

DOUBLE-BLIND CONTROLLED TRIAL OF γ -HYDROXYBUTYRATE AND CLOMETHIAZOLE IN THE TREATMENT OF ALCOHOL WITHDRAWAL

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Abstract — The aim of this double-blind, comparative study was to assess the efficacy and safety of γ -hydroxybutyrate (GHB) in ameliorating the symptoms of alcohol withdrawal. Newly admitted alcohol-dependent patients ($n = 98$) were randomized to receive either clomethiazole 1000 mg daily (CLO group) ($n = 33$), or 50 mg GHB/kg body wt ($n = 33$) or 100 mg GHB/kg body wt ($n = 32$). This dose was administered for 5 days, halved on day 6, and on days 7 and 8 only placebo was given. As CLO is available as capsules and GHB as syrup, a double-dummy method was used to try to ensure blindness. The groups were matched in terms of baseline demographic and alcohol-related variables. There was no difference between the three treatments in ratings of alcohol withdrawal symptoms nor requests for additional medication. After tapering off the active medication, there was no increase in withdrawal symptoms, indicating that physical tolerance did not develop to either GHB or CLO within the 5-day treatment period. The most frequently reported side-effect of GHB was transient vertigo, particularly after the evening double dose.

INTRODUCTION

Sudden withdrawal of alcohol after heavy and regular use may lead to a number of complications, some of which are life-threatening (Yost, 1996; Hall and Zadar, 1997). In this situation, sedative drugs are required and a variety have been used. Diazepam (Kramp and Rafaelsen, 1978) is widely used in Europe, whereas chlordiazepoxide (Sereny and Kalant, 1965; Saitz, 1994) is the drug of choice in the USA. In addition, barbiturates (Harfst *et al.*, 1967; Kramp and Rafaelsen, 1978) and meprobamate (Wegner and Fink, 1965) are sometimes used for this indication. Clomethiazole, a thiamine derivative, whose efficacy is well documented (Ritola and Malinen, 1981), is also frequently used. It has been shown to be equal to chlordiazepoxide (Lapierre *et al.*, 1983) and superior to placebo (Glatt *et al.*, 1966). Clomethiazole's side-effects often require dose adjustments, and, after long-term therapy, discontinuation can reveal dependency symptoms. Also, after intravenous administration, it can increase bronchial secretion. Therefore, other agents have been examined as potential alternatives: carbamazepine, dopaminergic agents (such as tiapride), and compounds that reduce sympathetic activation (such as β -blockers and α_2 -adrenergic agonists) (Bjorkvist, 1975; Sellers *et al.*, 1977; Murphy *et al.*, 1981; Ritola and Malinen, 1981). However, the efficacy of these newer drugs has not been fully established (Lesch and Nimmerrichter, 1993; Lesch and Walter, 1994; Mayo-Smith, 1997; Williams and McBride, 1998).

γ -Hydroxybutyrate (GHB) is a neurotransmitter that occurs naturally in the mammalian brain, where it seems to have a role in sleep induction (Van Cauter *et al.*, 1997). This property was first used in clinical practice over 30 years ago, when GHB was administered as a sedative and anaesthetic. When administered intravenously in the dose range of 50–100 mg/kg body wt/day, it is generally well tolerated. GHB has no effect on respiratory function, but it may lead to a slight increase in systolic blood pressure and a decrease in heart rate. Rarely, myoclonia may occur.

GHB has been used in the treatment of alcoholism for withdrawal and in relapse prevention. Oral GHB has been successfully used for the short-term treatment of alcohol withdrawal (Gallimberti *et al.*, 1989; Nimmerrichter *et al.*, 1997). There is some evidence that it is effective both as an anticraving substance (Maremanni *et al.*, 1996), and as a support for abstinence during long-term treatment of alcohol-dependent subjects (Addolorato *et al.*, 1996, 1998). GHB received regulatory approval for both these indications in Italy in 1993 and has been submitted for similar registration in Austria, Hungary, Portugal and France. The pharmacological profile of GHB with its inhibitory action on the central nervous system, anxiolytic property, and its profound effects on the dopaminergic system is the rationale for using it as treatment for both withdrawal symptoms and controlling ethanol consumption (Cash, 1994; Maître, 1997; Agabio *et al.*, 1998). In the double-blind, placebo-controlled study of Gallimberti *et al.* (1989), withdrawal symptoms of 11 participants treated with GHB 50 mg/kg body wt were compared to those of 12 participants taking placebo. Di Bello *et al.* (1995) demonstrated in an open study the effectiveness of GHB in 55% of cases in a dose range from 50 to 150 mg/kg body wt/day. The methodological weaknesses of these studies included the small number of participants, the lack of a control group, and insufficient description of the participants. In the study of Gallimberti *et al.* (1989) 28% had used illicit drugs in the past. Di Bello *et al.* (1995) did not describe the previous drug use of their subjects.

