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Gamma-Hydroxybutyrate Reduces both Withdrawal Syndrome and Hypercortisolism in Severe Abstinent Alcoholics: An Open Study vs. Diazepam

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Abstract: In 42 alcoholic inpatients we performed an open randomized study to compare the effects of diazepam and gamma-hydroxybutyrate (GHB) on the suppression of severe alcohol withdrawal syndrome and hypercortisolism. Both diazepam (0.5 mg/kg bodyweight, q.i.d.) and GHB (50 mg/kg bodyweight, q.i.d.) were orally administered for three weeks. During all study period, GHB was more able than diazepam in reducing both withdrawal syndrome and hypercortisolism. These effects were evident during the first week of treatment and persisted throughout the study period. The results confirm a strict correlation between high levels of plasma cortisol and alcohol withdrawal symptoms and they show a slight superiority of GHB over diazepam in the suppression of both ethanol withdrawal and hypercortisolism. Taken together, our data suggest that GHB may act as potent anti-withdrawal agent in severe abstinent alcoholics.

Keywords: Alcohol withdrawal syndrome, diazepam, gamma-hydroxybutyrate, plasma cortisol level

F.N. designed the study, analyzed the data, and wrote the article. S.F., E.M., W.C., and A.L. collected and analyzed the data. G.L.G. supervised the study.

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INTRODUCTION

Alcohol withdrawal syndrome is a serious medical condition that may lead to a number of severe complications such as seizures, delirium tremens, and disturbed electrolyte and vitamin levels, some of which are life-threatening (1, 2).

The management of withdrawal syndrome represents only the first step in the alcohol dependence treatment that is essentially based on intervention through psycho-social support and the use of drug therapy (3–9). The treatment of alcohol-withdrawal syndrome is usually carried out with diazepam or chlordiazepoxide (6, 10–13).

Although benzodiazepines are the safest and the most effective drugs used in the relief of alcohol withdrawal, they may be contraindicated in a small percentage of patients such as those with severe hepatic impairment (if using long-acting compounds) or seizures (if using short-acting compounds). Moreover, there are no data showing that benzodiazepines in comparison with other drugs are more effective in term of success rates (13). Consequently, in the latest years, other agents have been examined as potential alternatives: compounds that reduce sympathetic activation (such as clonidine, propranolol, atenolol) (14–16), anticonvulsants (such as carbamazepine, phenytoin, valproex sodium, and gabapentin) (17–25), dopaminergic agents (such as tiapride, bromocriptine, and cyamemazine) (26–30), mood stabilizers (such as lithium) (31), and other drugs such as chloromethiazole (a thiamine derivative) (17, 26, 32) or baclofen (a GABA_B agonist) (33). Although the above drugs are largely used, their efficacy has not been fully established and some of them recognize important side effects such as dependence (3, 6).

Recently, gamma-hydroxybutyrate (GHB), a naturally occurring short-chain fatty acid related to gamma-aminobutyric acid (GABA) (34, 35), formerly used as hypnotic/anaesthetic agent (36), has been shown as effective in reducing narcolepsy at the dose range of 2–4.5 g/day (37, 38), and alcohol withdrawal syndrome, ethanol use and craving at the dose range of 50–150 mg/kg body weight/day (39). In particular, five studies have addressed the efficacy of GHB in the suppression of alcohol-withdrawal symptoms in humans (40–44). Moreover, different studies have also proven that GHB may induce and maintain alcohol abstinence in 11–78% of alcoholics (45–50). Although all previous studies have shown that GHB is safe, well-tolerated, and effective, they also warn that the major risk of its use may be a dependence state that may occur in the 10–15% of patients receiving the drug for the treatment of alcoholism (48, 51). With regard to the risk of dependence some studies have shown that GHB abuse liability may be reduced under a strict clinical surveillance and supervision by members of family and of alcohol rehabilitation.
programs (52). If the above precautions are taken in account during GHB administration, its use may represent a potential effective and safe drug for the management of alcohol withdrawal.

