



BRIEF OBSERVATION

Baclofen in the Treatment of Alcohol Withdrawal Syndrome: A Comparative Study vs Diazepam

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ABSTRACT

PURPOSE: Benzodiazepines are the drugs of choice in the treatment of alcohol withdrawal syndrome (AWS). Recent data have shown that baclofen may reduce AWS symptoms. At present, no comparative studies between baclofen and any benzodiazepine used in AWS treatment are available. Accordingly, the present study was designed to compare efficacy, tolerability and safety of baclofen versus diazepam in the treatment of AWS.

SUBJECTS AND METHODS: Thirty-seven patients with AWS were enrolled in the study and randomly divided into 2 groups. Baclofen (30 mg/day for 10 consecutive days) was orally administered to 18 patients (15 males, 3 females; median age: 46.5 years). Diazepam (0.5-0.75 mg/kg/day for 6 consecutive days, tapering the dose by 25% daily from day 7 to day 10) was orally administered to 19 patients (17 men, 2 women; median age: 42.0 years). The Clinical Institute Withdrawal Assessment (CIWA-Ar) was used to evaluate physical symptoms of AWS.

RESULTS: Both baclofen and diazepam significantly decreased CIWA-Ar score, without significant differences between the 2 treatments. When CIWA-Ar subscales for sweating, tremors, anxiety and agitation were evaluated singly, treatment with baclofen and diazepam resulted in a significant decrease in sweating, tremors and anxiety score, without significant differences between the 2 drug treatments. Both treatments decreased the agitation score, although diazepam was slightly more rapid than baclofen.

CONCLUSION: The efficacy of baclofen in treatment of uncomplicated AWS is comparable to that of the “gold standard” diazepam. These results suggest that baclofen may be considered as a new drug for treatment of uncomplicated AWS. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Alcohol withdrawal syndrome; CIWA-Ar; Baclofen; Diazepam

Alcohol withdrawal syndrome (AWS) is a life-threatening condition affecting alcohol-dependent patients who discontinue or decrease their alcohol consumption.¹ Symptoms usually develop within 6-24 hours after the last drink² and include increase in blood pressure and pulse rate, tremors, hyperreflexia, irritability, anxiety and depression in light to

moderate AWS forms. These symptoms may progress to more severe forms characterized by seizures³ and coma;⁴ in these forms, cardiac arrest and death occurs in 5% to 10% patients.^{5,6}

The main objectives of the clinical management of AWS are to decrease the severity of symptoms, prevent more severe withdrawal clinical manifestations such as seizure and delirium, and facilitate entry of the patient into a treatment program in order to attempt to achieve and maintain long-term abstinence from alcohol.⁷ At present, benzodiazepines (eg, diazepam, 0.5-0.75 mg/kg/day) are the drugs of choice in the treatment of AWS.^{8,9}

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Baclofen is a stereoselective γ -aminobutyric acid_B (GABA_B) receptor agonist used at present to control spasticity.¹⁰ However, recent lines of experimental evidence have suggested the ability of baclofen to suppress alcohol withdrawal signs in rats;¹¹ accordingly, recent preliminary data have shown how baclofen rapidly suppressed AWS severity in human alcoholics,¹² even when manifested in its severe form complicated by *delirium tremens*.¹³

Currently, no comparative studies between baclofen and benzodiazepines used in the management of AWS are available. The aim of the present study was, therefore, to compare the efficacy, tolerability and safety of baclofen versus the benzodiazepine diazepam in the treatment of moderate/severe acute uncomplicated AWS.

METHODS

Patients and Treatment

Between September 2001 and October 2004, 130 subjects affected by current alcohol dependence referring to our Alcohol Treatment Unit to request alcohol detoxification treatment were consecutively considered for the study. Inclusion criteria were: age between 18 and 75 years; a daily alcohol consumption of more than 80 g alcohol/day during the previous 24 hours; diagnosis of alcohol dependence according to DSM-IV criteria.¹⁴ Exclusion criteria were the current presence of: *delirium tremens* or hallucinosis; severe psychiatric diseases (eg, major unipolar depression and schizophrenia); epilepsy; severe cardiac failure; diabetes mellitus; severe liver impairment; liver encephalopathy; kidney failure; neoplastic diseases; lack of cooperating relatives; abuse of or dependence on other drugs, with the exception of nicotine.

