AN OPEN MULTICENTRIC STUDY EVALUATING 4-HYDROXYBUTYRIC ACID SODIUM SALT IN THE MEDIUM-TERM TREATMENT OF 179 ALCOHOL DEPENDENT SUBJECTS

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Abstract — We report the results of an ‘open’ multicentre study evaluating the use, tolerability and therapeutic efficacy of the sodium salt of 4-hydroxybutyric acid (GHB) for the medium-term treatment of withdrawal symptoms in 179 patients with alcohol dependence followed up as outpatients. The follow-up of patients was 6 and 12 months after drug discontinuation. Following a daily oral administration of 50 mg/kg for approximately 6 months, no serious systemic or single-organ consequences leading to drug discontinuation were reported, and tolerability was fair in all patients. Eleven subjects (10.1%) showed craving for the drug and voluntarily increased their doses (6–7 times the recommended levels). GHB led to complete abstinence during drug administration in 78.0% of the patients. A significant reduction of compulsive desire (‘craving’) was observed in parallel, as deduced from evaluation of a specific questionnaire, the Alcohol Craving Scale. At follow-up examination, 43 of the treated subjects remained abstinent at 6 months, and 30 subjects were abstinent for 1 year after drug discontinuation.

INTRODUCTION

The principles of alcohol dependence therapy are essentially based on intervention through psychological support (Bien et al., 1993) and the use of drug therapy. The role of drug therapy, however, has not yet been well established (US Department of Health and Human Services, 1990). Psychological and behavioural support interventions include various rehabilitation programmes (for example the Minnesota system, psychoeducational interventions, systemic family and group therapies) (Alcoholics Anonymous, 1978; Emrick, 1987; Jacobson et al., 1989; O’Farrel, 1989; US Department of Health and Human Services, 1990; Hermos, 1992; Addolorato et al., 1993a; Bien et al., 1993).

At present, pharmacotherapy comprises numerous non-specific drugs, such as vitamins, minerals, drugs acting on the central nervous system (CNS) (anxiolytics, antidepressants and the major tranquillizers), and also specific drugs. Besides interdiction/aversion drugs (disulfiram, metronidazole, apomorphine etc.), substances with a compulsive desire (craving) reduction activity (fluoxetine, methadoxine, S-adenosyl-methionine, naltrexone, acamprosate) have been employed (Fuller et al., 1986; Lhuintra et al., 1990; Lieber et al., 1990; Gorelick and Paredes, 1992; O’Malley et al., 1992; Inturri et al., 1993; Gasbarrini et al., 1994; Soyka, 1995). Among the latter group, gamma-hydroxybutyric acid (GHB) has been introduced recently into clinical practice (Gallimberti et al., 1989, 1992; Addolorato et al., 1993b; Di Bello et al., 1995).

GHB, a metabolite of GABA, formerly used as a hypnotic/anaesthetic agent (Laborit et al., 1960; Mamelak et al., 1986), has been found in large quantities in the hypothalamus and basal ganglia and has been assigned neurotransmitter and neuromodulatory functions (Mamelak et al., 1986; Vayer et al., 1987). GHB administration is effective in preventing the abstinence syndrome in both experimental animals and man (Gallimberti et al., 1989) and in inducing short-term abstinence (Gallimberti et al., 1992). Since the majority of

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treatment failures occur within the first 6 months and studies on the medium-term effect of GHB in alcoholism treatment are lacking and, after having conducted a pilot study on 15 alcohol-dependent patients with promising results (Addolorato et al., 1993b), we performed a multicentre study, firstly to evaluate the usefulness, tolerability and safety of GHB, and, secondly, to obtain an indication of GHB activity in prolonged outpatient weaning, using the parameters of abstinence and craving as measures of outcome.

PATIENTS AND METHODS

Nineteen centres from various Italian regions participated in the study.