Recently, some evidence suggests that GHB may have a dual mechanism of action in the brain (35). In particular, biochemical data indicate that the intrinsic neurobiological activity of GHB may be due to the activation of their own receptors, while the most important clinical effects may be mediated via the GABA_B receptors (35). Newer studies suggest that GHB may act on specific receptors inducing a perturbation in GABA, dopamine, and opiate release in several regions of the brain (35, 53, 54). Today, the molecular mechanisms of GHB effects on alcohol intake, craving and withdrawal are still unclear but several studies indicate that they may be related to the ethanol-mimicking action of the drug on the central nervous system (48, 51). In fact, several data suggest that GHB may act as a “substitute” of the alcohol on the central nervous system (48, 51), an effect that is not shared with the other classes of drugs used to treat alcoholism.

A previous clinical work has suggested that GHB is as effective as diazepam in the treatment of alcohol withdrawal syndrome (42). Interestingly, the above study showed that GHB seems to be quicker in reducing anxiety, agitation, and depression in abstinent alcoholics (42). Up to now, no studies were performed to compare the diazepam and GHB effects on the responsivity of hypothalamic-pituitary-adrenocortical (HPA) axis in abstinent alcoholics. Since a large body of evidence suggests that the severity of alcohol withdrawal syndrome may be strictly correlated to hypercortisolism (55–62) we would expect that GHB would be more effective than diazepam at reducing both withdrawal syndrome and hypercortisolism in alcoholics. As a proof-of-concept test of this hypothesis, we did an open randomized study to compare the effects of GHB and diazepam at reducing withdrawal syndrome and hypercortisolism in individuals who are in severe alcohol abstinence.

METHODS

We recruited patients in Lombardia region (Italy) who provided informed consent and agreed to participate in the study. To be included in the research, participants were required to meet the following criteria: (1) DSM-IV TR diagnosis for alcohol dependence; (2) age 18 years or older; (3) no pregnancy; (4) no axis I psychiatric or other drug-dependence disorders; (5) no HIV antibodies; (6) no serious physical illness (e.g., active tuberculosis, acute hepatitis or cirrhosis, renal and cardiovascular illness, unstable diabetes); (7) no previous pharmacological
treatment for drug abuse. Individuals who met the above criteria were evaluated by medical history and physical examination, chest-X ray, EKG, and chemistry, haematology, alcohol breath test, and urinalysis testing.

Only patients with severe alcohol-withdrawal syndrome were eligible for inclusion in the study. The severity of the withdrawal syndrome had to reach ≥20 points on the Clinical Institute Withdrawal Scale—revised (CIWA-Ar) (64, 65).

The study consisted of an inpatient program for the treatment of alcohol withdrawal syndrome lasting three weeks. The research was advertised by notices, word of mouth, and written information. If the above eligibility criteria were met, participants came to the inpatient clinic on the morning before the admission day to give their informed consent to participate in the study, and they were invited to stop immediately their alcohol use. Those who returned the following day in alcohol withdrawal were randomly assigned to either diazepam or GHB; standard vitamin supplementation (vitamin B1) was given to all patients. The randomization assignment was generated via computer software. No other sedative or ancillary medications were allowed.

Of 55 participants screened, 8 were excluded for medical reasons, 3 were excluded for reasons of current treatment with psychotropic medications, and 2 declined participation. Thus, a total of 42 patients were randomized to study conditions. The participants were enrolled in two groups:

1) 21 patients received a treatment with GHB) (50 mg/kg/day of bodyweight fractionated in four daily doses);
2) 21 patients received a treatment with diazepam (.5 mg/kg/day bodyweight fractionated in four daily doses).