The study we report here compares low and high dosage of GHB with clomethiazole (CLO). Both drugs were evaluated for effects on acute withdrawal symptoms, craving for alcohol, and rebound phenomena after treatment discontinuation.

SUBJECTS AND METHODS

Study design

The study was double-blind, double-dummy with randomization to one of three treatments, two dosages of GHB and one of CLO, over 8 days. The study design followed the Guidelines of The Plinius Maior Society (1994) and was approved

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by the Ethics Committee of the Vienna University Clinic. The trial was conducted in compliance with the current revision of the Declaration of Helsinki.

Inclusion/exclusion criteria

During the period of the study, 967 patients were admitted to the Anton-Proksch-Institute. Of these, 101 were considered potential participants and were asked for informed consent (all other patients were either already detoxified, pre-medicated, or dependent on substances other than alcohol). Informed consent was given by 98 patients and these were screened. All participants fulfilled at least three DSM-IV (American Psychiatric Association, 1994) and ICD-10 criteria (World Health Organization, 1992) for the diagnosis of alcohol dependence. The 'Münchener Alkoholismustest' (MALT) (Feuerlein *et al.*, 1979) was applied to confirm the diagnosis. Only patients with severe alcohol dependence and 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 (CIWA-Ar) (Sullivan *et al.*, 1989; Stuppaeck *et al.*, 1994), with at least 12 points scored on items 4 (tremor), 5 (sweating), and 11 (nervousness/anxiety), as these were deemed the core symptoms of physical withdrawal, in the following referred to as CIWA-Ar-short. Participants also had to have an elevated γ -glutamyltransferase (GGT; ≥ 1.3 times the upper normal range) and/or mean corpuscular volume (MCV; ≥ 95 fl) and/or relative carbohydrate-deficient transferrin (%CDT) levels ($\geq 2.5\%$) in order to include an objective measure for the severity of the alcohol problem.

Exclusion criteria were: illnesses such as decompensated liver cirrhosis, acute pancreatitis, reduced respiratory function, acute pulmonary or bronchial disease, myocardial infarction during the preceding 6 months and cardiac arrhythmia; dementia, schizophrenia, polysubstance misuse or dependence or use of benzodiazepines and hypnotics (all participants underwent urinary drug screening for illegal drugs and sedatives); suspected sleep apnoea syndrome; an allergy to either of the study drugs; epileptic seizures, except those forms occurring exclusively during alcohol withdrawal. A history of delirium associated with alcohol withdrawal was not a reason for exclusion.

Treatments administered

After giving written informed consent, participants were randomized to one of the three treatments by means of a computerized randomization schedule. Patients with severe withdrawal symptoms (≥ 20 points on the CIWA-Ar) at admission received the first drug dose after inclusion into the study. In the case of intoxicated participants the first administration was possible after completing screening procedures and only after the blood-alcohol level had dropped to $\leq 0.1\%$ (100 mg/dl). At admission and also during the study period, alcohol abstinence was checked by a breathalyser at least once every day. Specially appointed research personnel were responsible for administering the tests and supervising intake of the study medication.

All medications were administered four times a day (at 08.00, 12.00 and 16.00) with double doses in the evening (20.00). Thus, from day 1 (day of admission and start of treatment) to day 5, the daily dosage administered was either 1000 mg of CLO according to the prescribing advice for Austria or 50 mg of GHB/kg body wt (GHB₅₀) or 100 mg of GHB/kg body wt

(GHB₁₀₀). On day 6, participants received only half the daily dose, with the other half of the dose being substituted by placebo. On days 7 and 8, only placebo was given. Placebo was administered either as capsules of identical shape, size, taste and colour, or as a syrup. During the first 5 days, an additional administration of GHB or CLO was allowed at midnight. Participants asking for an additional dose at night were analysed separately, but remained in the study. No other sedative medication was allowed.

