Plasma Aldosterone During Haemodialysis in Patients with Terminal Renal Failure

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Haemodialysis normally leads to a reduction in sodium, potassium and water. Since all these factors may influence the secretion of aldosterone either by acting directly upon the adrenals or through the renin-angiotensin system, we investigated the effect of haemodialysis on plasma aldosterone concentrations in patients with terminal renal failure.

PATIENTS AND METHODS

Twenty patients with terminal renal failure were studied. The diagnosis of renal disease was made by biopsy in 13 cases and by clinical symptoms and laboratory data in the remaining 7 cases.

The patients were on a regular haemodialysis programme 2-3 times a week. The duration of haemodialysis ranged between 3 and 40 months. Coil or Cordis Dow capillary artificial kidneys were used. Sodium concentration in the dialysate was 130 mEq/l and potassium concentration was 2 mEq/l.

The patients were divided into three groups:

Group 1 consisted of 5 patients whose blood pressure was normal before the start of haemodialysis.

Group 2 included 11 patients with a high blood pressure that could be controlled by haemodialysis and antihypertensive therapy.

Group 3 consisted of 4 patients whose high blood pressure could not be controlled by haemodialysis and antihypertensive therapy.

Plasma aldosterone (PA), plasma renin activity (PRA), plasma cortisol (PC), plasma sodium and potassium concentration and body weight were determined immediately before and 30 minutes after haemodialysis — after the patients had been in the supine position for at least one hour.

In addition, 6 patients with controllable high blood pressure were dialysed at constant serum sodium and potassium concentrations. These experiments
were performed by using electrolyte concentrations in the dialysate which corresponded to the concentration of sodium or potassium in plasma. When the patients were dialysed at constant serum potassium concentration, they were pre-treated with Resonium-A (Winthrop). Patients whose serum potassium concentration was higher than 5 mEq/l the day before haemodialysis received 3 x 15g Resonium-A orally, whereas patients with a serum potassium lower than 5 mEq/l had 15g only.

PA was measured by radioimmunoassay (Vetter et al., in preparation). PRA was determined using a radioimmunoassay for angiotensin I (Haber et al., 1969). PC was measured by a protein binding method (Murphy et al., 1963). Plasma sodium and potassium were measured by flame spectrometry.

Between 120-150 mEq sodium per day, our normal supine values for PA are 40-120 pg/ml and for PRA 0-3ng/ml/3h. Our normal range for PC is 2-25µg/100ml.

Statistical analysis was performed by Student’s t-test and by calculation of the correlation coefficient.

RESULTS

Group 1: Patients with Normal Blood Pressure (Cases 1-5, Table I)

In all 5 patients in this group PA and PRA were either within the normal range or slightly elevated before and after haemodialysis. During haemodialysis PA showed a weak decrease in 2 patients (cases 1, 3), remained almost unchanged in one (case 4) and increased in 2 patients (cases 2, 5). In one patient the increase in PA was associated with a rise in PRA while PC declined (case 5), whereas in patient 2 the increase in PA occurred together with a marked rise in PC while PRA declined.

PRA decreased in 2 patients (cases 1, 2), was undetectable before and after haemodialysis in patient 3 and showed an increase in the remaining 2 patients. In patient 4 the increase in PRA was not associated with a rise in PA.

PC decreased with the exception of one patient (case 2), who showed a marked rise in PC in response to haemodialysis.

The average decrease in plasma sodium and plasma potassium concentration was 1.2 and 1.1 mEq/l respectively.

The mean loss of body weight was 0.8kg.

