Effect of Fludrocortisone Acetate in Patients With Subarachnoid Hemorrhage

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In this study with randomized controls, we administered fludrocortisone acetate to 46 of 91 patients with subarachnoid hemorrhage in an attempt to prevent excessive natriuresis and plasma volume depletion. Fludrocortisone significantly reduced the frequency of a negative sodium balance during the first 6 days (from 63% to 38%, \( p=0.041 \)). A negative sodium balance was significantly correlated with decreased plasma volume during both the first 6 days (\( p=0.014 \)) and during the entire 12-day study period (\( p=0.004 \)). Although fludrocortisone treatment tended to diminish the decrease in plasma volume, the difference was not significant (\( p=0.188 \)). More patients in the control group developed cerebral ischemia (31% vs. 22%) and, consequently, more control patients were treated with plasma volume expanders (24% vs. 15%), which may have masked the effects of fludrocortisone on plasma volume. Fludrocortisone therefore reduces natriuresis and remains of possible therapeutic benefit in the prevention of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. (Stroke 1989;20:1156-1161)

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Delayed cerebral ischemia is a major complication occurring after aneurysmal subarachnoid hemorrhage.1-5 One possible causal factor is a decrease in plasma volume,6-7 associated with excessive natriuresis6-8 and hyponatremia.6-12 In patients with hyponatremia after subarachnoid hemorrhage, fluid restriction leads to an increased risk of cerebral infarction.11 Several authors have reported a partial or complete reversal of signs and symptoms of cerebral ischemia after plasma volume expansion, with or without induced arterial hypertension.13-15 Maintenance of an adequate intravascular volume is therefore important in patients with subarachnoid hemorrhage. In a small nonrandomized study,7 the mineralocorticoid fludrocortisone acetate16,17 appeared to prevent plasma volume depletion in the first 6 days after the hemorrhage. The aim of our study was to investigate the effect of fludrocortisone acetate on sodium balance, fluid balance, and plasma volume in a randomized trial of patients with subarachnoid hemorrhage.

**Subjects and Methods**

The trial commenced in January 1986 and ended in May 1987. Three centers participated: the Department of Neurosurgery, Royal Free Hospital, London; the Department of Neurology, University Hospital Rotterdam; and the Department of Neurology, University Hospital, Utrecht. The ethics committee at each center approved the study.

Patients with signs and symptoms of subarachnoid hemorrhage and with confirmatory evidence on the initial computed tomogram18-19 or in the cerebrospinal fluid were eligible. Reasons for exclusion were a lapse of >72 hours since the presenting hemorrhage; age of >70 years; previous treatment with diuretics or corticosteroids; presence of endocrine, renal, or cardiac disease; or computed tomographic evidence of a cause for the subarachnoid hemorrhage other than aneurysm.18,19 If death appeared imminent, entry was delayed.

The amount of cisternal blood on the initial computed tomogram was graded separately for each of the 10 cisterns on a scale of 0 to 3 (maximum score 30 points) as previously described.4,10 Similarly, intraventricular blood was graded separately for each of the four ventricles on a scale of 0 to 3 (maximum score 12 points).4,10 Four-vessel angiography and aneurysm surgery were performed depend-
ing on the patient’s clinical condition. Surgery was planned between Days 7 and 10 in London and on Day 12 in Rotterdam and Utrecht. The level of consciousness was assessed at entry by means of the 14-point Glasgow Coma Scale.20

Eligible patients were randomized after informed consent was obtained. Randomization was stratified per center, according to random number tables by means of a sealed-envelope technique. Treatment with fludrocortisone acetate was always started ≤72 hours after the hemorrhage. The drug was administered intravenously or orally, 400 μg/day in two doses, for a maximum duration of 12 days. Treatment was discontinued if signs of heart failure developed. Antihypertensive drugs were given only if the patient was receiving this treatment before admission. Corticosteroid treatment was started (in those who were eligible for aneurysm surgery) 48 hours before the operation. All patients received tranexamic acid intravenously before the first 4 days after admission, in six doses of 1 g/day. During the first 12 days, fluid intake was maintained at 3 l/day either orally or intravenously (isotonic saline). For every degree of body temperature above 38°C, an additional 500 ml/day fluid was administered. When signs of cerebral ischemia developed, extra fluid in the form of dextran 40, polygelin (in London), or 20% albumin (in Rotterdam and Utrecht) was given. Serum electrolytes, blood urea nitrogen, serum creatinine, and routine blood hematologic values were measured daily.

