Effect of alcohol withdrawal on blood pressure, plasma renin activity, aldosterone, cortisol and dopamine \( \beta \)-hydroxylase


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Summary

1. Sixty-five alcoholic patients admitted for detoxification had blood pressure, withdrawal symptoms, plasma cortisol (PC) and plasma aldosterone (PA) levels, plasma renin activity (PRA), and serum dopamine \( \beta \)-hydroxylase (DBH) levels measured on the first and fourth days after admission.

2. On the morning after admission blood pressure was elevated (>140/90) in 32 patients (49%) and was 160/95 mmHg or more in 21 (32%). PRA was initially elevated in 41 patients, PA levels in 14, and 13 patients had raised PC levels. By the fourth day, blood pressure and biochemical measures had fallen significantly while urine volume and sodium output, low on admission, had increased significantly. On admission urinary metanephrine levels were raised in four out of the 31 patients who had them measured.

3. The height of both the systolic and diastolic blood pressures was significantly related to the severity of the alcohol withdrawal symptoms. Of the biochemical parameters measured, PC level correlated with systolic but not diastolic pressure, and urinary volume was inversely correlated with the height of the diastolic pressure. No relationship was found between blood pressure and PRA or PA level.

4. The pressor effect of alcohol withdrawal could be due to sympathetic nervous system overactivity, or possibly to hypercortisolaemia. The first hypothesis seems more likely.

Introduction

Alcoholic patients admitted to hospital for detoxification have a high prevalence of hypertension; their blood pressures return to normal after alcohol withdrawal symptoms have abated and they remain normal if they continue to abstain [1]. Patients who resume drinking sustain a rise in blood pressure to their former high levels. To study the mechanisms of the pressor effect of alcohol withdrawal, we studied 65 alcoholic patients and measured plasma levels of aldosterone (PA) and cortisol (PC), plasma renin activity (PRA), and serum levels of dopamine \( \beta \)-hydroxylase (DBH) together with urinary sodium and metanephrine excretion in relation to changes in blood pressure during detoxification.

Patients and methods

Sixty-five alcoholic patients who had been referred either from general practitioners or from the Alcohol Addiction Unit were admitted for detoxification and investigation of blood pressure and liver function. All had been drinking heavily (at least 100 g of ethanol per day) up to 24 h before admission although none were intoxicated at the time of the study. Patients with incidents, anaemia or decompensated cirrhosis...
were excluded. Blood pressure was measured by one observer using a standard mercury sphygmo-
manometer, phase V being used for the diastolic
pressure. Alcohol withdrawal symptoms were
graded on the first and fourth mornings after
admission on a scale of 0-7 modified from that of
Gross et al. [2], using estimates of tremor, sweating,
eating disturbance, fits and delirium tremens.
Alcohol withdrawal symptoms were treated with
oral chlormethiazole in reducing dosages in 60
patients; five patients with severe symptoms also
received alcohol to a maximum of 80 g per day up
to the third day after admission.

Blood specimens were taken after overnight
recumbency and fasting on the first and fourth
mornings after admission for estimation of PA and
PC concentrations and PRA. Serum DBH concen-
trations were measured in 32 patients. Urine was
collected for estimation of 24 h volume, sodium
and metanephrine concentrations. PRA was
determined by measuring the production of angio-
tensin I with radioimmunoassay, PA by using the
method of Fraser et al. [3], PC with radioimmuno-
assay, and DBH with the spectrophotometric
method of Nagatsue & Udenfriend [4]. We know
of no evidence that either ethanol or chlor-
methiazole interfere with the radioimmunoassay
of PRA, PA or PC. None of the patients received
any antihypertensive medications during the
study.

Statistical analysis was performed by using sub-
programs of the statistical package for Social
Sciences [5] on the ICL 1906A computer at the
University of Birmingham. Within-group com-
parisons were done by means of paired t-test.
Correlations were determined by using Pearson's
correlation test. Multiple linear regression analysis
with age as an independent variable was used to
determine the interrelationship of the various
clinical and biochemical measurements and their
changes with time. The study was approved by the
ethical committee of the hospital and informed
consent obtained from all patients.

