SEX HORMONES DURING ALCOHOL WITHDRAWAL:
A LONGITUDINAL STUDY OF 29 MALE ALCOHOLICS
DURING DETOXIFICATION

JAAN RUUSA, BO BERGMAN* and MONA-LISA SUNDELL

Department of Clinical Neuroscience and Family Medicine, Psychiatry Section, Karolinska Institute, Huddinge Hospital, Huddinge, Sweden

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Abstract — It is a well-known fact that alcohol affects sex hormone levels in males. Even in the absence of liver dysfunction, there is still a direct toxic effect of ethanol on testosterone synthesis resulting in acutely decreased values. This study is based on 29 male alcoholics without severe signs of liver disease treated on the alcohol detoxification ward at Huddinge hospital in Stockholm, Sweden during 1995. The aim was to study levels of sex hormones in male alcoholics during detoxification with benzodiazepines and after 3 weeks of sobriety. Blood samples were taken three times: one day after admission (day 2) when the patient was sober, at discharge (day 5) and after 3 weeks of sobriety (day 21). Levels of testosterone and sex hormone-binding globulin (SHBG) showed the same pattern during detoxification and follow-up. They were both low, but generally within normal limits, on days 2 and 5, but raised after 3 weeks of sobriety. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) were initially high, but were substantially depressed during detoxification. Levels of FSH recovered after 3 weeks, whereas LH remained at the same level. Most patients exhibited generally low levels of both FSH and LH, however. Levels of oestrone decreased steadily. There were no correlations between levels of sex hormones and the number of milligrams of oxazepam administered to the patients during detoxification either at admission, at discharge or at follow-up. In summary, the endocrinological response to alcohol intake is complex. This study suggests that the duration of endocrinological recovery after drinking is a quite long-lasting process, that different hormones need different times to recover and that the normal glandular-pituitary feed-back processes may be partly put out of order.

INTRODUCTION

It is a well-known fact that alcohol affects sex hormone levels in males. Alcoholic males with chronic liver disease or cirrhosis have been reported to have a decreased testosterone concentration and an increased level of luteinizing hormone (LH) (Galvao-Teles et al., 1973; Välimäki et al., 1982; Kley and Teschke, 1985). However, Lindholm et al. (1978a) and Bahnsen et al. (1981) found no correlation between liver condition and testosterone levels, and the latter authors noticed only an increased LH concentration. There are even observations of patients with moderately affected liver function exhibiting raised serum concentrations of testosterone and LH compared to healthy controls (Gluud et al., 1983). Although sex hormone-binding globulin (SHBG) and testosterone generally are positively related (Myking et al., 1987; Bergman and Brismar, 1994; Ruusa and Bergman, 1996), there are studies in which negative correlations have been found (Galvao-Teles et al., 1973; Gluud et al., 1987). Other researchers have reported raised SHBG and more or less unaffected serum testosterone levels in male alcoholics (Lindholm et al., 1978b; Bahnsen et al., 1981; Myking et al., 1987). Altogether, these studies illustrate the complexity of the relationship between sex hormones produced in endocrine glands and the influence of the liver in situations where alcohol is involved.

Even in cases where the liver seems not to be affected, there is still a direct toxic effect of ethanol on testosterone synthesis resulting in acutely decreased values. Thus, testosterone is decreased among healthy male non-alcoholics during alcohol intoxication (Mendelson et al., 1983). With testosterone levels falling, the negative feedback mechanism on the pituitary gland is weakened and LH release is increased.
1977). Daily alcohol consumption for a period of 25 days by healthy males results in a reduction of testosterone plasma levels and androgen production (Gordon et al., 1976). Ylikahri et al. (1974) reported an acute effect on testosterone levels in healthy subjects, with a maximum decrease 10–20 h after ethanol intake. Välimäki et al. (1984) reported an increase in testosterone concentration 1 week after alcohol withdrawal among non-cirrhotic alcoholics. Heinz et al. (1995) found diverging testosterone levels (increased and decreased), although within normal limits, after 3 weeks of abstinence. These latter two studies indicate a great recovery potential with regard to sex hormone production.

