VASOPRESSIN RESPONSE IN HAEMODIALYSIS PATIENTS

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Summary

Ten patients underwent repeated haemodialysis under circumstances of manipulated change in plasma osmolality and blood volume. Basal plasma arginine vasopressin (AVP) levels were significantly higher than in normal controls, but no linear correlation between basal plasma osmolality and AVP levels was found. In 38 of 44 studies there was an appropriate response of AVP to change in plasma osmolality or blood volume. We conclude that the quantitative response of AVP in dialysis patients is not linear and differs markedly as compared to normals. Changes in blood volume may play a more dominant role in the control of AVP release.

Introduction

Under normal circumstances arginine vasopressin (AVP) secretion is controlled by a number of factors, the most important being plasma osmolality [1]. According to the studies of Robertson et al [2] a change in plasma osmolality of 1% is sufficient to evoke a change of approximately 1 pg/ml in plasma AVP, and this response is linear between osmolalities of 281 to 295 mOsm/kg. There is still much debate on the issue of whether there is an ‘osmotic threshold’ for AVP release or whether below a certain osmolality there is no linear correlation [3–5]. Other major stimuli to AVP secretion are changes in blood volume and blood pressure; however, it would appear that these stimuli are too gross to be major factors in AVP modulation [6]. Stress, smoking and various medications may play a secondary role in control of AVP release [7].

In recent years a variety of endocrine dysfunctions have been described as part of the uraemic syndrome [8–11], however very little is known on the control of AVP in uraemia [12]. The present study is an attempt to define the behaviour of AVP in response to its major known stimuli. We chose to study haemodialysis patients since haemodialysis presents a unique opportunity to alter individually the components that regulate AVP release.
Material and Methods

We studied 10 patients ranging in age from 20 to 45 years and maintained on chronic intermittent haemodialysis 12–15 hours weekly for 8–80 months. Original renal disease was chronic glomerulonephritis, chronic interstitial nephritis or chronic obstructive uropathy. Residual renal function was extremely low with creatinine clearance in all cases below 1ml/min and daily urinary volume under 100ml. Other than vitamins and aluminium hydroxide, the patients received no other drug therapy. Blood was drawn prior to and following dialysis of 4 hours duration; the sample prior to dialysis being drawn 30 minutes following venepuncture and recumbency, to minimise the effect of stress on AVP release. Smoking was forbidden before and during dialysis. Changes in body weight and blood pressure were monitored during and following dialysis.

Dialysate contained 2mEq/L potassium, 200mg/100ml glucose, and 3mEq/L calcium. Dialysate sodium was manipulated to be between 130–140mEq/L. Similarly blood volume was altered by varying the degree of ultrafiltration. Each patient was studied during five haemodialyses. On each occasion a different combination of osmolality and blood volume was induced.

Plasma AVP was measured by radioimmunoassay [13]. Plasma renin activity was measured by radioimmunoassay of angiotensin I (125)I [14]. Osmolality was measured by freezing point depression, and effective plasma osmolality was estimated by correction for the abnormal levels of BUN. Change in blood volume was estimated from change in haematocrit using a standard formula [15]. Levels of plasma glucose, urea nitrogen, creatinine, sodium, potassium and calcium were measured by standard methods.

Results

1 Mean predialysis AVP levels were 4.95 (SEM ±0.56)pg/ml compared to 1.0 (SEM ± 0.5)pg/ml for normal controls (Figure 1).

2 At commencement of dialysis we were unable to find a linear correlation between measured or effective plasma osmolality, and plasma AVP (Figure 2).

3 In 15 of 44 studies we found an increase in AVP levels following haemodialysis (Table I). In 7 of these the rise in AVP appeared to be appropriate to increasing effective osmolality and decreasing blood volume. In a further 8 studies, however, there was a rise in AVP levels despite a significant decrease in effective plasma osmolality, but in accordance with a decrease in blood volume.

4 In 29 studies there was a decrease in AVP levels following haemodialysis (Table I). In 23 of these AVP decreased appropriately to a significant decrease in effective plasma osmolality despite a small decrease in blood volume. In 6 studies AVP decreased despite both a small increase in effective plasma osmolality and a small decrease in blood volume.

5 The relationship of plasma AVP to other variables that have been said to influence AVP secretion during haemodialysis were investigated. No
Figure 1. Baseline AVP levels for all 44 studies. The shaded area represents results of normal controls for this laboratory.

