Effects of ursodeoxycholic acid on systemic, renal and forearm haemodynamics and sodium homoeostasis in cirrhotic patients with refractory ascites

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ABSTRACT

Systemic arterial vasodilatation has been implicated in the pathogenesis of sodium retention in cirrhosis. Hydrophobic bile acids, which have vasodilatory actions, may be involved. Ursodeoxycholic acid, a hydrophilic bile acid, could potentially decrease systemic arterial vasodilatation, possibly due to its antioxidant effects, and improve sodium handling in cirrhosis. The effects of ursodeoxycholic acid on systemic, renal and forearm haemodynamics, liver function and renal sodium handling were assessed in vasodilated cirrhotic patients with refractory ascites treated with a transjugular intrahepatic porto-systemic shunt (TIPS). Eight cirrhotic patients with refractory ascites without TIPS placement served as controls for the sodium handling effects of ursodeoxycholic acid. From 1 month post TIPS, seven patients were studied before, after 1 month of treatment with ursodeoxycholic acid (15 mg·day⁻¹·kg⁻¹) and at 1 month follow-up. Lipid peroxidation products were used as indices of its antioxidant effects. Ursodeoxycholic acid caused a significant reduction in sodium excretion in both groups (P < 0.05). This, in the post-TIPS patients (urinary sodium excretion: 35±8 mmol/ day at 1 month versus 93±21 mmol/ day at baseline, P < 0.05), was due to a significant increase in sodium reabsorption proximal to the distal tubule (P < 0.05), without any significant changes in systemic, renal or forearm haemodynamics, or in liver function. No significant change in lipid peroxidation products was observed. We conclude that: (i) in cirrhotic patients with refractory ascites, ursodeoxycholic acid causes sodium retention, (ii) the abnormality in sodium handling in the post-TIPS cirrhotic patients appears to be the result of a direct effect on the proximal nephron, suggesting that factors other than systemic vasodilatation also contribute to sodium retention in cirrhosis, (iii) caution should be exercised in administering ursodeoxycholic acid in cirrhotic patients with ascites.

Key words: ascites, cirrhosis, sodium retention, transjugular intrahepatic porto-systemic shunt, ursodeoxycholic acid, vasodilatation.

Abbreviations: MAP, mean arterial pressure; MDA, malondialdehyde; RBF, renal blood flow; RPF, renal plasma flow; RVR, renal vascular resistance; TIPS, transjugular intrahepatic porto-systemic shunting; UDCA, ursodeoxycholic acid.

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INTRODUCTION

Profound haemodynamic changes associated with progressive sodium retention complicate the clinical course of chronic liver disease [1]. The circulation is hyperkinetic with increased cardiac output and decreased systemic vascular resistance [2]. The pathogenesis of the systemic arterial vasodilatation is not well understood. Possible mechanisms include an enhanced production of endogenous vasodilators [3] and reduced responsiveness to vasoconstrictors [4,5]. The resultant mismatch between vascular capacitance and the intravascular volume leads to the activation of various neurohumoral pressor systems to enhance renal sodium retention [6]. This concept, known as the ‘Peripheral Arterial Vasodilatation Hypothesis’, has been generally accepted as the theory governing the pathogenesis of sodium retention in cirrhosis. However, in recent years, well-compensated cirrhotic patients have consistently demonstrated subtle sodium handling abnormalities in the absence of arterial underfilling [7–9]. More importantly, about one-third of patients with recent onset cirrhotic ascites have no evidence of arterial underfilling as evidenced by normal plasma renin activity, and yet they avidly retain sodium [10,11]. This suggests that other mechanism(s) such as a direct hepatorenal interaction may be responsible for sodium retention, especially in the earlier stages of cirrhosis.