Results
Forty-eight men and 17 women were studied.
During the study ten patients took their own
discharge from hospital; their results have been
excluded from the calculations of changes in
blood pressure and biochemical variables. Fifty
patients underwent liver biopsy; only nine (14%)
had histological evidence of cirrhosis, the most
common lesion being fatty change (Table 1). Men
were slightly older (mean 42 years) than women
(mean 37 years) and drank more alcohol, but
initial alcohol withdrawal scores were similar
(Table 1).

Systolic blood pressure was elevated (>140
mmHg) in 28 patients (43%) and diastolic blood
pressure (>90 mmHg) in 17 (26%). Thirty-two
patients (49%) had either an elevated systolic or
diastolic pressure. Blood pressure was 160/95
mmHg or more (W.H.O. criteria) in 21 patients
(32%). Fifty-seven patients (88%) had some
alcohol withdrawal symptoms (score >0) on the
first day and their blood pressures were signifi-
cantly higher than those with zero withdrawal
scores (t = 2.72, P<0.01 for systolic; r = 2.83,
P<0.05 for diastolic). At this time 41 patients
(63%) had elevated PRA, 13 (20%) had elevated
PC levels and 14 (22%) had elevated PA levels.
Urinary metanephrines were elevated in four of
31 patients who had these measured on admission.

A highly significant positive correlation was
found between both systolic and diastolic blood
pressures on admission and the severity of the
alcohol withdrawal symptoms (r = 0.001) (Table

**Table 1. Characteristics of 65 alcoholics and liver biopsy appearances**

Withdrawal score was coded on a clinical scale of 0-7. 20 g of alcohol = 1 pint of beer = 2 measures
(U.K.) of whisky

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Age (years)</th>
<th>Mean daily alcohol intake in previous 3 months (g)</th>
<th>Mean alcohol withdrawal score</th>
<th>Liver biopsy</th>
<th>No biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(range)</td>
<td></td>
<td></td>
<td>Normal</td>
<td>Fatty liver</td>
</tr>
<tr>
<td>Males</td>
<td>48</td>
<td>19-63</td>
<td>314</td>
<td>2.5</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Females</td>
<td>17</td>
<td>23-71</td>
<td>266</td>
<td>2.4</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>19-71</td>
<td>301</td>
<td>2.5</td>
<td>10</td>
<td>28</td>
</tr>
</tbody>
</table>
TABLE 2. Correlation matrix for blood pressure, withdrawal score and biochemical variables

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
<th>Plasma</th>
<th>24 h urinary volume</th>
<th>24 h urinary sodium output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td>0.30**</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood</td>
<td></td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td>-</td>
<td></td>
<td>-0.27*</td>
<td></td>
</tr>
<tr>
<td>Withdrawal score</td>
<td>0.46***</td>
<td>0.37***</td>
<td>0.42***</td>
<td>0.28*</td>
<td>0.42***</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01, ***P = 0.001.

2). No correlations were found between the various biochemical parameters measured and blood pressure except for a positive correlation between systolic but not diastolic pressure and PC concentration (P < 0.01). Diastolic blood pressure inversely correlated with urinary volume (P < 0.05). PC and PA levels and PRA were all positively correlated with the severity of the withdrawal symptoms (Table 2).

Blood pressures fell over the period of withdrawal and were significantly lower by day 4 (Table 3). On the fourth morning after admission blood pressure exceeded 140/90 mmHg in only eight patients (14%) and 160/95 mmHg in two (3%). Significant falls occurred in PRA and in PA, PC and DBH concentrations between day 1 and day 4 (Table 3). Packed cell volume was high normal on day 1 and showed a small but significant fall by day 4. Mean 24 h urine volume and sodium output, low on admission, had risen significantly by day 4 although urinary potassium excretion remained low (Table 3). Multiple linear regression analysis using age as an independent variable showed that the variation in age accounted for 5% (β = 0.21) and PC levels for 9% (β = 0.30) of the variability of systolic blood pressure on admission. Urine volume accounted for 7% (β = -0.27) of the variability of diastolic blood pressure on admission. None of the other biochemical variables significantly contributed to the blood pressure. No correlation was found between the changes in blood pressure and any of the other variables measured between admission and day 4.

