Suppression of plasma renin activity by intravenous infusion of antidiuretic hormone in man

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Summary

1. Ten patients on maintenance diuretic treatment received an intravenous infusion of antidiuretic hormone at a low rate for 1 h.
2. A gradual reduction in mean plasma renin activity was observed and this was significant at 60 min.
3. There was a significant correlation between the initial value and the extent of the fall in plasma renin activity. There was no consistent change in blood pressure, heart rate and blood volume.
4. The results point to an intrarenal site of action of antidiuretic hormone.

Key words: antidiuretic hormone, renin, vasopressin.

Abbreviations: ADH, antidiuretic hormone; PRA, plasma renin activity.

Introduction

Inhibition of renin release by administration of antidiuretic hormone in physiological doses has been demonstrated in various settings in dogs (Bunag, Page & McCubbin, 1967; Vander, 1968; Tagawa, Vander, Bonjour & Malvin, 1970; Malvin, 1971; Shade, Davis, Johnson, Gotshall & Spielman, 1973). Recently inhibition of renin release from isolated rat kidney by ADH has also been reported (Vandongen, 1975). In man prolonged administration of ADH failed to suppress plasma renin activity in spite of demonstrable fluid retention (Goodwin, Ledingham & Laragh, 1970).

The aim of the present study was to examine the effect of intravenous infusion of ADH for 1 h on PRA in man. Patients on maintenance diuretic treatment were chosen since PRA suppression is more readily revealed when elevated initial values are present.

After the completion of this study renin suppression in normal man by ADH infusion was reported by Khokhar, Slater, Forsling & Payne (1976).

Patients and procedures

The study comprises an ADH-treated group of ten patients and a control group of four patients (see Table 1). All in the control group and all but one in the ADH group were on maintenance diuretic treatment (bumetanide, frusemide, spironolactone) with potassium supplementation, on liberal salt and water intake.

ADH group protocol

On the morning of the investigation no diuretics were given. After 1 h lying supine, the subject was injected intravenously with a priming dose of 100 munits of ADH dissolved in 2.5 ml of sodium chloride solution (150 mmol/l; saline), followed by the intravenous infusion of 20 munits of ADH/min in saline for 60 min, at a rate of 0.5 ml/min by an infusion pump (Braun Melsungen, Germany).

A synthetic lysine vasopressin preparation (Vasopressin, Sandoz) was used. The activity of
### Table 1. Clinical data for patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Medical treatment</th>
<th>Initial PRA (ng h⁻¹ ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADH group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>Liver cirrhosis</td>
<td>Bumetanide (4 mg), spironolactone (100 mg)</td>
<td>16-3</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>Ischaemic heart disease</td>
<td>Bumetanide (4 mg), digoxin (0-188 mg)</td>
<td>16-0</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>Aortic regurgitation</td>
<td>Bumetanide (2 mg), digoxin (0-25 mg)</td>
<td>2-1</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>M</td>
<td>Aortic and mitral valve prostheses</td>
<td>Frusemide (120 mg), digoxin (0-188 mg), verapamil (120 mg)</td>
<td>2-1</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>Ischaemic heart disease</td>
<td>Bumetanide (1 mg), digoxin (0-125 mg)</td>
<td>2-8</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>Bumetanide (4 mg), digoxin (0-50 mg), spironolactone (100 mg)</td>
<td>6-7</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>F</td>
<td>Ischaemic heart disease</td>
<td>Bumetanide (4 mg), digoxin (0-25 mg), allopurinol (300 mg)</td>
<td>2-6</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>M</td>
<td>Mitral valve prosthesis</td>
<td>Frusemide (80 mg), digoxin (0-25 mg)</td>
<td>22-5</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>F</td>
<td>Mitral stenosis and regurgitation</td>
<td>Bumetanide (4 mg), spironolactone (100 mg), digoxin (0-188 mg)</td>
<td>8-4</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>F</td>
<td>Mitral stenosis, bronchial asthma</td>
<td>Bumetanide (4 mg), digoxin (0-25 mg)</td>
<td>50-9</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>F</td>
<td>Ischaemic heart disease</td>
<td>Bumetanide (3 mg), digoxin (0-25 mg), proxiphyllin (1200 mg)</td>
<td>5-8</td>
</tr>
<tr>
<td>12</td>
<td>58</td>
<td>F</td>
<td>Aortic valve prosthesis</td>
<td>Bumetanide (2 mg), digoxin (0-375 mg)</td>
<td>11-3</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>M</td>
<td>Ischaemic heart disease</td>
<td>Bumetanide (2 mg), proxiphyllin (200 mg)</td>
<td>8-2</td>
</tr>
<tr>
<td>14</td>
<td>35</td>
<td>M</td>
<td>Ischaemic heart disease</td>
<td>Bumetanide (4 mg), spironolactone (100 mg), digoxin (0-50 mg)</td>
<td>10-3</td>
</tr>
</tbody>
</table>

**Median age:** 57

**Median PRA:** 7-6

**Control group protocol**

The patients were studied at the same time in the morning as the ADH patients. After they had been supine for 1 h a saline infusion (0-5 ml/min) without ADH was given for 60 min. PRA was determined before and 60 min after start of the infusion.