All medications were administered four times a day (at 8.00 a.m., 12.00 p.m., 4.00 p.m., and 8.00 p.m.). In the case of intoxicated subjects, the first administration was possible after completing screening procedures and only after the blood-alcohol level had dropped to <.1% (100 mg/dl). At admission and also during the study period, alcohol abstinence was checked by a breath analyzer at least once every day. Illegal drugs were also monitored every week by urine analysis using an immunoassay technique.

Starting from the first week of treatment, and only if the CIWA-Ar score was <5, both medications were gradually tapered according to clinical response. After three weeks of inpatient treatment, all patients had the possibility to receive, in an outpatient clinical setting, a maintenance program including a drug therapy plus psycho-social support.
(consisting in weekly counselling sessions and cognitive-behaviour and skill-training therapies).

All patients were followed for three weeks. The alcohol withdrawal syndrome was evaluated at 8.00 a.m. before the first daily medication dose using the CIWA-Ar. The alcohol withdrawal symptoms on CIWA-Ar were evaluated every day during the course of the study. Plasma cortisol levels were evaluated at admission, and at the first day of the first, second, and third week of treatment, respectively. The blood samples were collected to detect plasma cortisol levels at 12.00 p.m. On the day of cortisol measurement, the pharmacological treatment was given after the blood collection. The plasma cortisol level was determined using a radioimmunoassay technique (Diagnostic Product Corporation, Los Angeles, CA, USA). Cortisol intra- and inter-assay coefficients of variation were 2.5 and 6%, respectively.

Data were analyzed using the Statistical Package for the Social Science (SPSS) version 11.0. Analysis of variance (ANOVA) was used to test for differences in continuous variables. Comparison between groups was performed by a two-way ANOVA, a Student’s t-test or a chi-square analysis as appropriate. For ANOVA analysis, post-hoc comparison was carried out using a Student-Newman–Keuls test. All statistical tests were two-tailed and all significance levels were set at \( p < .05 \).

The study was approved by the local ethic committee and was conducted according to the principles of the Helsinki Declaration, the good clinical practice consolidate guidelines, and the Italian law on privacy of personal data.

RESULTS

The two groups of patients were well matched in terms of demographic characteristics, living situation, and alcohol use.

Both pharmacological treatments reduced the withdrawal syndrome and decreased hypercortisolism (Figure 1 and Table 1). In particular, as depicted in Figure 1, GHB was more effective than diazepam at reducing both withdrawal syndrome (measured as CIWA-Ar total score) and hypercortisolism. Interestingly, as reported in Table 1, GHB was also more able to reduce several of CIWA-Ar mean subscores such as tremor, paroxysmal sweats, anxiety, and agitation at the different times of observation (including the first week of treatment).

In both groups the drug tapering started from the second week of treatment. In particular, the tapering in the GHB group interested 16 subjects, while in the diazepam group, only 1 patient.
In the GHB-treated group, a significant relationship between a reduction of plasma cortisol levels and a decrease of alcohol withdrawal symptoms was noted ($r = .95$, $p = .02$). On the contrary, in the diazepam group, this correlation was not observed ($r = .82$, $p = .09$).

After completion of the three-week inpatient study, all 42 subjects accepted to enter in the outpatient treatment.

All subjects completed the study without drop-out, severe adverse effects, or medical complications.

**DISCUSSION**

In agreement with a previous work, GHB was able more than diazepam to reduce alcohol withdrawal syndrome at the different times of observation (42). Interestingly, this effect was also observed during the first week of treatment on some of CIWA-Ar mean subscores and it is in accord with a previous work suggesting that GHB may be quicker than diazepam to reduce some symptoms of withdrawal such as anxiety and agitation (as measured on CIWA-Ar), and depression (as measured on the Zung self-rating depression scale) (42). The effects of GHB on alcohol withdrawal may be due both to GHB ethanol-mimicking and anticraving actions, able to decrease in short time some of the most important symptoms strictly associated with alcohol withdrawal. In spite of the study of Addolorato et al. (42) that find no significant differences in terms of
Table 1. CIWA-Ar sub-mean scores at baseline and at different times of the study in the diazepam and GHB group, respectively

