COMPARISON OF CYANAMIDE AND PLACEBO IN THE TREATMENT OF ALCOHOL DEPENDENCE OF ADOLESCENTS

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Abstract — Aims: About 50% of alcoholic patients relapse within 3 months of treatment. Previous studies have suggested that cyanamide may help to prevent such relapse. The aim of our study was to assess the efficacy and safety of long-term cyanamide treatment in alcohol dependence of adolescents. Methods: In this double-blind, placebo-controlled study, we recruited 26 patients, aged 16–19 years, with chronic (frequent and regular) or episodic (frequent, but irregular) alcohol dependence. Patients were randomly allocated treatment with cyanamide (200 mg daily) or a placebo for 90 days. Patients were assessed on the day the treatment was started, and on days 30 and 90, by interview, self-report, questionnaire and laboratory screening. Patients were classified as abstinent, relapsing or non-attending. Time to first treatment failure (relapse or non-attendance) was the primary outcome measure. Results: The cyanamide (n = 13) and placebo (n = 13) groups were well matched in terms of baseline demographic and alcohol-related variables. Mean cumulative abstinence duration was significantly greater in the cyanamide group than in the placebo group. Apart from occasional diarrhoea, there was no difference in side effects between groups. Conclusions: Cyanamide seems to be an effective and well tolerated pharmacological adjunct to psychosocial and behavioural treatment programmes for the treatment of some adolescent alcohol-dependent patients. Because of reported hepatotoxic, haematological and dermatological side effects, patients should be observed continuously by experienced clinicians. Further studies are necessary to prove the efficacy of cyanamide in adolescents.

INTRODUCTION

About 50% of alcoholic patients relapse within 3 months of completion of treatment (Feuerlein, 1986). Several studies have reported various results with opiate antagonists. O’Malley et al. (1992), Volpicelli et al. (1992) and Mason et al. (1994) reported a significant reduction of relapse severity, whereas Krystal et al. (2001) reported no significant effect. With drugs that affect transmission of serotonin: Naranjo and Kadlee (1991) reported a significant effect; dopamine: Shaw et al. (1994) and Borg (1983) reported a significant effect, whereas Walter et al. (2001) reported an increase in relapse rates caused by D1 and D2 antagonists; γ-aminobutyric acid (GABA): Gallimberti et al. (1992) reported a significant effect; and acamprosate: Lesch et al. (2001) reported a good effect only in special subgroups of patients.

Cyanamide is an aldehyde dehydrogenase (ALDH) inhibitor used as a pharmacological adjunct in the aversive treatment of chronic alcoholism. Its elimination half-life and total plasma clearance values range from 42.2 to 61.3 min and its oral bioavailability is 70% at a 1.0 mg/kg dose (Colom et al., 1999). Cyanamide blocks ethanol metabolism by inhibition of both the low- and high-Km forms of ALDH (Loomis and Brian, 1983a, b; Cederbaum and Dicker, 1985) in a pH-dependent manner [at pH < 7.5 formation of an irreversible form, at pH > 8.5 formation of a reversible form (DeMaster et al., 1998)]. As a result of this inhibition an increase is induced in acetaldehyde concentrations in blood and liver. This is responsible for the alcohol deterrent activity of cyanamide, because it induces a severe reaction (the toxic acetaldehyde syndrome) characterized by tachycardia, hypotension, flushing and dyspnea (Brien et al., 1978, 1979).

The mechanism of the inhibition of ALDH by cyanamide remains unclear. Some authors postulate that this inhibition is achieved by one active metabolite (DeMaster et al., 1979). Prufonosa et al. (1989, 1991) suggested that the metabolic conversion of cyanamide to an active inhibitory form does not take place, and that ALDH activity thus appeared to be irreversibly inhibited in vitro in the presence of catalase and NAD+ . So far, cyanamide pharmacokinetic studies have been carried out in experimental animals (Deitrich et al., 1976; Obach et al., 1986) and in most of these studies the doses administered were higher than the therapeutic doses.