Patients with a blood alcohol concentration (BAC) lower than 0.1 g/L were assessed using the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale, a scoring system for quantitative evaluation of physical symptoms of AWS.¹⁵ Only subjects with a CIWA-Ar score equal to or higher than 10 (defined as moderate or severe AWS

requiring pharmacological treatment) were ultimately enrolled in the study.

Among the 130 potential subjects, 49 (37.7%) met the study criteria. Thirty-seven (28.5%) agreed to take part in the study (32 men [86.5%] and 5 women [13.5%], with a mean age of 45.0 ± 1.9 years [range: 21-73 years]). Their mean daily alcohol intake was 223.1 ± 18.2 g alcohol/day (median value: 200.0 g; range: 90-600 g); their mean duration of addiction was 14.8 ± 1.6 years (median value: 13.0 years; range: 3-39 years). These data were confirmed by patients and collateral interviews. All subjects were randomly divided into 2 groups by a 1:1 randomization procedure. The 2 groups were comparable in terms of sociodemographic characteristics (Table 1).

Baclofen Group

Eighteen alcoholics with a range of daily alcohol consumption of 130-440 g (mean 256.7 ± 19.3 g)

and a range of years of addiction of 3-39 years (mean 13.6 ± 2.6 years), were treated with oral doses of baclofen of 30 mg/day, fractionated in 3 daily administrations for 10 consecutive days. The baclofen dose was chosen on the basis of results obtained in a previous study from this laboratory.¹²

Diazepam Group

Nineteen alcoholics with a range of daily alcohol consumption of 90-600 g alcohol/day (mean: 191.3 ± 28.9 g; $P < .005$, Mann-Whitney test, respect to baclofen group) and a time range of addiction of 3-39 years (mean: 15.8 ± 1.9 years $P > .05$, Mann-Whitney test, respect to baclofen group), were treated with oral doses of diazepam. Specifically, a total of 0.5-0.75 mg/kg diazepam was divided in 6 daily administrations for 10 consecutive days. Doses were tapered by 25% daily from day 7 to day 10.¹⁶ This protocol was selected due to the ease of application in clinical practice and on the basis of results obtained in a previous study from this laboratory.¹⁷

CLINICAL SIGNIFICANCE

- The GABA_B receptor agonist baclofen is capable of reducing alcohol withdrawal symptoms (AWS).
- Baclofen can cut AWS with an efficacy comparable to that of the "gold standard" diazepam.
- Baclofen and diazepam significantly decreased AWS, without differences between treatments.
- Baclofen may be considered a new drug for treatment of AWS, also in view of its safety and manageability.

Table 1 Sociodemographic Characteristics of the Sample

| | Baclofen Group (n = 18) | Diazepam Group (n = 19) | P Value |
|-------------------------------|----------------------------|----------------------------|----------------------------|
| Age (years), mean \pm SEM | 42.3 ± 2.7 | 42.0 ± 2.4 | $>.05$, Mann-Whitney test |
| Male, n (%) | 15 (83.3) | 17 (89.5) | $>.05$, chi-squared test |
| Married, n (%) | 11 (61.1) | 7 (36.8) | $>.05$, chi-squared test |
| >13 years of education, n (%) | 5 (27.8) | 3 (15.8) | $>.05$, chi-squared test |
| Employed, n (%) | 16 (88.9) | 15 (78.9) | $>.05$, chi-squared test |

Study Procedure

The drug therapy was administered by the principal investigator from 8 AM to 8 PM and by the referred family member from 8 PM to 8 AM.

All subjects were checked as outpatients. BAC were evaluated at each control. On days 1 and 10, after a 12-hour fast, blood samples were drawn from each patient for determination of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (GGT), and mean cellular volume (MCV) value. Patients of both groups and their relatives were informed of the possibility of receiving a trial drug; only those who gave their written consent were included in the study. With the exception of nicotine, no psychoactive drugs were permitted; no other medications potentially acting as a confounding factor for the study were administered during the detoxification period.