If peripheral arterial vasodilatation was solely responsible for sodium retention in cirrhosis, then any manoeuvre that reduces the systemic arterial vasodilatation should improve renal sodium handling in these patients. Ursodeoxycholic acid (UDCA), a stereoisomer ofchenodeoxycholic acid, and a relatively more hydrophilic bile acid, has been shown experimentally to produce minimal vasodilatation on precontracted arterial rings when compared with chenodeoxycholic acid and deoxycholic acid [12]. In contrast, hydrophobic bile acids induce vasodilatation via a direct relaxant action on vascular smooth cells [13], as well as by increasing the generation of oxygen free-radicals [14,15]. Plasma levels of hydrophobic bile acids are elevated in cirrhosis [16,17], and therefore these could potentially be involved in the systemic arterial vasodilatation in cirrhosis [18,19]. Hence, altering the hydrophilic/hydrophobic ratio of bile acids towards hydrophilicity should theoretically reduce systemic arterial vasodilatation and, according to the ‘Peripheral Arterial Vasodilatation Hypothesis’, should also improve renal sodium handling in cirrhosis.

Therefore, the aim of this study was to assess the effect of altering the hydrophilic/hydrophobic balance of bile acids using UDCA on systemic haemodynamics and on renal sodium handling in cirrhosis and the mechanism(s) involved. Patients with decompensated cirrhosis and refractory ascites treated with a transjugular intrahepatic porto-systemic shunt (TIPS) were selected for the study, since they have marked exacerbation of systemic arterial vasodilatation [20,21] which persists for at least 12 months after TIPS insertion [21], and this is thought to at least partly contribute to the delay in the onset and the magnitude of the natriuresis.

METHODS

Ethics approval for the study was granted by the Ethics Committee of the Toronto Hospital, University of Toronto, and all patients gave their informed consent.

Patients

All study patients were recruited from both the Liver Clinics and the Hepatology Ward of the Toronto Hospital. The post-TIPS patients consisted of five males and two females, mean age 52 ± 4 (41–69) years, with biopsy proven cirrhosis and refractory ascites. Eight patients (six males and two females), mean age 61 ± 3 years (52–70 years), with cirrhosis and refractory ascites who did not receive a TIPS served as controls. All patients had had refractory ascites for more than 6 months and those patients with alcoholic cirrhosis had abstained from alcohol for at least 6 months before entry into the study. The definition for refractory ascites has been reported previously [22]. All patients who received TIPS fulfilled the selection criteria [23], and had a successful TIPS insertion from January 1995 to December 1995 at the Toronto Hospital. Baseline clinical and biochemical data and the severity of liver disease according to Pugh’s classification [24] are shown for both groups in Table 1.

Study protocol

The study was conducted in the Clinical Investigation Unit of the Toronto Hospital. Control patients were enrolled once they met the criteria for refractory ascites [20]. The post-TIPS patients were enrolled at a mean period of 3.7 ± 0.6 months after TIPS insertion, when significantly increased arterial vasodilatation is usually observed in these patients [16,17]. This also eliminates the confounding effects of haemodynamic instability and volume shifts which occur in the early post-TIPS period. At the time of entry, all post-TIPS patients were in a diuretic phase without diuretic therapy; three had eliminated their ascites but still had some pedal oedema. After a stabilization period of 5 days without diuretic therapy, while being maintained on a diet of 22 mmol of sodium and 1 litre of fluid per day, control patients underwent assessment of their renal sodium handling. Their daily 24-h urinary sodium excretion (U\textsubscript{Na}V) was measured after the administration of UDCA at a dose of 15 mg·day\textsuperscript{−1}·kg\textsuperscript{−1}. Detailed haemodynamic studies were
Table 1 Clinical, haematological measurements and liver function in both controlled patients and ascitic patients treated with TIPS before, during and after UDCA administration for 4 weeks

