LOW-MOLECULAR-WEIGHT METABOLITES RELEVANT TO ETHANOL METABOLISM: CORRELATION WITH ALCOHOL WITHDRAWAL SEVERITY AND UTILITY FOR IDENTIFICATION OF ALCOHOLICS

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Abstract — The blood levels of ethanol, acetaldehyde, acetate, methanol, acetone, lactate, pyruvate, and glucose were measured in 23 male alcohol-dependent patients on days 2 to 6 after hospitalization and in 22 healthy male blood donors. Correlations between the biochemical parameters and 17 symptoms of the alcohol-withdrawal syndrome (AWS) were calculated. Abnormally high levels of ethanol, methanol, acetate, and acetone as well as hypoglycaemia were found on day 2, but lactacidaemia and pyruvataemia were pronounced throughout the observation period. AWS severity correlated positively with the acetone content on day 2 and with the acetate content on days 2 to 6. Negative correlations were found between ethanol levels and craving for alcohol, methanol levels and craving for alcohol, and between psychopathologic disorders and the total AWS severity score. The results suggest that concentrations of blood ethanol, methanol, acetate, and acetone exceeding their normal endogenous levels can be used only as indicators of recent heavy drinking. Linear discriminant analysis using the levels of the nine parameters studied enabled the correct classification of 91% to 96% of alcoholic patients during 1 week of abstinence and 100% of control subjects. The most informative parameters in the discrimination between alcoholics and controls were lactate, pyruvate, the lactate/pyruvate ratio, acetate, and acetone.

INTRODUCTION

Some low-molecular-weight substances, such as acetaldehyde, methanol, acetone, acetate, lactate, and pyruvate are closely related to ethanol metabolism and have specific features in heavy drinkers. Abnormally high levels of acetate (Nuutinen et al., 1985), methanol (Jones, 1986; Bonte and Sprung, 1987; Gilg et al., 1987) acetone and isopropanol (Iffland et al., 1988, 1994) were found in alcoholics during drinking periods and it was suggested that they be used as biochemical markers of heavy drinking. However, little and contradictory information is available on these metabolites in alcoholic patients during periods of abstinence.

High levels of acetaldehyde and methanol metabolites were found to persist in the blood of alcoholics for several days after the cessation of drinking (Magrinat et al., 1973). These authors speculated that the metabolites may be the primary factor in the severity of withdrawal. More recent studies, however, have demonstrated concentrations of blood acetaldehyde being within the low micromolar range in alcoholics during withdrawal (Peterson and Polizzi, 1987; Helander et al., 1993).

Alcohol-associated ketoacidosis has been described in alcoholic patients as a complication during alcohol withdrawal. However, the information on its frequency is controversial (Williams, 1984; Wrenn et al., 1991). Acetone concentrations in the breath are also higher in alcoholics abstaining from alcohol, compared to healthy subjects (Phillips et al., 1989).

Several blood tests have been used as composite indices in the detection of heavy drinking and alcoholism and, supplemented by discriminant function analysis as a classification procedure, have produced promising results (Eckhardt et al., 1984; Cowan et al., 1985; Morvai et al., 1989). Of
the parameters measured, only lactate, pyruvate, and glucose were included in the test batteries used for discriminant function analysis (Stewart et al., 1983) and we were interested in whether the blood levels of other metabolites determined in alcoholics during the early phase of abstinence could be used for discrimination between alcoholics and healthy controls.

Some investigators believe that the deficiency of substrates such as acetate, lactate, and 3-hydroxybutyrate (Derr et al., 1981; Derr, 1984) or glucose and pyruvate (Kosenko and Kaminsky, 1988) may be of importance in the development of the alcohol-withdrawal syndrome (AWS) symptoms. A further aim of this work was therefore to study the correlation between the blood concentrations of low-molecular-weight substances related to ethanol metabolism and the severity of the AWS.