Figure 2. Baseline plasma AVP levels plotted against baseline effective plasma osmolality.
<table>
<thead>
<tr>
<th></th>
<th><strong>RISE IN ADH</strong></th>
<th><strong>FALL IN ADH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>'Appropriate'</td>
<td>'Inappropriate'</td>
</tr>
<tr>
<td>Number of studies</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>$\Delta$ ADH (pg/ml)</td>
<td>$3.1 \pm 0.7$</td>
<td>$6.2 \pm 1.5$</td>
</tr>
<tr>
<td>$\Delta$ E Osm (mOsm/kg)</td>
<td>$5.1 \pm 1.6$</td>
<td>$10.7 \pm 1.1$</td>
</tr>
<tr>
<td>Baseline E Osm (mOsm/kg)</td>
<td>$289 \pm 2.0$</td>
<td>$289 \pm 2.5$</td>
</tr>
<tr>
<td>$\Delta$ fall in BV (%)</td>
<td>$6.5 \pm 1.2$</td>
<td>$7.9 \pm 1.2$</td>
</tr>
</tbody>
</table>

correlation between AVP and serum calcium or plasma renin activity could be found.

**Discussion**

Our results indicate that the basal level of plasma AVP in dialysis patients is significantly higher than that of normal controls. It is tempting to suggest that the high plasma AVP is due to higher plasma osmolality, since there is no evidence for decreased catabolism or renal clearance for the hormone in anephric patients [16,17]. However, we were unable to find a linear correlation between plasma AVP and measured or effective plasma osmolality prior to dialysis. Moreover we were unable to show any correlation between plasma sodium and AVP despite the fact that sodium is the major plasma solute contributing to plasma osmolality. Similarly we found no correlation between change in plasma AVP and potassium, creatinine, or glucose, whose levels change during haemodialysis therapy. In contrast to a previous report we were unable to confirm a correlation between plasma AVP and change in serum calcium [18]. Other non-osmolar factors that may effect AVP control were examined. No correlation between change in AVP and plasma renin activity or blood pressure could be found [19].

In 7 of the 15 studies where AVP increased following haemodialysis this rise appeared to be appropriate to increasing effective osmolality and decreasing blood volume. However in a further 8 studies AVP rose despite a significant decrease in effective plasma osmolality but in accordance with a decrease in blood volume. It is noteworthy that the rise in AVP in these 8 studies was double that of the first group, however basal effective plasma osmolality and decrease in blood volume was not markedly different. We therefore suggest that this 'inappropriate' rise in AVP despite a decrease in plasma osmolality may in fact represent an exaggerated response to decreasing blood volume.

In 23 of 29 studies where a decrease in AVP was documented, this drop was appropriate to a large decrease in effective plasma osmolality, but occurred despite a small decrease in blood volume. However in 6 studies AVP decreased despite both a small increase in effective plasma osmolality and a small decrease in
blood volume. The increase in AVP in this group was almost double that of the first, but the difference in change in blood volume between the two groups was not statistically significant. It is notable, however, that the baseline effective osmolality of 279 ± 2.8 mOsm/kg is notably lower than that of all other groups investigated (289 ± 2.0 mOsm/kg) and it is possible therefore, that at this low baseline 'subthreshold' level of plasma osmolality the changes in blood volume and plasma osmolality were inadequate to produce a rise in AVP.

Hence in 30 of 44 studies AVP responded as expected to change in osmolality while in a further 8 studies the response was possibly to a change in blood volume. In 6 studies we were unable to explain change in AVP level by change in osmolality, blood volume, or other monitored factors that change during dialysis.

In patients undergoing haemodialysis with multiple factors changing and interchanging it was not possible to predict in any given study to which stimulus AVP would respond. We therefore conclude that the quantitative response of AVP in this population is not linear and differs markedly compared with normals. Changes in blood volume in dialysis patients may play a more dominant role in the control of AVP.

Acknowledgments

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References

1 Dunn, FL, Brennan, TJ, Nelson, AE and Robertson, GL (1973) J. clin. Invest., 52, 3212
17 Baumann, G and Dingman, JF (1976) J. clin. Invest., 57, 1109
18 Pastoriza-Munoz, E, Eastling, RE and Malvin, RL (1976) Nephron, 16, 449

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Open Discussion

BAKER (London) Could you say something about the reproducibility of your ADH radio-immunoassay and its specificity?

NORD There was a very good interassay correlation of 5%.

HAMMER (Copenhagen) Do you have any blood pressure data on these patients?

NORD Blood pressure was monitored every 15–20 minutes during dialysis and there was no correlation between the changes in the blood pressure and vaso-pressin level.

HAMMER Those patients you have made your calcium investigations on, did they have normal calcium concentrations or were they hypercalcaemic?

NORD They were in the normal range; if anything a little low.