CIWA-Ar was administered once a day (immediately before the first daily administration of the drug) on days 1, 2, 3, 4, 5 and 10. Baseline values were those collected on day 1 before the first drug administration. The whole study was performed on a single blind design; in particular, investigators who performed CIWA-Ar at the different times of treatment were always the same and were unaware as to which drug was being administered to patients.

A rescue protocol was available; specifically, if the patient did not respond to treatment with baclofen and the CIWA-Ar remained higher than 10 or increased during the first 2 hours, an oral dose of 0.75 mg/kg diazepam¹⁶ or an intramuscular dose of 10 mg haloperidol¹⁸ would be administered.

The study protocol complied fully with the guidelines of the Ethics Committee of the Università Cattolica del Sacro Cuore in Rome, Italy.

Statistical Analysis

Statistical evaluation of patients' age, years of addiction, and quantity of daily alcohol consumption in the baclofen and diazepam groups was performed by the Mann-Whitney test. Possible differences in proportions were assessed using a chi-squared test and odds ratios with 95% confidence intervals.

Analysis of the efficacy of the 2 drugs on the severity of AWS was intended to be performed with the intention-to-treat principles¹⁹ (ie, entering into the analysis any randomized patient, including dropouts). Analysis of the effect of baclofen and diazepam on CIWA-Ar score and its 4 subscales (anxiety, agitation, sweating and tremors), as well as changes in AST, ALT, GGT and MCV, was performed by (a) 2-way (time, treatment) analysis of variance (ANOVA) with repeated measures on the factor time or (b) analysis of covariance (ANCOVA), with repeated measures on the factor time and baseline data as covariance, when baseline data were significantly different (Mann-Whitney test); in the latter case, the effect of each drug was analyzed by a one-way ANOVA, with repeated measures.

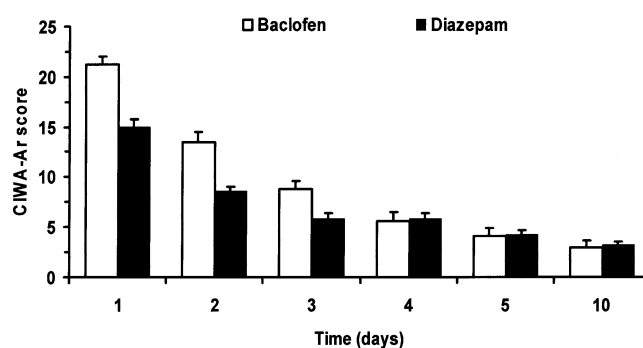


Figure 1 Score of the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale in patients treated for 10 consecutive days with baclofen (30 mg/day, per os; n = 18) and diazepam (0.5-0.75 mg/kg/day on days 1-6, tapering the dose by 25% daily from day 7 to day 10; n = 19). CIWA-Ar administration occurred once a day, on days 1, 2, 3, 4, 5 and 10, immediately before the first daily administration of drugs (scoring of day 1 acting as baseline).

RESULTS

All 37 patients completed the study, with no dropouts in either group, and no difference in the patients' compliance to treatment was found between groups. No patients needed the application of the rescue protocol. BAC lower than 0.1 g/L were found in all patients at each control.

At baseline, mean total CIWA-Ar score (ie, the sum of all items) was significantly higher in baclofen than diazepam group ($P < .0001$, Mann-Whitney test) (Figure 1). When analyzed separately, both baclofen and diazepam treatments significantly decreased the CIWA-Ar score (one-way ANOVA for baclofen: $F[5,85] = 115.48$, $P < .0001$; one-way ANOVA for diazepam: $F[5,90] = 80.82$, $P < .0001$), with no significant differences between the 2 treatments (2-way ANCOVA: $F[1,140] = 0.91$, $P > .05$) (Figure 1).

