ORIGINAL ARTICLE

The role of glucocorticoids in sodium retention in cirrhotic patients: A double blind, randomized, crossover study

MARTIN HOJMARK HANSEN1,3, STEFFEN SKOTT KRISTENSEN1,3, OVE B. SCHAFFALITZKY DE MUCKADELL1,3, HELLE CHARLOTTE THIESSON2,3, RUTH ANDREW4 & ANNETTE DAM FIALA1

1Department of Medical Gastroenterology, Odense University Hospital, Odense C, Denmark, 2Department of Medical Nephrology, Odense University Hospital, Odense C, Denmark, 3University of Southern Denmark, Odense M, Denmark, and 4Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Abstract

Objective. Cirrhotic patients have an increased ratio of urinary cortisol to cortisone metabolites, indicating decreased renal 11-β-hydroxysteroid dehydrogenase type-2 activity. This suggests that cortisol — by activation of the mineralocorticoid receptor — may contribute to the abnormal sodium retention evident in cirrhosis. The aim was to elucidate the role of glucocorticoids in sodium retention in decompensated cirrhotic patients. Methods. A randomized, double-blind, placebo-controlled, crossover study was performed in nine patients with alcoholic cirrhosis of the liver. A washout interval of 14 days separated the two periods. After a basal period of 36 h, dexamethasone (0.5 mg every 6 h) or placebo was given for two days. Urine was collected for 12 h periods, and the concentrations of sodium, potassium, creatinine, cortisol and cortisol metabolites were determined. Blood samples for hemoglobin, glucose, sodium, potassium, creatinine, aldosterone and cortisol were obtained daily. Results. Dexamethasone treatment decreased S-cortisol 92.3% (82.9-93.4%) (median and range) compared with that in the basal period. Natriuresis (dexamethasone — placebo) increased 55.1 (-26.4-168.7) mmol/day (median and range). No statistically significant differences (dexamethasone — placebo) were found in changes in body weight (0.00 (-0.45-2.20) kg/day), diuresis (0.56 (-0.35-1.43) L/day) or mean arterial pressure (8.33 (-16.0-41.3) mmHg) (median and range) in reference to the preceding 24 h basal period. Conclusion. These results indicate that endogenous glucocorticoids contribute to the sodium retention in patients with alcoholic cirrhosis of the liver.

Key Words: 11-β-hydroxysteroid dehydrogenase type 2, cirrhosis, cortisol, liver, mineralocorticoid receptor, sodium retention

Introduction

The prognosis of liver cirrhosis is poor, and is characterized by increased morbidity and mortality, with a 10-year relative survival of 34% [1]. Survival rate is lower if complications such as ascites, variceal bleeding or encephalopathy are present at the time of diagnosis [2]. A better understanding of the pathophysiology leading to complications may lead to an adequate and improved treatment [3].

According to the forward theory of ascites formation, a relative underfill of the central vascular compartment increases the activity of renin-angiotensin-aldosterone system (RAAS) and other anti-natriuretic systems. This leads to increased water and sodium retention causing plasma volume expansion leading to ascites formation [4]. In addition a forward increase in splanchnic capillary pressure leads to increased lymph production which contributes to the ascites formation [3,5]. However, not all cirrhotic patients have increased levels of aldosterone when accumulating ascites [6].
Aldosterone is a steroid hormone which acts on the nuclear mineralocorticoid receptor (MR), thus leading to an increased synthesis of a number of proteins. Most important is the epithelial sodium channel (ENaC), which increases sodium reabsorption in the distal tubule and the collecting ducts. This leads to an osmotic gradient across the epithelium, which in turn causes water to be reabsorbed [7].

Cortisol is another steroid hormone produced in the adrenal glands. Chemically cortisol resembles aldosterone and is able to act on the MR. Furthermore, the affinity of cortisol to the MR is similar to that of aldosterone but cortisol exists in a 100–1000 times higher concentration in plasma. The selective access of aldosterone to MR is ensured by the enzyme 11-β-hydroxysteroid dehydrogenase type 2 (11-β-HSD2), which converts cortisol into the inactive metabolite, cortisone, and thus protects MR from activation mediated by cortisol [8,9]. In patients lacking active 11HSD2, inappropriate occupation of MR by cortisol can be attenuated by administration of dexamethasone, a synthetic glucocorticoid drug [8]. Dexamethasone has low affinity to the MR [10] but exerts negative feedback effects on the hypothalamic-pituitary-adrenal axis via the glucocorticoid receptor, reducing the production of cortisol [11].