Group 2: Patients with Controllable Hypertension (Cases 6-16, Table I)

Before haemodialysis 6 of the 11 patients showed above normal elevated PA (cases 6, 7, 8, 10, 11, 12), whereas 4 patients had abnormally high PRA (cases 8, 9, 10, 16). From the 6 patients who showed elevated PA before haemodialysis only 2 had high PRA (cases 8, 10). Three of the 4 patients with high PA
Table I. Plasma aldosterone (PA), plasma renin activity (PRA), plasma cortisol (PC), plasma sodium and potassium and body weight (BW) (b) before and (a) after haemodialysis in 20 patients with terminal renal failure. Normal blood pressure (cases 1-5), controllable hypertension (cases 6-16) and uncontrollable hypertension (cases 17-20)

<table>
<thead>
<tr>
<th>Case No</th>
<th>PA pg/ml</th>
<th>PRA ng/ml/3h</th>
<th>PC pg/100ml</th>
<th>Sodium mEq/l</th>
<th>Potassium mEq/l</th>
<th>BW kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126</td>
<td>100</td>
<td>3.4</td>
<td>1.5</td>
<td>8.4</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>96</td>
<td>3.4</td>
<td>2.9</td>
<td>5.8</td>
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</tr>
<tr>
<td>3</td>
<td>66</td>
<td>50</td>
<td>&lt;0.16</td>
<td>&lt;0.16</td>
<td>6.8</td>
<td>5.6</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>62</td>
<td>1.6</td>
<td>3.3</td>
<td>6.0</td>
<td>4.7</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>86</td>
<td>0.9</td>
<td>1.6</td>
<td>8.4</td>
<td>7.3</td>
</tr>
</tbody>
</table>

mean 1-5
| 73 | 79 | 1.9 | 1.86 | 6.7 | 6.6 | 139 | 137.8 | 4.9 | 3.8 | 55.5 | 54.7 |

mean 6-16
| 132 | 117 | 3.7 | 5.0 | 8.7 | 7.6 | 137 | 133 | 5.3 | 3.7 | 63.8 | 62.6 |

mean 17-20
| 339 | 405 | 13.7 | 11.1 | 6.9 | 5.1 | 137.5 | 132.5 | 5.4 | 3.8 | 63.8 | 62.5 |

and normal PRA had a high plasma potassium concentration (cases 6, 11, 12). Only one patient (case 7) had a PA elevated above normal. It was associated with neither an abnormally high PRA nor with a plasma potassium concentration higher than 5 mEq/l. One patient with excessively high PRA before haemodialysis showed low PA (case 16).

In 2 patients PA showed a marked increase in response to haemodialysis (cases 9, 16), rose slightly in one patient (case 8) and remained unchanged or decreased in the other patients. In one patient (case 8) the increase in PA coincided with a rise in PRA while PC declined. In patient 9 PA increased together with PRA and PC and in one patient (case 16) the increase in PA
was associated with a marked rise in PC while PRA remained unchanged.

PRA decreased or remained unchanged in response to haemodialysis in 6 of the 11 patients (cases 7, 10, 12, 13, 15, 16) and increased in the remaining 5 patients (cases 6, 8, 9, 11, 14).

PC decreased or showed no change during haemodialysis except in patients 9, 10 and 16.

Plasma sodium decreased from a mean of 137 mEq/l to 133 mEq/l.

The average decrease in plasma potassium was 1.6 mEq/l.

The mean reduction in body weight was 1.2kg.

**Group 3: Patients with Uncontrollable Hypertension (cases 17-20, Table I)**

All 4 patients in this group showed above normal elevated PA and PRA both before and after haemodialysis.

Only one patient (case 17) showed a marked rise in PA in response to haemodialysis. This increase in PA was associated with a rise both in PRA and PC. In the remaining 3 patients PA remained unchanged or decreased during haemodialysis.

PRA increased in 2 patients (cases 17, 19) and decreased in patients 18 and 20.

PC declined, except in patient 17.

The average decrease in plasma sodium was 5 mEq/l, and the average fall in plasma potassium was 1.6 mEq/l.

The average reduction in body weight was 1.3kg. Only one patient (case 17) showed a loss of body weight greater than 2kg.