Treatment with baclofen and diazepam resulted in a marked decrease in the severity of sweating, tremors, anxiety and agitation score. Mean baseline sweating score was significantly higher in the baclofen than in the diazepam group ($P < .001$, Mann-Whitney test) (Figure 2, panel A); both drug treatments significantly decreased the sweating score when analyzed separately (one-way ANOVA for baclofen: $F[5,85] = 46.66$, $P < .0001$; one-way ANOVA for diazepam: $F[5,90] = 22.53$, $P < .0001$), with no significant differences between the 2 treatments (2-way ANCOVA: $F[1,140] = 2.81$, $P > .05$) (Figure 2, panel A). Mean baseline tremor score did not differ between the 2 groups ($P > .05$, Mann-Whitney test) (Figure 2, panel B); both drug treatments significantly decreased the tremor score, without differences between treatments (2-way ANOVA: $F_{\text{time}}[5,175] = 51.64$, $P < .0001$; $F_{\text{treatment}}[5,175] = 0.52$, $P > .05$) (Figure 2, panel B). Mean baseline anxiety score was significantly higher in the baclofen than in the diazepam group ($P < .005$, Mann-Whitney test) (Figure 2, panel C); both drug treatments decreased anxiety score (one-way ANOVA for baclofen: $F[5,85] = 77.01$, $P < .0001$; one-way