<table>
<thead>
<tr>
<th>Nausea and vomiting</th>
<th>Tremor</th>
<th>Paroxysmal sweats</th>
<th>Anxiety</th>
<th>Agitation</th>
<th>Tactile disturbances</th>
<th>Auditory disturbances</th>
<th>Visual disturbances</th>
<th>Headache, fullness in head</th>
<th>Orientation and clouding of sensorium</th>
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<tbody>
<tr>
<td><strong>Diazepam treatment (n = 21)</strong></td>
<td></td>
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</tr>
<tr>
<td>1st day</td>
<td>2 ± 0</td>
<td>3.67 ± .48</td>
<td>5.19 ± 1.08</td>
<td>5.33 ± .97</td>
<td>4.71 ± .56</td>
<td>2 ± 0</td>
<td>2 ± 0</td>
<td>1 ± 0</td>
<td>1 ± 0</td>
</tr>
<tr>
<td>2nd day</td>
<td>2 ± 0</td>
<td>3.71 ± .46</td>
<td>3.28 ± .48</td>
<td>5.42 ± .92</td>
<td>5.42 ± .92</td>
<td>2 ± 0</td>
<td>2 ± 0</td>
<td>1 ± 0</td>
<td>1.09 ± .43</td>
</tr>
<tr>
<td>3rd day</td>
<td>2 ± 0</td>
<td>3.84 ± .21</td>
<td>4.09 ± .43</td>
<td>4.38 ± .49</td>
<td>4.19 ± .40</td>
<td>2.19 ± .40</td>
<td>2 ± 0</td>
<td>1.61 ± .49</td>
<td>1.23 ± .53</td>
</tr>
<tr>
<td>4th day</td>
<td>1.57 ± .50</td>
<td>3.59 ± .51</td>
<td>3.23 ± .43</td>
<td>3.52 ± .52</td>
<td>4.12 ± .51</td>
<td>2.57 ± .92</td>
<td>1.61 ± .66</td>
<td>1.28 ± .46</td>
<td>.38 ± .49</td>
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<tr>
<td>5th day</td>
<td>1.90 ± .30</td>
<td>3.53 ± .51</td>
<td>3.28 ± .46</td>
<td>3.90 ± .30</td>
<td>3.82 ± .40</td>
<td>2 ± 0</td>
<td>2.14 ± .65</td>
<td>1 ± 0</td>
<td>.71 ± .46</td>
</tr>
<tr>
<td>6th day</td>
<td>.66 ± .48</td>
<td>2.71 ± .46</td>
<td>3.33 ± .48</td>
<td>3.61 ± .49</td>
<td>3.95 ± .49</td>
<td>1.61 ± .49</td>
<td>1.04 ± .21</td>
<td>.66 ± .48</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>7th day</td>
<td>.33 ± .48</td>
<td>3.24 ± .62</td>
<td>2.90 ± .30</td>
<td>3.81 ± .60</td>
<td>3.43 ± .51</td>
<td>1.19 ± 6.68</td>
<td>1 ± 0</td>
<td>.33 ± .48</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>14th day</td>
<td>0 + 0</td>
<td>1.48 ± .51</td>
<td>1.48 ± .51</td>
<td>1.48 ± .51</td>
<td>2.05 + 1.02</td>
<td>.89 + .42</td>
<td>.90 + .30</td>
<td>.48 + .51</td>
<td>.43 + .51</td>
</tr>
<tr>
<td>21st day</td>
<td>0 + 0</td>
<td>.95 + .67</td>
<td>.90 + .70</td>
<td>.85 + .67</td>
<td>1.14 + 1.01</td>
<td>.05 + .22</td>
<td>.24 + .44</td>
<td>.24 + .44</td>
<td>.29 + .46</td>
</tr>
<tr>
<td><strong>GHB treatment (n = 21)</strong></td>
<td></td>
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</tr>
<tr>
<td>1st day</td>
<td>2 ± 0</td>
<td>3.71 ± .46</td>
<td>5.38 ± 1.28</td>
<td>5.42 ± .92</td>
<td>5.04 + .86</td>
<td>2 ± 0</td>
<td>1.71 + .46</td>
