictures later in the course. The additive effect by cytotoxic bile acids can hypothetically aggravate this damage and orally given UDCA may here have the potential to exert a cytoprotective effect, resembling the effects observed in conditions with bile acid retention.

Absorption of orally given cyclosporine, at least the classic formulation, is low and variable [33]. In cholestatic liver disease and in conditions of bile duct obstruction the bioavailability is further reduced [34], sometimes making it necessary to revert to intravenous administration of cyclosporine to maintain adequate blood levels. In the early phase after liver transplantation when the bile is usually diverted through a T-tube, absorption of cyclosporine A is constantly low [35]. Bile refeeding as well as T-tube clamping then reverses the decreased absorption of cyclosporine [36]. In dogs, the bile acid chenodeoxycholic acid improves cyclosporine absorption when administered together with lecithin [37]. Trials in man with UDCA have so far failed to show a similar effect [38]. In this prospective study we have investigated the effect of prophylactic orally administered UDCA on bile flow, bile acid composition, and cyclosporine requirement in the early phase after liver transplantation. The effect on ischemic damage and early graft function has also been evaluated.

Materials and methods

Patients and experimental design

From 1 September 1992 to 31 May 1994, 102 liver transplant patients from Denmark, Finland, Norway, and Sweden entered a trial of prophylactic UDCA. Thirty-three of these patients were transplanted at our institution and have been further investigated in this study. The patients were randomized in a double-blind design to receive either capsule of UDCA 15 mg/kg per day (17 patients) or placebo (16 patients). The UDCA and the placebo capsules had an identical appearance and taste and were kindly provided by Dr Falk, (Pharma, Freiburg, Germany). There were no significant differences between the two groups regarding recipient age, gender, graft cold ischemia time, duration of operation, intraoperative blood loss, recipient disease, or donor age (Table 1). Donor livers were obtained from heart-beating cadaveric donors and all grafts were full sized. No children below 15 years of age were included in the study. University of Wisconsin solution was used for preservation. Bile duct anastomosis was performed as a choledochocholedochostomy over a T-tube in all cases. The baseline immunosuppressive treatment consisted of triple drug therapy with prednisolone, azathioprine, and cyclosporine (Sandimmune; Sandoz, Basel, Switzerland). Protocol biopsy was performed 7 days after transplantation. All the patients received total parental nutrition for the first 3 days. After that most of the patients were commenced on a normal hospital diet. The number of patients who were unable to have a gradual increase of orally taken food during the first 10 days did not differ significantly between the two groups. No early (day 1–5) rejection episode was found in either of the groups. The drug was administered twice daily through a nasogastric tube beginning on the 1st postoperative day and was discontinued after 3 months. Bile was continuously collected from the T-tube and the volume was monitored. The T-tube was clamped no earlier than 10 days after transplantation. Samples (5 ml) of bile for analysis of total and individual bile acids were obtained after an overnight fast during the first 5 days. The samples were frozen at −20 °C before being analyzed.

Bile acid analysis

The total bile acid concentration was determined using a 3-alpha hydroxysteroid dehydrogenase assay. The individual bile acids were determined in portions of bile hydrolyzed in 1 mol/l KOH at

110 °C for 12 h. After acidification, the conjugated bile acids were extracted with diethylether, and the methyltrimethylsilyl ethers were prepared and analyzed by gas liquid chromatography using a 1% Hi-Eff BP 8 column.

Cyclosporine requirement analysis

Cyclosporine concentration trough levels were measured daily by a whole blood monoclonal RIA. Requirement analysis was performed between days 16 and 20. Patients who received cyclosporine intravenously at the time of analysis or had an open T-tube were excluded in the analysis. A cyclosporine index was calculated by dividing the trough level with the quotient of dose and the weight of the patient. By this a higher index will indicate a lower requirement of cyclosporine to achieve a given concentration.

Statistical analysis

Results are expressed as mean ± SEM. Differences were tested using Student's t-test and paired t-test for comparisons within groups. The time course of biochemical variables was compared by means of analysis of variance for repeated measurements. $P < 0.05$ was considered as statistically significant.

