Advantages of treatment of ascites without sodium restriction and without complete removal of excess fluid

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SUMMARY Two modifications of the standard method of treatment of ascites in chronic liver disease were investigated in three separate randomised trials involving a total of 201 patients. These modifications were (1) an unrestricted sodium intake and (2) limitation of diuresis to partial removal of ascites, to the point of relief of abdominal tension. Mean serum sodium fell significantly in all patient groups receiving the low sodium diet and did not fall in the groups given an unrestricted diet. Mean serum urea nitrogen rose significantly in the patient groups undergoing complete diuresis and did not change in the groups undergoing partial diuresis. Mean serum uric acid rose only in the groups undergoing complete diuresis. We concluded that the advantages of these two modifications of therapy of ascites were increased dietary palatability and decreased likelihood of hyponatraemia and of rise in serum urea nitrogen and uric acid. Disadvantages included dissatisfaction of patients over incomplete clearing of ascites, occasional difficulty in performing diagnostic studies because of prolonged ascites, and unsuitability of a high sodium intake in patients whose ascites is highly refractory to treatment.

In recent years, standard therapy of ascites caused by chronic liver disease has consisted of stringent restriction of sodium intake and administration of diuretics to promote natriuresis and weight loss until the ascites is gone. Suggested modifications of this approach have included an initial period of observation without diuretic therapy to detect spontaneous natriuresis and weight loss until the ascites is gone. Suggested modifications of this approach have included an initial period of observation without diuretic therapy to detect spontaneous natriuresis and weight loss until the ascites is gone.

The objectives of our study were to assess possible benefit from two additional modifications of the standard approach to the treatment of ascites. The first modification was elimination of sodium restriction in the diet, now practical because of the greatly increased potency of available diuretics. The second modification tested was limitation of diuresis to partial removal of ascites, to the point of relief of abdominal tension.

Methods

The research included three separate studies covering a span of several years. Similar patients were involved in all three studies. They had ascites due to subacute or chronic liver disease and were hospitalised on the University of Southern California Liver Service at John Wesley County Hospital in Los Angeles. Approximately 90% of the patients had alcoholic liver disease. Before instituting diuretic therapy they were placed on a low sodium diet (10 mmol/day) and one or more 24-hour urine samples were collected for analysis of sodium and creatinine content. At the onset of diuretic therapy serum sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, and uric acid2 were measured by standard methods and these measurements were repeated two or three times weekly during diuretic therapy and at the time of its discontinuance. Twenty-four hour urine measure-

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2Uric acid was not measured in Study II.
ments of sodium and creatinine output were made two or three times weekly during diuresis.

Patients were randomly allocated to different types of therapeutic regimens if they were not undergoing spontaneous natriuresis, were able to take food, did not have hepatic encephalopathy or active gastrointestinal bleeding, had a serum creatinine below 1·5 mg/dl and agreed to partake in the study.

STUDY I
Patients were randomly assigned to three subgroups. Patients in subgroup A continued to receive the low sodium diet and were given diuretics until ascites was minimal or absent. Patients in subgroup B were given a diet unrestricted in sodium and also received diuretics until ascites was minimal or absent. Patients in subgroup C were given an unrestricted diet and sufficient diuretics to relieve partially the ascites and maintain it at a level consistent with the patient’s comfort. The diuretics used in these three subgroups of patients were spironolactone (usually 100 mg daily) and ethacrynic acid (50-200 mg daily, as needed). Patients in subgroup C received spironolactone daily and ethacrynic acid intermittently. In all three subgroups, supplements of potassium chloride (10% solution) and lysine monohydrochloride (10% solution) were used at the discretion of the treating physicians to prevent hypokalaemia and alkalosis.

STUDY II
This was similar to Study I in all respects except that frusemide 80-320 mg daily was used in place of ethacrynic acid.