Efficacy and safety measures

The primary efficacy variable was reduction of the withdrawal syndrome on the CIWA-Ar compared to the individual baseline level, in the intention-to-treat (ITT) group. We were interested specifically in the main symptoms of physical withdrawal, such as anxiety, sweating and tremor. The severity of the withdrawal syndrome was measured at eight times on day 2, between 07.30 and 14.30, using CIWA-Ar. On days 3–5, withdrawal symptoms were assessed once, and only the main items constituting withdrawal were assessed, namely items 4 (tremor), 5 (sweating) and 11 (anxiety) of the CIWA-Ar, which we have termed CIWA-Ar-short.

On days 1 and 8, clinical and biological parameters, including electrocardiogram, CDT, MCV, GGT, aspartate aminotransferase (ASAT), and alanine aminotransferase (ALAT) were measured. Side-effects of the study treatment were determined by open questions: the investigator asked the participant how he had been feeling since the last application of the study medication.

Tests administered

The severity of the desire for alcohol was measured using the 'Lübeck Craving-Risk-Relapse questionnaire' (LCRR-1), which includes a visual analogue rating scale for the intensity of craving and verbal information concerning the frequency of craving (Veltrup, 1994). The LCRR-1 craving scale was used to assess a possible increase in craving symptoms during the reduction phase of the study (from day 6 onwards). Details of this analysis will be published elsewhere.

All participants were classified according to Lesch's typology with the 'Lesch Alcoholism Typology Questionnaire' (Lesch *et al.*, 1991) and rated on the 'Addiction Severity Index' (ASI) (McLellan *et al.*, 1980), which was administered when the patient was recovering from alcohol withdrawal, on day 5.

Additional medication requested was documented daily.

Statistical analyses

A sample size of 30 per group was chosen according to therapeutic experiences with CLO and GHB. Most of the earlier studies with GHB were placebo-controlled without active comparator. In these studies, the coefficient of variation (CV%) in CIWA-Ar scores was $\sim 20\%$. Thus, it was concluded that, when using 20% CV%, an α of 0.05 and a power of 0.8, a difference between treatment groups of 1.5 points according to the CIWA-Ar scale would yield a significant result, if 30 participants per group were evaluated. The primary parameter for the evaluation of efficacy was the effect of the study treatments on the symptoms of withdrawal measured on the morning of day 6 and the detection of possible rebound phenomena after discontinuation of the study treatments on day 8 (measured as an increase in the CIWA-Ar score compared with that of day 6). A statistical analysis was performed using

analysis of variance based on the ITT group. The ITT group was defined as those who received at least one dose of the trial medication, and had at least one post-baseline assessment on the primary efficacy variable (CIWA-Ar scale). If the data were not normally distributed or variances were not homogeneous, the non-parametric Kruskal–Wallis *H*-test was used. For between-group comparisons, multiple comparisons by Nemenyi were used. Two-tailed tests were used throughout, testing for levels of significance at $\alpha = 0.05$. The secondary parameters were number of drop-outs, additional administration of GHB or CLO in the evening, and sedation. LOCF (last observation carried forward) was used for the primary criterion in the ITT group. Patients diagnosed as Type IV alcoholics according to Lesch *et al.* (1991) were excluded from the per protocol (PP) group, but not from the ITT group.

RESULTS

Study population

The ITT group consisted of 98 participants. Twenty-one participants were discovered to have had major protocol violations: five participants did not have the required elevation of liver enzymes, in four participants the drug screening tests were positive for benzodiazepines, and 12 participants had non-alcohol related epileptic seizures in the past. Eleven participants discontinued the study prematurely. The reason for discontinuation is described in the corresponding paragraph. Thus, the PP group consisted of 65 participants. The groups were well matched in terms of demographic and alcohol-related baseline variables (Table 1). Of the 98 patients in the ITT group, 33 participants were assigned to CLO, 32 to the GHB₁₀₀ group, and 33 to the GHB₅₀ group. There were no significant differences between the GHB groups and the CLO group in the proportions of male and female participants, age or weight. The laboratory data showed that participants in all groups had clear signs of chronic excessive alcohol intake with GGT exceeding the normal upper limit markedly, abnormal hepatic enzymes with elevated ASAT and ALAT activities,

and %CDT. The ratio ASAT/ALAT >1 in all groups is also clearly associated with heavy alcohol consumption.

The MALT, in which a total score of 11 is indicative for alcohol dependence, showed that participants were severely dependent, with no significant difference in scores between groups. There were no differences between groups in Lesch typology.