**Statistical analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 vs Group 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA before haemodialysis</td>
<td>group 1 vs group 3</td>
<td>p &lt;0.01</td>
</tr>
<tr>
<td>PRA before haemodialysis</td>
<td>group 1 vs group 3</td>
<td>p &lt;0.01</td>
</tr>
<tr>
<td>Before haemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA / PRA</td>
<td>r = 0.835</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>PA / K</td>
<td>r = 0.475</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>PA / PRA / K</td>
<td>r = 0.890</td>
<td>p &lt;0.001</td>
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<tr>
<td>After haemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA / PRA</td>
<td>r = 0.475</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>PA / K</td>
<td>no correlation</td>
<td></td>
</tr>
<tr>
<td>PA / PRA / K</td>
<td>r = 0.458</td>
<td>p &lt;0.05</td>
</tr>
</tbody>
</table>

**Haemodialysis at Constant Plasma Sodium Concentration**

Six patients with controllable hypertension (cases 6-11) were dialysed against a sodium concentration in the dialysate which corresponded to their actual serum sodium concentration. As shown in Table II, no decrease in plasma sodium occurred under these conditions. Mean plasma sodium concentration remained almost unchanged (136.7 mEq/l before, 137.2 mEq/l after haemodialysis). Mean decrease in plasma potassium was 1.2 mEq/l compared to
Table II. Plasma aldosterone (PA), plasma renin activity (PRA), plasma cortisol (PC), plasma sodium and potassium and body weight (BW) (b) before and (a) after haemodialysis at constant plasma sodium concentration (cases 6Na–11Na) and at constant plasma potassium concentration (cases 6K–11K) in 6 patients with controllable hypertension. For comparison the means + SD of the results obtained under regular haemodialysis are listed (means 6-11+SD).

<table>
<thead>
<tr>
<th>Case No</th>
<th>PA pg/ml</th>
<th>PRA ng/ml/3h</th>
<th>PC µg/100ml</th>
<th>Sodium mEq/l</th>
<th>Potassium mEq/l</th>
<th>BW kg</th>
</tr>
</thead>
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<tr>
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<td>94</td>
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<td>10.2</td>
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<tr>
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<td>138</td>
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<td>6.0</td>
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<tr>
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<td>4.9</td>
<td>2.9</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>10_Na</td>
<td>168</td>
<td>116</td>
<td>6.4</td>
<td>4.9</td>
<td>6.8</td>
<td>15.5</td>
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<tr>
<td>11_Na</td>
<td>56</td>
<td>48</td>
<td>4.1</td>
<td>1.5</td>
<td>31.0</td>
<td>19.0</td>
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<tr>
<td>mean 6-11 Na</td>
<td>125</td>
<td>78</td>
<td>5.6</td>
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<td>SD</td>
<td>37</td>
<td>40</td>
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<tr>
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<td>57</td>
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<tr>
<td>7_K</td>
<td>88</td>
<td>232</td>
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<tr>
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<td>106</td>
<td>66</td>
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<td>12.5</td>
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<td>4.8</td>
</tr>
<tr>
<td>9_K</td>
<td>36</td>
<td>42</td>
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<td>1.2</td>
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</tr>
<tr>
<td>10_K</td>
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<td>86</td>
<td>4.3</td>
<td>1.4</td>
<td>7.4</td>
<td>3.3</td>
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<tr>
<td>11_K</td>
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<td>46</td>
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<td>3.6</td>
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<tr>
<td>mean 6-11 K</td>
<td>71</td>
<td>88</td>
<td>4.0</td>
<td>5.0</td>
<td>9.4</td>
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</tr>
<tr>
<td>SD</td>
<td>26</td>
<td>72</td>
<td>2.8</td>
<td>5.3</td>
<td>7.5</td>
<td>2.6</td>
</tr>
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</table>

1.6 mEq/l on regular haemodialysis (Table II).

Average reduction in body weight was 1.6kg and thus was 0.4kg higher than under regular conditions.

In all 6 patients PA decreased during haemodialysis. This decrease was statistically significant (p < 0.01). The decrease in PA coincided with a decrease in PRA. PRA decreased from a mean of 5.6ng/ml/3h to a mean of 3.4ng/ml/3h. The decrease in PRA was statistically significant (p < 0.05).
PC remained almost unchanged in one patient (case 6), decreased in 2 patients (cases 9, 11) and showed an increase in the remaining 3 patients (cases 7, 8, 10).