Plasma volume was measured during the first 24 hours after admission and was again on Days 6 and 12. Plasma volume was determined by the isotope dilution technique. A total dose of 148 kBq of 5 mg radioiodinated human serum albumin (iodine-125 in London and iodine-131 in Rotterdam and Utrecht) in isotonic saline was injected intravenously.21 Blood was sampled before injection and at given times after injection (in London at 10, 20, 30, and 60 minutes; in Rotterdam and Utrecht at 8 and 13 minutes). Isotope activity was analyzed with a Gammatrac 1191 (Tracor Analytic, Elk Grove Village, Illinois).22 We expressed the results as total plasma volume and calculated the percentage change between the second (Day 6) and the first measurements and between the third (Day 12) and the first measurements. Because bed rest alone may cause a certain decrease in plasma volume after 1 week,23 we considered only a drop in plasma volumes of >10% relevant, and we referred only to this as “decreased plasma volume.”

Sodium balance was calculated daily for the first 12 days or until surgery for the aneurysm by subtracting sodium excretion from sodium intake. Patients who were well enough to eat were placed on a specially prepared low-sodium diet as well as on intravenous fluids to minimize errors in sodium intake calculations. Sodium excretion was measured in 24-hour urine samples. Fluid balance was calculated daily by subtracting total urine production from total fluid intake. Cumulative sodium and fluid balances were analyzed for the first 6 days and for the entire 12-day study period.

Clinical deterioration occurring within 28 days or until aneurysm surgery was investigated by clinical examination and, where possible, by repeated computed tomography. Cerebral events were defined as probable delayed cerebral ischemia (gradual development of focal neurologic signs, with or without deterioration in the level of consciousness, without confirmation by computed tomography or autopsy) and definite delayed cerebral ischemia (gradual or sudden deterioration in the level of consciousness, or the development of focal signs, or both, with computed tomographic or autopsy confirmation of cerebral infarction). Outcome was assessed according to the 5-point Glasgow Outcome Scale.24 The fourfold tables were analyzed with Fisher’s exact probability test.

Results

Ninety-one patients were randomized; 46 (treated) patients received fludrocortisone and 45 (control patients) did not. Except for a slightly higher proportion of treated patients with little external blood (score 0–6) on the initial computed tomogram entry characteristics were well matched between the groups (Table 1). Antibiotic treatment was administered in one of the 46 treated patients and in four of the 45 control patients. No other drug that might affect renal function was administered.

We measured plasma volume in 82 patients on Day 1, in 64 patients on Day 6, and in 47 patients on Day 12, which enabled us to calculate plasma volume changes in 62 patients for the first 6 days and in 46 patients for the entire 12-day study period. In the remaining patients, measurements were omitted because of early death, aneurysm surgery, the finding of a cause for subarachnoid hemorrhage other than aneurysm, or technical problems. Fluid balance and sodium balance were calculated for the first 6 days in 78 and 77 patients, respectively, and for the entire 12-day study period in 62 and 61 patients, respectively. This included all patients with complete measurement of plasma volume. Cumulative sodium balance and decreased plasma volume could be correlated in 61 patients for the first 6 days and in 46 patients for the entire 12-day study period; we were able to compare cumulative sodium balance and fluid balance in 77 patients for the first 6 days and in 61 patients for the entire 12-day study period.

Fluid intake and sodium intake were well matched in the groups. Mean daily fluid intake in the treated group was 3,261 ml during the first 6 days and 3,352 ml during the entire 12-day study period; in the control group these values were 3,341 and 3,264 ml, respectively. Mean daily sodium intake in the treated group was 219 mmol during the first 6 days and 222...
mmol during the entire 12-day study period. In the control group these values were 208 and 202 mmol, respectively.

Fludrocortisone treatment significantly reduced the incidence of a negative cumulative sodium balance during the first 6 days ($p=0.041$) and during the entire 12-day study period ($p=0.002$, Table 2). There was no effect of fludrocortisone treatment on cumulative fluid balance.

A negative cumulative sodium balance during the first 6 days was correlated with decreased plasma volume (48% vs. 18%, $p=0.014$) and with a negative cumulative fluid balance (18% vs. 0%, $p=0.012$, Table 3). During the entire 12-day study period, a negative sodium balance correlated significantly with decreased plasma volume ($p=0.004$) but not with a negative fluid balance ($p=0.113$, Table 3).