All participants showed signs of severe withdrawal (Table 2). The time of the first drug administration was considered as the baseline. At baseline, the participants showed a mean total score (sum of all items of the CIWA-Ar) of 27.1 ± 4.4 SD with no difference between the treatment groups. In the CIWA-Ar-short scale, the mean sum of items (tremor, sweating, and anxiety) (\pm SD) was 13.0 ± 1.1 in the GHB₅₀ group, 13.4 ± 1.7 in the GHB₁₀₀ group, and 13.1 ± 1.3 in the CLO group (Table 2). The differences between groups were non-significant.

Efficacy

Effect on acute withdrawal symptoms. The minimum score in the CIWA-Ar scale is 11 points (no symptom of withdrawal at all) and in the CIWA-Ar-short (consisting of items 4, 5 and 11) 3 points, which is when a patient does not show any tremor, sweating or anxiety. In all groups, withdrawal symptoms improved with almost no residual symptoms on day 2 (Table 2). By 07.30 on day 2, all participants had achieved a clinically relevant improvement of their withdrawal symptoms on CIWA-Ar. Similarly, participants scored in the item 'anxiety' 2.1 ± 1.0 , 2.1 ± 1.1 and 2.2 ± 1.3 (mean \pm SD) in groups GHB₅₀, GHB₁₀₀ and CLO, respectively. There was no statistically significant difference between the three treatments on day 2, neither in the CIWA-Ar nor in the CIWA-Ar-short. Thus, the main effect of all three treatments occurred within the first 48 h (Fig. 1).

From day 3 onwards, participants showed few, mild symptoms of withdrawal. There was no major deterioration during the rest of the study period. In accordance with the study protocol, participants did not receive any active drug on days 7 and 8. There was no change in CIWA-Ar when the active medication was completely tapered off and placebo only was given (days 6–8), i.e. no rebound effects were seen.

Table 1. Patient characteristics

Parameter	CLO (<i>n</i> = 33)	GHB ₁₀₀ (<i>n</i> = 32)	GHB ₅₀ (<i>n</i> = 33)
Sex (male/female)	29/4	30/2	30/3
Age (years)	39.0 ± 7.3	41.6 ± 9.1	42.9 ± 7.9
Weight (kg)	72.0 ± 13.7	75.7 ± 11.8	73.1 ± 12.5
Blood-alcohol level % at admission	1.99 ± 0.045	1.09 ± 0.049	1.01 ± 0.05
MCV (fl) (uln 101)	97.9 ± 7.9	94.9 ± 5.5	99.3 ± 7.0
%CDT (uln $\leq 2.5\%$)	5.9 ± 6.1	5.3 ± 4.8	4.8 ± 5.3
GGT (IU/l) (uln 28)	199 ± 312	187 ± 396	204 ± 255
ASAT (IU/l) (uln 18)	40.2 ± 36.4	35.2 ± 32.6	44.7 ± 40.8
ALAT (IU/l) (uln 22)	36.8 ± 27.6	30.2 ± 30.4	39.2 ± 40.8
ASI (sum score) <i>n</i> = 28, 31, 32 respectively	20.6 ± 8.3	24.7 ± 9.0	22.7 ± 9.0
MALT	36.8 ± 5.5	38.7 ± 6.3	36.3 ± 6.1
MALT-F	4.6 ± 0.9	4.8 ± 1.0	4.4 ± 1.1
MALT-S	19.1 ± 3.0	19.5 ± 3.5	18.7 ± 3.6
Lesch type (I/II/III/IV)	2/13/14/3	2/15/10/4	2/17/9/5

Values are means \pm SD or in numbers.

ASI, addiction severity index; CLO, chlomethiazole; GHB₁₀₀, 100 mg/kg daily dose of γ -hydroxybutyrate; GHB₅₀, 50 mg/kg daily dose of GHB; uln, upper limit of normal; MALT, Munich alcoholism test; MALT-F, Munich alcoholism test: objective part; MALT-S, Munich alcoholism test: subjective part. For other abbreviations, see text.