Low testosterone levels may even be related to symptomatology during alcohol withdrawal. Thus healthy non-alcoholic males with low levels of testosterone reported more severe hangover symptoms (Ylikahri et al., 1974) and alcoholics with low levels of testosterone exhibited more pronounced neurasthenic symptoms than those with a good supply of testosterone (Ruusa and Bergman, 1996).

The aim of this investigation was to study levels of sex hormones in male alcoholics during detoxification with benzodiazepines and after 3 weeks of sobriety.

**MATERIALS AND METHODS**

This study included 29 male alcoholics aged 29–61 years treated on the alcohol detoxification ward at Huddinge hospital in southern Stockholm, Sweden, during 1995. The mean age of the patients was 45 years (SD 10.7). Twenty-five were Swedes and four were Finns. The patients constituted ~6% of all detoxifications carried out on that ward in 1995. They were not randomly selected, as patients with known liver damage or disease, like hepatitis or cirrhosis, or other serious somatic or psychiatric illness, were excluded. Further, patients with a history of use/abuse of benzodiazepines, cannabis or other drugs were also excluded. The patients went through a comprehensive, systematic physical examination and those exhibiting signs of liver disease were excluded. Blood samples were taken on three occasions: day 2 (i.e. 1 day after being admitted), day 5 (the day of discharge) and day 21 (after 3 weeks of sobriety). The taking of the third blood test was contingent on the patient managing to stay absolutely sober after discharge. The nursing staff on the ward in question had a great deal of knowledge about the patients, many of whom were very frequent ‘visitors’ to the ward, and based on their judgement quite a lot of patients were excluded as it was deemed unlikely that they would be able to stay sober for 3 weeks after discharge. Thus, there was a positive selection of patients; the two major criteria for being included were the absence of any serious illness, especially diseases of the liver, and being able to stay sober at least 3 weeks after discharge. Due to these criteria our group of patients may be regarded as being more psychosocially stable than the general patient population, e.g. a greater proportion were married and employed. The patients stated that the mean amount of liquor consumed during the week prior to admittance was 621 cl of 40% vodka or similar spirits (range 74–1260 cl) corresponding to ~2070 g of pure ethanol (range 247–4200 g of pure ethanol).

The detoxification followed a 5-day routine which was the same for all patients. Depending on the status of the patient, a ‘large’ or a ‘small’ oxazepam schedule was prescribed by the doctor; in the former cases the patient received 315 mg of oxazepam and in the latter 165 mg of oxazepam during these 5 days. Some patients needed extra oxazepam and those with a history of seizures were also prescribed carbamazepine, usually 200 mg × 3 during hospitalization.

The aim of the study was to establish levels of sex hormones on repeated occasions. Thus, blood samples were taken and some other tests were performed three times: 1 day after admission (hereafter called day 2) when the patient was sober and at the culmination of abstinence, then at discharge (day 5) and finally after 3 weeks of sobriety (day 21). The first two blood tests and examinations were performed during inpatient care, whereas the third was during an outpatient visit. The blood tests were carried out between 12:00 and 14:00. Levels of the following hormones were established on day 2, day 5 and day 21: testosterone, SHBG, oestrone, follicle stimulating hormone (FSH) and LH. The above procedure was adopted concerning pulse rate, diastolic and systolic blood pressure and body temperature. All blood tests and measurements were performed by the third author of this paper.
Table 1. Serum levels (μkat/l) of ALAT, ASAT, GGT and bilirubin among male alcoholics at admittance for inpatient detoxification