MATERIALS AND METHODS

Subjects and protocol

Twenty-three male patients aged 24–58 years (mean 37.8 years) suffering from alcohol dependence were admitted to the alcoholism treatment department of the Hospital of the Grodno Regional Psychoneurologic Dispensary. The patients gave their informed consent to the investigation. The study protocol was approved by the Hospital Ethics Committee. The patients met the criteria for the second stage of alcoholism according to the classification of Portnov and Pyatnitskaya (1973) and the ICD-10 criteria for alcohol dependence (World Health Organization, 1992). They had compulsive craving for alcohol with loss of quantitative, and decrease of situational, control, AWS, high tolerance to alcohol, changed forms of intoxication, excessive alcohol intake, and personality disorders of the alcoholic type. The duration of alcohol abuse ranged from 3 to 24 years with a mean of 9.8 years. The last alcohol drink was about 24 h before admission in 10 patients and more than 24–48 h in the other 13 subjects. The control group consisted of 22 healthy male blood donors, aged from 20 to 48 years (mean 36 years). They abstained from alcohol for between 3 to 30 days before the tests.

Psychological and clinical assessments

To assess the severity of the AWS, the patients were rated according to Bokij and Lapin (1976) on days 2, 3, 4, and 6 at the same time of day (10:00) by the same physician. The AWS symptoms were scored on a four-point scale. Depending on the severity, 0 indicated a lack of symptoms, whereas 3 showed the presence of a pronounced symptom. For other cases, the symptoms were scored by one or two points. The following AWS symptoms were assessed: craving for alcohol, anxiety, irritability, depressed mood, sleep disturbances, elementary perception disorders, asthenia, tremor, thirst, decreased appetite, nausea, elevated blood pressure, quickened pulse, sweating, headache, Romberg’s sign, and cardiac pain. Based on these symptoms, summarized severity of psychopathologic and affective disorders, autonomic disorders, somatic and gastrointestinal disorders, and total AWS severity were calculated.

During detoxification, the alcoholic patients were treated with glucose (400 ml of a 5%, w/v, solution during the first 2 days, i.v.), sodium hyposulphite (10 ml of a 30% solution for 3–5 days, i.v.) or unithiol (an analogue of dimercaprolum, sodium 2,3-dimercaptopropanesulphonate, 3–5 ml of a 5% solution, i.m., for 5–7 days) as sulphydryl group-containing compounds, and magnesium sulphate. Some of the patients received plasma substitute haemodesum (neocompensan), 200–400 ml i.v. for 1 day. A B-multivitamin preparation with ascorbic acid was given orally during the whole 6-day study period. In addition to the detoxification, patients with severe AWS were prescribed a combination of neuroleptics and tranquillizers to attain a rapid and marked sedative effect and a reduction of withdrawal symptomatology and craving for alcohol. The patients were given: perphenazine (n = 15), thioridazine (n = 4), tofisopam (n = 4), diazepam (n = 4), and other neuroleptics and tranquillizers (n = 5). Twelve patients showed symptoms of depression and were treated with amitriptyline.

The patients were examined on the second, third, fourth, and sixth days after admission. The first examination was usually performed between 10 and 20 h after hospitalization.

Laboratory analyses

To determine blood metabolites, we used samples of capillary blood (0.4 ml) obtained by puncture of a fingertip. Blood was deproteinized immediately by the addition of 0.4 ml of a 12%
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Table 1. Blood concentrations of some metabolites and alcohol withdrawal severity score in alcoholic subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy controls (n = 22)</th>
<th>Alcoholic patients during detoxification (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>[Ethanol] (µM)</td>
<td>9.9 ± 1.1</td>
<td>139.8 ± 60.7*</td>
</tr>
<tr>
<td>[Acetaldehyde] (µM)</td>
<td>0.06 ± 0.03</td>
<td>0.56 ± 0.27</td>
</tr>
<tr>
<td>[Methanol] (µM)</td>
<td>6.3 ± 1.1</td>
<td>24.6 ± 9.0*</td>
</tr>
<tr>
<td>[Acetone] (µM)</td>
<td>8.7 ± 0.9</td>
<td>28.8 ± 9.2*</td>
</tr>
<tr>
<td>[Acetate] (mM)</td>
<td>0.28 ± 0.04</td>
<td>0.44 ± 0.07*</td>
</tr>
<tr>
<td>[Lactate] (mM)</td>
<td>0.55 ± 0.03</td>
<td>3.7 ± 31***</td>
</tr>
<tr>
<td>[Pyruvate] (mM)</td>
<td>0.06 ± 0.005</td>
<td>0.11 ± 0.01**</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio</td>
<td>10.8 ± 0.9</td>
<td>53.1 ± 10.7***</td>
</tr>
<tr>
<td>[Glucose] (mM)</td>
<td>6.4 ± 0.3</td>
<td>4.4 ± 0.23***</td>
</tr>
<tr>
<td>AWS severity (score)</td>
<td>—</td>
<td>26.2 ± 1.7</td>
</tr>
</tbody>
</table>

