BACLOFEN EFFICACY IN REDUCING ALCOHOL CRAVING AND INTAKE: A PRELIMINARY DOUBLE-BLIND RANDOMIZED CONTROLLED STUDY

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Abstract — Aims: The γ-aminobutyric acid (GABA) receptor agonist, baclofen, has recently been shown to reduce alcohol intake in alcohol-preferring rats and alcohol consumption and craving for alcohol in an open study in humans. The present study was aimed at providing a first evaluation of the efficacy of baclofen in inducing and maintaining abstinence and reducing craving for alcohol in alcohol-dependent patients in a double-blind placebo-controlled design. Methods: A total of 39 alcohol-dependent patients were consecutively enrolled in the study. After 12–24 h of abstinence from alcohol, patients were randomly divided into two groups. Twenty patients were treated with baclofen and 19 with placebo. Drug and placebo were orally administered for 30 consecutive days. Baclofen was administered at the dose of 15 mg/day for the first 3 days and 30 mg/day for the subsequent 27 days, divided into three daily doses. Patients were monitored as out-patients on a weekly basis. At each visit alcohol intake, abstinence from alcohol, alcohol craving and changes in affective disorders were evaluated. Results: A higher percentage of subjects totally abstinent from alcohol and a higher number of cumulative abstinence days throughout the study period were found in the baclofen, compared to the placebo, group. A decrease in the obsessive and compulsive components of craving was found in the baclofen compared to the placebo group; likewise, alcohol intake was reduced in the baclofen group. A decrease in state anxiety was found in the baclofen compared to the placebo group. No significant difference was found between the two groups in terms of current depressive symptoms. Conclusions: Baclofen proved to be effective in inducing abstinence from alcohol and reducing alcohol craving and consumption in alcoholics. With the limits posed by the small number of subjects involved, the results of this preliminary double-blind study suggest that baclofen may represent a potentially useful drug in the treatment of alcohol-dependent patients and thus merits further investigations.

INTRODUCTION

In recent years, the use of pharmacotherapy together with psychosocial interventions (including Alcoholics Anonymous and various counselling approaches) has enhanced the percentage of success in maintaining alcoholic patients in remission and assisting the development of a lifestyle compatible with long-term alcoholic abstinence. However, to date, drugs with proven efficacy are very few (see Garbutt et al., 1999; Swift, 1999; Kranzler, 2000) and the discovery of new medications capable of positively affecting the components of alcohol dependence syndrome, such as craving and loss of control on drinking or protracted abstinence symptoms, would represent an important step forward in the treatment of patients with alcohol problems (see Garbutt et al., 1999).

Baclofen is a potent and stereoselective γ-aminobutyric acid (GABA_B) receptor agonist used clinically to control spasticity (Davidoff, 1985). Recent preclinical experiments have demonstrated the efficacy of baclofen in suppressing both alcohol withdrawal signs in rats made physically dependent on alcohol and voluntary alcohol intake in alcohol-preferring rats (Colombo et al., 2000, 2002). Moreover, preliminary clinical open studies have confirmed the ability of baclofen to reduce alcohol craving and intake (Addolorato et al., 2000b) and alcohol withdrawal symptoms (Addolorato et al., 2002) in alcohol-dependent patients.

The present double-blind randomized placebo-controlled study was performed in order to determine the efficacy of short-term baclofen administration on craving for alcohol, alcohol intake and abstinence from alcohol in patients affected by alcoholism.

PATIENTS AND METHODS

A total of 39 alcohol-dependent patients (mean age ± SD: 47.3 ± 10.5 years; mean daily drinks: 14.2 ± 7.9; mean years of addiction: 11.8 ± 4.2) were consecutively admitted to the study. Inclusion criteria were: (1) age ranging from 18 to 70 years; (2) diagnosis of current alcohol dependence according to DSM-IV criteria (American Psychiatric Association, 1994); (3) last alcohol intake reported to have taken place in the 24 h preceding observation; (4) presence of a referred family member. Exclusion criteria were the presence of: (1) severe liver, kidney, heart or lung diseases; (2) psychopathological illness undergoing treatment with psychoactive drugs, epilepsy or epileptiform convulsion; (3) addiction to drugs other than nicotine. Each patient was required to provide his/her informed consent after having received information on the characteristics, dosing rate and possible side-effects of the drug, as well as on the possibility of dropping out of the study at any time. The study protocol fully complied with the guidelines of the Ethics Committees of the Università Cattolica in Rome and of the University of Bologna, where the study was performed.

