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Ability of Baclofen in Reducing Alcohol Craving and Intake: II—Preliminary Clinical Evidence

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Background: Accumulating evidence shows the efficacy of the γ-aminobutyric acid ($GABA_B$) receptor agonist baclofen in reducing alcohol intake in rats, but no studies have been performed in alcoholics. In the present preliminary study we investigated the effect of short-term baclofen administration on craving for alcohol, ethanol intake, and abstinence from alcohol in alcoholic individuals.

Methods: Ten male current alcoholic individuals were admitted to the study. Baclofen was orally administered for 4 weeks, at a dose of 15 mg/day refracted in three times per day for the first 3 days, with the dose increased to 30 mg/day for the remaining 27 days. Each subject was checked as an outpatient every week for the 4 weeks; at each visit (T0-T4) craving level was evaluated by the Alcohol Craving Scale (ACS), and abstinence from alcohol was assessed based on the individual's self-evaluation, family member interview, and the main biological markers of alcohol abuse. A self-reported alcohol intake was recorded as the mean number of standard drinks consumed per day.

Results: Nine subjects completed the study; of these, two subjects continued to drink alcohol although they substantially reduced their daily drinks in the first week of treatment, whereas seven maintained abstinence throughout the experimental period. Craving was significantly reduced from the first week of the drug administration ($p < 0.01$) and remained so throughout the entire treatment period. Participants also reported that obsessional thinking about alcohol disappeared. Values of γ-glutamyltranspeptidase, alanine aminotransferase, and mean cellular volume significantly decreased by the end of the study. Tolerability was fair in all participants; headache, vertigo, nausea, constipation, diarrhea, abdominal pain, hypotension, increased sleepiness, and tiredness were present as side effects in the first stage of the treatment. No participants showed craving for the drug.

Conclusions: With the limitations of the low number of individuals evaluated and the open design, this preliminary clinical study supports the preclinical evidence on the effect of baclofen in reducing alcohol intake. The anticraving properties of the drug suggest a possible role of baclofen in the treatment of individuals with alcohol problems.

Key Words: Baclofen, Alcoholism, Craving, Obsessional Thinking, Pharmacological Treatment for Alcohol Addiction.

AFTER THE ACUTE symptoms of alcohol withdrawal subside, the main objectives in treating individuals affected by alcohol abuse and/or addiction are to prevent relapse and dropout and to maintain abstinence or alternatively to reduce alcohol consumption. In the last few years, the mechanism of craving for alcohol has gained great interest in alcoholism treatment studies, because craving is a frequent cause of relapse and treatment failure in terms of abstinence. It has recently been hypothesized that serotonin may play a major role in craving for alcohol (Anton, 1996; Kranzler and Anton, 1994), but other neurotransmitters may be involved such as γ-aminobutyric acid (GABA), dopamine, acetylcholine, and opioids (Erickson, 1996; Secretary of Health and Human Services, 1997).

Although psychological approach and counseling are essential components in reducing craving and achieving alcohol abstinence (Dall'Aglio et al, 1997; Edwards and Rollnick, 1997), pharmacotherapy may also be necessary in treating individuals who are not helped by psychosocial therapies alone (Anton, 1996). Several pharmacological

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decreased ethanol intake in rats (Agabio et al., 1998) and humans (Gallimberti et al., 1992), induced alcohol abstinence in alcoholics (Addolorato et al., 1996, 1998a,b), and was effective in treating alcohol withdrawal syndrome in both experimental animals (Fadda et al., 1989) and humans (Gallimberti et al., 1989), with a similar efficacy to benzodiazepine (Addolorato et al., 1999b). It has been hypothesized that the effects of GHB on alcohol intake, craving, and withdrawal syndrome are related to its ethanol-mimicking effect on the central nervous system (Colombo et al, 1995).

Baclofen (beta-(4-chlorophenyl)-γ-aminobutyric acid) is a lipophilic derivative of GABA; it is a potent and stereoselective $GABA_B$ receptor agonist (Allan and Harris, 1989) and has a structural homology with GHB. At present it is used clinically to control spasticity (Davidoff, 1985).

Different lines of experimental evidence suggest that baclofen and GHB share several pharmacological effects. For instance, baclofen exerted discriminative stimulus effects (the animal correlate of human subjective feelings perceived after intake of a psychoactive drug) similar to those of GHB, as recently shown by a drug discrimination study in rats (Colombo et al., 1998). Moreover, similar to GHB, baclofen reduced voluntary alcohol intake and intensity of alcohol withdrawal signs in rats (Colombo et al., 2000). On the basis of the latest promising results, and because no studies have been performed on alcohol craving and alcohol abstinence utilizing baclofen in alcoholics, we decided to carry out a preliminary study to investigate the effect of short-term baclofen administration on craving for alcohol in individuals affected by current alcoholism; variation on alcohol intake and abstinence from alcohol were also evaluated as outcome measures in treated subjects.