Alcohol-dependent patients were admitted to the study on the basis of DSM-III-R criteria (American Psychiatric Association, 1987). Eligible patients gave their informed consent. Pregnancy, severe kidney, heart or lung disease, decompensated liver cirrhosis, psychopathology under treatment with psychoactive drugs and epilepsy or epileptiform convulsions constituted exclusion criteria.

On the basis of such criteria, 179 alcohol-dependent subjects were enrolled and administered GHB. Of these, 131 subjects were males and 48 were females, between the ages of 18 and 73 (mean age 46), under outpatient treatment at the above centres. According to the DSM-III-R criteria, of the 179 patients enrolled in the study, 59 (32.9%) had an alcohol dependence of mild severity, 55 (30.7%) had a moderate alcohol dependence and 65 (36.3%) had a severe alcohol dependence. The drug and its administration were entrusted to a designated family member; the drug was orally administered, at a dose of 50 mg/kg three times/day for 24 weeks.

All the patients were strongly advised against the use of drugs that can potentially influence the desire for alcohol consumption.

Each subject was checked as an outpatient every 3 weeks for the 24-week duration; at each visit, routine psychological support counselling was provided and the patient was requested to complete the Alcohol Craving Scale (ACS). The questionnaire contained 14 items, each of which required a yes or no answer, corresponding to 1 or 0 points, respectively; thus, the maximum craving score was 14 (Gallimberti et al., 1992; Di Bello et al., 1995).

Abstinence was evaluated on the basis of the patients’ self-evaluation and on that by the family member, and laboratory tests, including blood alcohol concentration, gamma GT (GGT), mean cell volume (MCV), aspartate aminotransferase (AST), alanine aminotransferase (ALT), determination of alcohol in saliva by the QED saliva alcohol test (by Enzymatics Inc., Horsham, UK). Laboratory tests were repeated at 3 months and at the end of the study. The follow-up of the patients was at 6 months and 12 months after drug discontinuation.

Statistical analysis was carried out by means of the Mann–Whitney U-test for within-group comparison, and by the Wilcoxon test for comparisons between the different groups as regards ACS; Student’s paired t-test was used to compare the results of laboratory tests before and after the study, and to compare the data between the different subgroups of patients.

RESULTS

Of the 179 patients enrolled in the study, 70 subjects (of whom 17 were females) dropped out (39.1%), whereas 109 subjects (31 of whom were females) continued drug therapy with GHB (60.9%).

Of the 109 subjects, 84 (25 females and 59...
males) became and remained abstinent throughout the experiment (78.0%) (Fig. 1), whereas 25 subjects (6 females and 19 males) relapsed; the majority of these (19 subjects) voluntarily discontinued the drug, in part complaining of a lack of reduced craving (14 subjects) or fear of side-effects due to concomitant intake of alcohol and drugs (9 subjects).

In the following 1-year period of observation, of the 84 subjects who maintained abstinence until termination of the treatment, 43 (51.2%) remained abstinent at 6 months of drug suspension (Fig. 1), whereas in 41 (48.8%) treatment failed (26 withdrew and 15 relapsed); at 1 year among abstinent patients this led to 35.7% (30 subjects) complete abstinence (Fig. 1).

Some sporadic benzodiazepine intake was recorded both during the treatment time and the follow-up, without any significant difference between abstinent patients and relapsed ones. No serious systemic or single-organ side-effects leading to drug cessation were reported. Tolerability was fair in all patients; ~36% of the subjects reported vertigo, which resolved after about 3 weeks of treatment; another 28% reported increased sleepiness and tiredness, which resolved after 2–3 weeks of drug intake and did not recur.

Eleven subjects showed craving for the drug (10.1%) and voluntarily increased their doses (6–7 times the recommended level) to obtain anxiolytic and hypnotic effects. Seven of these showed ACS mean score higher than 8.5; the DSM-III-R scores showed scattered values.