The renal glucocorticoid-metabolizing enzyme 11-β-HSD2 is downregulated in bile duct-ligated cirrhotic rats and it has recently been shown that cirrhotic patients have an increased ratio of urinary cortisol to cortisone metabolites, indicating decreased renal 11-β-HSD2 activity (unpublished observations). Furthermore, it has been demonstrated that in bile duct-ligated rats, urinary sodium excretion level increased when the rats were treated with dexamethasone [12]. These findings suggests that cortisol — by activation of MR — may play a role in the abnormal sodium retention evident in cirrhosis.

The aim of this study was to elucidate the role of glucocorticoids in sodium retention in decompensated cirrhotic patients.

**Methods**

**Screening process**

The study was performed according to the Declaration of Helsinki and approved by the local ethics committee (VF20040245). The participants were recruited from among patients with alcoholic liver cirrhosis from the Department of Medical Gastroenterology at Odense University Hospital. The patients were either seen in the outpatient clinic in the period January 2010–July 2011 and identified by the ICD-10 diagnostic code K70.3, cirrhosis hepatitis.
Table I. Patient characteristics. Baseline equals the basal period from the first admission regardless of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants N</td>
<td>9</td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
</tr>
<tr>
<td>Male/Female</td>
<td>N</td>
</tr>
<tr>
<td>B-Hgb mmol/L</td>
<td>8.2 (5.35-9.55)</td>
</tr>
<tr>
<td>INR IU</td>
<td>1.3 (1-1.9)</td>
</tr>
<tr>
<td>P-Albumin g/L</td>
<td>33 (28-49)</td>
</tr>
<tr>
<td>P-Bilirubin µmol/L</td>
<td>22 (10-115)</td>
</tr>
<tr>
<td>P-Na mmol/L</td>
<td>138.5 (126-141.5)</td>
</tr>
<tr>
<td>P-CsCr µmol/L</td>
<td>83.5 (54.5-132.5)</td>
</tr>
<tr>
<td>Child Pugh Score (A/B/C) N</td>
<td>2/6/1</td>
</tr>
<tr>
<td>MELD Score Points</td>
<td>8 (0-16)</td>
</tr>
<tr>
<td>Heart Rate Beats/min</td>
<td>70.3 (57.33-93.67)</td>
</tr>
<tr>
<td>Sodium excretion mmol/day</td>
<td>142.5 (12.14-282.9)</td>
</tr>
<tr>
<td>Diuretics Yes/No</td>
<td>N</td>
</tr>
<tr>
<td>Spironolactone Yes/No</td>
<td>N</td>
</tr>
<tr>
<td>Furosemide Yes/No</td>
<td>N</td>
</tr>
<tr>
<td>Amiloride Yes/No</td>
<td>N</td>
</tr>
</tbody>
</table>

alcoholics, or as inpatients in the periods, February–April and August–October 2011. In total, 212 patients were screened through a systematic review of patient files. Only 37 patients were eligible and contacted as possible participants (Figure 1).

Inclusion criteria were patients with alcoholic liver cirrhosis and age above 18 with presence of ascites or diuretic treatment due to ascites. Exclusion criteria were diagnosed diabetes mellitus, suspicion of hypercorticism, transjugular intrahepatic portosystemic shunt, dialysis due to renal insufficiency, abdominal cancers, or non cooperation.

Patients who fulfilled the criteria were given verbal and written information about the study design and the participant’s written consent was obtained. An abdominal ultrasound examination was subsequently performed in order to verify the presence of ascites.

Study design

The study was a randomized double-blind crossover design. A washout interval of fourteen days separated the periods. Each period consisted of five days (Figure 2). On day 1, height and blood pressure were measured. On day 3, after a basal period of 36 h, the patient was given either dexamethasone or a placebo. The tablets were encapsulated in white opaque capsules to secure double blinding. One capsule was administered every 6 h until day 5 at 2 a.m. The patients were randomized to receive dexamethasone or placebo in period one, and thus placebo or dexamethasone in period two.

Patients were instructed to attempt identical sodium intake, using diet sheets, in the two periods. Intake of fluid was standardized to 2 L. During both periods the patients received their normal daily medicine, which was identical in the two periods.

The patient was weighed every morning at 8 a.m. using an electronic scale. The blood pressure and heart rate were measured two times a day, at 8 a.m. and 8 p.m. using an electronic blood pressure monitor.

Urine collection

Urine was collected into 12 h samples. The volume was determined by weight measurement. The urine

Figure 3. Change in urinary sodium excretion in the placebo and dexamethasone period (p < 0.05, n = 9).

