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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 drink[2] 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 seizures[3] 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]

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

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

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]

Table 1 Sociodemographic Characteristics of the Sample

	Baclofen Group (n = 18)	Diazepam Group (n = 19)	P Value
Age (years), mean ± 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