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>Normal value</th>
<th>No. of patients within/above normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-ALAT</td>
<td>1.2</td>
<td>0.9</td>
<td>0.3–4.4</td>
<td>&lt;0.80</td>
<td>10/19</td>
</tr>
<tr>
<td>S-ASAT</td>
<td>1.3</td>
<td>1.1</td>
<td>0.4–5.0</td>
<td>&lt;0.80</td>
<td>11/18</td>
</tr>
<tr>
<td>S-GGT</td>
<td>6.1</td>
<td>12.2</td>
<td>0.3–59.6</td>
<td>&lt;1.30</td>
<td>10/19</td>
</tr>
<tr>
<td>S-Bilirubin</td>
<td>17.7</td>
<td>10.1</td>
<td>5.0–46.0</td>
<td>&lt;26.0</td>
<td>26/3</td>
</tr>
</tbody>
</table>

S-ALAT, serum alanine aminotransferase; S-ASAT, serum aspartate aminotransferase; S-GGT, serum γ-glutamyltransferase.

(M.L.S.), who also kept in touch with the patients after discharge to ensure that they had not started drinking.

A few patients were not able to remain sober while waiting for the third tests. In such cases the patients were either excluded or were given a second chance later on to prove that they had achieved 3 weeks of sobriety, e.g. by visiting an outpatient alcohol clinic. Virtually all patients drank in a typically 'Scandinavian way', i.e. 'all or nothing'. Thus, when starting to drink they were not able to stop and their chances of concealing such an episode from the nursing staff were extremely limited. Thus, we are almost 100% certain that all our patients had a 3-week period of sobriety at day 21.

With two exceptions, the effect on the liver was moderate (Table 1). Thus, approximately two-thirds of the patients exhibited moderately elevated serum levels of liver enzymes (alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase). Two patients had extremely high values of serum γ-glutamyltransferase (33.4 and 59.6 μmol/l) and two patients had high levels of serum bilirubin (41.0 and 46.0 μkat/l). If these patients were excluded from the analysis in Table 1 the mean values decreased to 3.1 μmol/l (GGT) and 15.8 μkat/l (bilirubin) respectively.

Assay methods

Serum concentrations of testosterone were determined by direct radioimmunoassay using a commercial kit (Coat-a-Count) obtained from Diagnostic Products Corp., Los Angeles, CA, USA. Serum oestrone was determined after extraction with diethyl ether and in-house radioimmunoassay developed at the Hormone Laboratory, Department of Obstetrics and Gynaecology, Huddinge University Hospital. The method uses anti-oestrone-6-O(carboxymethyl)imine–ovalbumin (BioClin Ltd, Cardiff, UK), tritiated E1 tracer and dextran-coated charcoal separation. FSH and LH were determined by chemiluminescence enzyme immunoassay using commercial kits (Immulite) obtained from Diagnostic Products Corp., Los Angeles, CA, USA. SHBG was determined by time-resolved fluorescence immunoassay using a commercial kit (Auto-Delfia) obtained from Wallac OY, Turku, Finland. Detection limits and within- and between-assay coefficients of variation were for testosterone 0.1 nmol/l, 6 and 10%; for oestrone 30 pmol/l, 7 and 10%; for FSH 0.1 U/l, 6 and 8%; for LH 0.7 U/l, 6 and 10%, and for SHBG 0.5 nmol/l, 5 and 3% respectively.

Statistics

Paired t-test (two-tailed) and Pearson’s product-moment correlation coefficient have been used according to the SPSS for windows software (Norusis, 1993).