STUDY III
This was designed to determine if unrestricted sodium intake and less vigorous diuresis could be applied successfully to a broader spectrum of patients. The Fellows and residents on the Liver Service were asked to consider randomisation of all patients in whom diuretic therapy for ascites was undertaken with the single exception of patients whose serum creatinine was above 1·4 mg/dl. Patients were randomly assigned to two subgroups. Subgroup A received the low sodium diet and diuretics (spironolactone and frusemide) continuously until ascites was minimal or absent, as in subgroup A of the two previous studies. Subgroup B patients were given a diet unrestricted in sodium. The intent was to use diuretics as in subgroup C of the prior studies—that is, in an amount sufficient to remove partially the ascites and then maintain it at a level consistent with the patient’s comfort. In reviewing the records it was apparent that the latter objective of plan B was not attained in most of the patients who, in fact, received diuretics until ascites was gone. There were several reasons for the failure to attain our objective in subgroup B. In the first two studies, each patient was directly managed by one of the investigators. In the third study, patients were managed by all of the resident and Fellow staff of the Liver Service and it was evident, in retrospect, that we had sometimes not made our objective clear to each physician. Additionally, practical considerations often prevailed; diagnostic studies such as liver biopsy, hepatic vein catheterisation, and laparoscopy were more easily performed in patients whose ascites had been totally relieved. The only consistent difference, therefore, between subgroups A and B in Study III was in the amount of sodium in the diet.

Results
Body weight, serum electrolytes, urea nitrogen, creatinine, and uric acid at the onset of diuretic therapy were compared with the values when ascites was judged to be gone (subgroups A and B of Studies I and II, subgroup A of Study III, and many patients in subgroup B of Study III), or at the time of hospital discharge if ascites remained and diuretic therapy was continued (subgroup C of Studies I and II and some patients in subgroup B of Study III). Patients in whom diuretic therapy was discontinued because they developed hepatic encephalopathy after substantial diuresis are included in the above analysis. However, when diuretic therapy was discontinued because of gastrointestinal bleeding before a significant amount of weight had been lost (once), hepatic encephalopathy (twice), or recognition of the hepatorenal syndrome (twice) the patients were excluded. Three patients were withdrawn early from Group III-B because the responsible physician was dissatisfied with the slow rate of weight loss. Four additional patients were excluded, one because of premature discharge from the hospital against medical advice, one because of failure to find ascites on diagnostic paracentesis, and two because the wrong diet was given. This left 201 patients for data analysis.

DIURESIS
Table I contains data concerning diuresis. Urinary sodium values before diuretic therapy were similar in all subgroups and reflect the fact that patients undergoing spontaneous natriuresis were eliminated from the study. In most patients, 24-hour urine collections were satisfactory as indicated by the creatinine content. However, in Study III, in order to permit the inclusion of data from a few patients whose urine collections were erratic, we have expressed urinary sodium as mmol per gram of urinary
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creatinine.

Total weight loss was smallest, as expected, in the three patient subgroups I-C, II-C, and III-B where the intent was to remove the ascites partially rather than completely. Average daily weight loss was also least in two of these subgroups, I-C and III-B. The marked difference in mean daily weight loss in two similarly designed studies in subgroups I-C and II-C is explained by the shorter period of hospitalisation in subgroup II-C. In both groups of patients a relatively rapid initial rate of diuresis was achieved in order to relieve abdominal tension. Thereafter a smaller 'holding' dose of diuretics was used in an attempt to remain in balance with sodium intake. The patients in subgroup II-C were discharged earlier from the hospital (mean 17 days of treatment versus 25 days for patients in subgroup I-C).

Urinary sodium values during diuresis reflect both the rate of weight loss and the dietary sodium intake. The high value in subgroup I-C is misleading as ethacrynic acid was given intermittently and 24-hour urine sodium measurements were made only on days when it was given.

**SERUM SODIUM AND CHLORIDE**

Serum sodium fell significantly in all three subgroups receiving a low sodium diet (Table 2). There was a mean fall of 2·1 mmol/l in subgroup I-B not treated with sodium restriction, but the fall was not statistically significant. There was no change in serum sodium in the remaining four subgroups given an unrestricted diet.

Changes in serum chloride in general paralleled those in serum sodium but were greater in magnitude, at least partially explained by concomitant changes in acid-base balance as reflected in the serum bicarbonate.