AWS = alcohol-withdrawal syndrome.
Significant differences between the healthy subjects and the alcoholic patients are shown as *P < 0.05, **P < 0.01, ***P < 0.001. — Denotes not determined.

(w/v) solution of sulphosalicylic acid + 0.38% thiourea. Blood sampling was performed at 08:00 after an overnight fast. Ethanol, acetaldehyde, methanol, and acetone concentrations were determined simultaneously by a head-space gas chromatographic technique (Shishkin et al., 1988). Deproteinized supernatants (0.2 ml), containing n-propanol (3.2 mg/ml) as internal standard, were transferred to 6-ml glass vials and 0.2 g anhydrous potassium carbonate was added. The vials were kept in a water bath at 65°C for 15 min. One ml of head space was then injected into a column by a heated gas-tight syringe. A 3700 model gas chromatograph fitted with a hydrogen flame ionization detector (Chromatograph, Moscow) was used. The artefactual acetaldehyde formation was studied in blood samples to which ethanol had been added to obtain concentrations from 1–20 mM. Acetate was analysed by a different head-space gas chromatographic method (Giles et al., 1986) in deproteinized blood samples (0.25 ml). Lactate and pyruvate were determined enzymatically (Hohorst, 1957). Glucose concentration was analysed by an o-toluidine method using a reagent kit from Lachema N.P., Brno (Czech Republic).

Statistical analysis

Data are expressed as means ± SEM. Student’s t-test, Pearson’s correlation and stepwise linear discriminant analysis were used as statistical procedures. The values of significance (P) of the differences in the correlation coefficients of the same pairs of parameters calculated for different days of observation were determined. The correlation coefficients were assumed to be stable if their values were not statistically different (Genkin, 1996).

RESULTS

Ethanol and methanol concentrations were different in the group of subjects consuming alcohol for 24 h before admission (n = 10) and the group of patients abstaining from alcohol for more than 24 h (n = 13). On day 2 the patients from the first group had higher ethanol (405.1 ± 112.1 µM, P < 0.01) and methanol levels (46.4 ± 15.9 µM, P < 0.05) compared to the second group (13.7 ± 4.5 and 9.2 ± 3.4 µM, respectively). The acetate concentrations were not significantly different on day 2 in these groups of patients (0.48 ± 0.1 and 0.40 ± 0.04 mM, respectively). On day 3 of treatment the methanol, ethanol, acetate, and acetone levels started returning to normal values.

The concentrations of various substances in the alcoholic group as a whole and in the controls are shown in Table 1. Concentrations of all of the volatiles (ethanol, acetaldehyde, methanol, and acetone) were higher in alcoholics as a whole than in the controls. Acetaldehyde values were below...
1 μM for the entire abstinence observation period. Abnormally high lactate and pyruvate concentrations and lactate/pyruvate ratios were also found throughout the observation periods (Table 1). Hypoglycaemia was noted within the first 2 days. The AWS severity was pronounced on days 2 and 3 after admission.

In healthy individuals, significant positive correlations were found between the concentrations of glucose and acetate \((r = 0.61, P < 0.01)\), glucose and lactate \((r = 0.59, P < 0.01)\), and acetate and lactate \((r = 0.43, P < 0.05)\). In contrast to healthy subjects, significant correlations between ethanol and its metabolites were observed in alcoholic patients. On day 2, there were positive correlations between ethanol and acetaldehyde \((r = 0.86, P < 0.01)\), ethanol and methanol \((r = 0.50, P < 0.05)\), methanol and acetaldehyde \((r = 0.52, P < 0.05)\), acetaldehyde and acetate \((r = 0.49, P < 0.05)\), and acetone and acetate \((r = 0.48, P < 0.05)\).