RESULTS

In Table 2, mean values of sex hormones, ranges, SDs and the numbers of patients with values below or above the normal ranges are presented at day 2, day 5 and day 21. The majority of the patients exhibited values within normal limits concerning testosterone, SHBG and oestrone, although the ranges were large. Levels of LH and FSH were generally low, with ~30–80% of the patients exhibiting values below normal limits.
Table 2. Hormone levels during inpatient detoxification and follow-up for 29 male alcoholics

<table>
<thead>
<tr>
<th>Hormone/day</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>No. of patients with values below/above normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-testost/2</td>
<td>16.4</td>
<td>5.5</td>
<td>2.4–32</td>
<td>2/-*</td>
</tr>
<tr>
<td>S-testost/5</td>
<td>16.3</td>
<td>6.4</td>
<td>5.0–29</td>
<td>5/-*</td>
</tr>
<tr>
<td>S-testost/21</td>
<td>18.2</td>
<td>6.1</td>
<td>7.6–35</td>
<td>1/-*</td>
</tr>
<tr>
<td>S-SHBG/2^a</td>
<td>37.7</td>
<td>18.0</td>
<td>8.0–88</td>
<td>3/2</td>
</tr>
<tr>
<td>S-SHBG/5</td>
<td>37.1</td>
<td>16.2</td>
<td>13.0–80</td>
<td>0/2</td>
</tr>
<tr>
<td>S-SHBG/21</td>
<td>44.8</td>
<td>23.1</td>
<td>16.0–98</td>
<td>0/3</td>
</tr>
<tr>
<td>S-LH/2^a</td>
<td>4.4</td>
<td>2.7</td>
<td>0.80–12</td>
<td>9/2</td>
</tr>
<tr>
<td>S-LH/5</td>
<td>2.6</td>
<td>1.6</td>
<td>0.70–6</td>
<td>16/0</td>
</tr>
<tr>
<td>S-LH/21</td>
<td>3.0</td>
<td>1.5</td>
<td>0.70–7</td>
<td>9/0</td>
</tr>
<tr>
<td>S-FSH/2^b</td>
<td>4.3</td>
<td>3.1</td>
<td>1.0–13</td>
<td>19/0</td>
</tr>
<tr>
<td>S-FSH/5</td>
<td>3.4</td>
<td>2.6</td>
<td>0.70–12</td>
<td>23/0</td>
</tr>
<tr>
<td>S-FSH/21</td>
<td>4.5</td>
<td>3.1</td>
<td>1.0–13</td>
<td>19/0</td>
</tr>
<tr>
<td>S-oestrone/2</td>
<td>268</td>
<td>130</td>
<td>97–640</td>
<td>1/8</td>
</tr>
<tr>
<td>S-oestrone/5</td>
<td>235</td>
<td>74</td>
<td>93–382</td>
<td>1/2</td>
</tr>
<tr>
<td>S-oestrone/21</td>
<td>199</td>
<td>96</td>
<td>115–584</td>
<td>0/1</td>
</tr>
</tbody>
</table>

The figure following the hormone, e.g. FSH/2, corresponds to day 2, FSH/5 to day 5 and FSH/21 to day 21 after admission.

^a Normal value: 20–50 years > 9.9 nmol/l; > 50 years: > 7.9 nmol/l.
^b Normal value: 20–50 years: 15–56 nmol/l; > 50 years: 19–76 nmol/l.
^c Normal value: 20–54 years: 3–9 IU/l; > 50 years: 3–13 IU/l.
^e Normal value: 20–29 years: 150–400 pmol/l; > 29 years: 75–325 pmol/l.
* There is no upper limit.

Levels of testosterone and SHBG showed the same pattern during detoxification and at follow-up. They were both low at days 2 and 5 and raised after 3 weeks of sobriety. Mean testosterone levels increased from 16.3 to 18.2 nmol/l (not significant), whereas SHBG increased from 37.7 to 44.8 nmol/l ($t = -2.61, P = 0.015$) (Table 2). There was a positive correlation between levels of testosterone and SHBG when compared at days 2, 5 and 21 ($r = 0.64, P = 0.000; r = 0.55, P = 0.002; r = 0.38, P = 0.041$ respectively). Levels of FSH and LH were initially high (4.3 and 4.4 IU/l respectively), but were subsequently depressed to 3.4 and 2.6 IU/l during detoxification ($t = 4.9, P = 0.000; t = 4.1, P = 0.000$). Levels of FSH recovered (4.5; $t = -4.1, P = 0.000$) after 3 weeks, whereas LH remained at the same level (Table 2). However, after 3 weeks of sobriety, 19 of the 29 patients still exhibited levels of FSH below normal limits (the same was true for LH concerning nine of the patients). Levels of oestrone decreased steadily. The decrease started during the days in hospital (268–236 pmol/l; $t = 4.9, P = 0.000$) and ended at 199 on day 21 ($t = 3.1, P = 0.005$ from day 2 to day 21) (Table 2). There were no correlations between levels of sex hormones and the number of milligrams of oxazepam administered to the patients during detoxification either at admission, at discharge or at follow-up on day 21.