Comparing laboratory investigations before and immediately after GHB administration in abstinent patients versus the relapsed ones, we observed a significant difference in final values of GGT (from mean value of 161 U/l to 55 U/l, for abstinent patients, $P < 0.001$, and from a mean value of 1194 U/l to 129 U/l, for relapsed patients). The reduction in AST (from mean starting value of 51 U/l to a final value of 35 U/l, for abstinent patients, $P < 0.001$, and from 58 U/l to a final mean of 39 U/l, for relapsed patients, $P < 0.001$) and ALT (from mean value of 52 U/l to 33 U/l, for abstinent patients, $P < 0.001$, and from 52 U/l to 38 U/l, for relapsed patients, $P < 0.001$) did not differ between the two groups.

The ACS mean score (Table 1) in the 109 treated subjects at the start was 9.01 ± 2.64 and was 3.72 ± 2.84 at the end of the study ($P < 0.001$); in patients maintaining abstinence throughout the period of treatment (group A) the mean score on entrance was 9.16 ± 2.71, and at the end of the study was 3.09 ± 2.53 ($P < 0.001$). On the other hand, in patients who reached, but did not maintain, abstinence (group B), the mean score on starting was similar to group A (8.51 ± 2.32), but on termination of treatment it was significantly higher (5.75 ± 2.95) ($P < 0.01$) (Table 1). In patients, subgroup individuals who relapsed at 1 year (group D) showed starting values of craving significantly lower than patients complying with the therapy (group C) (Table 1).

### Table 1. The alcohol craving score of patients treated with gamma-hydroxybutyrate

<table>
<thead>
<tr>
<th>Patients</th>
<th>Start</th>
<th>End</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group</td>
<td>9.01 ± 2.64</td>
<td>3.72 ± 2.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group A</td>
<td>84</td>
<td>9.16 ± 2.71</td>
<td>3.09 ± 2.53</td>
</tr>
<tr>
<td>Group B</td>
<td>25</td>
<td>8.51 ± 2.32</td>
<td>5.75 ± 2.95</td>
</tr>
<tr>
<td>Group C</td>
<td>30</td>
<td>10.1 ± 3.17</td>
<td>3.07 ± 1.80</td>
</tr>
<tr>
<td>Group D</td>
<td>54</td>
<td>7.75 ± 2.96</td>
<td>3.37 ± 1.66</td>
</tr>
</tbody>
</table>

Group A: subjects abstinent throughout the period of treatment; Group B: subjects not abstinent throughout the period of treatment; Group C: subjects abstinent 1 year after drug discontinuation; Group D: subjects not abstinent 1 year after drug discontinuation.

* $P$ between the mean values before and after the study within the sub-groups; ** $P$ between the mean values from the different groups at the start of treatment; *** $P$ between the mean values from the different groups at the end of the study.
DISCUSSION

The drug proved to be very manageable, giving rise to few side-effects. In particular, unwanted dizziness, sleepiness and tiredness early during treatment, due to GHB’s CNS action, were foreseeable and their extent and transience supported in general the acceptability of the drug.

Liver function test values in the treated subjects improved significantly and this is generally attributable to cessation of alcohol intake. The parallel reduction in indices of hepatocellular damage, however, support the general safety of the drug. On the other hand, a number of patients abused the drug, seeking its psychotropic effects.

Within the limits of an open study, we observed a fair efficacy of the drug in improving the abstinence rate that is comparable with the best results obtained with other types of treatment, which vary between 24% and 60% (US Department of Health and Human Services, 1990; Bien et al., 1993). The parallel reduction in the mean ACS score of responding patients and the expected better response in patients with a higher ACS mean score add indirect support to the possibility of a link between GHB’s alleged anti-craving action and its clinical efficacy. The increase in relapse in the 6 months following the end of GHB administration not only outlines the efficacy of the drug, but also draws attention to its limitations, and also favours an indirect mechanism of action of the drug. It is conceivable that GHB improves the abstinence rate, rather than influence directly alcohol dependence. Our results thus warrant a double-blind placebo-controlled study to establish the therapeutic role of GHB in alcoholism.


REFERENCES


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