Cyanamide may also have some side effects, which fortunately could be observed in only a few cases: Brugueras et al. (1987), Yokoyama et al. (1995), Suzuki et al. (2000) and Tamai et al. (2000) reported the possible development of ground-class inclusion bodies in the hepatocytes, Ajima et al. (1997) observed cyanamide-induced granulocytopenia, Yerro et al. (2000) even reported cyanamide-induced pancytopenia. Rios-Herranz et al. (1992) reported the development of aplastic anaemia. Dermatological side effects of cyanamide have also been observed: Abajo et al. (1999) reported cyanamide-induced eczematous erythroderma, Kawana et al. (1997) reported exfoliative dermatitis and Torrelo et al. (1990) reported lichen-planus-like eruptions.

No data reporting the benefit of cyanamide for alcohol-dependent adolescents have been reported. That is why we undertook a double-blind, placebo-controlled trial of 90 days’ treatment with cyanamide; the endpoint for analysis was continuous abstinence. Because of the reported side effects, a continuous observation of the patients included in our study was essential.

SUBJECTS AND METHODS

Eligible patients were those who presented to our hospital that treats in-patients with alcohol dependence of chronic (frequent and regular) or episodic (frequent but irregular) type (DSM-III criteria) (American Psychiatric Association, 1980) because of national documentation rules. Patients had to be aged 16–19 years; to have been abstinent for at least 5 days

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before the study; to have a $\gamma$-glutamyl transferase ($\gamma$GT) value of at least twice the upper limit of the normal range or a mean corpuscular volume (MCV) of 93 fl or more, or both; and their parents gave written informed consent. We used the CAGE questionnaire’s (Ewing, 1984) four clinical interview questions on cutting down, annoyance by criticism, guilty feelings, and eye-openers to assess the severity of patients’ alcoholism.

We excluded patients with serious coexisting disease (inadequately controlled juvenile diabetes mellitus, hypertension, cardiac failure, septicaemia, active tuberculosis, neoplastic disease; renal failure with a serum creatinine concentration of 120 $\mu$mol/l or more and hypercalcaemia of all aetiologies; epilepsy unrelated to alcoholism; and psychiatric disorders that might necessitate specific drug treatment, polytoxikomanic patients, patients with severe personality disorders). In 2000, we screened 36 patients, of whom three were excluded because of coexisting disease. Thus, 33 patients were recruited. The study was conducted according to the European Good Clinical Practice Guidelines and the Declaration of Helsinki under the auspices of an Ethic Commission.

Under the intention-to-treat principle, all randomized patients are eligible for analysis irrespective of whether they fulfil the conditions of the protocol. We used a slightly modified approach, in that we excluded seven patients who had been randomized but who did not attend the assessment on day 0 and, therefore, did not receive any medication. Lehert (1993) proposed this modification for alcohol studies because it is more practicable than the standard intention-to-treat approach for studies of patients with very high withdrawal rates and low motivation.

The remaining 26 patients underwent an in-patient, pharmacologically supported, alcohol-withdrawal treatment. After abstinence for at least 5 days they were reassessed and baseline measurements for safety and efficacy calculations were made. Patients were then randomly assigned to cyanamide or a placebo. In our assessment, day 0 was the day when cyanamide or placebo treatment was started. Cyanamide and placebo tablets were identical in appearance. Patients received 200 mg daily (two tablets in the morning, one at midday, and one in the evening). Patients in the placebo group took the same number of tablets. Patients were classified as abstinent or relapsed on day 0 and on days 30 and 90 according to their self-reports. The investigator recorded their judgements of whether the self-report was likely to be true and biological markers ($\gamma$GT, MCV). The duration of double-blind treatment was 90 days. All patients received additional psychosocial and behavioural treatment. Patients who missed a visit, but attended the next one, were not withdrawn. Patients who relapsed during treatment were able to continue in the study on an out-patient basis, or were admitted to hospital for alcohol withdrawal where they continued to take their coded medication; however, if such patients could not be returned to the community within 15 days they were withdrawn from the study. The variables used in assessment were: red and white blood cell count, prothrombin time (70–120%); and electrolytes, blood urea nitrogen, creatinine, uric acid, fasting blood glucose, total bilirubin, triglycerides and albumin, as well as the alcoholism-related variables (Table 1). MCV and $\gamma$GT values were also measured on the day of selection and at each assessment during follow-up, so that relapse could be confirmed or detected biochemically.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cyanamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>8/5</td>
<td>7/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$17.1 \pm 0.9$</td>
<td>$17.8 \pm 1.2$</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>118 ± 14</td>
<td>112 ± 9</td>
</tr>
<tr>
<td>GOT (U/l)</td>
<td>16 ± 5</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>GPT (U/l)</td>
<td>20 ± 4</td>
<td>21 ± 8</td>
</tr>
<tr>
<td>$\gamma$GT (U/l)</td>
<td>14 ± 2</td>
<td>15 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