Patients were randomized in two groups; 20 patients were treated with baclofen (mean age: 45.8 ± 10.6 years; mean daily drinks: 17.6 ± 7.5; mean years of addiction: 12.6 ± 4.8).
and 19 patients with placebo (mean age: 48.8 ± 10.4 years; mean daily drinks: 10.7 ± 6.7; mean years of addiction: 11.0 ± 3.4). Patients were recruited among those contacting our Alcohol Treatment Units. Randomization was performed as follows: the 39 consecutive patients received either baclofen or placebo in a double-blind fashion. Baclofen and placebo were entrusted to a referred family member. Placebo tablets were identical in size, colour, shape and taste to baclofen tablets. Baclofen or placebo was orally administered for 4 consecutive weeks. For the first 3 days, baclofen was administered at a dose of 15 mg/day refracted in three times/day; subsequently, the daily dose of baclofen was increased to 30 mg/day refracted in three times/day. The dose prescribed was chosen on the basis of the results obtained in a previous open clinical study (Addolorato et al., 2000b), and represents the minimum therapeutic dosage recommended by the drug manufacturer in order to avoid side-effects.

In cases where symptoms of alcohol withdrawal could not have been controlled effectively by baclofen or placebo, a ‘rescue’ protocol would have been adopted, based on administration of diazepam (0.5–0.75 mg/kg body weight). However, no patients required this treatment intervention.

All patients were strongly advised against the use of drugs capable of potentially affecting craving for alcohol. Specifically, the use of benzodiazepines, antidepressants, metadone, naltrexone, acamprosate, γ-hydroxybutyric acid (GHB), as well as alcohol-sensitizing drugs (e.g. disulfiram) was not allowed during the study period and subsequent follow-up.

Each subject was checked as an out-patient every week for the duration of the study; at each visit, routine psychological support counselling as previously described (Addolorato et al., 1993) was provided by the same professional staff. Craving level was evaluated by administration of the Obsessive–Compulsive Drinking Scale (OCDS) at the start of the study (T0) and at each weekly out-patient visit (T1–T4). The OCDS is a validated scale consisting of two subscales which evaluate the obsessive and compulsive components of craving (Anton et al., 1995). Abstinence from alcohol was evaluated, at each out-patient visit, on the basis of: (1) patient’s self-evaluation [reporting alcohol intake as the mean number of standard drinks consumed per day (one standard drink equal to 12 g of absolute alcohol) (Secretary of Health and Human Services, 1997)]; (2) family member interview; (3) determination of alcohol concentration in blood and saliva by QED (Enzymatics Inc., Horsham, UK). Cumulative abstinence duration (CAD), defined as the total number of days of abstinence, was also calculated in both the baclofen and placebo groups. Furthermore, main biological markers of alcohol abuse [aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltranspeptidase (GGT) and mean cell volume (MCV)] were determined at the start (T0) and at the end (T4) of the study. Finally, possible changes in state anxiety and current depression were assessed by means of the State and Trait Inventory test, Y1 axes (Spielberg et al., 1983), and Zung Self-Rating Depression Scale (Zung et al., 1965), respectively.

At drug discontinuation, the presence of possible side-effects due to drug suspension was recorded on a weekly basis for the first 4 weeks.