**Haemodialysis at Constant Plasma Potassium Concentration**

The same patients were dialysed against a potassium concentration in the dialysate which corresponded to their serum potassium concentration determined immediately before haemodialysis. As shown in Table II only a minimal decrease in plasma potassium occurred under these conditions. Mean serum potassium decreased slightly from 4.4 mEq/l before haemodialysis to 4.3 mEq/l after haemodialysis. The mean decrease in serum sodium and body weight was similar to the decrease in sodium and weight observed under regular haemodialysis (Table II).

From the 6 patients one (case 7) showed a marked increase in PA in response to haemodialysis. This increase was associated with a rise in PRA and PC. One patient (case 8) showed a fall in PA despite a marked rise in PRA. During haemodialysis the mean PA slightly increased as did PRA (Table II). Except in one patient (case 7) PC decreased. In all 6 patients the values obtained for PA before haemodialysis were significantly lower than the values found before regular haemodialysis (p < 0.001). This coincided with significantly lower plasma potassium concentrations than those found before regular haemodialysis (p < 0.001).

**DISCUSSION**

Four factors are known to be involved in the regulation of aldosterone secretion: the renin-angiotensin system, ACTH and the concentrations of sodium and potassium in blood (Blair-West et al, 1963; Ganong et al, 1966; Davis et al, 1968).

In this study plasma aldosterone determined before haemodialysis correlated well with plasma renin activity (r = 0.835, p < 0.001) indicating that in patients with terminal renal failure the renin-angiotensin system may be the prime factor in regulating the secretion of aldosterone. However, the statistical significant correlation (r = 0.475, p < 0.05) between plasma aldosterone and plasma potassium concentration seems to document that in these patients potassium may also be involved in the regulation of aldosterone secretion. The importance of both factors, renin and potassium, is demonstrated by the high combined correlation between plasma aldosterone, renin activity and potassium (r = 0.890, p < 0.001). Similar findings were already reported by Weidmann et al (1972a, 1973).

In 20 patients with terminal renal failure plasma aldosterone and plasma renin activity determined before haemodialysis ranged from low to excessively high. Patients with uncontrollable hypertension showed significantly higher
plasma aldosterone and plasma renin activity than patients with normal blood pressure (p < 0.01). In patients with controllable hypertension both normal and above normal elevated values for aldosterone and renin activity were found. Though in some of these patients the high plasma aldosterone was found to be associated with hyperkalaemia and normal plasma renin activity, two patients remained who showed both high aldosterone and high plasma renin activity. The latter seems to be a consistent finding in our patients with uncontrollable hypertension. Regular haemodialysis includes reduction in sodium, potassium and water. Each of these changes may influence the secretion of aldosterone either through the renin-angiotensin system or through direct action upon the adrenal gland (Blair-West et al, 1963; Ganong et al, 1966; Davis et al, 1968).

Nine of the 20 patients described in this study showed an increase in plasma renin activity during haemodialysis. These increases, however, were with few exceptions small. In only one patient the reduction in body weight was greater than 2kg. In each of the 3 groups of patients the average loss of weight in response to haemodialysis was less than 1.5kg. Our results are partly in contrast to results published by Brown and co-workers (Brown et al, 1969) who found that marked loss of body weight (>2kg) increased plasma renin concentration, whereas lesser reduction in weight (< 2kg) normally produced a fall in plasma renin concentration. Kotchen and co-workers (Kotchen et al, 1970) found in most of 27 patients an increase in plasma renin activity with an average loss of body weight of 2.3kg.

Only 4 of the 9 patients, who increased plasma renin activity in response to haemodialysis, showed a simultaneous rise in plasma aldosterone concentration. The failure of 5 patients to increase plasma aldosterone despite a stimulus from the renin-angiotensin system could have been caused by the administration of heparin, which is known to inhibit the secretion of steroids but does not alter the secretion of renin (Schlatmann et al, 1964; Bailey & Ford, 1969). However, no alterations in plasma aldosterone concentration were observed in anephric patients following an intravenous infusion of heparin (Bayard et al, 1971; Weidmann et al, 1972b).

Another possible explanation could be that in these patients the suppressing effect of the decreasing potassium overrides the stimulating effect of the renin-angiotensin system.

