Sex-related differences in the haematological effects of excessive alcohol consumption

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SUMMARY Mean corpuscular volume (MCV) was measured at presentation in 320 hospital patients with a history of excessive alcohol consumption. The MCV of the 94 women thought to be actively drinking more than 80 g/day of alcohol was 101.3 fl compared with 96.7 fl in their male counterparts. Alcohol consumption, age, smoking habits, prevalence of inadequate diet, or serum and red cell folate levels did not differ significantly between men and women. It is suggested that MCV is a better indicator of excessive alcohol consumption in women than in men, and that women are more susceptible to the haematological toxicity of alcohol.

There is increasing evidence to support the clinical impression that women are more susceptible than men to a variety of alcohol-related diseases (Lancet, 1977; Ashley et al., 1977). Several studies have concluded that women appear to develop cirrhosis with or without alcoholic hepatitis after a shorter period of excessive alcohol consumption (Spain, 1945; Wilkinson et al., 1969; Pequignot et al., 1974; Levi and Chalmers, 1978), and Morgan and Sherlock (1977) and Krasner et al. (1977) have found a significantly higher prevalence of severe alcoholic liver disease among their female patients.

The widespread use of electronic cell counters in haematology has confirmed that an increase in mean corpuscular volume (MCV) is frequently found in hospital patients with known excessive alcohol consumption (Wu et al., 1974, 1975; Buffet, 1976; Morin and Porte, 1976; Davidson and Hamilton, 1978). A previous report from this hospital (Wu et al., 1975) was the first to point out that women who drink heavily tend to have higher MCVs than their male counterparts. This might be because women are more susceptible to the haematological toxicity of alcohol, or, alternatively, it could be due to differences in such factors as alcohol consumption or the pattern of drinking between the two sexes. We have therefore attempted to answer some of these questions by studying sex-related differences in a larger group of patients.

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transpeptidase (GGTP) was measured in 250 patients by the method of Rosalki et al. (1970). Percutaneous liver biopsy was performed in 210 patients with clinical or biochemical evidence of liver disease, and further details of the mode of presentation and histological findings have been described elsewhere (Levi and Chalmers, 1978).

To obtain comparative values for MCV we also prospectively studied 88 new patients referred to a gastroenterology outpatient clinic (44 men and 44 women), whose average alcohol intake was assessed as being less than 20 g daily. None of these patients was subsequently diagnosed as having any haematological disorder, gastrointestinal bleeding, or malabsorption.

These studies were approved by the hospital Ethical Committee, and the data were analysed using $2 \times 2 \chi^2$ or t tests. As the values for GGTP showed a log normal distribution logarithmic conversion was performed before statistical calculations.

**Results**

Of the 320 patients with high alcohol consumption, 218 were men and 102 women, giving a sex ratio of 2:14:1. Mean corpuscular volumes at presentation of the 301 patients thought to be actively drinking (defined as those drinking regularly until at least two weeks before presentation) are shown in Fig. 1, together with the results from 88 gastroenterology outpatients drinking less than 20 g/day. The mean MCV of the women 'drinkers' (101·3 fl, standard deviation 8·0 fl) was significantly higher than in the men (96·7 ± 7·2 fl, p < 0·001), and both high alcohol consumption groups had higher MCVs than the gastroenterology outpatients (p < 0·001). In the latter group, there was no significant difference between the MCV of the women (86·4 ± 3·2 fl) and of the men (86·0 ± 3·1 fl).

Thus 94% of the women actively drinking more than 80 g/day had MCVs above the upper limit of the reference range (80-92 fl) compared with only 71% of the men. The remaining 19 patients (11 men and 8 women) with a past history of excessive drinking or currently drinking less than 80 g/day had a mean MCV of 87·7 fl (women 85·7 fl, men 89·1).