The physiological parameters are presented in Table 3. Blood pressure and pulse rate normalized during detoxification and were the same on day 5 as day 21. Body temperature was normal throughout the whole observation period. There were two significant correlations between physiological parameters and hormone levels. Both were observed on day 5. The first one was between systolic blood pressure and LH ($r = 0.43; P < 0.05$) and the second between oestrone and body temperature ($r = 0.46; P < 0.05$).

### DISCUSSION

This is a longitudinal study of sex hormone levels in 29 alcoholics during inpatient detoxification with benzodiazepines. In order to minimize the influence of any liver dysfunction on hormone levels, we did not select the patients randomly. Thus, patients in poor general condition were not included and the same was true for those exhibiting signs of serious liver disease, like cirrhosis. Further, blood liver enzyme results were, with a few exceptions, at levels usually seen among patients admitted for inpatient detoxification.
ification. This procedure does not guarantee the absence of serious liver dysfunction, and a liver biopsy, which was not possible for practical reasons, would have been a useful complement. A second selection was made mainly by the staff and the purpose was to include patients capable of staying sober for the duration of the study, i.e. 3 weeks. No systematic procedure was followed for this selection, which was based on previous knowledge of the patients. Taking these two selection procedures together, it is reasonable to assume that the patients included in the study were on average psychosocially more stable and healthier than the average alcoholic patient. This raises the question of whether our results are representative for alcoholics in general. It is possible that a study based on randomly selected material would have yielded different findings. However, one should bear in mind that the threshold for being admitted is quite high and that all cases of inpatient detoxification are warranted by strict medical reasons. The vast majority of detoxifications are performed at outpatient clinics. Thus, the patients included in the study were all seriously alcohol-dependent and deemed incapable of being detoxified on an outpatient basis.

During the 5 days of hospitalization, the mean testosterone levels were the same at day 2 and day 5 and showed a modest increase after 3 weeks of sobriety. Most values were within normal limits, however. Although not identical, our results do not necessarily contradict those reported by Välimäki et al. (1984), who found an increase in testosterone after 2 weeks of sobriety. Their study was also based on non-cirrhotic male alcoholics. In a recent study of alcoholics in India, reduced testosterone levels were found after up to 20 days of sobriety (Sudha et al., 1995). One may speculate as to whether the weak increase noted in our study after 3 weeks only reflects the start of a recovery process.

As we have not been able to find any published information on testosterone levels during detoxification with benzodiazepines, this raises the question as to whether the intake of oxazepam affected these levels. The present study did not include any group without oxazepam, so very little can be concluded regarding the possible effects of oxazepam on hormone levels. However, there was no correlation between levels of testosterone and the amount of benzodiazepines the patients had received. Further, despite the daily reduction of oxazepam dosage, the levels of testosterone were stable during detoxification and did not show any signs of increase during the days in hospital. The effects of oxazepam, as used in this study, of modifying the withdrawal syndrome and perhaps attenuating the testosterone levels, should not be ignored. A direct toxic suppressing effect of ethanol on testosterone synthesis has been reported by several authors. Perfusion with ethanol in vitro of isolated rat testes resulted in decreased testosterone production (Cobb et al., 1978) and experiments in vivo on rats gave the same result (Orpana et al., 1990). On a biochemical level, there are reports of ethanol and acetaldehyde inhibition of the conversion of androstendione to testosterone by decreasing the activity of 17-β-hydroxysteroid oxidoreductase (Cicero and Bell, 1980). Our results do not conflict with these findings of a direct toxic suppressing effect by ethanol on testosterone, although the benzodiazepine administration, which may be a confounding factor, limits the possibility of drawing any conclusions in this regard.

