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ACAMPROSATE IN KOREAN ALCOHOL-DEPENDENT PATIENTS: A MULTI-CENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Abstract — Aims: A multi-centre, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and the safety of acamprosate over 8 weeks in Korean alcohol-dependent patients. **Methods:** One hundred and forty-two alcohol-dependent patients in 12 centres were randomized to 8 weeks treatment with either acamprosate (n = 72) or a placebo (n = 70) in combination with out-patient psychosocial intervention. They were predominantly male (95.8%), with a mean age of 44.3 ± 8.3 years; 76.1% were married; 59.9% were employed; 58.5% had received previous alcoholism treatment (previous mean number of admissions in alcoholism in-patient programmes 4.6 ± 6.9). At visits to the clinic (weekly for 4 weeks, then biweekly for 4 weeks), a record was made of alcohol use (Time-Line Follow-Back), alcohol craving using a Korean version of the Obsessive Compulsive Drinking Scale and a visual analogue scale, and adverse events. Serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase (GGT), blood urea nitrogen and creatinine levels were measured on weeks 0, 2, 4 and 8. **Results:** In the acamprosate group (A), 71.4% had had alcohol within the 2 days prior to starting medication, against 65.2% of patients in the placebo group (P); (P > 0.05). One hundred and one subjects (71.1%) completed 8-weeks of treatment (A, 73.6%; P, 68.6%; P > 0.05). During the 8-week treatment period, 37, (A) (n = 72) and 32% (P) (n = 70) achieved continuous abstinence (P > 0.05), and 40, (A) and 39% (P) remained without relapse (P > 0.05) (defined as a day when a man consumed five or more drinks or a woman four or more drinks). The percentage of days abstinent during the 8-week treatment period was 81.2, (A) and 78.5% (P) (P > 0.05), and the percentage of days without heavy drinking 86.1 (A) and 84.9% (P) (P > 0.05). The mean amount drunk per drinking occasion was 7.2, (A) and 8.6 standard drinks (P) (P > 0.05). No statistically significant differences in changes in the serum GGT level or craving scores from baseline to the end-point of treatment were found between the two groups. Recency of drinking prior to commencing study drug predicted percentage of days abstinent in the first 2 weeks on treatment; however, when ANOVAs were conducted using treatment outcomes as a dependent variable, medication condition as an independent variable and the period of abstinence prior to treatment as a covariate, a significant effect of medication condition was still not seen. **Conclusions:** Acamprosate was ineffective in reducing drinking in this Korean sample. The result differs from that of most European acamprosate trials. This might be explained by our sample's relatively severe alcohol dependence, and low social support, or the fact that many patients were still drinking near to their first medication. The variability of the psychosocial support, ethnicity (which might also affect acamprosate pharmacokinetics) and the Korean drinking style, which differs from that of Europeans, might have contributed to our negative result.

INTRODUCTION

Alcohol dependence is one of the most important health issues throughout the world. Its prognosis is known to be poor. Korea is no exception in this respect, and, for these reasons, acamprosate has drawn the attention of many clinical investigators.

Acamprosate (calcium acetylhomotaurinate) has been postulated to be a helpful adjunct to conventional out-patient treatment after detoxification for the treatment of alcohol dependence. Most European clinical trials of acamprosate in detoxified alcoholics have demonstrated a statistically significant lengthening of time to first drink, a reduction in drinking days, and an increase in the percentage attaining complete abstinence (Lhuintre *et al.*, 1985; Pelc *et al.*, 1992, 1997; Ladewig *et al.*, 1993; Paille *et al.*, 1995; Sass *et al.*, 1996; Whitworth *et al.*, 1996; Barrias *et al.*, 1997; Geerlings *et al.*, 1997; Poldrugo, 1997; Tempesta *et al.*, 2000). However, these findings have not yet been replicated outside Europe.