Results

Bile flow

All liver grafts produced bile within 24 h after revascularization. In both of the groups there was an increasing bile flow for each day until day 5 after transplantation. The increase was more pronounced in the UDCA group where the flow on day 2 reached a mean value of 183 ± 28 ml/day compared to 106 ± 17 ml/day in the placebo group ($P < 0.05$). Between day 5 and day 10, the volume of bile produced each day stabilized and there were no significant differences day by day in volumes of bile produced by the grafts in the two groups (Fig. 1). However, when the first 10 days was taken together, the average daily bile production was found to be higher in the UDCA group compared to the placebo group (242 ± 20 ml/day vs 176 ± 18 ml/day, $P < 0.02$).

Total bile acid output

As the bile flow increased during the first 5 postoperative days there was a concomitant tendency for higher total bile acid excretion in the UDCA group compared to the placebo group; the difference, however, was not significant. In the UDCA group, the maximal bile acid output was observed at the 5th postoperative day with a mean value of 3.81 ± 0.85 μmol/min. The output thereafter successively decreased until day 10 when the mean daily output was monitored to 0.98 ± 0.29 μmol/min ($P < 0.02$). In the placebo group no significant differences in the daily bile acid output was found over time; maximal mean value was observed at day 8 with 2.43 ± 0.92 μmol/min (Fig. 2). The correlation between bile flow and bile acid output as measured by linear regression was similar in both groups, indicating that the increased bile flow observed in the UDCA group is strongly bile acid dependent (Fig. 3).

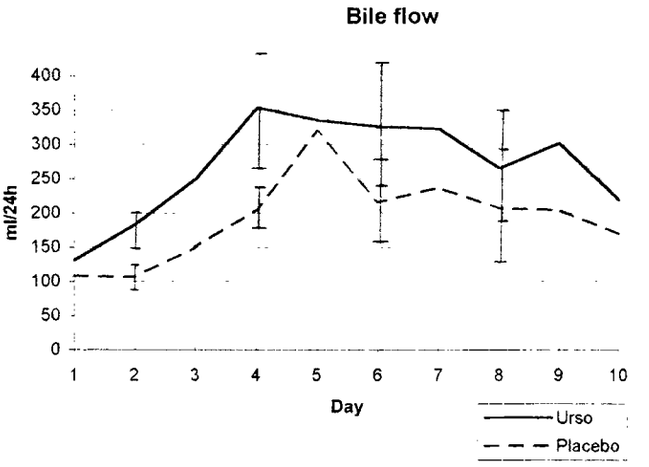

Fig. 1 Comparison of bile flow between the ursodeoxycholic acid (UDCA) and placebo groups. Results are expressed as mean ± SEM ml/24 h

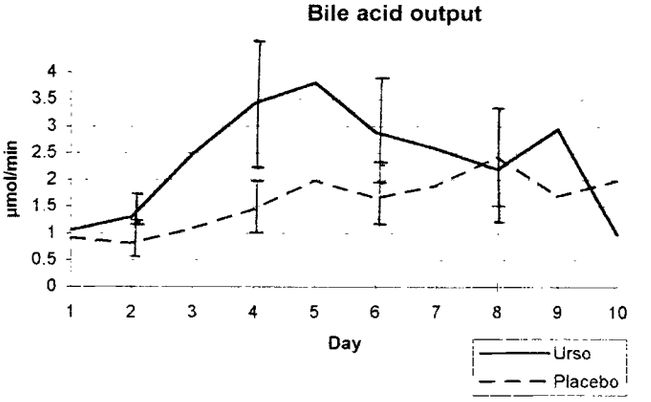

Fig. 2 Comparison of bile acid excretion through the drainage between the UDCA and placebo groups. Results are expressed as mean ± SEM μmol/min

Individual bile acids

When analyzing the composition of the bile in the placebo group it was found that the fractions of individual bile acids changed over time gradually increasing amounts of cholic acid and with a corresponding decrease in the portions of chenodeoxycholic acid and

