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Sodium oxybate in maintaining alcohol abstinence in alcoholic patients with and without psychiatric comorbidity

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Abstract

Sodium oxybate (SMO) is a GABA-ergic drug currently used for the treatment of alcohol-dependence in some European countries. In particular, clinical studies have shown a role of SMO in promoting alcohol abstinence, as well as in relieving withdrawal symptoms. The aim of this study was to describe alcohol abstinence and the onset of craving for and abuse of SMO in alcohol-dependent subjects with and without psychiatric co-morbidity. Forty-eight patients were enrolled and classified into two groups: group A (20 alcoholics without any psychiatric co-morbidity) and group B (28 alcoholics with a psychiatric co-morbidity). All patients were treated with oral SMO (50 mg/kg of body weight t.i.d.) for 12 weeks. Alcohol abstinence as well as alcohol drinking during the 12 weeks of treatment did not differ between the two groups at the end of treatment ($p=0.9$). In addition, a reduction of alcohol intake in both groups has been observed ($p<0.0001$). On the other hand, craving for SMO was significantly more frequent in group B than group A ($p=0.001$). Cases of SMO abuse were observed in almost 10% of group B patients. In conclusion, alcohol abstinence achieved through SMO administration does not differ in patients with and without psychiatric co-morbidity. However, alcoholics with co-morbid

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borderline disorders appear to be at high risk of developing craving for and abuse of the drug; therefore, SMO may not be indicated in these patients.

1. Introduction

Sodium oxybate (SMO) is a short-chain fatty acid structurally similar to the inhibitory neurotransmitter γ-amino-butyric acid, which exerts an ethanol-mimicking effect on the central nervous system (Colombo et al., 1995; Agabio et al., 1998; Gessa et al., 2000). In 2002, SMO was approved by the Food and Drug Administration for the treatment of cataplexy in narcoleptic patients (Pardi and Black, 2006). However, in the last 10 years, SMO has become a common drug of abuse in many countries (Ricaurte and McCann, 2005; Snead and Gibson, 2005). In some European countries, such as Italy and Austria, where the use of SMO as a recreational drug is not widespread, this drug is currently employed in treating alcohol dependence with encouraging results (Addolorato et al., 2009; Caputo et al., 2009a; Caputo & Bernardi, 2010). In particular, from 40 to 70% of alcoholic patients receiving SMO achieved and maintained abstinence (Addolorato et al., 2009; Caputo et al., 2009a; Caputo & Bernardi, 2010) and a recent Cochrane review highlighted that SMO is more effective than naltrexone and disulfiram in maintaining alcohol abstinence, and than disulfiram in reducing alcohol craving (Leone et al., 2010). When SMO is used at therapeutic doses and under careful medical control, craving for and abuse of SMO are a limited phenomenon (10%) (Addolorato et al., 2009; Caputo et al., 2009a, Caputo & Bernardi, 2010). Nonetheless, this issue still needs to be further and thoroughly investigated. Namely, it would be important to identify the features of those alcoholics who tend to abuse SMO. In this respect, we recently demonstrated that the risk of SMO abuse is higher in patients with poly-drug addiction (Caputo et al., 2009b).

Psychiatric co-morbidity is currently described in 30–50% of alcoholic patients following a rehabilitation program (Grant et al., 2004; Kessler, 2004; Conway et al., 2006; Queyen and Mausbach, 2007). Epidemiological and clinical studies have shown that an Axis I psychiatric diagnosis can be found in 6–50% of alcoholics (Le Fauve et al., 2004), and the prevalence of antisocial and borderline personality disorders – the most frequently diagnosed Axis II psychiatric disorders among individuals with alcohol and other drug dependence – ranges between 15% and 50% (Ralevski et al., 2007). However, despite their high prevalence in alcoholics, psychiatric conditions often represent an exclusion criterion in controlled clinical trials dealing with the induction and maintenance of abstinence from alcohol.

The present study aimed at describing alcohol abstinence and the onset of craving for and abuse of SMO in alcohol-dependent patients with or without a co-morbid diagnosis of a psychiatric disorder during a 12-week SMO treatment period.

2. Experimental procedures

We enrolled patients consecutively admitted over a period of 24 months to three outpatient clinics belonging to the "G. Fontana" Centre for the Study and Multidisciplinary Treatment of Alcohol Addiction, University of Bologna, the Unit for Addiction Treatment, Department of Mental Health of Bologna, and the Department of Internal Medicine, SS. Annunziata Hospital, Cento (Ferrara). The primary end-point of the study was maintenance of alcohol abstinence; onset of craving and abuse of SMO were secondary end-points.

Inclusion criteria were: 1) alcohol dependence, with or without Axis I and Axis II psychiatric co-morbidity; 2) completion of detoxification treatment for alcohol dependence; 3) maintenance of abstinence from alcohol for 7 days. The conditions reported under 1) were defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria (American Psychiatric Association, 2000).

Exclusion criteria were: severe liver, kidney, heart or lung disease, epilepsy, poly-drug addiction according to DSM-IV-TR criteria, Axis I and II psychiatric disorders for which the pharmacological treatment took priority over treatment for alcohol dependence, unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, and previous treatment with SMO.

After providing their informed consent, being aware of the aims of the study, dosing rate and possible side-effects of the drugs they were going to receive, as well as the possibility of dropping out of the study at any time or the fact that the investigator could consider (for safety and/or efficacy reasons) the need for a specific pharmacological treatment or a psychotherapy to control worsening of their psychiatric condition, the patients were classified into two groups according to DSM-IV-TR criteria (American Psychiatric Association, 2000): group A (diagnosis of alcohol dependence without any Axis I or Axis II psychiatric co-morbidity) group B (diagnosis of both alcohol dependence and any Axis I or Axis II psychiatric co-morbidity). Both groups were treated with oral doses of SMO (50 mg/kg of body weight t.i.d.) for 12 weeks. The drug and its administration were entrusted to a referred family member.

Each subject was checked weekly as an outpatient for 12 weeks, recording continuous abstinence from alcohol and amount of daily alcohol intake (expressed as standard US drinks; one standard US drink = 12 g of absolute alcohol) (O'Connor and Schottenfeld, 1998), and relapse into heavy drinking (relapse = five or more drinks on one occasion for men and four or more drinks on one occasion for women) (O'Malley et al., 1992). These parameters were assessed on the basis of participant self-evaluation, the interview of a family member and the determination of alcohol concentrations in the blood and saliva (Assay for the Qualitative Detection of Alcohol in Saliva; Alcohol OnSite, Varian Inc., USA). On admission to the study and at the end of treatment, we also evaluated the alcohol craving level, by administering the Alcohol Craving Scale (ACS) (Gallimberti et al., 1992), and assessing laboratory parameters of alcohol abuse [aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltraspeptidase (GGT), and mean red blood cell volume (MCV)]. As previously tested, craving for SMO was assessed using a simple questionnaire (Caputo et al., 2009b). A more accurate investigation about the quantity of the abused SMO was obtained with the assistance of patients and their family member to whom SMO had been entrusted.

On admission to the study, cigarette smoking was also investigated. Current smoking was defined as having smoked ≥100 cigarettes during lifetime and having smoked every day or some days (Centers for Disease Prevention Control, CDC, 2001). In addition to weekly counselling sessions and pharmacological therapy, self-help groups, such as Alcoholics Anonymous (AA) and social services, were offered.