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Short communication

The effect of acamprosate on alcohol and food craving in patients with alcohol dependence

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Abstract

Introduction: The balance between inhibitory (gamma aminobutyric acid; GABAergic) and excitatory (glutamatergic) neurotransmission is thought to be associated with craving for alcohol and food. The anticraving effect of acamprosate is thought to be mediated through modifying the balance of GABA and glutamate. Recent studies in animals have suggested that acamprosate may have non-selective effects on craving for both alcohol and food.
Methods: The influence of acamprosate for reducing craving for alcohol and food was assessed in 204 in-patients with alcohol dependence (96 patients treated with acamprosate, PWA; 108 patients were not treated PNA) was assessed at baseline and following 1, 2, and 4 weeks of treatment.
Results: There was a significant reduction in craving for alcohol over 4 weeks of treatment in both PWA and PNA groups, but without significant group differences. In contrast, a reduction in food craving was observed only in the PWA group. In addition, there was a significant increase of body mass index (BMI) in the PNA group but not the PWA group over the 4-week period.
Discussion: These results demonstrate acamprosate nonselective effects on craving for drinking and eating in alcoholic patients.

Keywords: Acamprosate; Craving; Food; Body mass index

1. Introduction

Acamprosate (calcium-acetyl homotaurinate) is a pharmacological option for the treatment of alcohol dependence which promotes abstinence and reduces relapse (Boismare et al., 1984; Gewiss et al., 1991; Le Magnen et al., 1987). In a majority of studies, including large-scale meta-analysis, acamprosate has been shown to be a more effective treatment than placebo (Garbutt et al., 1999). However, more recent studies have been mixed with respect to the effectiveness of acamprosate treatment for alcohol dependence (Roussaux et al., 1996; Feeney et al., 2006; Morley et al., 2006; Namkoong et al., 2003). These studies varied in terms of social and cultural circumstances, severity of the alcohol dependence and time between the start of treatment and last drinking episode (Morley et al., 2006; Namkoong et al., 2003).

At present, there is no definitive mechanism for acamprasate's effect in alcohol dependence, although the molecule resembles glutamate (Littleton, 1998). With alcohol withdrawal, there is an increase in glutamate release and hyperactivity of both ionotropic and metabotropic glutamate receptors (mGluR) (Littleton and Zieglgansberger, 2003). In rats, acamprosate blocks this increase in glutamate in the nuclear acumbens and reduces neurotoxicity in cortical and hippocampal cultures (Dahchour et al., 1998). Acting as an antagonist to the glutamate receptor, acamprosate may inhibit the glutamate releasing feedback loop (Harris et al., 2003). Consistent with the observation that acamprosate reduced neuronal excitability during

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alcohol withdrawal, Boeijinga et al. (2004) suggested that the inhibition of glutamatergic transmission by acamprosate might be responsible for its clinical efficacy.

Glutamate antagonists have been shown to be effective in the prevention of relapse in other substance abuse disorders (Kenny and Markou, 2004). Memantine and dextromethorphan, low-affinity NMDA receptor channel blockers, reduced the severity of physical withdrawal symptoms in human opiate dependent subjects (Bisaga et al., 2001). The antagonist treatment of metabotropic glutamate receptors in mice and rat studies have demonstrated increased cocaine administration thresholds and decreased cocaine, nicotine, and ethanol self-administration (Kenny and Markou, 2004). Furthermore, mice with a deletion of the metabotropic glutamate receptor gene did not acquire cocaine self-administration behavior (Chiamulera et al., 2001).

Abnormal consummatory behaviors, such as binge eating and craving, are common pathological features of both alcoholism and eating disorders (Addolorato et al., 2005; Blum et al., 2000). High rates of comordity of alcohol abuse and eating disorders have commonly been established, more so with those engaging in bulimic and binge-eating behaviors (BED) (Sinha and O'Malley, 2000). Additionally, dysfunctional eating has begun to be classified as an addictive behavior; Davis and Claridge (1998) found eating disordered patients scored comparably to alcoholics and drug abusers on measures of addictive personality. Also, upon recovery from alcohol dependence, the co-occurrence of obesity and dysfunctional eating has been documented (Shaper, 1991).