It is generally believed that Asians have a lower rate of alcoholism, because of the flushing reaction to ethanol due to a reduced level of aldehyde dehydrogenase (Goedde *et al.*, 1984). However, the lifetime prevalence of alcohol dependence in Korea by Diagnostic Interview Schedule (DIS)/DSM-III was found to be 10.3%, which is higher than was found using the same method in western countries as well as in other Asian countries (Helzer *et al.*, 1990; Namkoong *et al.*, 1990). In addition, Koreans have their own unique concept of alcoholism and drinking style, compared with other Asian peoples.

Given the emerging role of genetic and cultural issues in drug treatment, it was considered important to evaluate the efficacy and safety of acamprosate for alcohol dependence in different ethnic groups, such as in this Korean sample.

PATIENTS AND METHODS

This study was a multi-centre, randomized, double-blind, placebo-controlled clinical trial undertaken to evaluate the efficacy and safety of acamprosate for the treatment of Korean alcohol-dependent patients. Following baseline assessment, 142 alcohol-dependent patients were randomized to receive either acamprosate or a placebo over a period of 8 weeks. This treatment was combined with an out-patient psychosocial treatment programme.

Subjects

Subjects were recruited through newspaper advertisements or as patients seeking treatment at the out-patient clinics of seven university general hospitals and five psychiatric hospitals, which had an alcohol treatment programme.

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An initial screening examination and assessment was conducted within 4 weeks of the end of detoxification. Detoxification may have been carried out on an in-patient or out-patient basis for patients who were clinically assessed to be in need of detoxification. Patients had to be free of benzodiazepines and were instructed not to drink alcohol between the initial screening and randomization session (week 0). Patients who had a positive breathalyser result on day 0 were required to return on the next day. Individuals from 21 to 65 years of age were eligible to participate if they: (1) met the DSM-IV criteria (American Psychiatric Association, 1994) for alcohol dependence; (2) were able to read and write Korean; (3) had a stable residence and a telephone. Criteria for exclusion included: (1) current misuse or dependence on a substance other than alcohol or nicotine; (2) acute major psychiatric illness or psychotic illness; (3) liver cirrhosis or renal problem (serum creatinine > 1.2 mg/dl); (4) unstable medical condition; (5) current use of disulfiram or regular use of psychotropic medication; (6) previous treatment with acamprosate; (7) among women, pregnancy, nursing or refusal to use a reliable form of birth control.

Written informed consent was obtained at the initial screening session. The protocol was approved by the Internal Review Board of each centre and the National Food and Drug Administration, and was conducted in accordance with the amended Declaration of Helsinki (World Medical Association, 1997).

An unspecified number of subjects were approached for initial screening by investigators in each centre. Of a total of 153 patients meeting initial eligibility criteria, 11 potential participants declined to participate or dropped out prior to randomization for the following reasons: they were unable to abstain for just 1 day (n = 2), lost to follow-up (n = 4), refused treatment (n = 3), and refused to take medication (n = 2) between assessment and randomization. Enrolment in the study took place only after an examination by a psychiatrist, a physical examination and after blood and urine laboratory tests had been completed.

A total of 142 subjects were randomized with respect to the medication according to age, sex and body weight, and actually attended the first treatment session at which study medications were dispensed. Seventy-two of the subjects were randomized to acamprosate, and 70 to a placebo treatment. Rates of treatment enrolment and study completion are displayed in Fig. 1.