GOT, glutamic-oxaloacetic transaminase; GPT, glutamate pyruvate transaminase.

To assess side effects, the investigator questioned the patients on all assessment days and recorded the presence or absence of severe adverse side effects, which were rated for association with the study medication.

The variables used to assess efficacy were alcohol consumption, physical signs of alcoholism, tremor index, $\gamma$GT concentration and MCV.

No drugs acting on the central nervous system were allowed during the trial. We required that patients who had been treated with benzodiazepines for withdrawal symptoms had stopped such treatment on the day of selection. Random (almost bi-weekly), albeit infrequent, drug checks (opiates, benzodiazepines) showed no positive results. At each assessment, the patient was classified as abstinent or relapsed according to his or her self-report, checked by an investigator and through biological markers.

Time to first occurrence of treatment failure was the principal outcome measure. The percentage of treatment failures was calculated by the life-table method of Kaplan and Meier (1958) and the treatment groups were compared by the Mantel–Cox test. The possibility of later improvement during the treatment period was ignored in this analysis. The cumulative abstinence duration — the total number of days of abstinence — was the secondary outcome measure. We calculated this measure as the sum of only the periods of complete abstinence. When relapse was reported at a visit, the total period from the previous visit to that visit was classified as a period of relapse. Groups were compared by $t$-test applied to the square-root-transformed cumulative abstinence duration data.

### RESULTS

Seven of the 33 patients recruited did not receive study medication and were therefore not included. Two were admitted to hospital for more than 15 days during the study. They were withdrawn from treatment, but were included in the intention-to-treat analysis. The groups were well matched in terms of demographic and alcohol-related baseline variables on the day of selection and on day 0. There were no differences between the cyanamide and placebo groups in quantity (>70 g alcohol daily) and frequency of drinking (daily), signs of psychological (6.3 vs 6.2) and physical dependence (5.9 vs 5.6) (as measured by a score from the DSM-III criteria for alcohol dependence), and Hamilton depression scores (29 vs 26) (Hamilton, 1960).

Thirteen cyanamide-treated and 13 placebo-treated patients completed the treatment phase: of those withdrawn, seven
(one vs six) relapsed, five (three vs two) refused to continue treatment, three (one vs two) had concurrent illness, and two (one vs one) had adverse side effects. The proportion of patients who remained abstinent (i.e. had not had treatment failure) was higher in the cyanamide group than in the placebo group throughout the 90 days of treatment ($P = 0.0069$, Mantel–Cox test). On day 90, significantly more cyanamide-treated patients had been continuously abstinent ($P = 0.0012$) (Table 2). Mean cumulative abstinence duration was significantly greater in the cyanamide group than in the placebo group (Table 2). The commonest reason for withdrawal was relapse in both groups. More than 50% of withdrawals occurred within the first 30 days of treatment; thereafter the rate diminished progressively.

There were no significant differences between the cyanamide and placebo groups for the side effects [gastrointestinal (3.4 vs 3.0), dermatological (2.9 vs 2.8), muscular (3.1 vs 3.4), neurological/psychological (7.7 vs 7.3), genito-urinary/sexual (4.1 vs 4.0), cardiovascular/pulmonary (6.4 vs 6.2)]. The complex nature of both alcohol dependence and the symptoms of alcohol withdrawal meant that we were not always able to distinguish between alcohol-related symptoms and adverse side effects.

We could not observe a significant correlation between the severity of patients’ alcoholism and the prevention effect of cyanamide [cutting down (cyanamide 5.4, placebo 5.9), annoyance by criticism (cyanamide 4.9, placebo 4.8), guilty feelings (cyanamide 3.6, placebo 4.1), and eye-openers (cyanamide 3.4, placebo 3.7)].