Despite the relations between fludrocortisone treatment and sodium balance and between sodium balance and plasma volume, the direct relation between fludrocortisone treatment and plasma volume was not significant ($p=0.588$ and $p=0.188$, respectively, for the first 6 days and for the entire 12-day study period; Table 2, Figure 1).

Of the 46 patients treated with fludrocortisone, only seven (15%) received plasma volume expanders, compared with 11 (24%) of the 45 control patients. Plasma volume expanders were adminis-
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TABLE 2. Comparison of Control and Fludrocortisone-Treated Patients With Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Treated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>n</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Negative cumulative sodium balance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 6 days</td>
<td>25</td>
<td>40</td>
<td>63*</td>
<td>14</td>
</tr>
<tr>
<td>Entire 12-day period</td>
<td>23</td>
<td>33</td>
<td>70\†</td>
<td>8</td>
</tr>
<tr>
<td>Negative cumulative fluid balance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 6 days</td>
<td>3</td>
<td>40</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Entire 12-day period</td>
<td>4</td>
<td>33</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Decreased plasma volume (&gt;10%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>11</td>
<td>32</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Day 12</td>
<td>8</td>
<td>25</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>14</td>
<td>45</td>
<td>31</td>
<td>10</td>
</tr>
</tbody>
</table>

\*tp<0.05, 0.003, respectively, different from control by Fisher's exact probability test.

The incidence of cerebral ischemia was lower in the treated group, but the difference was not significant. Of the treated 46 patients, 10 (22%) developed delayed cerebral ischemia (seven definite and three probable) compared with 14 of 45 control patients (31%, seven definite and seven probable, \(p=0.349\); Table 2). This trend was seen in each center.

Outcome was similar in the two groups; independent outcome was achieved in 29 (63%) of the 46 treated patients and in 30 (67%) of the 45 control patients \(p=0.827\).

Fludrocortisone treatment was discontinued in two patients because of pulmonary edema, but in the control group pulmonary edema also occurred in two patients. No other side effects developed except hypokalemia. The effect of fludrocortisone treatment on blood pressure was investigated by comparing mean blood pressure on Days 1, 6, and 12 in patients admitted in Rotterdam (44% of all patients). No differences in mean blood pressure between the groups were found.

Discussion

Our study confirms that patients with subarachnoid hemorrhage may have excessive natriuresis, as almost half of our patients in whom it was assessed had a negative sodium balance during the first 6 days after admission. This excessive natriuresis cannot be explained by a high sodium intake before admission followed by a low intake after admission since the mean daily sodium intake in our patients matched that in the average North American and Western European population (174–261 mmol).\(^{25}\)

The release of a natriuretic factor after subarachnoid hemorrhage is a more likely explanation for this sodium loss.\(^{8–12}\)

A negative sodium balance was correlated significantly with a negative fluid balance during the first 6 days and with decreased plasma volume during both the first 6 days and the entire 12-day study period. It is therefore reasonable to assume that any means of preventing the development of a negative sodium balance would help maintain plasma volume. Fludrocortisone treatment significantly reduced the occurrence of a negative sodium balance, during both the first 6 days and the entire 12-day study period. Although the results did suggest that plasma volume depletion was reduced by fludrocortisone treatment, the difference was not significant.

The effect of fludrocortisone in preventing plasma volume depletion may have been masked by the administration of plasma volume expanders. These were administered when the clinicians in charge

TABLE 3. Correlation of Cumulative Sodium Balance With Plasma Volume and Fluid Balance After Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Cumulative sodium balance</th>
<th>Negative</th>
<th></th>
<th>Positive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>n</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Decreased plasma volume (&gt;10%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>13</td>
<td>27</td>
<td>48*</td>
<td>6</td>
</tr>
<tr>
<td>Day 12</td>
<td>10</td>
<td>23</td>
<td>43\†</td>
<td>1</td>
</tr>
<tr>
<td>Negative fluid balance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 6 days</td>
<td>7</td>
<td>39</td>
<td>18*</td>
<td>0</td>
</tr>
<tr>
<td>Entire 12-day period</td>
<td>4</td>
<td>31</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

\*tp<0.02, 0.005, respectively, different from positive cumulative sodium balance by Fisher's exact probability test.
was observed not only between the two groups in cerebral ischemia but also between fludrocortisone-treated group and that this trend was higher in those with cerebral ischemia. To show such a benefit would require many more patients in each group.

Despite this, it is of interest that the proportion of patients with cerebral ischemia was lower in the fludrocortisone compared to controls and therefore remains of possible therapeutic benefit in patients with subarachnoid hemorrhage.

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