**SERUM UREA NITROGEN AND CREATININE**

There was a significant rise in serum urea nitrogen in all subgroups except I-C and II-C (Table 2). These

Defined as p < 0·01, Student's t test.

### Table 1 Average values relating to diuresis in eight groups of patients with ascites due to chronic liver disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (no.)</th>
<th>Treatment duration (days)</th>
<th>Weight loss</th>
<th>24-hour urine Na</th>
<th>Diuretic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total (kg)</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before treatment</td>
<td>During treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mEq/g</td>
<td>mEq/g</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I A</td>
<td>22</td>
<td>11</td>
<td>12</td>
<td>1·1</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>25</td>
<td>8</td>
<td>11</td>
<td>1·4</td>
<td>8</td>
</tr>
<tr>
<td>C</td>
<td>18</td>
<td>25</td>
<td>7</td>
<td>0·28</td>
<td>5</td>
</tr>
<tr>
<td>II A</td>
<td>10</td>
<td>19</td>
<td>10·8</td>
<td>0·57</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>27</td>
<td>10·7</td>
<td>0·4</td>
<td>5</td>
</tr>
<tr>
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<td>9</td>
<td>17</td>
<td>8·7</td>
<td>0·5</td>
<td>13</td>
</tr>
<tr>
<td>III A</td>
<td>59</td>
<td>21</td>
<td>10·3</td>
<td>0·58</td>
<td>7*</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>24</td>
<td>6·9</td>
<td>0·30</td>
<td>8†</td>
</tr>
</tbody>
</table>

*Not representative, as ethacrynic acid was given twice weekly and urine sodium measurements were made only on these days.
†mEq/g urinary creatinine (1 mmol 1 g = 0·113 g/g).

### Table 2 Number of episodes of diuretic-related hepatic encephalopathy and mean serum values at beginning and end of study period in eight groups of patients with ascites treated with various diuretic schedules

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (no.)</th>
<th>Serum</th>
<th>Episodes of encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Na</td>
<td>K</td>
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<td></td>
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<td>(mEq/l)</td>
<td>(mEq/l)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a†</td>
<td>b†</td>
</tr>
<tr>
<td>I A</td>
<td>22</td>
<td>134</td>
<td>128*</td>
</tr>
<tr>
<td>B</td>
<td>25</td>
<td>134</td>
<td>132</td>
</tr>
<tr>
<td>C</td>
<td>18</td>
<td>133</td>
<td>133</td>
</tr>
<tr>
<td>II A</td>
<td>10</td>
<td>139</td>
<td>134*</td>
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<tr>
<td>B</td>
<td>9</td>
<td>135</td>
<td>134</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>135</td>
<td>135</td>
</tr>
<tr>
<td>III A</td>
<td>59</td>
<td>133</td>
<td>131*</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>133</td>
<td>134</td>
</tr>
</tbody>
</table>

*p < 0·01 when compared with value at beginning of study period. (SI conversion factors: 1 mmol = 1 mEq urate (mmol) x 0·0595; urea nitrogen (mmol) x 0·714; creatinine (mmol) x 0·844).
†Values at beginning of study period.
‡Values at end of study period.
§Encephalopathic episodes ascribed to use of diuretics.
two groups consisted of patients whose ascites was not removed completely; they had a smaller total amount of ascites removed and in group I-C the rate of weight loss was less than in the other groups. Serum creatinine rose along with urea nitrogen but to a lesser degree and the increase was significant only in groups I-A, I-B, II-A, III-A, and III-B.

**SERUM URIC ACID**
Serum uric acid rose significantly with diuresis in four of the five patient subgroups in whom measurements were made (Table 2). There was only a small increase, not significant, in subgroup I-C where ascites was not totally removed. Uric acid was not measured in the other subgroup where ascites was not completely removed (II-C). The magnitude of the rise was greatest in the two subgroups I-A and I-B where the rate of diuresis was greatest. These two subgroups received ethacrynic acid but so did the patients in subgroup I-C where there was no significant increase in urate.