Finally, limited research has been conducted to address the selectivity of acamprosate treatment. Escher and Mittleman (2006) suggested that acute and chronic acamprosate treatment was relatively non-selective in effects on alcohol and water self-administration in rats, though other studies do suggest selectivity for attenuation of alcohol consummatory behavior in rodent (Czachowski et al., 2001).

Based on the pathologies, behavioral interactions and potential commonality in addictive pathways between alcohol and food abuse, we hypothesized that acamprosate treatment would reduce both alcohol and food craving in human subjects with alcohol dependence. This hypothesis was tested in a large cohort of alcohol dependent subjects during in-patient treatment.

2. Methods

Overall, 204 male in-patients were included in this study, recruited from the Department of Neuropsychiatry, Chun-Cheon National Hospital from August 2003 through October 2004 and Incheon Eun Hye Hospital from March 2005 to December 2006. All aspects of the clinical protocol were reviewed and approved by the Institutional Review Board (IRB) at the Chun-Cheon National Hospital. Study subjects were diagnosed with alcohol dependence in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) classification and provided written informed consent to participate in this investigation.

The goals of the research and procedures were explained to the patients who provided written informed consent. Patients with an endocrine disorder including excessive obesity (body mass index > 37) (Lee and Wang, 2005), hyperlipidemia and diabetes mellitus, or with any history of mental illness or other substance abuse were excluded from this study.

In total, 287 in-patients with alcohol dependence were screened. Of this number, 83 were excluded from the study. Use of antipsychotics, antidepressants or anticonvulsants excluded 39 patients. Prior to the end of the study, 29 subjects were discharged from the clinical sites. Additionally, 15 patients had other psychiatric or medical problems: 3 with schizophrenia, 4 with bipolar disorder, 4 with major depression, and 4 patients had diabetes mellitus.

During a 2-week detoxification period, all patients received lorazepam and thiamine as well as cognitive behavior therapy, group therapy and education for alcohol dependence during the research period. For a 4-week period following detoxification, liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin), weight, and height of study subjects were recorded: at baseline (end of detoxification period), 1, 2, and 4 weeks later. Diazepam, zolpidem, and propranolol as PRN drugs were used for managing tremor, anxiety and insomnia. Body weight was measured before breakfast. Additionally, a seven-point visual analogue scale was applied to check craving for alcohol and food at baseline, 1, 2, and 4 weeks later.

The study subjects were divided into two groups; patients with acamprosate (PWA) and patients without acamprosate (PNA). In the group of PWA, patients with a bodyweight of <60 kg received acamprosate 1332 mg/day, whereas those with a bodyweight of ≥60 kg received 1998 mg/day (Gual and Lehert, 2001; Tempesta et al., 2000).

Changes in craving for alcohol and food from baseline to 1, 2, and 4 weeks of treatment were analyzed with repeated measures analysis of variance (ANOVA). Correlations between the change of body mass index (BMI, kg/m^2) and craving for alcohol and food were checked by Pearson correlation. Statistical significance was defined at an alpha level of less than 0.05, two tailed. All analyses were performed using Statistica 6.0.

3. Results

There were no significant differences in age, alcohol use, onset age, alcohol drinking type, education, marital status, or economic status between patients in the PWA and PNA groups (Table 1). There were no differences in liver function tests (AST, ALT, and albumin) between the two groups over the duration of treatment. There was no correlation between lorazepam dose, thiamine dose, and craving for alcohol and food.

Both PWA ($F = 34.51$, $p < 0.01$) and PNA ($F = 30.42$, $p < 0.01$) groups showed a significant reduction in craving for alcohol over 4 weeks of treatment. However, there was only a weak trend for a greater reduction in craving for alcohol in the PWA group, compared to the PNA group ($F = 2.15$, $p = 0.09$).

In contrast, the PWA group showed a different change of food craving during the treatment period, compared to the PNA