Discussion

This study confirms our previous observation of a relationship between the alcohol withdrawal
least 36 h after the patient's last alcoholic drink and the height of the blood pressure was related to the severity of the withdrawal symptoms. Further, the blood pressure rose in those patients who developed evidence of withdrawal whilst being studied. In the five patients that were given alcohol to control their symptoms, blood pressures either remained unchanged or fell.

Studies in normal subjects [6] and in alcoholics [7] have reported increased PRA and PA levels during withdrawal from alcohol. These changes may be due to increased sympathetic nervous activity in response to the 'stress' of alcohol withdrawal. Alternatively, the raised PRA may result from dehydration after an ethanol-induced natriuresis [8, 9], though none of the patients became hypotensive. Further evidence for dehydration was the fall in packed cell volume during detoxification and the rise in the initial low 24 h urinary volume and sodium excretions. Beard & Knott [10], however, have reported isosmotic overhydration in chronic alcoholics during the early withdrawal period. Our results differ from that study as we found much lower initial 24 h urinary volume and sodium excretions.

The elevation of PC in alcoholics is well known, some patients even demonstrating an alcohol-induced Cushing's syndrome [11]. Stokes [12], however, has shown rising PC levels in chronic alcoholics during alcohol withdrawal, and these levels decreased after detoxification. Merry [13] has also shown that PC levels increase during withdrawal and this elevation is suppressed by alcohol. The increased levels may be due to stimulation of adrenocorticotrophic hormone production directly or by potentiation of corticotrophin-releasing factor by arginine vasopressin [14, 15]. Another possible mechanism for the raised PC level is impaired hepatic metabolism due to alcoholic liver damage [16]. All our patients were studied at least 36 h after their previous alcohol consumption and were withdrawing at the time of measurement so it is unlikely that the changes observed were due to a direct effect of ethanol. Ramsay [17] has postulated that the elevated cortisol levels may be a contributing factor in alcohol-associated hypertension. The exact mechanism by which cortisol may influence hypertension is unclear. It may be related to a mineralocorticoid effect, increased plasma renin substrate [18] or catecholamine hypersensitivity [19]. Although our results show a correlation between PC levels and blood pressure, this does not necessarily mean a direct causal relationship.

The symptoms of alcohol withdrawal, tremor, sweating, and tachycardia, might all be explained on the basis of increased peripheral [20] and central adrenergic activity [21] and increased catecholamine release [22, 23]. Serum DBH level was used as an indicator of sympathetic nervous activity but no relationship was found between it and blood pressure although urinary metanephrine excretion was elevated in four patients. Plasma and urinary catecholamines have been shown to be raised after acute alcohol ingestion [24] and during alcohol withdrawal [22]. Our findings of normal levels of DBH may reflect the poor relationship between DBH and sympathetic activity. Thus the hyperadrenergic state may account for not only the symptoms of alcohol withdrawal but also the associated hypertension.

During alcohol withdrawal there are complex changes in the renin aldosterone axis and also in adrenal cortical and medullary function. There are thus several possible pressor mechanisms present, and our data suggest a possible role of cortisrol or catecholamine-mediated hypertension rather than that involving the renin aldosterone system. One possible mechanism for the relationship between alcohol intake and blood pressure seen in patients with ischaemic heart disease [25] and hypertension [26] as well as in population studies [27] is that the association reflects bouts of alcohol withdrawal. In clinical practice, blood pressure is most likely to be measured when patients are not acutely intoxicated and therefore are in a state of sub-clinical withdrawal. Alternatively, the raised blood pressure in alcoholics may have a different origin from that seen in epidemiological studies.

References
Blood pressure and alcohol withdrawal