**Methods**

PRA was measured by a radioimmunoassay as described by Haber, Koerner, Page, Kliman & Purnode (1969) with an Angiotensin-I¹²⁵I kit (New England Nuclear Corp.). The normal range of PRA in our laboratory is 0-67-2-90 ng h⁻¹ ml⁻¹. The measurement had a coefficient of variation ±3%. Plasma colloid osmotic pressure was measured in duplicate with a

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this preparation is controlled by Sandoz by a bioassay (U.S.P. XVII), with the third international standard of oxytocic, vasopressor and antidiuretic substances used as reference substances.

Blood pressure, heart rate, PRA, packed cell volume and plasma colloid osmotic pressure were determined 15 min and just before, and 10, 20, 30, 45 and 60 min after, the priming dose of ADH. Plasma osmolality, plasma sodium and potassium concentrations were determined before and after ADH infusion in six patients.

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colloid osmometer (Hansen, 1961); the 95% confidence limits of a single measurement with all errors compounded was ±0.7 cm water. In our laboratory determination of plasma colloid osmotic pressure has proved a more sensitive indicator of changes in plasma volume than packed cell volume (Hesse, Nielsen & Lund-Jacobsen, 1975) and plasma protein concentration, determined by rocket electrophoresis (unpublished data). Packed cell volume was determined as microhaematocrit, plasma osmolality by the freezing-point depression method (Advanced Osmometer 65-31, Advanced Instruments, Massachusetts, U.S.A.), and plasma sodium and potassium concentrations by flame photometry (Auto-Analyzer SMA 6/60). The results are shown as the mean values of duplicate estimations.

Significance of differences was tested by the Wilcoxon test for paired comparison and the Mann-Whitney's U-test for unpaired comparison.

Results

ADH group

The two PRA values before ADH infusion were similar (mean 13.1 and 12.9 ng h⁻¹ ml⁻¹), at -15 and 0 min respectively. In two patients with normal initial PRA values no change was observed. In the remainder, PRA gradually decreased during the infusion (Fig. 1); after 30 min the median value of all ten patients was 32.4% lower than the control value \( (P<0.01) \), and after 60 min 41.2% lower than the control value \( (P<0.01) \).

The decrease at 60 min was closely correlated with the initial PRA value (Fig. 2: \( r = 0.99, P<0.001 \)). If the mean of initial and final values is used instead of initial value (a statistically more correct approach) the correlation coefficient is still 0.97.

Mean blood pressure increased in three patients (16, 17 and 18 mmHg), but was virtually unchanged in the remainder \((-5, -1, 0, 2, 4, 4\) and 5 mmHg). Heart rate decreased slightly (median value -4/min; range: -12 to +4, \( P<0.10 \)). There was no significant correlation between change in heart rate, blood pressure or PRA. Plasma colloid osmotic pressure and packed cell volume (Fig. 3) as well as plasma sodium and potassium concentrations and plasma osmolality remained constant.

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**Fig. 1.** Plasma renin activity (PRA) from ten patients during intravenous infusion of antidiuretic hormone for 1 h. Note the logarithmic scale on the ordinate, adopted to show the decline of PRA in the whole range of measurement. Times are related to time of starting the infusion.

**Fig. 2.** Correlation between initial values and decreases in plasma renin activity after ADH infusion for 60 min. \( r = 0.99, P<0.001 \).

**Fig. 3.** Mean values ± se of packed cell volume (▲) and plasma colloid osmotic pressure (cm water) (●) during ADH infusion. There were no significant changes.
Control group

PRA decreased slightly in two of the patients after 60 min, by 15 and 19% respectively. In the two other patients PRA was unchanged. The mean decrease in the control group (8.5%) was significantly lower than that of the ADH group \((P < 0.02)\).

Discussion

In the present study, the marked and rapid suppression of PRA confirms the recent finding of Khokhar et al. (1976) in normal subjects. It is not likely that heart disease as such played any role in the demonstrated effect, since the patients had heart diseases of various aetiologies and severity, and the response of PRA was strikingly homogeneous, reflected by the rectilinear correlation between decrement in PRA and initial PRA (Fig. 2). The same relation between initial value and decrease has been observed with PRA suppression by propranolol (unpublished work).

Our results differ from those of Khokhar et al. (1976) in one respect: they observed a decrease in plasma protein concentration parallel to that of PRA and suggested that plasma volume expansion at the expense of extracellular volume contraction caused the reduction in renin secretion rate. We found no evidence of plasma volume expansion (unchanged plasma colloid osmotic pressure and packed cell volume; Fig. 3). This disagreement is not likely to be explained by differences in protocol, and remains unexplained. However, the finding of PRA suppression in both studies—with or without plasma volume expansion—speaks against the mechanism of renin suppression suggested by Khokhar et al. Our finding of no consistent change in blood pressure, heart rate and blood volume points to an intrarenal site of action.

The ADH plasma levels induced by the infusion in our study and that of Khokhar et al. (1976) is probably within the ranges of ADH levels present in certain fluid disturbances in man. An interaction between ADH and PRA should be taken into account in the assessment of the role of the renin–aldosterone system in oedematous states.

Furthermore, some of the earlier reports on renin and aldosterone suppression by volume expansion need re-evaluation since ADH administration was included in the experiments (Bartter, Biglieri, Pronove & Delea, 1958; Newsome & Bartter, 1968).

Acknowledgments

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References


Vandongen, R. (1975) Inhibition of renin secretion in the isolated rat kidney by antidiuretic hormone. Clinical Science and Molecular Medicine 49, 73–76.