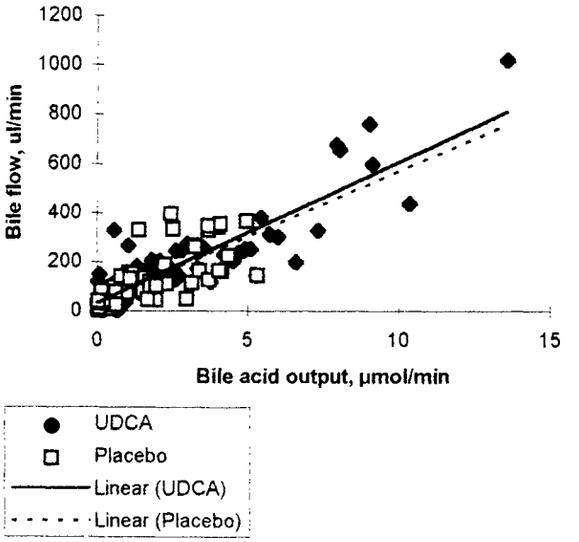

Fig. 3 Relationship between bile acid secretion rate and bile flow in UDCA- and placebo-treated patients. The equations of the regression lines were $y = 34.4 + 59.0x$ (correlation coefficient: 0.88) for the UDCA group and $y = 35.4 + 55.2x$ (correlation coefficient: 0.74) for the placebo group

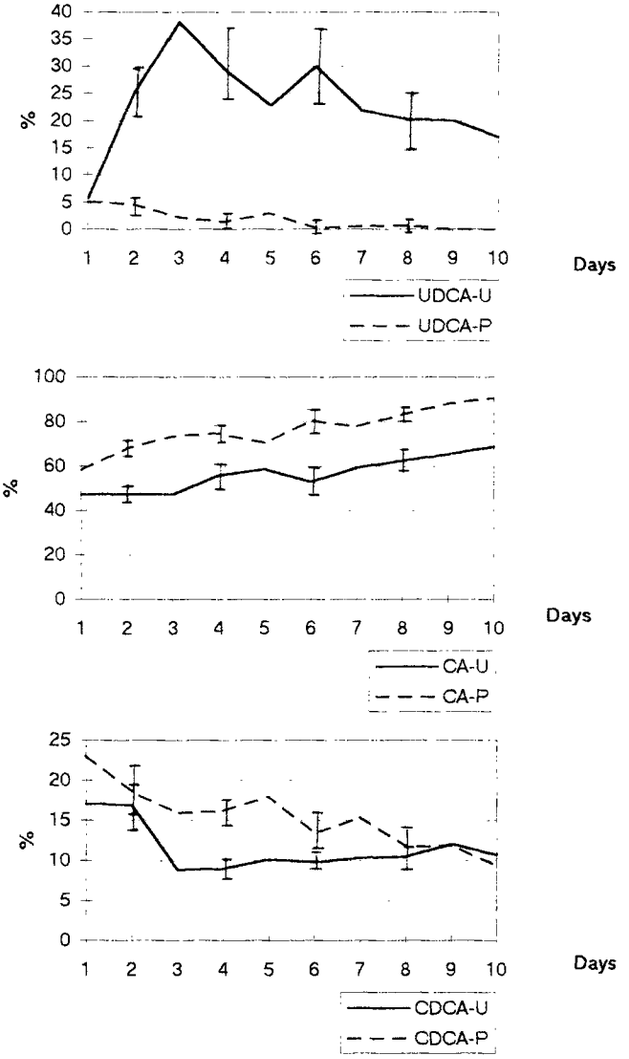

Fig. 4 Analysis of individual bile acids. The fractions of *UDCA*, cholic acid *(CA)*, and chenodeoxycholic acid *(CDCA)* during days 1–10 are shown. Results are expressed as mean ± SEM. *U* UDCA-treated group, *P* placebo-treated group