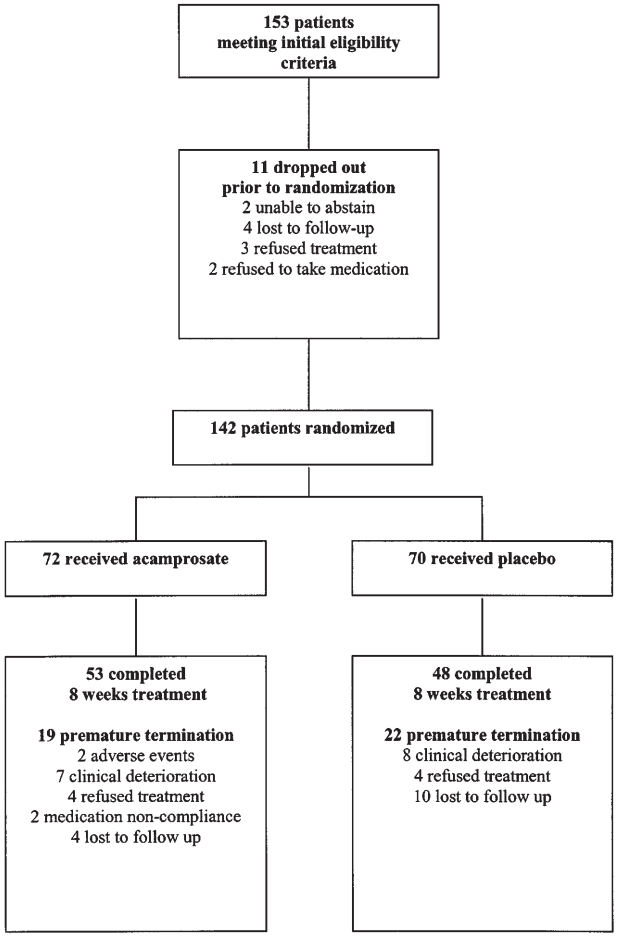

Fig. 1. Patient enrolment and discontinuation.

Treatments

After the initial screening session, eligible patients were randomized to receive acamprosate or placebo by the principal investigator (K.N.), using a computer-generated schedule. Investigators remained blind to the medication assignment.

Patients visited the clinic weekly for the first 4 weeks, and biweekly for the second 4 weeks. At each visit, 1332 mg/day (<60 kg body weight) or 1998 mg/day (≥60 kg) of acamprosate or equivalent numbers of identically presented placebo tablets were dispensed, and the subjects also underwent the clinic's usual psychosocial treatment, which included medical counselling, brief psychotherapy, and encouragement to attend AA sessions or cognitive behavioural therapy.

Assessments

At intake, a record was made of sociodemographic characteristics, physical examination, laboratory testing (liver and renal function) and psychiatric status. Drinking behaviour for the preceding 4 weeks prior was assessed using Time-Line Follow-Back (TLFB) (Sobell and Sobell, 1992). Diagnoses of substance use disorders and other psychiatric disorders were obtained from a psychiatrist's clinical interview, according to DSM-IV criteria (American Psychiatric Association, 1994).

At every visit, alcohol use from the time of the previous visit was recorded using TLFB. Breathalyser tests were administered at all assessment sessions. Alcohol craving was measured using a Korean version of the Obsessive Compulsive Drinking Scale (OCDS) (Anton *et al.*, 1995, 1996) and a visual analogue scale (VAS). Serum total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), blood urea nitrogen (BUN) and creatinine levels were measured at weeks 0, 2, 4 and 8. Finally, adverse events were monitored at each visit using the SAFTEE–GI (Levine and Schooler, 1986). To determine medication compliance, returned tablets were counted.

Statistical analyses

Following the intention-to-treat (ITT) principle, any randomized patient who took at least one dose of study medication was entered into the analysis. Primary outcome variables and statistical methods were as follows: (1) length of time to the first drink and the length of time to the first relapse. Time to

the first relapse was defined as days until the first day of heavy drinking, defined as five or more drinks in a day (males) or four or more drinks (females). Kaplan–Meier survival analysis was used to examine differences in these between the acamprosate and the placebo groups. (2) Per cent days abstinent, per cent days without heavy drinking, and mean consumption per drinking occasion was summarized for the entire study period. For these measures, differences between the two medication groups were examined using the Student's *t*-test.

Secondary outcome variables were the following: (1) per cent days abstinent, per cent days without heavy drinking, and mean drinking amount per drinking occasion, summarized over each 4-week period. Longitudinal outcomes with repeated measures were analysed by random coefficient regression analyses using the PROC MIXED procedure of Statistical Analysis System (SAS). Summary scores during the baseline 4 weeks were treated as time point 0 for the model. Medication by time interactions were tested on a period-by-period basis to evaluate how they changed with time. Because the distribution of scores of the number of drinks per drinking day was highly skewed, these scores were square-root-transformed prior to analysis. (2) Changes in a measure of craving for alcohol provided by the OCDS and VAS. (3) Changes in the GGT level from baseline to the end-point carried forward. Analysis of variance (ANOVA) with repeated measure was used to examine differences between the groups.