Two of the 20 patients showed an increase in plasma aldosterone which was not associated with a rise in plasma renin activity. Both patients, however, showed a marked rise in plasma cortisol indicating an increase in ACTH-secretion. Further evidence that ACTH may also be involved in the regulation of aldosterone secretion during haemodialysis is given by the observation that the greatest increase in plasma aldosterone was found in a patient who showed a rise both in plasma renin activity and plasma cortisol.
To evaluate the effect of changes in sodium and potassium during haemodialysis 6 patients with controllable hypertension were dialysed with serum sodium and potassium concentrations which were held constant each in turn by adjusting dialysate sodium and potassium. When these patients were dialysed at constant plasma sodium concentration while plasma potassium was allowed to fall, plasma aldosterone significantly decreased in response to haemodialysis (p < 0.01). However, this decrease was associated with a decrease in plasma renin activity (p < 0.05). Thus, it remains unsettled whether in these patients the observed decrease in plasma aldosterone was mediated through the decrease in plasma potassium or through the diminishing stimulus of the renin–angiotensin system.

When the patients were dialysed at constant plasma potassium while plasma sodium decreased, the observed changes in plasma aldosterone were not qualitatively different from those found in response to regular haemodialysis. These results do not exclude a stimulatory effect of sodium on the secretion of aldosterone independent from the renin–angiotensin system, but most probably this effect is of minor importance. This is consistent with results reported by others who failed to document a stimulatory effect of sodium depletion on aldosterone secretion in anephric patients (Weidmann et al., 1972b; Peart, 1970). Following the administration of Resonium-A, in each patient plasma aldosterone concentration determined before haemodialysis was significantly lower than in standard haemodialysis (p < 0.001). This coincided with markedly lower plasma potassium concentrations (p < 0.001). Again, these results highlight the importance of potassium in the regulation of aldosterone secretion in patients with terminal renal failure.

CONCLUSIONS

In 20 patients with terminal renal failure plasma aldosterone ranged from low to excessively high values.

Before haemodialysis the high correlation between plasma aldosterone, plasma renin activity and the concentration of potassium in plasma (r = 0.890, p < 0.001) indicates that both the renin–angiotensin system and potassium are the major determinants which regulate the secretion of aldosterone in patients with terminal renal failure.

However, the markedly lower correlation obtained after haemodialysis between aldosterone, renin activity and potassium (r = 0.458, p < 0.05) seems to document that factors other than the renin–angiotensin system and potassium participate in the regulation of aldosterone secretion during haemodialysis.

One of these factors was probably ACTH, since in some patients increases in plasma aldosterone coincided with increases in plasma cortisol while plasma renin activity declined.
When 6 of the 20 patients were dialysed at constant plasma potassium concentration while plasma sodium declined, no increases in plasma aldosterone were observed which were independent from changes in plasma renin activity. Thus, the reduction of sodium during haemodialysis most probably exerts no stimulatory effect on the secretion of aldosterone which is not mediated through the renin-angiotensin system.

When the same patients were dialysed at constant plasma sodium concentration while plasma potassium declined, all 6 patients showed a decrease both in plasma aldosterone and in plasma renin activity. Therefore, it remains unsettled whether the decrease in plasma aldosterone was mediated through the fall in plasma potassium or through the diminishing stimulus of the renin-angiotensin system.

ACKNOWLEDGMENT

The authors would like to thank Mr A Alig and the nursing and secretarial staff of the Haemodialysis Unit, Stadtspital Waid, Zürich, for their kind support.

REFERENCES

Ganong, W. F., Biglieri, E. G. and Mulrow, P. J. (1966) Recent Progress in Hormone Research, 22, 381

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OPEN DISCUSSION

T DRUEKE (Paris): You observed a rise in PRA activity when the plasma potassium fell. Did you avoid ultrafiltration and sodium depletion at the same time?

ARMBRUSTER: We did have a little ultrafiltration and sodium depletion at the same time. A rise in PRA with high sodium depletion and ultrafiltration has been described and therefore in order to ensure a potassium effect one should avoid having any ultrafiltration.

SCHWARZBECK (Mannheim): Do you have any pathological explanation for your good correlation between potassium and renin-aldosterone activity?

ARMBRUSTER: No.