UDCA. The main bile acid was found to be cholic acid which accounted for 70.5 ± 4.3% of the total bile acids during day 5. The portion of UDCA was low and decreased from 5.1% (day 1) to 1.4% (day 5). In the UDCA group, there was a significant increase in the portion of UDCA compared to the placebo group from the 2nd postoperative day (25 ± 3.9% vs 4.6 ± 1.5%, $P < 0.003$). The fraction of UDCA then remained high during the whole study period with a peak at day 3, when 38.1 ± 6.6% of the bile acids consisted of UDCA (Fig. 4). Following the increase of UDCA, a corresponding decrease of the portion of mainly cholic acid but also chenodeoxycholic acid was observed. The fraction of deoxycholic acid in the bile remained unaffected by orally given UDCA.

Cyclosporine requirement

In order to compare the cyclosporine requirement for both groups a cyclosporine index was calculated by dividing the trough level with the quotient of the dose and weight of the patient. During the first 10 postoperative days, bile was diverted externally with poor absorption of orally given cyclosporine. Intravenously administered cyclosporine was frequently added in order to reach acceptable trough levels and no calculations were performed during that period. When investigating the cyclosporine requirement during days 16–20, no significant differences between the two groups were found as judged by the cyclosporine dose, cyclosporine concentration, or cyclosporine index (Fig. 5).

Biochemical parameters

The time course of the biochemical test results showed lower values of ALT for UDCA-treated patients throughout the study period, reaching a significant difference during the 4th and 5th postoperative days (Fig. 6). There was a corresponding tendency for lower peak ALT in the UDCA group (18.7 ± 3.1 µkat/l) compared to the placebo group (32.0 ± 8.4 µkat/l); however,

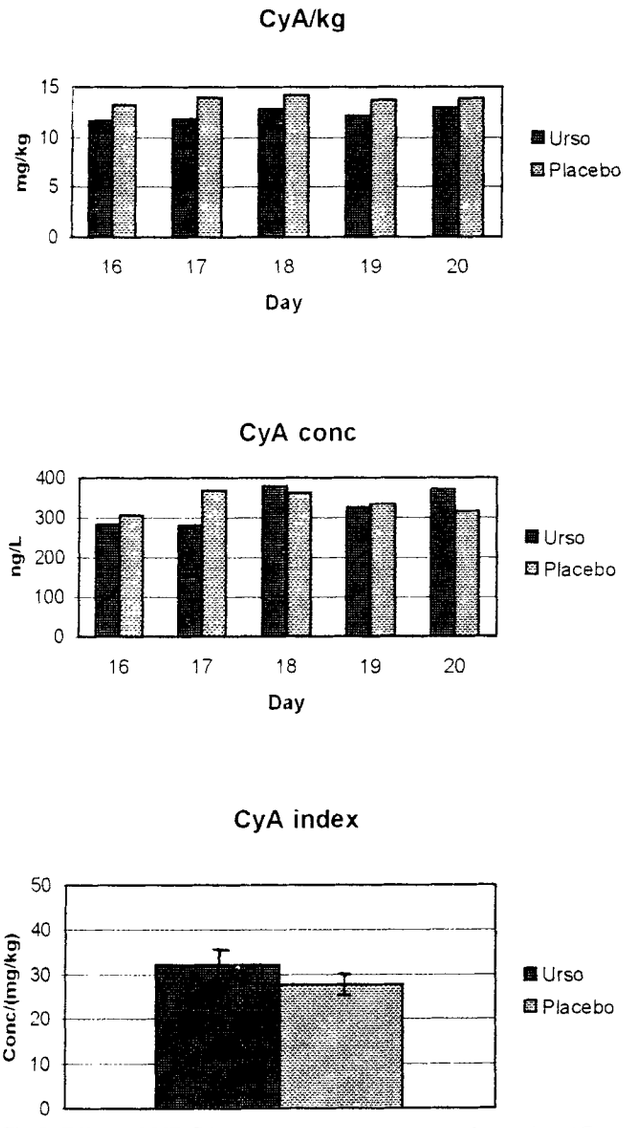

Fig. 5 Effect of UDCA treatment on average cyclosporine *(Cya)* requirement between days 11 and 20. CyA index is defined as CyA concentration *(conc)*/(CyA/kg). Data are given as mean ± SEM