Figure 4. Median cortisol levels during the placebo (■) and dexamethasone (○) period (p < 0.05, n = 9).
was analyzed for sodium, potassium, creatinine, and cortisol by standard automated procedures and metabolites of cortisol. Metabolites were determined by gas chromatography-mass spectrometry [13]. This enabled us to estimate the activity of 11-β-HSD2, given as urinary cortisol and cortisone ratio [14]. Cortisol metabolites were calculated as the sum of a-cortolone, b-cortolone, a-cortol, b-cortol, cortisone (E), cortisol (F), 5b-tetrahydrocortisol (THF), 5a-tetrahydrocortisol (a-THF), and tetrahydrocortisone (THE).

Blood samples

The blood samples were collected every morning at 8 a.m. Each sample was analyzed for hemoglobin, glucose, sodium, potassium, creatinine, cortisol, and aldosterone. S-aldosterone was measured using a commercial kit (Coat-A-Count). On day 2 samples were further analyzed for bilirubin, INR, albumin, and coagulation factors in order to calculate MELD score and Child Pugh Score [15–17].

Statistics and calculations

All calculations and graphic design were performed using Microsoft Office Excel 2007. To compare the dexamethasone period with the placebo period, Wilcoxon signed rank test was used. Mann-Whitney test was performed in order to rule out the possibility of carry-over effects and period effects. Levels of significance were $p < 0.05$.

Results are — unless otherwise stated — presented as median and range.

Results

Twelve patients participated in the study. Three were later excluded: two due to previously unknown diabetes mellitus and one did not wish to complete the study. Of the remaining nine patients the Child Pugh score, at the time of inclusion, was A in two patients, B in six patients and C in one patient. Other patient characteristics are shown in Table I. No carry-over effect or period effects were demonstrated.
Table II. Results from day 3 and day 5 in the two periods.

<table>
<thead>
<tr>
<th></th>
<th>Day 3</th>
<th>Day 5</th>
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<tbody>
<tr>
<td></td>
<td>µg/12 h</td>
<td>µg/12 h</td>
</tr>
<tr>
<td>Cortical melanos (n = 6)</td>
<td>1246 (1015-1592)</td>
<td>1246 (1015-1592)</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>255 (147-930)</td>
<td>295 (147-930)</td>
</tr>
<tr>
<td>Urine Na/K ratio</td>
<td>58 (43-71)</td>
<td>58 (43-71)</td>
</tr>
<tr>
<td>S-Na</td>
<td>82 (50-76)</td>
<td>82 (50-76)</td>
</tr>
<tr>
<td>Body Weight</td>
<td>76.2 (54.9-101.4)</td>
<td>76.2 (54.9-101.4)</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>92.7 (83-110)</td>
<td>92.7 (83-110)</td>
</tr>
<tr>
<td>Diuresis L/24 h</td>
<td>2.13 (0.26-2.08)</td>
<td>2.13 (0.26-2.08)</td>
</tr>
</tbody>
</table>

Urinary sodium excretion increased significantly (p < 0.05) in the dexamethasone period compared with the placebo period. The increase was 55.1 (−26.4-168.7) mmol/day (dexamethasone – placebo) (Figure 3).

During the placebo period S-cortisol was within normal range and did not change significantly, the median being 495.0 (314.0–654.0) nmol/L in the basal period and 436.0 (193.0–676.0) nmol/L on day 5. In the dexamethasone period S-cortisol changed significantly from 455.5 (252.5–843.0) nmol/L in the basal period to 40.0 (17.0–80.0) nmol/L on day 5, indicating significant suppression of cortisol production. The relative decrease in S-cortisol was 92.3% (82.7–93.4%) (Figure 4). In accordance with this, urinary excretion of cortisol metabolites declined significantly during treatment with dexamethasone.

No significant difference was found in sodium intake (Figure 5). As per the patients' diet sheets the median sodium intake in the placebo period was 118.0 (74.5–227.0) mmol/day. In comparison, the median sodium intake in the dexamethasone period was 109.3 (72.2–247.0) mmol/day.

When comparing the dexamethasone period with the placebo period the levels of B-glucose increased statistically significant 0.4 (−0.4–1.7) mmol/L/day. Median B-glucose level on day 5 in the dexamethasone period was 6.3 (5.5–9.6) mmol/L.