In our sample, cyanamide had no effect on haematology or serum biochemistry.

**DISCUSSION**

A study with unrestrictive selection criteria will inevitably recruit a heterogeneous population of patients, but such a sample is likely to reflect the mix of characteristics in the entire population with the disease in question, thus, the findings of such a study should be more generally applicable than the results from a highly selected group of patients. Avoidance of selection bias is especially important for disorders such as alcoholism, in which information on time of onset and the subsequent course is unreliable. This unreliability may lead to undetected differences between the treatment groups at recruitment.

We used conservative definitions of treatment outcome. Non-attending patients were classified as treatment failures and the whole period between two visits was counted as relapse, if the patient reported relapse at any time during the period. Although in using these conservative criteria we may over-estimate relapse rates and under-estimate cumulative abstinence duration, we believe that this approach more realistically reflects the usual course of alcohol dependence. This conservative approach to analysis of outcome must be kept in mind when our results are compared with those of other studies. Our study suggests that some alcoholic patients who respond to cyanamide should continue treatment.

A comparison of the efficacy of the various drugs used in the treatment of alcoholism is difficult because study populations, duration of treatment, inclusion and exclusion criteria, and outcome measures differ for each trial.

The study by Volpicelli et al. (1992) led to the registration of naltrexone, an opioid antagonist, for treatment of alcohol dependence in the USA. In their 12-week placebo-controlled, double-blind study, there was a significant difference in rates of relapse (defined as clinically significant). Recent work (Krystal et al., 2001) reported no significant difference in rates of relapse. By comparison, in our study on assessment day 90 (the nearest assessment to Volpicelli and colleagues’ 12 weeks), the relapse rate was 19%. We believe cyanamide compares favourably with naltrexone, because we had a less selective study sample; motivation was not an inclusion criterion as it was in Volpicelli and colleagues’ study. Another placebo-controlled study (O’Malley et al., 1992) found that, together with supportive therapy and coping skills, naltrexone was superior to the placebo in the reduction of alcohol consumption and was also associated with higher abstinence and lower relapse rates.

Gallimberti et al. (1992) investigated the effect of γ-hydroxybutyric acid in a 3-month double-blind placebo-controlled study of 82 alcoholic patients, who were asked not to drink alcohol; however, compliance was not mandatory. There were significant reductions in both intake and alcohol craving, and an increase in the percentage of abstinence days in the active-treatment group. Recent studies [see review by Kranzler, 2000] reported similar relapse rates.

In all these studies, the outcome measure was alcohol intake, rather than cumulative abstinence duration. However, the effects of this treatment for unselected patients in non-research settings remain to be seen.

The origin of alcoholism is complex and it is unlikely that a single cure will be found. Therefore, we believe that the treatment approach should include psychosocial as well as pharmacological components. Physicians should not assume that a patient will remain abstinent when prescribed a drug without additional psychosocial treatment. Perhaps the use of cyanamide should be restricted to specialized treatment facilities that have comprehensive programmes, so that misguided, and ultimately ineffective, application of the drug will be avoided.

Alcoholism in adolescents is very likely to become an important problem within the next few decades. The results of the present observations suggest that cyanamide may support abstinence rates of adolescents in some cases.

Our sample included only 26 patients. This small sample does not facilitate the interpretation of our results, but adolescents suffering from severe alcoholism are very rare and therefore our results should encourage the initiation of multicentre studies to replicate our findings.

Altogether, cyanamide seems to be a relatively safe and perhaps also effective adjunct to psychosocial alcohol

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**Table 2. Cumulative abstinence duration in the cyanamide and placebo groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cyanamide (mean ± SD)</th>
<th>Placebo (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-III-R criteria (n &gt; 5)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Relapse rate (day 30)</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Relapse rate (day 90)</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Abstinence on day 90</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Mean cumulative abstinence duration (mean ± SD)</td>
<td>77.7 ± 42.3</td>
<td>33.9 ± 21.0</td>
</tr>
</tbody>
</table>