<table>
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<th>Baseline</th>
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<th>1 month off UDCA</th>
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<tr>
<td>Post-TIPS patients</td>
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<tr>
<td>MAP (mmHg)</td>
<td>87 ± 2</td>
<td>84 ± 3</td>
<td>85 ± 3</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>74 ± 3</td>
<td>82 ± 9</td>
<td>75 ± 3</td>
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<tr>
<td>Serum albumin (g/l)</td>
<td>27 ± 2</td>
<td>31 ± 2</td>
<td>28 ± 3</td>
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<tr>
<td>Bilirubin (µmol/l)</td>
<td>54 ± 12</td>
<td>49 ± 7</td>
<td>42 ± 6</td>
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<tr>
<td>Prothrombin time (s)</td>
<td>15.9 ± 1.3</td>
<td>15.6 ± 0.4</td>
<td>15.8 ± 0.8</td>
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<tr>
<td>Pugh score</td>
<td>10.7 ± 0.8</td>
<td>9.3 ± 0.6</td>
<td>9.4 ± 0.6</td>
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<tr>
<td>Urinary sodium excretion (mmol/day)</td>
<td>17 ± 3</td>
<td>35 ± 8*</td>
<td>114 ± 22</td>
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<tr>
<td>Weight (kg)</td>
<td>72.1 ± 2.4</td>
<td>73.1 ± 4.2*</td>
<td>71.0 ± 2.8</td>
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*P < 0.05 compared with baseline.

only performed in the post-TIPS patients since they had significantly more severe systemic vasodilatation [20,21] and therefore UDCA would have a significantly greater effect. The post-TIPS patients were studied as inpatients on three occasions under the same sodium intake without diuretic therapy as the controls: at baseline, after 1 month of UDCA at the same dose and again after 1 month of no UDCA. On each occasion, metabolic studies were performed over 2 days. On day 1, renal and forearm haemodynamics and liver function tests were assessed in the morning, whereas systemic haemodynamics and central blood volume were measured by radionuclide angiography in the afternoon [25]. On day 2 after an overnight fast, blood was collected for measurements of pentane and ethane, markers of lipid peroxidation [26]. Blood was also collected for measurements of secondary reaction products, such as lipid hydroperoxides and malondialdehyde (MDA) [27]. Antioxidant vitamins were not permitted throughout the study [28]. Twenty-four-hour $U_{Na}$V was measured over 3 days on each of the three inpatient periods.

Glomerular filtration rate and renal plasma flow (RPF) were measured by inulin and para-aminohippurate clearances respectively and renal vascular resistance (RVR) was calculated. Lithium clearance was used as an indicator of sodium reabsorption proximal to the distal tubule [7,29]. Forearm blood flow was measured by venous occlusion plethysmography [30,31] and forearm vascular resistance was calculated from the mean arterial pressure (MAP) and forearm blood flow. Cardiac output and systemic vascular resistance were calculated from the MAP, heart rate and stroke volume measurements obtained during radionuclide angiography.

Procedures

Inulin, para-aminohippurate and lithium clearances

The techniques used to measure inulin and para-aminohippurate [32] and lithium clearances [7] have been described previously.

Central blood volume measurements

A detailed description of the technique of central blood volume measurements using radionuclide angiography can be found elsewhere [25]. Briefly, erythrocytes are labelled using $^{99m}$Tc-pertechnetate. The cardiac volumes are measured based on regional activity corrected for attenuation. The ejection fraction and volumes are analysed using semi-automated software. Quality assurance studies in our Nuclear Cardiology Laboratory have established the standard error of the estimate of left ventricular ejection fraction to be less than 2% using semi-automated techniques. The standard error of the estimate of ventricular volume is less than 5 ml [33].

Forearm blood flow

Total forearm blood flow was measured by venous occlusion plethysmography using mercury-in-elastic strain gauges [30], the technique of which has been described previously [34].