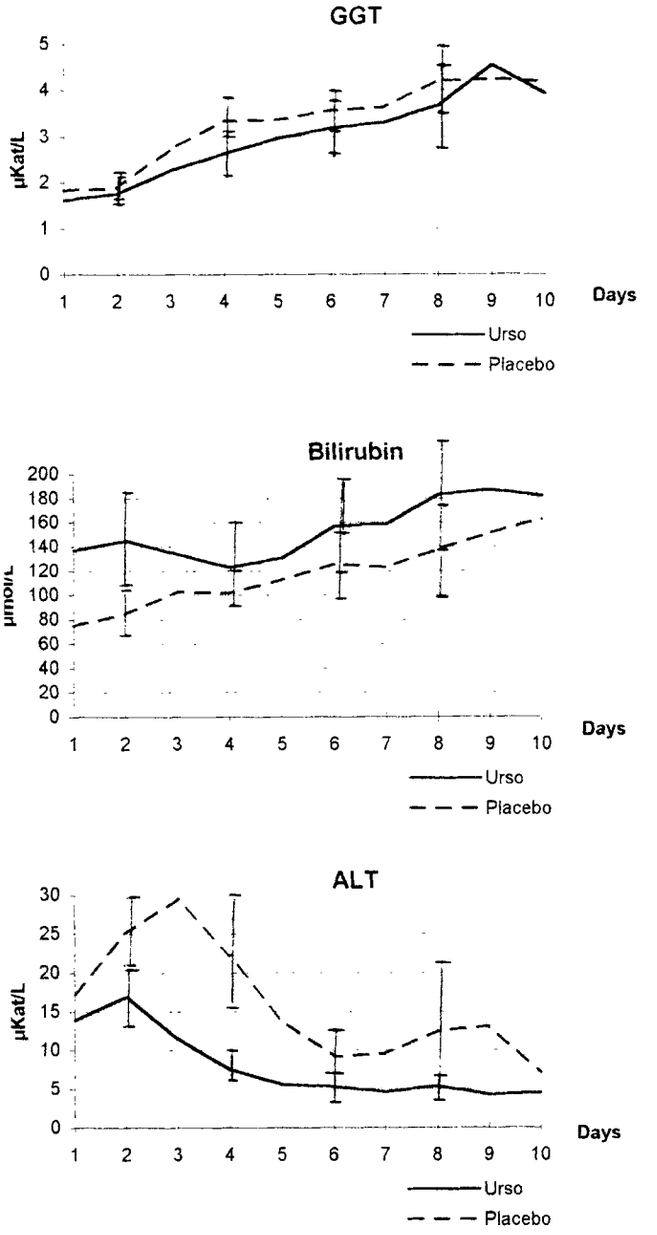

Fig. 6 Effects of 10 days treatment after liver transplantation on concentration of GGT, bilirubin, and ALT. Data are given as mean ± SEM

the difference was not significant ($P = 0.09$). There were no significant differences between the treatment groups for the levels of bilirubin or GGT.

Histopathology

When protocol liver biopsies on day 7 were analyzed, there were no differences between the two groups regarding the grade of ischemic injury, signs of toxicity, or rejection frequency (data not shown).

Discussion

In the Nordic multicenter study we have previously shown that orally given prophylactic UDCA does not affect the number of severity of rejection episodes in liver transplant patients [39]. In this paper we have studied in more detail the early effects of UDCA on graft function and biliary secretion in a single center population

of patients also included in the Nordic multicenter trial. The grafted liver constantly suffers from different degrees of anoxic injury in the early postoperative phase and since UDCA has been found to exert hepatoprotective properties both in vitro and in vivo we wanted to investigate whether there are also beneficial effects following liver transplantation.