<td>1.28 + .46</td>
<td>.85 + .35</td>
</tr>
<tr>
<td>2nd day</td>
<td>2 ± 0</td>
<td>*3.33 ± .48</td>
<td>*3.52 ± .51</td>
<td>*5.00 + .83</td>
<td>*4.71 ± 0.95</td>
<td>2 ± 0</td>
<td>*1 ± 0</td>
<td>* .85 + .35</td>
<td>.95 ± .21</td>
</tr>
<tr>
<td>3rd day</td>
<td>2 ± 0</td>
<td>*3.04 ± .21</td>
<td>*3.66 ± .48</td>
<td>*3.82 ± .46</td>
<td>*3.95 ± .21</td>
<td>*1.90 ± .30</td>
<td>2.09 ± .30</td>
<td>*1 ± 0</td>
<td>* .80 ± .46</td>
</tr>
<tr>
<td>4th day</td>
<td>1.57 ± .50</td>
<td>*3.19 ± .51</td>
<td>*2.83 ± .56</td>
<td>*3.12 ± .41</td>
<td>*3.52 ± .51</td>
<td>2.57 ± .92</td>
<td>1.61 ± .66</td>
<td>1.28 ± .66</td>
<td>.38 ± .49</td>
</tr>
<tr>
<td>5th day</td>
<td>*1.52 ± .51</td>
<td>*3.19 ± .51</td>
<td>*2.64 ± .43</td>
<td>*3.66 ± .48</td>
<td>*3.52 ± .51</td>
<td>*2.57 ± .92</td>
<td>*1.52 ± .67</td>
<td>* .57 ± .59</td>
<td>* .42 ± .50</td>
</tr>
<tr>
<td>6th day</td>
<td>* .47 ± .54</td>
<td>*2.38 ± .49</td>
<td>*2.57 ± .50</td>
<td>*3.04 ± .80</td>
<td>*2.90 ± .43</td>
<td>*1.04 ± .80</td>
<td>1 ± 0</td>
<td>.66 ± .48</td>
<td>*0 ± 0</td>
</tr>
<tr>
<td>7th day</td>
<td>* .05 ± .22</td>
<td>*2.33 ± .91</td>
<td>*2.24 ± .62</td>
<td>*2.48 ± .93</td>
<td>*3.81 ± .60</td>
<td>* .43 ± .60</td>
<td>* .48 ± .51</td>
<td>*0 ± 0</td>
<td>* .29 ± .46</td>
</tr>
<tr>
<td>14th day</td>
<td>0 + 0</td>
<td>* .38 + .50</td>
<td>* .71 + .56</td>
<td>* .76 + .44</td>
<td>* .90 + .30</td>
<td>* .19 + .40</td>
<td>*0 + 0</td>
<td>*0 + 0</td>
<td>*0 + 0</td>
</tr>
<tr>
<td>21st day</td>
<td>0 + 0</td>
<td>* .05 + .22</td>
<td>* .33 + .48</td>
<td>* .67 + .48</td>
<td>* .14 + .36</td>
<td>0 + 0</td>
<td>*0 + 0</td>
<td>*0 + 0</td>
<td>*0 + 0</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD* p < .05.
CIWA-Ar total scores between treatments, we observed that GHB was more able to reduce alcohol withdrawal syndrome. In particular, while Addolorato et al. (42) observed in GHB group a more significant reduction of anxiety on day 4, and of agitation on day 5, we noted that GHB was also able to reduce, at different times of observation, the mean of the CIWA-Ar subscores corresponding to tremor, paroxysmal sweats, anxiety, and agitation. The discrepancies in terms of results between the two studies may be due to several reasons. The most important of them are due to the differences in the characteristics of the samples and in the diazepam therapeutic regimen. In fact, the study of Addolorato et al. (42) recruited patients with a greater age range (19–63 years) and duration of alcoholism (2–42 years) and it used a more elevated and flexible therapeutic doses of diazepam (.5 to .75 mg/kg bodyweight).