Breath alkane expiration

Breath was collected by the subject breathing for 4 min through a cardboard mouthpiece connected to a 3-way Rudolph valve from a mylar bag (Aeroviroment, Monrovia, CA, U.S.A.) containing hydrocarbon-free air (< 0.1 p.p.m. total hydrocarbons expressed as methane;
Air, Ultra-Zero, Metheson Gas, Whitby, Ontario). The exhaled air was discarded; thus the initial atmospheric air with its hydrocarbon content was flushed from the patient’s lungs. During the succeeding 2.0 min while hydrocarbon-free air was being inspired, expired air was collected into another mylar bag for alkane analysis.

**Laboratory analysis**
Serum and urinary sodium and lithium concentrations were determined by standard flame photometry techniques. Plasma and urinary para-aminohippurate and inulin were estimated by chemical analyses using modified methods of Walser et al. [35] and Brun [36] respectively. Expired alkanes were analysed by gas chromatography (Shimadzu Seisugusho Ltd, Kyoto, Japan). Fifty millilitres of breath was passed through a stainless-steel loop packed with alumina and cooled to $-95 \, ^\circ \mathrm{C}$ to adsorb the injected sample. The loop was then heated to desorb the gas thermally. Pentane and ethane were analysed on a Porasil D column (Chromatographic Specialties Inc., Brockville, Ontario) by using a calibration curve derived from known concentrations of gases [28]. The concentrations of breath pentane and ethane were expressed in pmol min$^{-1}$kg$^{-1}$. Lipid peroxides, indirect products of lipid peroxidation, were assessed using a commercially available kit (Kamiya Biochemical Co., Thousand Oaks, CA, U.S.A.). MDA, a toxic metabolite that accumulates as a result of lipid peroxidation, was measured by reverse-phase HPLC in the form of a complex with thiobarbituric acid [37].

**Calculations**
Inulin and para-aminohippurate clearances were corrected for body surface area and expressed per 1.73 m$^2$. RVR = MAP/renal blood flow (RBF), where RBF = RPF/(1 – haematocrit). Sodium reabsorption proximal to the distal renal tubule was calculated using lithium clearance and glomerular filtration rate, whereas the distal tubular reabsorption was calculated from inulin clearance, serum sodium concentrations, urinary sodium concentrations and the urinary volume [38].

Central blood volume, a measurement affected by body size, was corrected for body surface area using the subject’s height and weight. Stroke volume, cardiac output and systemic vascular resistance were calculated from standard formulae [25]. The cardiac output was corrected for body surface area to yield the cardiac index. Cardiac and central vascular blood volume was calculated from total central blood volume minus right and left pulmonary vascular volumes.

**Statistical analysis**
All results were expressed as means ± S.E.M. Differences over time were assessed by repeated measures ANOVA. Dunnett’s test was used to determine the statistical significance of differences between the baseline value and repeated measurements of the same parameter. A $P$ value of less than 0.05 was considered statistically significant.

**RESULTS**
The control patients were in sodium balance at enrolment while on a diet of 22 mmol of sodium per day (Figure 1). Daily administration of UDCA resulted in a significant positive sodium balance by day 3 (9 ± 2 mmol/day compared with 17 ± 3 mmol/day at baseline, $P < 0.05$) (Figure 1). This continued for the remainder of the first week and $U_{Na}V$ decreased to 7 ± 2 mmol/day by day 7 ($P < 0.05$ compared with baseline). The control patients gained a mean weight of 1.2 ± 0.3 kg during the 7-day period. UDCA was therefore stopped after day 7.

The post-TIPS patients were in a diuretic phase after TIPS insertion when enrolled into this study. This was evidenced by their negative sodium balance. Their mean 24-h urinary sodium excretion over 3 days was 93 ± 21 mmol/day, despite being on a diet of 22 mmol of sodium per day and without diuretic therapy. The administration of UDCA for 1 month while maintained on 22 mmol of sodium per day resulted in a mean weight gain of 3.4 ± 0.8 kg. All seven patients developed increased leg oedema, but no patient developed increased ascites or any other untoward side effects. $U_{Na}V$ decreased significantly to 35 ± 8 mmol/day ($P < 0.05$ compared with baseline). One patient developed massive scrotal oedema and had difficulty walking. The excess fluid retained during UDCA treatment had disappeared 1 month after stopping the treatment, at which time $U_{Na}V$ returned to 114 ± 22 mmol/day ($P < 0.05$ compared with UDCA treatment).