S-aldosterone, urine Na/K-ratio, urine-cortisol–cortisone ratio, body weight, mean arterial pressure and diuresis (Figure 6) did not change significantly when comparing the dexamethasone period with the placebo period. S-aldosterone levels at baseline were 359.5 (32–970.06) pg/mL (normal range in the recumbent position being 10–160 pg/mL).

Discussion

In this study the aim was to elucidate the role of glucocorticoids in sodium retention in decompensated cirrhotic patients, and thereby the possible actions of glucocorticoids on the MR. To our knowledge this hypothesis has not previously been examined. This was accomplished by suppressing cortisol in plasma by administration of dexamethasone.

We found that the urinary sodium excretion increased significantly when S-cortisol was suppressed. This indicates that the renal sodium handling in patients with decompensated cirrhosis is dependent upon the presence of endogenous glucocorticoids.

The change in sodium handling was not caused by different levels of sodium intake in the two periods. Estimated from the patients' diet sheets, the difference between the two periods was small.
and could not account for the increase in sodium excretion.

Other parameters which might affect sodium handling were S-aldosterone and the activity of renal 11-3-HSD2. These did not change significantly after administration of dexamethasone and thus unlikely to account for the increase in urinary sodium excretion. The biological activity of MR is indirectly measured as urinary Na/K-ratio. This was increased—indicating decreased activation of the MR—during dexamethasone treatment, however, not within the limits of statistical significance. This supports the hypothesis that cortisol in cirrhotic patients activates the MR even though some cirrhotic patients may exhibit adrenal insufficiency [18]. The median S-aldosterone level indicates that our patients as a group have hyperaldosteronism. However, two patients had normal levels of S-aldosterone. In both patients the change in natriuresis was within the lower quartile.

The effect of dexamethasone on sodium excretion has previously been studied in healthy subjects given dexamethasone for five days. In this trial dexamethasone also caused increased urinary sodium excretion. However, the dosage used was 8 mg/day (four times higher dosage than given in our study). Furthermore, the increase in natriuresis was only attained after 4 days of treatment [19]. This suggests a different mechanism than the one seen in our study. In addition, dexamethasone does not functionally bind to the MR in vivo and does not influence the activity of the epithelial sodium channels [20]. Consequently, a direct effect of dexamethasone on natriuresis is unlikely.

Along with increased urinary sodium excretion one would expect an increase in the diuresis. In this study we found no statistically significant changes. There was, however, a clear tendency of increased diuresis when dexamethasone was administered (Figure 6). A larger study might demonstrate a significant difference.

In the present study we saw a small, but statistically significant increase in B-glucose levels. This is a known side effect of dexamethasone treatment. One might fear that increased B-glucose levels would lead to osmotic diuresis, but the median increase being 0.4 mmol/L it is unlikely to be of importance. However, one patient attained a B-glucose level of 9.6 mmol/L on day 5. This value, when combined with a meal, may have caused mild osmotic diuresis. This does not seem to be the case, since this patient's increase in diuresis equals the median increase. It is, therefore, unlikely that the increased natriuresis was due to glucosuria.

The increased natriuresis could also be caused by an increase in blood pressure. However, there was no significant difference in mean arterial pressure thus demonstrating no contribution to the increase in natriuresis.

The importance of 11-ß-HSD2 is illustrated by the clinical consequences of loss of function mutation in the 11-ß-HSD2 gene, which lead to the syndrome of apparent mineralocorticoid excess, a rare form of juvenile hypertension caused by activation of MR by glucocorticoids. Established treatment of this disorder includes dexamethasone [21], which support the importance of our findings in this study.

Thus the effect of dexamethasone on sodium handling in cirrhosis could be of clinical significance. It is well known that treatment with MR antagonists increases urinary sodium excretion significantly [22]. Most patients (eight out of nine) in this study already received diuretics. This treatment was identical for each patient in the two periods and changes in medication cannot be the cause of the increased sodium excretion seen in this study. The effect is, therefore, additional to the treatment with diuretics. As seven out of nine patients received an MR antagonist, the observed natriuresis after dexamethasone probably represented a blunted effect.

In summary this study demonstrated an increased renal sodium excretion in patients with decompensated cirrhosis when S-cortisol level was suppressed by the administration of dexamethasone. The effect was not due to changes in S-aldosterone or renal 11-ß-HSD2 activity. This suggests that the action of glucocorticoids on the MR plays a significant role in the renal sodium retention in patients with alcoholic cirrhosis of the liver. The impact of glucocorticoids in sodium retention should be investigated further in a larger and perhaps more heterogeneous group of cirrhotic patients and compared with the impact on sodium handling in normal subjects.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**