Relationship between the period of abstinence prior to treatment and the percentage of days abstinent during the treatment period was analysed by Pearson's correlation.

RESULTS

Sample characteristics

The sample was primarily male (95.8%), married (76.1%), well educated (high school graduate or beyond 69.0%) and employed (59.9%), and of mean ± SD age 44.3 ± 8.3 years. More than half of the subjects (58.5%) had received previous treatment for alcoholism. Their mean number of previous admissions to alcoholism in-patient programmes was 4.6 ± 6.9. Their mean ± SD baseline score on the Alcohol Dependence Scale (ADS) (Skinner and Horn, 1984) was 21.5 ± 8.4. Sixty-eight per cent of the sample had a drink within the previous 2 days of starting medication [71.4% of the acamprosate group (A), 65.2% of the placebo group (P); $P > 0.05$]. They drank for an average of 52.7 ± 32.7% of the 28-day pre-treatment baseline period, and consumed an average of 18.0 ± 11.7 standard drinks per drinking occasion.

The groups formed by randomization did not differ in terms of demographic, clinical characteristics or the number of days abstinent from alcohol before treatment (Table 1).

Treatment exposure

One-hundred and one patients (71.1%) completed the 8-week treatment period. Attrition was equal in both treatment groups: 19 patients (26.4%) on acamprosate and 22 patients (31.4%) on placebo. The reasons for premature termination are shown in Fig. 1.

There were no significant differences between the two groups with respect to medication compliance [percentage of tablets patient took: 80.5 ± 30.8% (A), 74.3 ± 32.2% (P); $t = 1.135$, df = 129, $P = 0.259$] or in the number of psychosocial treatment sessions attended [6.19 ± 3.10 (A), 6.17 ± 2.86 (P); $t = 0.046$, df = 140, $P = 0.963$].

Treatment effectiveness

Continuous abstinence and relapse rates in survival analysis. Figures 2 and 3 illustrate the cumulative rates of abstinence and time to the first relapse according to medication group. The median time to the first drink was 14 and 8 days for the acamprosate and placebo groups, respectively, and the corresponding median time to the first relapse was 21 (A) and 22 days (P). The proportion of patients achieving continuous abstinence over the entire 8-week treatment period was 37% (A) and 32% (P); 40% (A) and 39% (P) maintained abstinence or drank but without meeting the criteria for relapse to heavy drinking. There were no significant differences in the time to the first drink (log rank statistics = 0.36, df = 1, $P = 0.55$), or in the time to relapse (log rank statistics = 0.02, df = 1, $P = 0.90$), between the two groups.

Table 1. Demographic characteristics and drinking behaviours over the 4 weeks of baseline

Parameter (numbers or means)	Acamprosate ($n = 72$)	Placebo ($n = 70$)
Sex (% male)	69 (95.8)	67 (95.7)
Age (years) (mean ± SD)	44.7 ± 8.7	43.9 ± 8.0
Marital status (% married)	56 (77.8)	52 (74.3)
Educational level (years) (mean ± SD)	12.3 ± 3.8	12.2 ± 3.7
Employment (% employed)	45 (62.5)	40 (57.1)
Family history of alcoholism (% positive)	33 (45.8)	34 (48.6)
Previous episode of alcohol treatment (%)	43 (59.7)	40 (57.1)
In-patient detoxification before study (%)	27 (37.5)	29 (41.4)
Interval between last drink and the first medication		
Mean ± SD (days)	3.9 ± 6.6	3.8 ± 6.2
Range (days)	0–27	0–26
Patients who had a drink within the previous 2 days of starting medication	50 (71.4)	45 (65.2)
% Days drinking over 4 weeks of baseline (mean ± SD)	51.2 ± 32.4	54.1 ± 33.1
% Days heavy drinking over 4 weeks of baseline (mean ± SD)	47.6 ± 32.9	48.1 ± 31.9
Mean drinks per drinking occasion over 4 weeks of baseline (± SD)	18.4 ± 12.5	17.5 ± 10.9
Total score of Alcohol Dependence Scale (mean ± SD)	20.4 ± 8.2	22.7 ± 8.6

There were no significant differences in all variables.