On day 2, the alcoholic patients showed levels exceeding control values by ±2 SD concentrations of blood methanol in 21%, ethanol in 50%, acetone in 40%, acetate in 35%, lactate in 100%, and pyruvate in 60% of the cases. The glucose concentration was low in 26% of the patients.

The discriminant analysis indicated that these parameters correctly classified from 90.9% to 95.8% of our patients during the period of observation from day 2 to day 6 and 100% of the control subjects (Table 2). The most informative parameters in the discrimination between the alcoholics and the controls were lactate, pyruvate, the lactate/pyruvate ratio, and acetone (day 2), lactate, ethanol, and acetate (day 3), lactate, the lactate/pyruvate ratio, and pyruvate (day 4), lactate, acetate, and acetone (day 6).

The correlations of clinical features and biochemical parameters are presented in Table 3. On day 2, the acetone content correlated significantly

### Table 2. Stepwise discriminant analysis based on biochemical variables: classification matrix

<table>
<thead>
<tr>
<th>Group</th>
<th>Per cent correct</th>
<th>No. of cases classified by group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholics on day 2</td>
<td>90.9</td>
<td>20</td>
</tr>
<tr>
<td>Alcoholics on day 3</td>
<td>95.7</td>
<td>22</td>
</tr>
<tr>
<td>Alcoholics on day 4</td>
<td>95.8</td>
<td>23</td>
</tr>
<tr>
<td>Alcoholics on day 6</td>
<td>90.9</td>
<td>20</td>
</tr>
<tr>
<td>Controls</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>94.7</td>
<td>85</td>
</tr>
</tbody>
</table>

### Table 3. Correlation coefficient values for pairings of biochemical and clinical parameters in alcoholic patients during detoxification

<table>
<thead>
<tr>
<th>Parameter pairing</th>
<th>Correlation coefficient ((r))</th>
<th>Significance of difference between correlation coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>Acetone and psychopathological disorders</td>
<td>0.48*</td>
<td>0.39</td>
</tr>
<tr>
<td>Acetone and autonomic disorders</td>
<td>0.50*</td>
<td>0.30</td>
</tr>
<tr>
<td>Acetone and gastrointestinal disorders</td>
<td>0.37</td>
<td>0.28</td>
</tr>
<tr>
<td>Acetone and total AWS severity</td>
<td>0.59**</td>
<td>0.33</td>
</tr>
<tr>
<td>Acetate and psychopathological disorders</td>
<td>0.54*</td>
<td>0.36</td>
</tr>
<tr>
<td>Acetate and autonomic disorders</td>
<td>0.42*</td>
<td>0.33</td>
</tr>
<tr>
<td>Acetate and gastrointestinal disorders</td>
<td>0.33</td>
<td>0.40</td>
</tr>
<tr>
<td>Acetate and total AWS severity</td>
<td>0.415*</td>
<td>0.43*</td>
</tr>
<tr>
<td>Methanol and craving for alcohol</td>
<td>-0.13</td>
<td>-0.57**</td>
</tr>
<tr>
<td>Methanol and psychopathological disorders</td>
<td>0.04</td>
<td>-0.19</td>
</tr>
<tr>
<td>Methanol and autonomic disorders</td>
<td>-0.02</td>
<td>-0.51*</td>
</tr>
<tr>
<td>Methanol and total AWS severity</td>
<td>-0.06</td>
<td>-0.38</td>
</tr>
<tr>
<td>Ethanol and craving for alcohol</td>
<td>-0.1</td>
<td>-0.42*</td>
</tr>
<tr>
<td>Acetaldehyde and craving for alcohol</td>
<td>-0.23</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

AWS = alcohol-withdrawal syndrome.

*\(P < 0.05\); **\(P < 0.01\).