Table 2. Withdrawal symptoms during study period

Time	Symptoms and scores	Group		
		CLO (n = 33)	GHB ₁₀₀ (n = 32)	GHB ₅₀ (n = 33)
Baseline	Hyperhydrosis	4.5 ± 0.6	4.4 ± 1.0	4.4 ± 0.6
	Tremor	4.6 ± 0.7	4.8 ± 0.8	4.5 ± 0.6
	Anxiety	3.9 ± 0.9	4.2 ± 0.6	4.1 ± 0.7
	CIWA-Ar sub-score	13.1 ± 1.3	13.4 ± 1.7	13.0 ± 1.1
	CIWA-Ar total score	27.2 ± 4.9	27.2 ± 5.0	27.1 ± 3.2
Day 2 (07.30) ^a	Hyperhydrosis	2.2 ± 1.1	2.2 ± 1.2	2.0 ± 0.6
	Tremor	2.6 ± 1.2	2.5 ± 1.3	2.7 ± 1.2
	Anxiety	2.2 ± 1.3	2.1 ± 1.1	2.1 ± 1.0
	CIWA-Ar sub-score	7.0 ± 3.1	6.8 ± 3.0	6.8 ± 2.2
	CIWA-Ar total score	16.9 ± 4.9	16.7 ± 4.2	16.3 ± 3.6
Day 8 ^a	Hyperhydrosis	1.3 ± 0.8	1.4 ± 0.8	1.3 ± 0.6
	Tremor	1.5 ± 0.8	1.5 ± 1.0	1.3 ± 0.5
	Anxiety	1.5 ± 1.1	1.4 ± 0.8	1.1 ± 0.2
	CIWA-Ar sub-score	4.3 ± 2.4	4.3 ± 2.2	3.7 ± 1.1
	CIWA-Ar total score	12.8 ± 5.2	12.4 ± 4.0	11.7 ± 1.2
	Drop-outs	6	4	1

^aLast value carried forward.

For group abbreviations, see Table 1. For other abbreviations, see text.

There were no statistically significant differences between treatment groups (Table 2). This observation is further supported by the LCRR-1 scores (data not shown). At baseline, 20 participants in CLO, 18 in GHB₅₀, and 21 in GHB₁₀₀ reported craving. These feelings disappeared completely from day 4 onwards and did not reappear on days 6 or 7 (i.e. after discontinuation of GHB or CLO).

Statistical analysis revealed no differences between either GHB dosages as compared to CLO, nor between the two dosages of GHB, so that the results obtained with these treatment schemes can be considered as equal.

Premature discontinuation. Six participants in the CLO group discontinued the study (Table 2): one suffered a seizure on day 1, another withdrew his consent also on day 1, one did not respond adequately to therapy and discontinued on day 1, and three discontinued for other non-medical reasons (on days 2, 4 and 5). One patient from the GHB₅₀ group dropped out because of insufficient treatment response on day 4. Four from the GHB₁₀₀ group discontinued prematurely, two because of insufficient treatment response on day 2, one because of a grand mal seizure on day 3 and one for medical reasons other than withdrawal symptoms on day 4 (Table 2).

Additional medication. Additional study medication had to be given 25 times; five participants in the CLO group (total of 10 requests), four participants in the GHB₅₀ group (nine requests), and four participants in the GHB₁₀₀ group (six requests). Thus, administration of GHB at the lower dosage regimen did not lead to more requests for additional administration of medication than in the higher dosage group. Furthermore, there was no increased need for additional medication in either GHB groups, compared to CLO, despite GHB's half-life of 20 min.

Adverse events

Fifty-five participants complained of adverse events (Table 3). The most frequently reported adverse event was vertigo. Here, nine participants in the GHB₅₀ group suffered from 17 attacks of vertigo, 17 participants in the GHB₁₀₀ group reported 32

attacks and seven participants in the CLO group suffered from nine attacks. Rhinitis, a frequent side-effect of CLO treatment, was reported by four participants in the CLO group, three participants in the GHB₁₀₀ group and two participants in the GHB₅₀ group. With regard to the time when adverse events occurred, an unequal distribution was identified. More than two-thirds of the events were reported between 20.00 and 24.00 after administration of the evening dose (which was twice as high as the doses administered during daytime). During this 4-h period, 61% of the adverse events in the CLO group were reported, whereas at the same time 63% of all adverse events in the GHB₅₀ group, and 75% of the events in the GHB₁₀₀ group were reported. Therefore, it is reasonable to assume that the higher rate of adverse events was related to the higher evening dose.

There were two patients suffering seizures, one in the CLO group (suffering a seizure on day 1) and the other in the GHB₁₀₀ group (with a seizure on day 3).