Statistical evaluation of patients’ age, years of addiction and CAD in the baclofen and placebo groups was performed by the Mann–Whitney test. The number of drop-outs and of patients maintaining abstinence in the two groups were compared using the Fisher exact test for a 2 × 2 table [treatment (baclofen; placebo) × drop-out (presence; absence) or treatment (baclofen; placebo) × abstinence (presence; absence)]. The numbers of patients maintaining abstinence and CAD were analysed with the intention-to-treat principles (see Lehert, 1993), i.e. entering into the analysis any randomized patient, including drop-outs. In this analysis, it was assumed that all patients who terminated treatment before the end of the study were abstinence failures and CAD was calculated on the data available at the time of the last weekly visit. Analysis of the effect of baclofen on daily drinks, OCDS scales, scales of state anxiety and depression, and main biological markers of alcohol misuse was performed by the two-way (treatment × time) analysis of covariance (ANCOVA) with repeated measures on the time factor, and baseline data as covariance.

RESULTS

No statistically significant difference in mean age and mean years of addiction was found between the two groups (P > 0.05, Mann–Whitney test).

A schematic diagram on recruitment, group allocation, treatment retention and success in achieving and maintaining complete abstinence is presented in Figure 1. Although statistical significance was not reached (P = 0.06, Fisher’s exact test), the number of drop-outs was lower in the baclofen than in the placebo group; indeed, three subjects in the baclofen group (corresponding to 15.0%) and eight subjects in the placebo group (42.1%) dropped out and were excluded from further statistical analyses.

A significantly higher number of patients who achieved and maintained abstinence throughout the experimental period was found in the group of patients treated with baclofen (14 out of 20, corresponding to 70.0%) compared to subjects treated with placebo (four out of 19, or 21.1%) (P < 0.005; Fisher’s exact test). CAD was ~3-fold higher in baclofen- than

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placebo-treated patients [19.6 ± 2.6 and 6.3 ± 2.4 (mean ± SEM), respectively; \( P < 0.005 \), Mann–Whitney test].

Figure 2 shows daily alcohol intake in the two groups of patients at the different observation times of the study. ANCOVA revealed a significant effect of treatment on alcohol intake \( [F_{\text{treatment}}(1,78) = 10.71, P < 0.005; F_{\text{time}}(3,78) = 1.38, P > 0.05] \). In the baclofen group, the mean number of daily drinks was virtually completely suppressed within the first week of the treatment, being reduced from ~18 (value at T0) to <0.5 (values at T1–T4); in the placebo group, the daily drinks were reduced from approximately a mean number of 10 (T0) to 3.5–4.5 (T1–T4).

Figure 3 (top panel) shows the craving score in the two groups of patients at the different observation times. ANCOVA showed a significant effect of both treatment and time on total OCDS score \( [F_{\text{treatment}}(1,78) = 5.65, P < 0.05; F_{\text{time}}(3,78) = 10.30, P < 0.00005] \). From T1 to T4, the score in the baclofen group was constantly lower than that monitored in the placebo group. ANCOVA also revealed significant effects of treatment and time on both compulsive \( [F_{\text{treatment}}(1,78) = 4.60, P < 0.05; F_{\text{time}}(3,78) = 6.40, P < 0.0005] \) (Fig. 3, centre panel) and obsessive \( [F_{\text{treatment}}(1,78) = 5.06, P < 0.05; F_{\text{time}}(3,78) = 11.53, P < 0.00005] \) (Fig. 3, bottom panel) drinking subscales of OCDS, with scores in the baclofen groups constantly lower than those of the placebo group throughout T1–T4.

ANCOVA revealed significant effects of both treatment and time factors on state anxiety \( [F_{\text{treatment}}(1,78) = 4.62, P < 0.05; F_{\text{time}}(3,78) = 3.05, P < 0.05] \) (Fig. 4, top panel), with lower scores in the baclofen than placebo group at T1–T4. In contrast, no significant difference was observed in depression score \( [F_{\text{treatment}}(1,78) = 0.70, P > 0.05; F_{\text{time}}(3,78) = 2.28, P > 0.05] \) (Fig. 4, bottom panel).

Table 1 reports values obtained in laboratory investigations before and after baclofen or placebo administration.