The evidence showing that drug tapering occurred for both drugs after the second week of treatment may suppose that the observed superiority of GHB over diazepam may be a result of the use of low and fixed doses of diazepam during the first week of treatment. However, the data showing that the drug tapering started for both drugs after the second week of treatment and it interested in a more large number the subjects in the GHB treatment, may suggest that GHB over diazepam should be more able to control alcohol withdrawal syndrome during the first week of treatment.

As expected, GHB was more able than diazepam to reduce hypercortisolism, suggesting a possible correlation between the resolution of acute alcohol withdrawal and the return of plasma cortisol to control levels (61, 62). In accord with this hypothesis, our study showed, in the GHB group only, a significant correlation between the reduction of alcohol withdrawal syndrome and the decrease of hypercortisolism. This aspect may represent the most important novelty of the study and it may suggest that the slight superiority of GHB over diazepam may be due to its major ability to suppress hypercortisolism.

It has been well established that chronic alcohol use and withdrawal are associated with an altered hypothalamic pituitary adrenal axis (HPA) response (55–58, 61, 63, 66, 67). In particular, different studies have shown that chronic alcoholics show a blunted response of adrenocorticotropic hormone (ACTH) to several acute intervening stressors (59, 63, 66, 67), an effect that is predictive of a return to early drinking (68, 69). On the other hand, it has been recognized that hypercortisolism induced by alcohol withdrawal may underlie some of the clinical complications of alcoholism, including seizures and delirium tremens, and increased risk of psychiatric disorders (59, 62, 63). Moreover, an interesting study has demonstrated that a poorer cognitive performance in alcoholics may be related to higher cortisol levels during a recent withdrawal (70). Another research has suggested that in alcoholics higher plasma cortisol
concentrations are inversely correlated with the availability of raphe serotonin transporters and positively correlated with the severity of clinical depression (71). Considering the above evidence, an important goal of the pharmacological treatment of ethanol withdrawal syndrome should be the normalization of the HPA axis function, in order to better suppress the withdrawal syndrome and to prevent possible severe complications (including psychiatric disorders and relapse). In accord with our hypothesis, here GHB reduced more potently both hypercortisolism and abstinence symptoms, suggesting that the drug may act, normalizing the HPA axis function, as potent anti-withdrawal agent in severe abstinent alcoholics.

As previously demonstrated, both medications were safe, well-tolerated, and effective (10, 48, 49) and no patients dropped out.

Our study presents some limits. The first is the small size of the samples. The second is the time course of the cortisol measurements that consists of only four time points that may create some limitations on the ability to interpret causal relationship between plasma cortisol levels and withdrawal symptoms. Moreover, the plasma cortisol levels, that have a well-known circadian rhythms, were measured only once daily, at noon. Another bias of the study regarding the cortisol measurements may be represented by the influence that both medications may have on plasma cortisol levels since blood samples were always collected four hours after the first daily drug administration. The third is the doubt that the GHB doses used in the study are not exactly equivalent to those of diazepam given in the course of the study. In fact, the observed slight superiority of GHB over diazepam may be a result of the use of a relatively low and fixed dose of diazepam during the treatment. The fourth is that the study was not blinded. This aspect may represent a relevant limit of the study since the lack of blinding might have affected the CIWA-Ar scores and/or the plasma cortisol levels. However, despite the limitations of our study, we may suggest the use of GHB as a potent and safe anti-withdrawal agent in severe abstinent alcoholics.

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GHB Effects in Severe Abstinent Alcoholics


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