PARTICIPANTS AND METHODS

Ten males (mean age 44.0 ± 10.1 years; mean daily drinks 8.5 ± 3.5; mean years of addiction 14.8 ± 6.7) with current alcoholism according to DSM-IV criteria (American Psychiatric Association, 1994), who reported last alcohol intake in the 24 hr preceding observation, were consecutively admitted to the study. The presence of severe liver, kidney, heart, or lung diseases; psychopathology under treatment with psychoactive drugs; epilepsy or epileptiform convulsion; and polydrug addiction were exclusion criteria. The patients were included in the study after 12 to 24 hr of abstinence from alcohol. After receiving information about the characteristics, the dosing rate, and the possible side effects of the drug as well as information about the possibility of dropping out of the study at any time, eligible patients gave their informed consent.

The drug and its administration were entrusted to a referred family member; the drug was orally administered for 4 weeks, at a dose of 15 mg/day refracted in three times per day for the first 3 days, increased to 30 mg/day refracted in three times per day for the remaining 27 days. Because there are no clinical studies using baclofen in current alcoholics, we selected the present dose based on the minimum therapeutic dosage at the fractioning modality recommended by the drug manufacturer to avoid side effects.

All the individuals were strongly advised against using drugs that can potentially influence the craving for alcohol. In particular, the use of benzodiazepine, antidepressants, metadoxine, naltrexone, acamprosate, GHB, and antagonist-type drugs (i.e., disulfiram) was not allowed during the study period and the subsequent follow-up.

Each individual was checked as an outpatient every week for the duration of the 4 weeks; at each visit, psychological support counseling as previously described (Addolorato et al., 1993) was provided by the same professional staff. Counseling was performed as individual talks aimed, in particular, at identifying the cause and effect problems related to alcohol abuse and, in general, at the problems that the individual found difficult to resolve after a period of alcohol addiction. During part of such meetings, the family members living with the participant actively participated.

We evaluated craving level by administering the Alcohol Craving Scale (ACS) at the start of the study (T0) and at each weekly outpatient visit (T1–T4). ACS is a questionnaire containing 11 items, each of which requires a yes or no answer, corresponding to 1 or 0 points, respectively, and three multiple-choice questions, to which a score of 1 is attributed for affirmative answers; the maximum craving score was therefore 14 (Addolorato et al., 1998b; Gallimberti et al., 1992). Moreover, abstinence from alcohol was evaluated on the basis of the participant's self-evaluation and a family member interview, by determining blood alcohol concentration and alcohol in saliva by Q.E.D. (Quantitative Ethanol Determination) (Enzymatics Inc., Horsham, UK) at each outpatient control, and by measuring the main biological markers of alcohol abuse—aspartate aminotransferase (AST), alanine aminotranferase (ALT), gamma glutamyltranspeptidase (GGT), and mean cellular volume (MCV)—at the start and at the end of the study. Finally, self-reported alcohol intake was recorded as the mean number of standard drinks consumed per day (one standard drink = 12 g of absolute alcohol) (Secretary of Health and Human Services, 1997).

Statistical analysis was carried out by means of the Wilcoxon matched-pairs signed-ranks test for intragroup comparison, as regards ACS, the results of laboratory tests, and number of daily drinks.

Table 1. Alcohol Craving Score Median Value and (Range) of Subjects Treated With Baclofen at the Start of the Study (T0) and at Each Outpatient Weekly Visit (T1–T4)

Subjects	*n*	T0	T1	T2	T3	T4
Whole group	9	9 (3–14)	3 (0–8)*	1 (0–6)*	1 (0–4)*	0 (0–4)*
Group A	7	8 (3–14)	3 (0–8)*	1 (0–6)*	1 (0–4)*	0 (0–4)*
Subject 1		9	2	3	2	2
Subject 2		14	8	6	4	4

Group A: subjects abstinent throughout the experiment period; Subjects 1 and 2: subjects not abstinent throughout the experiment period. * $p < 0.01$ vs. T0.

RESULTS

Of the 10 individuals enrolled in the study, 1 dropped out and was therefore excluded from the statistical analysis. Of the 9 who completed the study, 2 continued to drink alcohol although they substantially reduced their daily drinks in the 1st week of treatment (median value and [range] T0: 8 [6–10]; T1: 2 [2–2]) and subsequently remained stable (T2: 1.5 [1–2]; T3: 1.5 [1–2]; T4: 1.5 [1–2]), whereas 7 achieved and maintained abstinence throughout the experimental period. They are still abstinent and undergoing psychological support (follow-up around 3 months; 2 subjects with occasional minor relapses).