SHBG concentration was found to be positively correlated with testosterone levels, the correlation being less pronounced on day 21, however. SHBG, in contrast to testosterone, increased significantly from day 5 to day 21. One possible interpretation is that SHBG recovers faster than testosterone after a period of drinking. The positive correlation between testosterone and SHBG was an expected finding among men with more or less unaffected liver function, as opposed to patients with fatty liver (Myking et al., 1987). In a study by Lindholm et al. (1978b), there was a connection between severely reduced spermatogenesis and high levels of SHBG. These latter authors, however, found no difference in SHBG concentration when cirrhotic and non-cirrhotic patients were compared.

FSH showed the most marked V-shaped curve, thus decreasing and then recovering to values noted at admission. FSH does not activate the testicular production of testosterone, but is responsible for spermatogenesis via the Sertoli cells. Gluud et al. (1983) reported raised FSH values in patients with liver cirrhosis. If the feedback process via the pituitary gland operates normally, our findings indicate that spermatogen-
eresis decreases during detoxification but recovers fully after 3 weeks of sobriety. Although the FSH concentrations recovered to values noted at admission, the vast majority of the patients still exhibited values below normal limits. This may indicate that the recovery process is prolonged and that it should be studied over an even longer time-period.

In our study, the LH levels decreased from day 2 to day 5 during detoxification. A decrease in LH has been reported after alcohol administration to rats (Cicero et al., 1978, 1979) and in male alcoholics during withdrawal when compared to non-alcoholics (Huttunen et al., 1976). Heinz et al. (1995) also reported decreased LH levels in alcoholics after 3 weeks of sobriety. However, the LH levels were still significantly higher than in healthy control subjects, which is in contrast to the findings in the present study in which the majority of the patients exhibited levels of LH below normal limits at day 5 and one-third at day 21. As testosterone levels are depressed after drinking, and LH, via the pituitary gland, stimulates the production of testosterone in Leydig cells, low levels of testosterone should activate LH production to increase testosterone. However, one may speculate as to whether the function or speed of this normal feed-back process is put out of order due to the direct toxic effect of long-term intake of ethanol, as discussed above. This hypothesis is supported by the fact that, among healthy subjects, no acute effect on levels of serum LH after alcohol administration has been observed (Ylikhari et al., 1974). With regard to both FSH and LH, one may speculate as to whether there is a deficit in the interaction between the hypothalamic and pituitary glands which may contribute to our findings.

Oestrone levels were initially high, but decreased during the 3-week observation period. One possible explanation is that there is an increased peripheral circulation in tissue where oestrone is produced after alcohol intake. Thus, after a period of sobriety, when peripheral circulation is improved, oestrone levels increase. Although liver function was moderately affected in our study, one cannot rule out completely the fact that the decrease of oestrone levels paralleled an improvement in liver function (Fredriksson and Pousette, 1994).

The physiological manifestations of abstinence were quite mild, which probably can be explained by the administration of benzodiazepines. The two, rather weak, significant correlations between levels of hormones and physiological measurements were probably coincidental. At discharge, all patients were in an acceptable physiological condition and considered to be able to continue treatment at an outpatient alcohol clinic.

In summary, the endocrinological response to alcohol intake is complex. This study suggests that the duration of endocrinological recovery after drinking is a quite long-lasting process, that different hormones need different periods of time to recover and that the normal glandular–pituitary feed-back processes may be partly put out of order.

REFERENCES