One participant of the GHB₁₀₀ group discontinued the study on day 4. After leaving the department, he was found in the street 12 h later, disoriented in place and situation. This patient seemed to respond well to the treatment as the CIWA-Ar score dropped from 32 (maximum score on day 1) to 15 (maximum score on day 2). On the last evaluation on day 4, he scored 2 points (on 6 possible points) on tremor and 2 points on sweating. At this evaluation, he did not show symptoms of anxiety.

DISCUSSION

The effectiveness of benzodiazepines and CLO in alcohol withdrawal treatment has been demonstrated, but both treatments have side-effects (Sereny and Kalant, 1965; Wegner and Fink, 1965; Glatt *et al.*, 1966; Kramp and Rafaelsen, 1978).

Pharmacotherapy is only one part of the therapeutic strategy in the treatment of alcoholism. Successful detoxification

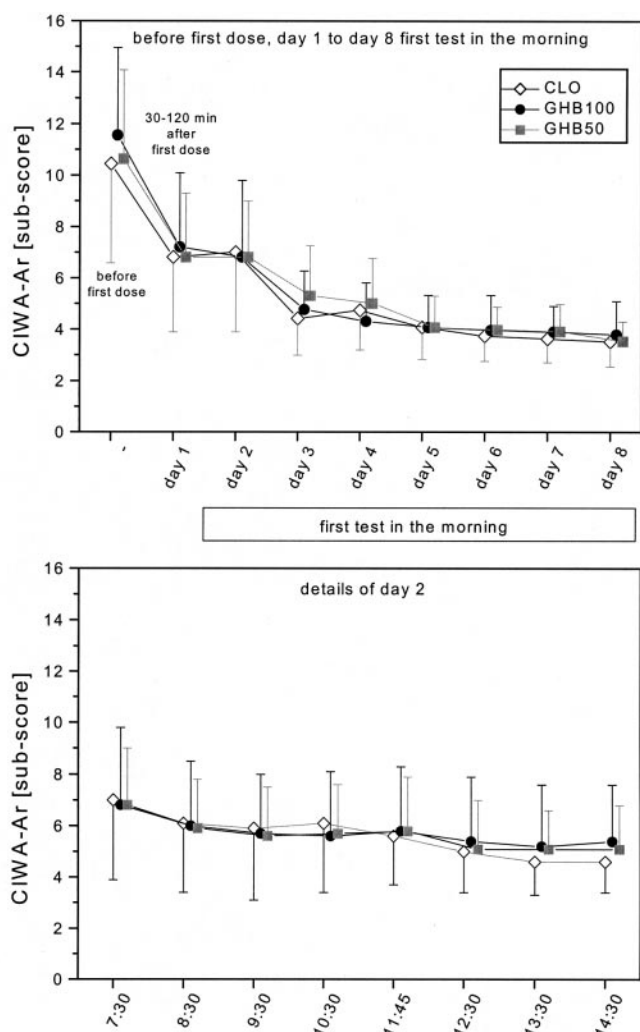


Fig. 1. Clinical Institute Withdrawal Scale (CIWA-Ar sub-score) for days 1–8, and details during day 2.

For numbers in each group, see Table 1. CLO, chlomethiazole; GHB₅₀, 50 mg γ -hydroxybutyrate/kg body wt; GHB₁₀₀, 100 mg GHB/kg body wt.

improves the motivation for further treatment and is an important precondition for relapse prevention (Lesch *et al.*, 1996; Nimmerrichter *et al.*, 1997). It can also reduce the length of withdrawal and thus the length of hospitalization (Poldrugo,

1997). A successful pharmacotherapeutic management of withdrawal will therefore promote a patient’s active participation in the treatment programme (Lesch, 1992).

GHB, a putative neurotransmitter or neuromodulator in the mammalian brain, produces a variety of neuropharmacological effects (Cash, 1994; Maître, 1997; Poldrugo and Addolorato, 1999), including reduction of ethanol consumption in animals (Agabio *et al.*, 1998) and in humans (Gallimberti *et al.*, 1992; Addolorato *et al.*, 1997, 1998). Furthermore, it has been shown to be effective in the treatment of alcohol withdrawal in rats (Poldrugo and Snead, 1984; Agabio *et al.*, 1998) and in humans (Gallimberti *et al.*, 1989; Nimmerrichter *et al.*, 1997). GHB exerts its effects via its own receptor which may be a target of ethanol action (Agabio *et al.*, 1998; Colombo *et al.*, 1998).