A significant reduction in craving was observed in the first week of the drug administration (ACS median score and [range]: T0: 9 [3–14] vs. T1: 3 [0–8]; $p < 0.01$); subsequently, the ACS median value was stable at the different times of observation (table 1). No notable difference in ACS median score was found between the abstinent sub-

jects and subjects who continued to drink at any evaluated time (Table 1).

The most common sensation reported by the participants was the disappearance of obsessional thinking about alcohol after some days of baclofen assumption. Obsessional thinking refers to a mental state in which alcoholic individuals, especially in the first stage of treatment, have a constant internal dialogue about whether to use alcohol or to resist (Anton, 1996). One of these individuals experienced GHB anticraving effects several years before but reported no change in his alcohol obsessional thinking with GHB therapy.

Comparing laboratory investigations before and after baclofen administration, we found a significant decrease in values of GGT (T0: 71.7 ± 44.2 U/liter vs. T4: 31.2 ± 18.0 U/liter, $p < 0.01$), AST (T0: 54.7 ± 13.4 U/liter vs. T4: 23.5 ± 10.0 U/liter, $p < 0.01$), ALT (T0: 55.1 ± 17.4 U/liter vs. T4: 21.7 ± 10.2 U/liter, $p < 0.01$), and MCV (T0: 96.3 ± 3.4 $\mu\mu^2$ vs. T4: 93.6 ± 2.4 $\mu\mu^2$, $p < 0.01$).

As for side effects, no serious systemic or single-organ events leading to drug cessation were reported and no participants discontinued the drug. In one participant the daily dose of the drug was reduced to 15 mg per day from the 2nd week of treatment due to headache, difficulty in concentrating, lack of appetite, and sedation. Tolerability was fair in all participants; 2 subjects reported headache, which resolved after about 2 weeks of treatment. Subjects also reported vertigo (1 subject), nausea (2 subjects), increased sleepiness and tiredness (5 subjects), constipation, diarrhea and abdominal pain (3 patients), and hypotension (1 subject), which resolved after 1 to 2 weeks of drug intake and did not recur.

No participants reported euphoria or other pleasant effects caused by the drug. No one showed craving for the drug; at drug discontinuation, we observed no drug with-

The present observations are in agreement with the data reported by Ling and Shoptaw (1998) about the cocaine anticraving effect of baclofen.

Moreover, the participants' self-reported sensation about the lack of alcohol-related obsessional thinking after the initial assumption of the drug must be stressed.

Previous studies showed that several neurotransmitters such as serotonin, GABA, dopamine, acetylcholine, and opioids play a fundamental role in the craving for, and obsessional thinking about, alcohol (Anton, 1996; Erickson, 1996; Kranzler and Anton, 1994; Secretary of Health and Human Services, 1997). The anticraving effect of baclofen could be due to the drug's ability to interfere with the neuronal substrates that mediate the reinforcing properties of ethanol. Accordingly, baclofen has been found to inhibit dopamine release in the nucleus accumbens of rats (Yoshida et al., 1994), a phenomenon likely linked to ethanol reward. Moreover, given the importance of dopamine antagonist substances in blocking the reinforcing effects of alcohol (Swift, 1999), this hypothesis could also explain the rapid disappearance of obsessional thinking about alcohol reported by our treated subjects.

In addition, Krupitsky et al. (1993), evaluating the effect of baclofen on affective disorders in alcoholics, showed that 3 weeks of treatment with the drug significantly decreased anxiety and depression in these individuals. Affective disorders, in particular anxiety and depression, and alcohol abuse frequently coexist (Helzer and Pryzbeck, 1988; Kessler et al., 1997), with a cooccurrence that varies from 16 to 68% (Davidson, 1995). The relationship between anxiety and depression disorders and alcohol abuse has been difficult to define; some authors have suggested that depressed mood is largely associated with the episode of drinking and may be due to the effect of chronic alcohol intoxication (Davidson, 1995), whereas others have shown

not seem to have the same pleasant effects. In particular, in previous studies a craving for GHB was reported by a number of treated individuals who abused the drug, seeking its pleasant psychotropic effects (Addolorato et al., 1996, 1997, 1999c); conversely, in the present study participants reported no pleasant effects caused by baclofen or craving for the drug. The lack of craving for the drug and its related abuse is an aspect worthy of consideration in the pharmacological treatment for alcohol or other substance addiction.

Finally, liver function laboratory tests in the treated subjects improved significantly, in both abstinent and nonabstinent subjects. This was obviously due to the suspension or reduction of alcohol intake, as indicated by the decrease

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