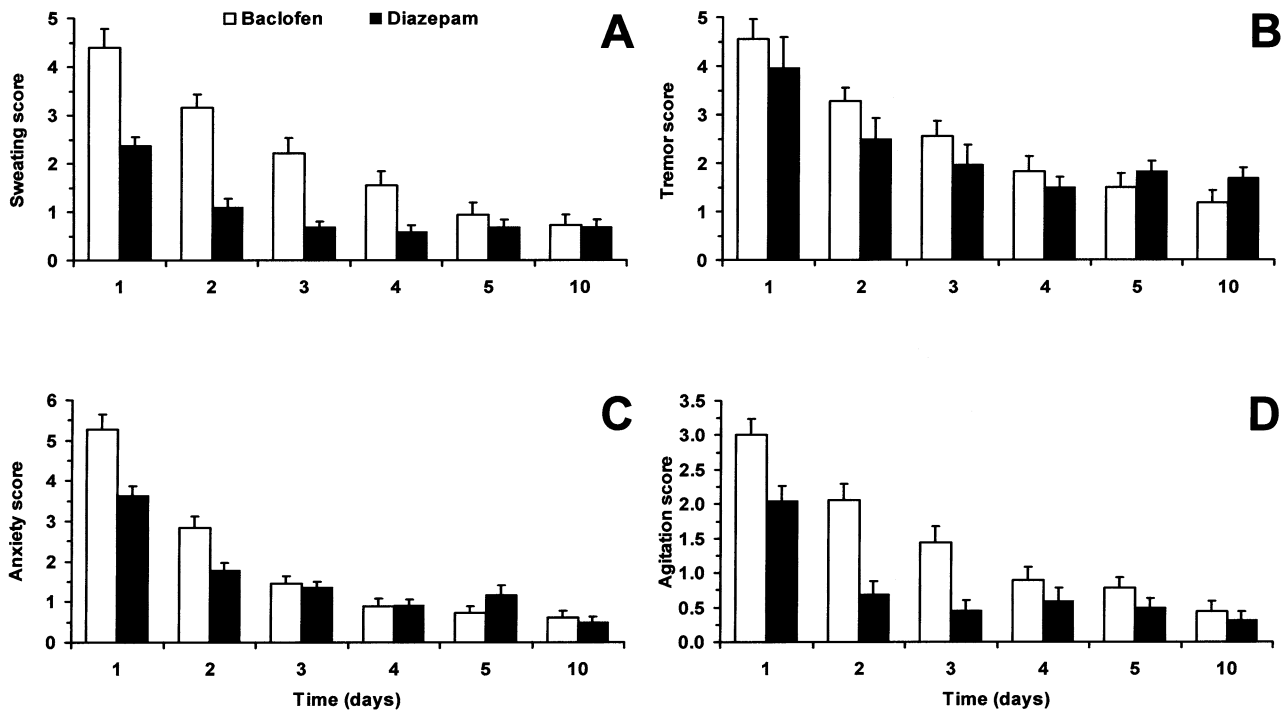


Figure 2 Score of 4 subscales—(A) sweating, (B) tremors, (C) anxiety, and (D) agitation—of the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale in patients treated for 10 consecutive days with baclofen (30 mg/day, per os; $n = 18$) and diazepam (0.5-0.75 mg/kg/day on days 1-6, tapering the dose by 25% daily from day 7 to day 10; $n = 19$). CIWA-Ar administration occurred once a day, on days 1, 2, 3, 4, 5 and 10, immediately before the first daily administration of drugs (scoring of day 1 acting as baseline).

ANOVA for diazepam: $F[5,90] = 56.19$, $P < .0001$, with no significant differences between the 2 treatments (2-way ANCOVA: $F[1,140] = 0.51$, $P > .05$) (Figure 2, panel C). Mean baseline agitation score was significantly higher in the baclofen than in the diazepam group ($P < .05$, Mann-Whitney test) (Figure 2, panel D); both drug treatments decreased the agitation score (one-way ANOVA for baclofen: $F[5,85] = 30.16$, $P < 0.0001$; one-way ANOVA for diazepam: $F[5,90] = 24.09$, $P < .0001$). Although baclofen was slightly slower than diazepam (2-way ANCOVA: $F[1,140]$

$= 4.19$, $P < .05$) (Figure 2, panel D), as indicated by significantly higher scores on days 2 and 3 in the baclofen versus the diazepam group, on subsequent days the efficacy of baclofen and diazepam was comparable.

A reduction in AST, ALT, GGT and MCV value was found in both baclofen- and diazepam-treated patient groups (Table 2).

No side effects were reported by either baclofen- or diazepam-treated patients. On discontinuation of treatment, no withdrawal symptoms or side effects were observed.

Table 2 Values of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), γ -Glutamyl Transferase (GGT) and Mean Cellular Volume (MCV) in Patients Treated for 10 Consecutive Days With Baclofen (30 mg/day, per os; $n = 18$) and Diazepam (0.5-0.75 mg/kg/day on Days 1-6, Tapering the Dose by 25% Daily from Day 7 to Day 10; $n = 19$)

| Blood Marker | Day 1 | | Day 10 | |
|--------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| | Baclofen Group ($n = 18$) | Diazepam Group ($n = 19$) | Baclofen Group ($n = 18$) | Diazepam Group ($n = 19$) |
| ALT | 108.3 \pm 17.0 | 59.2 \pm 9.5* | 66.5 \pm 11.6‡ | 25.7 \pm 2.8†† |
| AST | 112.1 \pm 18.1 | 97.2 \pm 17.5 | 55.1 \pm 8.5§ | 38.0 \pm 4.2§ |
| GGT | 367.2 \pm 95.0 | 301.4 \pm 54.1 | 197.2 \pm 43.8§ | 92.3 \pm 11.4§ |
| MCV | 97.7 \pm 2.0 | 89.8 \pm 1.4* | 90.0 \pm 5.1‡ | 81.9 \pm 0.9†† |

Each value is the mean \pm SEM of n subjects.

Blood samples were drawn on days 1 and 10, after a 12-h fast.

* $P < .05$ respect to day 1 level in baclofen group (Mann-Whitney test).

† $P < .05$ respect to day 10 level in baclofen group (Newman-Keuls test).

‡ $P < .05$ respect to day 1 level of the same group (Wilcoxon test).

§ $P < .05$ respect to day 1 level of the same group (Newman-Keuls test).

DISCUSSION

At present, benzodiazepines represent the “gold standard” in the management of patients with AWS.⁸ However, the use of benzodiazepines is associated with several side effects, such as risk of excess sedation, memory deficits and respiratory depression in patients with liver impairment, as is often the case in alcoholics.⁸ Moreover, benzodiazepines could have addictive properties, which constitutes a limitation to their use in subjects affected by substance abuse disorders.^{8,20} Consequently, the discovery of new potentially useful drugs for the treatment of AWS is of considerable practical importance.