NS denotes \(P > 0.05\) for insignificant difference between correlation coefficients.
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with the severity of psychopathological \((r = 0.48, P < 0.05)\), autonomic \((r = 0.5, P < 0.05)\), and somatic and gastrointestinal disorders \((r = 0.49, P < 0.05)\), as well as with the total AWS score \((r = 0.57, P < 0.01)\). The acetate levels correlated with the severity of psychopathological disorders \((r = 0.54, P < 0.01)\) and the total AWS score \((r = 0.415, P < 0.05)\).

On day 3, the number of significant correlations was lower than on day 2. Negative correlation was observed between the ethanol content and craving for alcohol \((r = -0.42, P < 0.05)\). The methanol concentrations correlated negatively with craving for alcohol \((r = -0.54, P < 0.05)\), and the severity of autonomic disorders \((r = -0.51, P < 0.05)\). A significant positive correlation was found between acetate levels and the total AWS score \((r = 0.45, P < 0.05)\).

On day 4, the acetone concentrations correlated positively with the gastrointestinal disorders severity \((r = 0.45, P < 0.05)\). The acetate content correlated with autonomic disorders \((r = 0.44, P < 0.05)\) and the total AWS score \((r = 0.56, P < 0.01)\). A negative correlation was observed between acetaldehyde and craving for alcohol \((r = -0.47, P < 0.05)\). A positive correlation was found between the lactate/pyruvate ratio and somatic and gastrointestinal disorders \((r = 0.43, P < 0.05)\).

Some significant correlations were also found on day 6. Methanol correlated negatively with the craving for alcohol \((r = -0.45, P < 0.05)\), the severity of psychopathological disorders \((r = -0.49, P < 0.05)\), and the total AWS severity score \((r = -0.46, P < 0.05)\). The acetate concentrations correlated positively with psychopathological disorders \((r = 0.49, P < 0.05)\) and the total AWS score \((r = 0.51, P < 0.05)\).

On different days of the observation period, correlations of the lactate, pyruvate, lactate/pyruvate ratio, and acetaldehyde with individual symptoms of somato-autonomic and psychopathological disorders were also found.

It can be seen from Table 3 that the values and signs of the correlation coefficients for the same pair of biochemical and clinical parameters from days 2 to 6 were similar in most of the cases. The correlation for acetone with AWS severity was consistently positive during the period of the study with a tendency to decrease in value after the second day, which is in agreement with the dynamics of the decrease in blood-acetone concentrations in the patients. The correlation for acetate with AWS severity was stable with negligible changes in values and significance. Most of the correlations for methanol, ethanol, and acetaldehyde were negative. The differences in the correlation coefficients of the same pairs on four different days of observation were not statistically significant (Table 3) and therefore may be taken as stable (Genkin, 1996).

**DISCUSSION**

The raised levels of blood ethanol and methanol found on day 2 of treatment may be attributed to previous alcohol intake. The very low concentrations of blood acetaldehyde observed throughout the 4-day period of withdrawal possibly reflect the persistence of haemoglobin-bound forms of acetaldehyde similar to those described by Peterson and Polizzi (1987) and Hernandez-Munoz et al. (1989). We found a 150- to 300-fold lower level of blood acetaldehyde during alcohol withdrawal, compared to the data of Magrinat et al. (1973) and believe this difference to be related to the absence of correction for acetaldehyde artefactually formed during analytical procedures, as suggested in almost all papers on human blood acetaldehyde published before 1983 (Eriksson and Fukunaga, 1993).

Increased acetone concentrations on day 2 of withdrawal might reflect the occurrence of mild alcoholic ketoacidosis. The positive correlations between the acetone concentrations and the psychopathological, autonomic, somatic, and gastrointestinal disorders as well as the AWS severity may reflect the contribution of alcoholic ketoacidosis to the development of some clinical signs of AWS. This assumption is supported by the observation that ketoacidosis during alcohol withdrawal plays an important role in the development of alcoholic cardiomyopathy (Tezikov et al., 1992).

Our data on the blood pyruvate and lactate levels being increased in alcoholic patients with early withdrawal disorders are in agreement with previous observations that patients with delirium tremens had elevated concentrations of these acids in their cerebrospinal fluid (Sytnisky, 1980).