![Figure 1](#)

**Figure 1** Daily urinary sodium excretion in cirrhotic patients with refractory ascites without TIPS placement during 1 week of UDCA administration

Values are means ± S.E.M. *$P < 0.05$ compared with baseline.
Renal haemodynamics and sodium homeostasis

In the post-TIPS patients, $U_{\text{Na}}V$ measured during the 3-h renal study period showed similar changes to the 24-h collection results. There was a significant reduction in $U_{\text{Na}}V$ and the fractional excretion of sodium ($P < 0.05$ compared with baseline) associated with UDCA administration, due mainly to a significant increase in sodium reabsorption proximal to the distal tubule ($P < 0.05$ compared with baseline) (Figure 2). All these parameters returned to baseline levels 1 month after stopping UDCA therapy (Figure 2). The calculated reabsorption of sodium distal to the site of lithium reabsorption remained unchanged throughout the study.

The positive sodium balance associated with UDCA in the post-TIPS patients was not due to any changes in renal haemodynamics. The renal circulation and glomerular filtration rate remained unchanged throughout the study period (Table 2). There was no apparent change in distribution of RBF as evidenced by an unchanged filtration fraction (20.9 ± 9.5% at baseline, 19.6 ± 4.0% with UDCA treatment and 18.1 ± 2.1% 1 month after stopping UDCA treatment).

Systemic and forearm haemodynamics

Systemic haemodynamic parameters, measured before and with UDCA treatment and 1 month after stopping UDCA in the post-TIPS patients, did not show any significant changes. The already elevated cardiac index and the already reduced systemic vascular resistance remained unchanged (Table 2). Likewise, forearm haemodynamics were not altered by the administration of UDCA (Table 2).

Central blood volume

Total central blood volume, pulmonary vascular volume and cardiac and central vascular volume in the post-TIPS patients were also unchanged from baseline throughout the study period (Table 3). MAP and heart rate also remained stable (Table 1).

Markers of lipid peroxidation

The administration of UDCA in the post-TIPS patients was associated with an increase in pentane production which continued even after UDCA was stopped (Table 4). Ethane production and lipid peroxide levels remained elevated throughout the study period and did not change significantly with UDCA (Table 4). In contrast, MDA production remained low throughout the study (Table 4).

Liver function

At baseline, the mean Pugh score in the post-TIPS patients was 9.4 ± 0.8. UDCA had no effect on liver function as measured by Pugh Score in these patients (Table 1).

DISCUSSION

UDCA, when administered to cirrhotic patients with refractory ascites with or without TIPS placement, resulted in a significant reduction in renal sodium excretion. This, in the post-TIPS patients, was mainly
Table 2  Systemic, renal and forearm haemodynamics in ascitic patients treated with TIPS before, during and after UDCA administration for 4 weeks