To determine if the sex difference in MCV in those who were actively drinking could be explained in terms of differences in alcohol consumption, type of beverage, smoking habit, diet, or age, the data were analysed as shown in Table 1. This shows that there was no statistically significant difference in age, prevalence of inadequate diet, or smoking habit between the two groups. Although the men tended to drink larger quantities of alcohol there was no

**Table 1** Comparison of 207 men and 94 women actively drinking more than 80 g/day of alcohol

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>50·5 ± 12·5</td>
<td>52·1 ± 12·8</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage with inadequate diet*</td>
<td>21·8</td>
<td>29·4</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking habit:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular smokers (%)</td>
<td>78·5</td>
<td>87·5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of cigarettes/day ± SD</td>
<td>18·1 ± 17·8</td>
<td>16·5 ± 13·2</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage of wine/spirit drinkers*</td>
<td>58·0</td>
<td>88·3</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Mean duration of excessive alcohol consumption (years)</td>
<td>15·9 ± 9·0</td>
<td>8·6 ± 6·0</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Mean present alcohol consumption† (g/day ± SD) (number)</td>
<td>159·1 ± 64·2 (182)</td>
<td>141·8 ± 55·7 (70)</td>
<td>&lt;0·05</td>
</tr>
<tr>
<td>(g/kg/day ± SD) (number)</td>
<td>2·2 ± 1·0 (120)</td>
<td>2·49 ± 1·3 (43)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not statistically significant.
*For definitions see text.
†Where sufficiently accurate information was available.
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Table 2  Laboratory investigations at presentation of patients actively drinking more than 80 g/day of alcohol

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.  ±SD</td>
<td>No.  ±SD</td>
</tr>
<tr>
<td>Mean haemoglobin (g/dl)†</td>
<td>204 14±8 1±74</td>
<td>91  13±5 1±85</td>
</tr>
<tr>
<td>Mean serum folate (ng/ml) (reference range 2-15)</td>
<td>169 7±13 4±9</td>
<td>80  6±05 4±7  NS</td>
</tr>
<tr>
<td>Mean red cell folate (ng/ml) (reference range 145-450)</td>
<td>146 300±6 165±6</td>
<td>75  267±0 174±0  NS</td>
</tr>
<tr>
<td>Mean serum B12 (pg/ml) (reference range 170-1000)</td>
<td>167 47±5 357±0</td>
<td>80  48±4 286±3  NS</td>
</tr>
<tr>
<td>Bone marrow % megaloblastic</td>
<td>87 28±7</td>
<td>51  37±3  NS</td>
</tr>
<tr>
<td>GGTP (IU/l) (reference range 0-50)</td>
<td>170 193±8 227±7</td>
<td>75  231±8 259±3  NS*</td>
</tr>
<tr>
<td>Liver histology % with cirrhosis ± alcoholic hepatitis</td>
<td>147 20±4</td>
<td>63  25±4  NS</td>
</tr>
</tbody>
</table>

NS = not statistically significant.
*After logarithmic conversion.
†Excluding six patients (3 men and 3 women) presenting with acute gastrointestinal bleeding.

A significant sex difference in consumption when this was calculated on a body weight basis. The most striking differences were that the women had a much shorter duration of excessive alcohol consumption, and the majority drank table wine, fortified wine, vermouth, or spirits rather than beer or cider.

The results of the other laboratory investigations are summarised in Table 2. Most of the patients were not anaemic, and, after excluding six patients with acute gastrointestinal bleed, only four (4%) women and seven (3%) men had haemoglobin concentrations below 10 g/dl. The women tended to have lower serum and red cell folate levels, but this was not statistically significant, and the majority of the values fell within the normal range. One-third of the sternal marrow aspirates showed megaloblastic erythropoiesis, and although proportionately more women had megaloblastic changes this was not statistically significant. This also the case with the increased prevalence of cirrhosis and higher GGTP values in the women.

The prevalence of folate deficiency in our patients and its relationship to MCV can be obtained from Figure 2. This shows that out of 221 patients whose red cell folate was measured, only 12.3% of the men and 20% of the women had low red cell folate values (serum B12 levels were normal in all these patients). The folate deficient patients had higher mean MCVs, but the majority of non-folate deficient patients were also macrocytic, and there was considerable overlap between the groups. Megaloblastic changes were present in some patients in both the folate deficient and non-folate deficient categories.