All participants included in our study had a severe alcohol withdrawal syndrome at baseline, with a CIWA score of ≥ 20 points. We showed that GHB at two dose levels (50 and 100 mg/kg body wt) is as effective as CLO in the dose we used (which is lower than the recommended dosage for the treatment of delirium tremens in some other countries). Sedatives administered in doses necessary to treat the alcohol withdrawal syndrome often induce cognitive dysfunction, which can prolong short-term treatment of withdrawal and impair the patient’s chances for a subsequent successful long-term treatment of addiction (Lesch and Nimmerrichter, 1993). In this respect, the use of less impairing substances like GHB may be an advantage (Lesch *et al.*, 1996).

In all three treatment groups, the withdrawal syndrome did not last longer than 3 days. At the end of day 2, participants showed no more than one or two mild symptoms (such as tremor, sweating or restlessness). Therefore, we believe that acute withdrawal can be treated within 2 or 3 days with effective medication. Subsequently, the medication should be tapered off, so that the patient does not need any sedative medication after 5 or 6 days. When participants in our study were switched from active medication to placebo on days 7 and 8, no rebound withdrawal symptoms occurred.

A short-acting treatment, such as GHB, may carry risks. The participant receiving the higher GHB dose who developed a delirium had discontinued medication for 12 h. There were no physiological symptoms indicating the development of a delirious state as long as he was under continuous medical treatment. The fact that this adverse event developed so fast could be explained by the short half-life of GHB. A longer-acting medication could have protected him.

Table 3. Summary of the most frequent adverse events

Symptom	Group					
	GHB ₅₀		GHB ₁₀₀		CLO	
	No. of patients	No. of complaints	No. of patients	No. of complaints	No. of patients	No. of complaints
Vertigo	9	17	17	32	7	9
Rhinitis	2	2	3	3	4	4
Nausea	1	1	2	2	0	0
Diarrhoea	4	4	3	3	3	3
Total	16	4	25	3	14	

For abbreviations, see Table 1.

A short and effective management of withdrawal symptoms not only reduces the inconvenience for a patient, but also saves costs. Furthermore, a successful withdrawal management with an early start of relapse prevention treatment might improve long-term prognosis.

We found no rebound effect on day 8, which indicates that administration of GHB for 5 days does not lead to drug dependence. Nevertheless, GHB is hotly debated as a drug of potential misuse. Addolorato *et al.* (1996) reported that 10.1% of patients prescribed GHB increased the dose of GHB to up to 6–7 times the therapeutic level. In addition, craving for GHB in detoxified subjects was noticeable and resulted in misuse of this drug (Addolorato *et al.*, 1997; Galloway *et al.*, 1997). For the same reason, the FDA banned the over-the-counter sale of GHB in the USA in November 1990 (Anonymous, 1991). Despite the ban, GHB is still manufactured and sold clandestinely as a street drug, which supposedly increases the risk of intoxication. Thus, it should be noticed that our data collected over a period of 6 days do not apply to medium- or long-term treatment with GHB. Our observations, as well as other reports (Poldrugo and Addolorato, 1999), indicate that GHB is a safe substance when used under strict medical supervision. The use of GHB for a longer period than detoxification should only take place under strict medical control.

There was no difference in the frequency of side-effects between CLO and GHB 50 mg/kg body wt. However, at the dosage of 100 mg GHB per kg body wt, 17 participants complained of vertigo, against only nine and seven participants in the GHB₅₀ group and in the CLO group, respectively.

During the clinical trial, two participants suffered seizures, one in the CLO group and one in GHB₁₀₀ group. GHB has been reported to induce absence-like seizures in rats (Aizawa *et al.*, 1997). In man, it is still debatable whether GHB can provoke EEG changes, which clinically resemble non-convulsive epilepsy (Cash, 1994). In our sample of 98 alcohol-dependent participants, no such petit mal seizures occurred.

It proved unnecessary to administer GHB at higher dosages. GHB showed considerably more side-effects, especially vertigo, at the larger dose of 100 mg/kg body wt. It seems that, for an average adult, single doses of GHB need not exceed 700 mg.

We conclude that GHB is equivalent in efficacy and tolerability to CLO used according to Austrian prescribing advice. In view of the equivalent efficacy of both dosages of GHB and the higher frequency of adverse events after administration of higher dosages, the lower dosage of 50 mg/kg body wt/day has proved sufficient for treating even severe symptoms of alcohol withdrawal.

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