**SERUM POTASSIUM AND BICARBONATE**
Changes in serum potassium and bicarbonate appear in Table 2. They were of relatively small magnitude though occasionally statistically significant. As stated previously, supplements of potassium chloride and lysine monohydrochloride were given to many patients in an uncontrolled fashion, as dictated by their serum potassium and bicarbonate measurements.

**HEPATIC ENCEPHALOPATHY**
Episodes of hepatic encephalopathy ascribed to diuretic administration occurred in all groups of patient (Table 2). There were fewer episodes in patients in subgroups I-C, II-C, and III-B where diuresis was less complete and serum urea nitrogen rose less or not at all but the differences are not great enough to be judged decisive.

**Discussion**

Hyponatraemia in patients with cirrhosis and ascites indicates relative water retention rather than sodium deficiency, as total extracellular fluid sodium content is markedly increased in such patients (Birkenfeld et al., 1958). The cause of water retention in this setting has not yet been definitely determined. Possible pathogenetic mechanisms include ‘appropriate’ vasopressin secretion mediated by volume-related stimuli, decreased degradation of vasopressin by the diseased liver (Skowsky et al., 1976), and abnormally high reabsorption of glomerular filtrate in the proximal nephron (Schedl and Barter, 1960). Our study made no attempt to explore these mechanisms. Though we did not prove that hyponatraemia in our patients was due to water excess rather than sodium deficiency, we regard this as the most likely possibility. Development of hyponatraemia during diuresis clearly was related to use of the low sodium diet, as there was a statistically significant fall in serum sodium only in the three groups of patients receiving this diet. Patients with liver disease and ascites probably have mechanisms activated both for water retention and sodium retention. If the diet is low in sodium and there is free access to water, there is more likelihood of development of hyponatraemia than when both sodium and water are ingested in normal proportions. We made no effort to restrict water intake in our patients nor did we attempt to measure fluid intake and fluid balance. It is entirely possible that treatment with both fluid and sodium restriction would have prevented hyponatraemia.

Increase in serum urea nitrogen and creatinine during the administration of diuretics in patients with ascites can be ascribed to reduction in plasma volume and glomerular filtration rate from the diuresis. This should be related both to the magnitude of the diuresis and the speed with which oedema fluid and ascites is mobilised into the circulation. In this study all subgroups except I-C and II-C showed highly significant increases in serum urea nitrogen and lesser increases in serum creatinine. There was no close correlation between the rate of weight loss and the amount of waste product increase. Particularly in subgroups I-A and I-B the rate of weight loss was high (1.1 and 1.4 kg/day) and exceeds the maximum rate of 0.6 kg/day recommended by Shear et al. (1970) on the basis of their findings regarding the speed of movement of ascitic fluid to the plasma. However, many of these patients had peripheral oedema and Shear et al. showed that peripheral oedema fluid was more easily transferred to the plasma than was ascitic fluid. Unfortunately, we failed to measure the peripheral oedema in our patients so we are not able meaningfully to compare rate of weight loss and development of renal impairment. In all of our subgroups of patients where serum urea nitrogen increased it did so to a greater degree than serum creatinine, consistent with renal impairment caused by reduction in plasma volume. The fact that renal impairment failed to develop in subgroups I-C and II-C where ascites was not completely removed suggests that diuresis is more likely to result in hypovolaemia as the last few litres of ascites are removed.

We conclude that management of ascites without sodium restriction and without attempting to remove all of the excess fluid is feasible in most patients and has certain advantages. Though the
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Dose of diuretic drugs required is higher, development of hyponatraemia is less frequent as is the occurrence of renal insufficiency and urate retention ascribable to diuretics. The incidence of hepatic encephalopathy may be decreased. There is rarely a change in diuretic requirement on hospital discharge, as dietary sodium is unlikely to change appreciably. On the other hand, this therapeutic approach does present some practical problems. Though patients appreciate the increased dietary freedom, they often object to prolonged presence of ascites, equating continued abdominal distention with failure to improve. Investigative procedures such as liver biopsy, liver scan, angiography, and barium meal are somewhat more difficult to perform or interpret when ascites is present. Patients with renal insufficiency and ascites that respond poorly to diuretics are difficult to manage without sodium restriction.

**References**


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