As most of the women drank wine and spirits which contain very little folic acid, it was possible that this might prove the explanation of their greater prevalence of macrocytosis. However, Table 3 shows that although wine/spirit drinkers had higher MCVs than beer/cider drinkers, the women wine and spirit drinkers had significantly higher MCVs than their male counterparts. The lower MCV of the beer/cider drinkers might have been a result of the higher folate levels, but this group also consumed significantly smaller amounts of alcohol.

Discussion

An electronic cell counter provides a very accurate and reproducible measure of red cell size. Values of MCV for normal men and women are very similar, and, if anything, women have slightly smaller cells (Kelly and Munan, 1977). Our results show that
women presenting to one district general hospital because of alcohol-related problems tended to have higher MCVs than men with equivalent alcohol intakes. In contrast to the drinking groups, outpatients from the same gastroenterology clinic with low alcohol consumption showed no significant sex-related differences in MCV, and nearly all the results fell within the reference range.

MCV has been shown to increase slightly with age (Kelly and Munan, 1977) and cigarette smoking (Helman and Rubenstein, 1975), but there was no significant difference in these factors between the men and women drinkers. As it is difficult to obtain accurate drinking histories from alcoholic patients, it is possible that the women might have underestimated their alcohol consumption to a greater extent than the men. However, some corroboration of alcohol intake was obtained from friends or relatives whenever possible, and we think it unlikely that consumption in the women was significantly higher.

In view of the difficulty of recognising excessive alcohol consumption in women it could be argued that we failed to identify women drinkers who were not macrocytic. We felt that this was unlikely to be the case as the sex ratio (M/F) was only 2:1:1, which is very similar to recent series of patients with alcoholic liver disease (Morgan and Sherlock, 1977; Krasner et al., 1977) that did not use macrocytosis as an aid to diagnosis. In addition, the sex difference in MCV was also seen in psychiatric patients with alcoholism who did not usually have blood counts performed before referral. We feel that the most likely explanation for our results is that women are more susceptible to the haematological toxicity of excessive alcohol consumption.

The mechanism of these changes remains unclear. Folate deficiency was found in less than 20% of our patients, and the sex difference in MCV was also found in the non-folate deficient groups. Although our dietary assessments were crude, we are in little doubt that macrocytosis can occur in patients who appear to be taking an adequate diet, and this seems to be due to some direct toxic effect of alcohol on the developing erythroblast. The macrocytosis did not appear to be clearly related to the presence or absence of cirrhosis, and we have found that MCV tends to fall in patients with alcoholic cirrhosis after alcohol withdrawal.

There is relatively little information about possible sex differences in human alcohol metabolism as most studies have been performed on men. However, Reed et al. (1976) found no difference in the calculated rates of alcohol metabolism in normal Caucasian men and women, and mean acetaldehyde concentrations were similar in both sexes. A partial explanation for the susceptibility of women might lie in differences in the volume of distribution of alcohol. Alcohol is distributed in tissues in proportion to their water content, and total body water as a percentage of body weight has been found to be approximately 10% higher in males (Delwaide and Crenier, 1973). As a result, peak alcohol levels after the same body-weight-adjusted dose tend to be higher in women than in men (Jenkins and Connolly, 1968; Jones and Jones, 1976). It is also of interest that this effect varies at different phases of the menstrual cycle (Jones and Jones, 1976).

Whatever the underlying mechanism, the practical importance of our findings is that a rise in MCV is a better indicator of excessive alcohol consumption in female hospital patients. This makes the MCV particularly useful in detection as these patients are often most reluctant to admit to excessive alcohol consumption (Levi and Chalmers, 1978). Finally, it is our experience that a woman whose MCV is well within the reference range is unlikely to be actively drinking large quantities of alcohol.

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