Effect of spironolactone on stool electrolyte losses during human cholera

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SUMMARY This study demonstrated that endogenous aldosterone, as determined by its transient competitive block by spironolactone, caused significant sodium and chloride retention during naturally acquired cholera. This beneficial effect of the hormone is accompanied, however, by a deleterious depletion of potassium. In addition, it was found that stool rate significantly altered the sodium and potassium concentrations in cholera stool despite minimal or absent aldosterone activity.

The ability of aldosterone to increase sodium absorption and potassium excretion in the distal tubule of the kidney (Laragh, 1967) is an important factor in the response to reduction in circulating vascular volume (Davis, Carpenter, Ayers, Holman, and Bahn, 1961). The action of pharmacological doses of aldosterone on electrolyte transport in colonic epithelium closely resembles its effect in the renal tubule (Shields, Mulholland, and Elmslie, 1966; Levitan and Goulston, 1967; Crocker and Munday, 1969).

The role of aldosterone has not been investigated during the volume-depleted state of acute cholera, and its influence on the electrolyte losses in the stool and the potassium depletion of cholera is unclear. This study explores the effect of aldosterone on stool electrolyte losses during cholera by employing spironolactone, a competitive antagonist of this hormone (Liddle, 1961; Porter, Bogoroch, and Edelman, 1964).

Patients and Methods

Twenty-three previously healthy adult male patients with bacteriologically confirmed cholera were selected for study. As stool rate is known to affect stool electrolyte composition (Watten, Blackwell, and Phillips, 1962), the patients were divided into two groups: one with constant stool rates during brisk diarrhoea, and the second group with declining stool rates during recovery from diarrhoea. All patients received intravenous therapy and standardized diets without salt restriction. The first group of 15 patients with constant stool rates was rehydrated but was maintained in a mildly hypovolaemic state with plasma specific gravities of 1.027 to 1.030 (normal = 1.024-1.027) in order to retain the hypovolaemic stimulus to aldosterone release. During the course of study these patients demonstrated mild clinical dehydration with no sweat and low jugular venous pressure, but care was taken to prevent oliguria, postural hypotension, and tachycardia. Stool and urine were collected for eight-hour periods and were analysed for sodium, potassium, chloride, and bicarbonate by standard methods. After two control periods a single oral dose of 100 mg spironolactone (Aldactone-A, Searle and Co.) was given. Stool and urine collections were continued for an additional 48 hours.

A second group of eight patients with declining stool rates was studied. These patients were kept well hydrated (plasma specific gravities were 1.022-1.026) with intravenous fluids to avoid any hypovolaemic stimulus to aldosterone release. In addition, they were given spironolactone 50 mg orally every eight hours to block any remaining aldosterone effect. Stool and urine volume and electrolytes were determined for eight-hour periods until diarrhoea had stopped.

Results

As shown in Fig. 1, spironolactone significantly raised the sodium:potassium ratio of choleraic stool. This was effected both by an increase in sodium and a decrease in potassium concentrations, the latter being smaller and thus changing the ratio more. The effect of spironolactone began in most patients...
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at four to eight hours with its peak effect at 12 to 16 hours. The average sodium : potassium ratio returned to the control value by 28 to 36 hours. Urinary sodium and potassium changes paralleled stool changes in both direction and time course. As seen at the top of Fig. 1, the average stool volume of each eight-hour period demonstrated that no significant change in stool rate occurred during the study period.

From the change in stool electrolyte composition between control periods and the peak effect of spironolactone, the retention of sodium and chloride and the loss of potassium due to the effect of aldosterone can be calculated (Table). The blocking action of spironolactone caused an additional daily loss of 74 m-equiv of sodium and 35 m-equiv of chloride as well as the retention of 71 m-equiv of potassium daily. Stool bicarbonate was not significantly influenced by spironolactone. Changes in urinary losses of sodium and potassium were smaller.

Figure 2 illustrates that as the stool rate declined in the second group of patients, the stool sodium : potassium ratio decreased, with both a decrease in sodium and an increase in potassium concentrations. Despite attempts at minimizing the influence of aldosterone by full hydration and administration of spironolactone, significantly lower sodium and greater potassium concentrations were present at slower stool rates.

Discussion

Aldosterone is known to play an important role in sodium and potassium metabolism (Yunis, Bercovitch, Stein, Levitt, and Goldstein, 1964; Gelb and Gerson, 1969). Spironolactone, because of its ability to compete with aldosterone at the target cell for a specific nuclear binding site, competitively antagonizes the action of aldosterone (Liddle, 1961; Porter

![Graph showing stool rate and potassium ratio over time following spironolactone administration.](image)

**Fig. 1** Effect of spironolactone (100 mg) on average stool sodium: potassium ratios (± 1 SEM) in 15 patients during cholera. Bar graph above shows there is no significant change of stool rate during the study period. Bottom graph shows average stool sodium: potassium ratios during 36 hours of study. Paired data show that the average rise in sodium : potassium ratio from control to peak (usually at 12-16 hours after spironolactone) is 4.63 (p < 0.001), and fall from peak to control values (by 28-36 hours after spironolactone) is 4.89 (p < 0.001).

<table>
<thead>
<tr>
<th>Control</th>
<th>At Peak Spironolactone Action</th>
<th>Net with Spironolactone</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>526 (110)*</td>
<td>600 (125)</td>
<td>+74</td>
</tr>
<tr>
<td>K</td>
<td>136 (28-6)</td>
<td>65 (13-6)</td>
<td>-71</td>
</tr>
<tr>
<td>Cl</td>
<td>90 (60-8)</td>
<td>325 (68-4)</td>
<td>+35</td>
</tr>
<tr>
<td>HCO³⁻</td>
<td>185 (38-7)</td>
<td>215 (45-9)</td>
<td>+30</td>
</tr>
</tbody>
</table>

**Table 1** Mean stool loss (m-equiv per 24 hours)¹

¹Mean stool volume was 4.775 l per 24 hours during study.

²Concentrations given in parentheses in m-equiv per litre.

³Mean urine volume was 1.230 l per 24 hours during study.
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**Fig. 2** Effect of spironolactone (50 mg every eight hours) on average stool sodium : potassium ratios during declining stool rates in eight well hydrated cholera patients. Correlation of stool rate with sodium : potassium ratios is highly significant (r < 0.001, n = 34). Regression equation with stool rate as the independent variable is y = 7.168 ± 2.510x; r = 0.5526.

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