The efficacy of baclofen in decreasing alcohol consumption and craving as well as maintaining abstinence from alcohol has recently been reported in human alcoholics.²¹⁻²³ Moreover, recent lines of clinical evidence suggest the efficacy of baclofen in rapidly reducing moderate to severe AWS symptoms,¹² even when complicated by *delirium tremens*.¹³ However, the small number of patients evaluated in previous studies,^{12,13} as well as the lack of any comparative analysis with other types of medication commonly used to treat AWS,^{8,9} rather limit the importance of the above studies and do not allow definitive conclusions to be drawn with regard to this use of baclofen.

The results of the present study show that the oral administration of doses of baclofen lower than those prescribed for spasticity¹⁰ are as effective as diazepam in the management of AWS, at least in its uncomplicated form, as shown by the similar decrease in CIWA-Ar score (a reliable and validated measure of AWS intensity) induced by baclofen and diazepam (Figure 1). Although baseline CIWA-Ar score differed significantly between the 2 groups, the proportion of the reducing effect of baclofen and diazepam was comparable. Moreover, when these data were statistically analyzed, the type 2 error was seen to be reasonably low.

Subsequently, the 4 most important items of CIWA-Ar scale were analyzed singly (Figure 2). No difference was found in the decreasing effect of either baclofen or diazepam on tremor intensity. Although baseline score for sweating, anxiety and agitation was significantly higher in the baclofen than in the diazepam group, both drug treatments produced comparable decrements in sweating and anxiety score, although baclofen was slightly slower than diazepam in reducing the agitation score (Figure 2, panel D).

These data are in close agreement with those of a recent study showing the efficacy of baclofen in improving symptoms of opiate withdrawal syndrome.²⁴

With regard to blood markers, ALT, AST, GGT and MCV values tended to decrease in both baclofen and diazepam groups, although this reduction appeared to be smaller in the baclofen than the diazepam group. It should be underlined that mean baseline values of ALT and MCV were significantly higher in the baclofen than the diazepam group, in agreement with the higher intake of alcohol reported by patients of the baclofen group. It is likely that the

reduction in blood marker values was secondary to cessation of alcohol intake; however, these data also suggest that treatment with either baclofen or diazepam did not induce any liver sufferance.

From a clinical point of view, it should be borne in mind that baclofen has been used for years as a particularly manageable and safe antispasticity drug.¹⁰ The results of the present study confirm the manageability and safety of the drug¹² because no patient in the baclofen group presented any side effects. Recently, the manageability and safety of baclofen in the treatment of alcoholism also has been reported by a self-case report on the complete and prolonged suppression of alcohol dependence achieved with extremely high doses of baclofen.²⁵ Finally, as previously reported in alcoholic patients,^{12,22,23} baclofen displayed no addictive properties,²⁵ a feature of paramount importance in the pharmacological treatment of patients with alcohol problems.

The results of the present study add further support to the hypothesis that the GABA_B receptor is part of the neural circuitry underlying AWS.¹¹ With regard to the mechanism of the action of baclofen on AWS, it has been hypothesized that baclofen-induced activation of GABA_B receptors might counterbalance AWS-associated enhanced function of glutamate excitatory neurotransmission, resulting in the observed attenuation of withdrawal symptomatology.¹¹

The observed suppressing effect of baclofen on AWS,¹² as in the present study, together with its efficacy in reducing alcohol craving and intake,^{22,23} feature baclofen as a promising and unique pharmacotherapy for alcohol dependence. This drug is of particular interest in view of its efficacy on 2 major aspects of the disorder, namely AWS and maintaining abstinence from alcohol intake. This specific ability of baclofen should theoretically result in a vastly simplified pharmacotherapy and higher compliance to treatment. Finally, it is of interest to note how the use of baclofen allowed AWS to be treated on an outpatient basis, with a significant reduction in the cost of treatment when compared with any inpatient AWS treatment.

In conclusion, the results of the present study indicate that the efficacy of baclofen in the treatment of uncomplicated forms of AWS is comparable with that of the “gold standard,” diazepam. Accordingly, baclofen may be considered as a new potentially useful drug for treatment of AWS.

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