<table>
<thead>
<tr>
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<th>Normal</th>
<th>Baseline</th>
<th>With UDCA treatment</th>
<th>1 month off UDCA</th>
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<tbody>
<tr>
<td>Cardiac index (ml/min/1.73 m²)</td>
<td>2.40–3.80</td>
<td>4.37 ± 0.76</td>
<td>4.91 ± 0.65</td>
<td>4.18 ± 0.37</td>
</tr>
<tr>
<td>SVR (dyne·s·cm⁻⁵)</td>
<td>700–1600</td>
<td>940 ± 164</td>
<td>830 ± 88</td>
<td>847 ± 73</td>
</tr>
<tr>
<td>GFR (ml·min⁻¹·1.73 m²)</td>
<td>124 ± 26</td>
<td>72.1 ± 17.9</td>
<td>83.5 ± 17.6</td>
<td>80.4 ± 18.3</td>
</tr>
<tr>
<td>RPF (ml·min⁻¹·1.73 m²)</td>
<td>654 ± 163</td>
<td>387 ± 68</td>
<td>438 ± 46</td>
<td>395 ± 42</td>
</tr>
<tr>
<td>RVR (dyne·s·cm⁻⁵)</td>
<td>6760 ± 530</td>
<td>14988 ± 3767</td>
<td>12542 ± 2446</td>
<td>11977 ± 2667</td>
</tr>
<tr>
<td>FBF (ml·min⁻¹·100 ml⁻¹ tissue)</td>
<td>2.3 ± 0.3</td>
<td>4.6 ± 0.9</td>
<td>4.2 ± 0.5</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>FVR (mmHg·ml⁻¹·min⁻¹·100 ml⁻¹ tissue)</td>
<td>50 ± 5</td>
<td>22.4 ± 3.8</td>
<td>21.6 ± 2.8</td>
<td>25.1 ± 2.7</td>
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Table 3  Total central blood volume, pulmonary vascular volume, cardiac and central vascular volume measurements in ascitic patients treated with TIPS before, during and after UDCA administration for 4 weeks

<table>
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<th>With UDCA treatment</th>
<th>1 month off UDCA</th>
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<tbody>
<tr>
<td>Central blood volume (ml/m²)</td>
<td>1280 ± 100</td>
<td>1472 ± 197</td>
<td>1505 ± 67</td>
<td>1551 ± 162</td>
</tr>
<tr>
<td>Right pulmonary vascular volume (ml/m²)</td>
<td>220 ± 20</td>
<td>177 ± 30</td>
<td>152 ± 21</td>
<td>188 ± 27</td>
</tr>
<tr>
<td>Left pulmonary vascular volume (ml/m²)</td>
<td>105 ± 18</td>
<td>151 ± 25</td>
<td>139 ± 9</td>
<td>150 ± 10</td>
</tr>
<tr>
<td>Cardiac and central vascular volume (ml/m²)</td>
<td>880 ± 80</td>
<td>1144 ± 149</td>
<td>1203 ± 59</td>
<td>1205 ± 153</td>
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Table 4  Levels of lipid peroxidation products in ascitic patients treated with TIPS before, during and after UDCA administration for 4 weeks

* P ≤ 0.05 compared with baseline.

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<tr>
<td>Pentane (pmol·min⁻¹·kg⁻¹)</td>
<td>6.1 ± 0.6</td>
<td>8.4 ± 3.9</td>
<td>16.7 ± 7.3</td>
<td>29.9 ± 6.4*</td>
</tr>
<tr>
<td>Ethane (pmol·min⁻¹·kg⁻¹)</td>
<td>11.4 ± 0.6</td>
<td>21.0 ± 7.0</td>
<td>21.2 ± 6.3</td>
<td>30.2 ± 7.1</td>
</tr>
<tr>
<td>MDA (nmol/ml)</td>
<td>0.50 ± 0.05</td>
<td>0.34 ± 0.12</td>
<td>0.25 ± 0.06</td>
<td>0.31 ± 0.19</td>
</tr>
<tr>
<td>Lipid peroxides (nmol/ml)</td>
<td>1–5</td>
<td>26.7 ± 3.4</td>
<td>15.9 ± 2.9</td>
<td>21.1 ± 6.7</td>
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due to an increase in sodium reabsorption proximal to the distal renal tubule, unaccompanied by any changes in systemic or renal haemodynamics. Forearm haemodynamics also remained stable with UDCA, as did markers of oxidative stress.

UDCA was first introduced as a treatment for gallstones [39]. In recent years, it has been used in cholestatic conditions [40] as well as for a variety of chronic liver diseases [41]. By inhibiting the solubilization of cholesterol and phospholipids in cell membranes by hydrophobic bile acids, UDCA has been shown \textit{in vivo} and \textit{in vitro} to protect against bile salt toxicity [42–44]. We proposed that UDCA might also counteract the direct vasorelaxant effect of hydrophobic bile acids and therefore be involved in the regulation of vascular tone. Theoretically it would seem advantageous to use UDCA in situations of excessive vasodilatation which may delay natriuresis in post-TIPS cirrhotic patients with ascites [45].