The significant accumulation of blood lactate and pyruvate up to day 6 of observation is not a
consequence of glucose administration, since the glucose solution was given to our patients in a relatively small dose during (and only for) the first 2 days, and blood sampling was performed on the next day after an infusion. Lactacidaemia and pyruvataemia associated with hypoglycaemia despite the detoxification treatment probably indicate disturbed aerobic glucose oxidation and gluconeogenesis from lactate in the alcoholics after the alcohol cessation.

Standard detoxification therapy was not sufficiently effective in eliminating the metabolic changes in alcoholics. The administration of glucose to our patients did not significantly increase the levels of blood glucose and the lactate and pyruvate concentrations remained high. It has been demonstrated that, in the liver of alcohol abusers, alcohol withdrawal could induce a state of hypermetabolism accompanied by the development of centrilobular liver cell hypoxia (Hadengue et al., 1988, French, 1991). Under hypoxia, glucose may possibly be utilized predominantly by the glycolytic pathway, with accumulation of pyruvate and lactate, whereas the utilization of lactate in gluconeogenesis is disturbed. The significant correlations between glucose, lactate, and acetate observed in healthy individuals were not seen in alcoholic patients. These differences may reflect indirectly the disturbed metabolism of energy-producing substances. The mechanisms of metabolic changes may be similar to those described in experimental animals when the cessation of alcohol intake after chronic intoxication leads to the accumulation of pyruvate, lactate, alanine, and glycogen in rat liver in combination with hypoglycaemia and failure of glycogen to act as an adequate source of blood glucose (Kosenko and Kaminsky, 1988).

Although acetate was elevated significantly in alcoholics on the second day of their admission to the hospital, this increase was not related to previous alcohol intake, since the concentrations of acetate did not differ from those in the groups of patients admitted for alcohol intoxication or withdrawal. Its level remained elevated by 25–36% on subsequent days, though this difference was not statistically significant in comparison with controls. It is suggested that this elevation may be due to the direct competition between acetate and lactate for lipogenesis and metabolism, as shown in animal experiments; the high lactate concentrations (3.9 mM, comparable to those found in our work) are known to inhibit acetate uptake by perfused rat liver (Snoswell et al., 1982). The concentration of acetate correlated positively with the severity of AWS and the extent of some withdrawal syndromes throughout the study. Our observations do not agree with the view (Derr et al., 1981) of acetate deficiency underlying AWS development. The experimental findings are contradictory. Although acetate weakens some manifestations of withdrawal in rats, it was shown that the application of acetate in detoxification enhanced alcoholic damage of cardiac muscle function (Tezikov et al., 1993).

The numerous significant correlations between biochemical parameters and the severity of AWS and the syndromes constituting AWS as well as the recurrence of some of the correlations on different days may indicate their regular nature. We can differentiate a group of negative correlations for AWS symptoms with ethanol, acetaldehyde and methanol. The craving for alcohol correlated negatively with ethanol concentration on the third day. These results agree with our earlier data. On the second and third days of treatment the ethanol levels correlated negatively with the presence of delirium tremens and the severity of withdrawal (Prónko et al., 1983; Ostrovsky et al., 1989). This is consistent with the views of the role of ethanol itself in the development of AWS (Bokij and Lapin, 1976). In early withdrawal a rapid decrease in ethanol levels may be important. On different observation days the correlations of methanol with craving for alcohol and with AWS severity were negative. The correlations may be explained in terms of both methanol and ethanol being of aetiological importance in alcohol dependence (Bonte et al., 1988).

The positive AWS correlations with acetone, acetate, pyruvate, and lactate, where levels were raised in many instances, may reflect a relationship between the severity of the AWS symptoms and the extent of the accompanying metabolic disturbances in the liver. Cause-effect relationships are complicated in this situation. It is known that the neuroendocrine changes characteristic of AWS aggravate ethanol-induced disturbances in the liver (Hadengue et al., 1988; French, 1991), but they, in their turn, can contribute to the severity of the patients' states and prolong the
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