UDCA has previously been shown to have a choleretic effect in non-transplanted livers [26, 27]. This has been taken as a possible mechanism by which toxic hydrophobic substances could be more rapidly eliminated and thereby reduce hepatocyte damage. In liver transplantation, laboratory signs of cholestasis are frequent, especially during the first 2 weeks after transplantation. Moreover, maintenance of an unimpaired bile flow is essential, thus preventing sludge formation and ascending cholangitis [40]. In this study we found that prophylactic treatment with UDCA increases bile flow as early as the 2nd postoperative day in liver transplant recipients. However, this increase did not correlate to an improved biochemistry of cholestasis as judged by GGT in the early phase after operation. The reason for this could be that there is a time lag between treatment and effect exceeding several weeks, which is consistent with previous findings both from liver transplant recipients and from patients with cholestatic disease [39, 41, 42].

Another possible mechanism by which UDCA may exert its effect is by replacing more toxic bile acids by less toxic ones, thus creating a bile acid pool that may protect the hepatocytes in the event of posttransplantation ischemia [16–19]. The results from this study show that there is a very rapid change in the pool of excreted bile acids, where chenodeoxycholic acid and cholic acid are replaced by UDCA. The fraction of UDCA was increased five-fold within 24 h of the first dose. This indicates an efficient absorption in spite of the decreased postoperative gastric motility normally found after major surgery. Interestingly, there is an early corresponding positive impact on the ALT levels in the UDCA group which could indicate a beneficial effect on perioperative anoxic and reperfusion injury.

Between the 5th and 10th postoperative days there was a significant decrease in the total amount of bile acids excreted in the UDCA group. This could not be found in patients who received the placebo. One explanation for this difference could be that there is a negative feedback mechanism on the absorption of bile acids (UDCA) from the distal ileum, with a gradually decreasing uptake as the load of UDCA in the enterohepatic circulation increases. However, a direct negative effect on endogenous bile acid de novo synthesis or, less likely, diversion toward an alternative excretion pathway of UDCA cannot be excluded.

In the placebo group, the composition of the bile during the very 1st postoperative day shows a pattern normally seen in healthy individuals and will reflect the bile acid composition by the donor liver as it was before explanation. The pattern of individual bile acids over time shows that the fractions of chenodeoxycholic acid, deoxycholic acid, and UDCA diminish significantly during the study period. This probably reflects the effect of the bile fistula which prevents the production of secondary bile acids. Since the synthesis of chenodeoxycholic acid is lower compared to cholic acid and bile acid production in this situation is dependent only on de novo synthesis, the cholic acid/chenodeoxycholic acid ratio increases over time, as previously observed [40, 43].

The dose of cyclosporine which was needed to achieve a given trough level concentration in blood immediately after clamping of the T-tube was not affected by orally given UDCA. This is in agreement with our previous findings when cyclosporine requirement was analyzed at a later stage after transplantation [39]. The effect on the area under the curve was not calculated in this study, but has previously been done showing no influence by UDCA at a dose of 10 mg/kg per day in patients with stable liver function [38].

We conclude that prophylactic orally given UDCA after liver transplantation gives a rapid change in bile acid composition and increases early postoperative bile flow. The increase is correlated to an improved liver function as judged by ALT, but not by bilirubin or histopathology of the liver. Absorption of cyclosporine when the T-tube is closed seems to be unaffected by orally given UDCA. The present study gives some support to the use of prophylactic UDCA as treatment for ischemic or reperfusion injury after liver transplantation. Although this study has only focused on early postoperative events, a beneficial long-term effect on laboratory cholestasis has previously been shown which can justify further usage of the drug in liver transplantation. However, the optimal time for administration of the drug is not yet established and a potential protective effect of UDCA may be even more pronounced if initiated before the donor organ is exposed to the peri- and postoperative transplant environment.

Acknowledgements We thank Ms Lisbet Benthin, Ms Lilian Larsson, and Ms Ingela Arvidsson for skilful technical assistance. This study was supported by grants from the Swedish Medical Research Council (034-4793).

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