No serious systemic or single-organ event leading to drug cessation was reported and no patient discontinued the drug. Tolerability was fair in all patients; as previously reported (Addolorato et al., 2000b), the most common side-effects were sleepiness (two patients), tiredness (one patient), vertigo (one patient) in the baclofen group and abdominal pain (one patient) in the placebo group, which resolved within 1–2 weeks of drug treatment and did not recur. No patient reported euphoria or other pleasant effects caused by the drug. No subject showed craving for baclofen. At drug discontinuation, neither drug withdrawal syndrome nor side-effect due to drug suspension was observed.

**DISCUSSION**

Recent preclinical (Colombo et al., 2000, 2002) and preliminary clinical data (Addolorato et al., 2000b, 2002) suggest that the GABA\(_B\) receptor agonist, baclofen, may be effective in the treatment of patients with alcohol problems. However, to date, no double-blind, randomized placebo-controlled study has been conducted. In spite of the limitation due to the low number of patients evaluated, the results of the present study indicate that administration of relatively
In agreement with our previous observation (Addolorato et al., 2000b), abstinence from alcohol or reduction in alcohol intake was achieved within the first week of baclofen treatment and was maintained throughout the treatment period. The increased efficacy of baclofen over placebo may be related to its suppressant effect on craving; indeed, the drug produced a rapid decrease in the ‘compulsive’ and ‘obsessive’ components of craving, as indicated by the immediate reduction in mean score of both OCDS subscales. It is noteworthy that an anti-craving effect of baclofen has already been observed with other substances of abuse, particularly cocaine in cocaine users (Ling et al., 1998). The anti-craving effect of baclofen may depend on its ability to interfere with the neuronal substrates mediating the reinforcing properties of ethanol. GABA<sub>B</sub> receptors located in the ventral tegmental area (VTA) have been reported to control the activity of mesolimbic dopamine neurons, a major neural pathway in the regulation of the reinforcing properties of addictive drugs, including alcohol (see Di Chiara, 1995; Koob et al., 1998; Spanagel and Weiss, 1999). Accordingly, pharmacological stimulation of VTA GABA<sub>B</sub> receptors has been found to inhibit the firing activity of these neurons (Kalivas, 1993) as well as basal (Yoshida et al., 1994) and alcohol-stimulated (Carta et al., 2001) dopamine release from their terminals in the nucleus accumbens.

Moreover, it is conceivable that the suppressing effect of baclofen on alcohol withdrawal symptomatology (Addolorato et al., 2002) may have helped the patients to achieve and maintain alcohol abstinence.

In contrast to the observation by Krupitsky et al. (1993) that baclofen ameliorates affective disorders in alcoholics, in the present study baclofen was found to be effective in reducing state anxiety, but not current depression. It may be hypothesized that the decrease in state anxiety found in the present study and the decrease in depression observed by Krupitsky et al. (1993) in alcoholics after a 3-week treatment with baclofen were secondary to the ability of baclofen to achieve both a rapid detoxification (Addolorato et al., 2002) and a decrease in craving, resulting in a rapid reduction of physical and psychological symptoms. Finally, it should be emphasized that the absence of a significant decrease in Zung depression scale score in the present study could be influenced by the relatively low score recorded in some patients at the start of the study.

In agreement with both previous observations (Krupitsky et al., 1993; Ling et al., 1998; Addolorato et al., 2000a), baclofen proved to be devoid of serious side-effects in alcoholics. Moreover, side-effects were present only during the first week of the treatment.

Preclinical data suggest that baclofen might be liable to misuse since the drug shares several pharmacological effects with the alcohol-mimicking agent, γ-hydroxybutyrate (GHB), and craving for and abuse of GHB have been observed in different alcoholic patients (see Addolorato et al., 2000a). However, baclofen failed to show euphorogenic effects and no patient consumed the drug above the prescribed dose. The lack of misuse liability of baclofen is an important factor in pharmacological treatments of alcohol and other substance addictions.

In conclusion, with the limits of the low number of patients recruited and the short time of observation, the results of the present preliminary double-blind study confirm that baclofen, because of its anti-craving and anti-reward action on the one
hand, and safety on the other, may have an important role in the treatment of patients with alcohol problems. Future studies with larger patient samples and longer periods of observation are surely warranted to confirm the results of the present study.

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REFERENCES