Our results did not show any changes in either systemic, forearm or renal haemodynamics after UDCA administration. Surprisingly, renal sodium excretion decreased significantly rather than improving while on UDCA, and this promptly reversed on stopping UDCA treatment. Patients with refractory ascites who did not receive TIPS also had significant sodium retention while on UDCA. From the results of the post-TIPS patients, the sodium-retaining effects of UDCA appear to be
localized to the nephron site proximal to the distal renal tubule. It must be noted that this increased sodium reabsorption occurred in the absence of any haemodynamic changes. Direct toxic tubular injury by UDCA at this site is a plausible explanation [46]. The sodium-retaining effects of UDCA may be peculiar to patients who have avid sodium retention, since this has not been reported in patients with cholestatic conditions with no ascites treated with UDCA. It is possible that high levels of UDCA, by virtue of its membrane-protective effects, increase the sensitivity of the proximal nephron to the heightened neurohumoral activities observed both in refractory ascitic patients without TIPS and post-TIPS patients [45], resulting in increased renal sodium retention.

We proposed that UDCA was an antioxidant, and any vascular effects of UDCA could be mediated via a reduction in oxidative stress. That is, UDCA reduced the hydrophilic bile acid-induced increase in lipid peroxidation, a marker of increased oxygen free-radical generation [12]. In the pretreatment period, breath alkane production was elevated, suggesting that patients with decompensated cirrhosis are oxidatively stressed. If UDCA was indeed an antioxidant, we would expect the level of oxidative stress in these patients to fall with treatment. The fact that pentane production did not fall with UDCA administration may partly reflect the severity of the underlying liver disease since pentane is partially metabolized by the liver. However, ethane production, which is the more reliable of the two alkane markers of oxidative stress, did not change with UDCA administration, nor did the levels of lipid peroxides or MDA. Our results therefore do not support the contention that UDCA reduces the oxidative stress in these post-TIPS cirrhotic patients. Heuman [47] proposed alternative explanations. He suggested that UDCA inhibited the hydrophilic bile acid-induced micellar solubilization of membrane lipids by forming simple micelles and sequestering more toxic bile acids, thereby preventing their toxicity. Furthermore, he suggested that the ability of UDCA to protect against the toxicity of a second bile acid was not a simple function of relative hydrophilicity, since taurocholic acid, while considerably more hydrophilic, was substantially less protective [44].

The unchanged liver function observed in this group of post-TIPS patients after UDCA differs from its beneficial effects in a variety of cholestatic and non-cholestatic conditions [48,49]. UDCA is known to be hepatoprotective, improving transaminase levels and liver histology [50]. However, in a rat model of hepatotoxicity, UDCA was ineffective in reducing the liver damage induced by carbon tetrachloride [51]. Furthermore, in some patients with advanced primary biliary cirrhosis, the administration of UDCA resulted in deterioration of liver function [52]. Although it is disappointing that UDCA did not improve liver function as measured by Pugh score in this group of post-TIPS patients, this may be related to the severe decompensated state of their liver disease.

In summary, UDCA, when administered to cirrhotic patients with refractory ascites, causes significant sodium retention, due mainly to an increased sodium reabsorption proximal to the distal tubule, possibly related to a direct toxic effect of UDCA at that nephron site, without any changes in systemic arterial vasodilatation or antioxidant status. This demonstrates a dissociation between systemic arterial vasodilatation per se and sodium retention in cirrhosis. UDCA does not affect liver function in post-TIPS patients. Caution should be taken when administering UDCA to cirrhotic patients, particularly in whom sodium retention is clinically significant.

ACKNOWLEDGMENTS

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