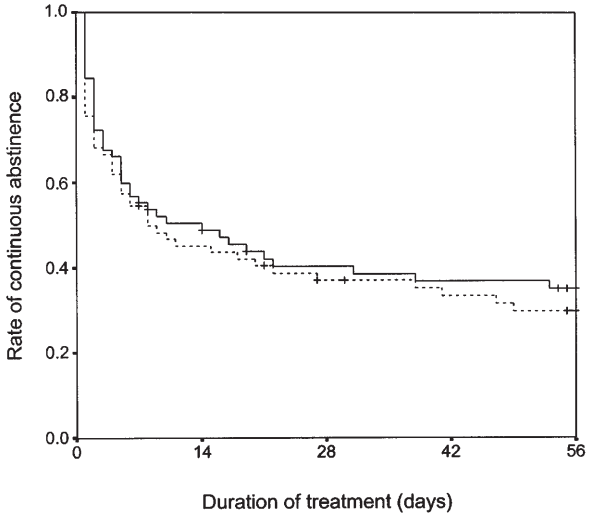

Fig. 2. Survival curve for continuous abstinence.
Log rank statistics = 0.36, df = 1, $P = 0.55$ in Kaplan–Meier survival analysis. (—) Acamprosate; (---) placebo.

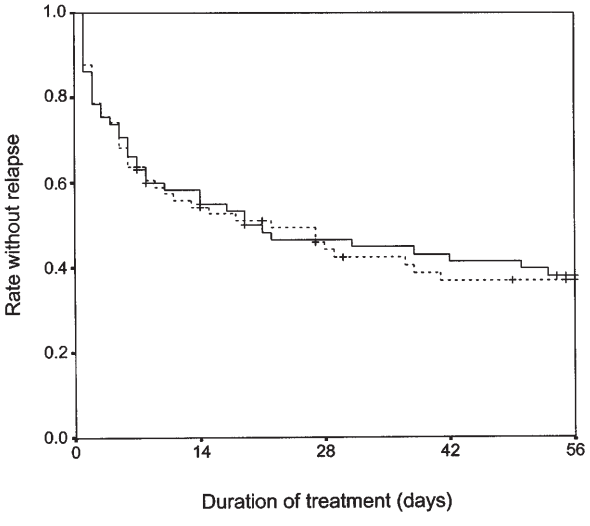

Fig. 3. Survival curve for no relapse.
Log rank statistics = 0.02, df = 1, $P = 0.90$ in Kaplan–Meier survival analysis. (—) Acamprosate; (---) placebo.

Drinking frequency and amount during the study period. In the ITT analysis for all subjects, acamprosate-treated subjects abstained for an average of 81.2% of the entire study days, whereas placebo-treated subjects abstained for 78.5% of the study days, and acamprosate-treated subjects did not drink heavily for an average of 86.1% of the entire study days, whereas placebo-treated subjects did not drink heavily for 84.9% of the study days. These differences, though slightly favouring the acamprosate group, were not statistically significant ($t = 0.60$, df = 129, $P = 0.55$; $t = 0.30$, df = 129, $P = 0.77$). Subjects receiving acamprosate drank a mean of 7.2 standard drinks per drinking occasion during the entire study period, whereas subjects receiving the placebo drank a mean of 8.6 standard drinks per drinking occasion, but this difference was not statistically significant ($t = 0.82$, df = 129, $P = 0.41$) (Table 2).

Change of drinking frequency and amount with time. Although both groups demonstrated higher levels of abstinent days and days without heavy drinking, and a lower number of drinks per drinking occasion, than during the pre-treatment period (Fig. 4), the random effects regression model did not reveal any significant medication by time interaction [$F(1,102) = 0.00$, $P = 0.96$; $F(1,102) = 0.02$, $P = 0.90$; $F(1,102) = 0.48$, $P = 0.49$, respectively].

Measure of alcohol craving and serum GGT. Alcohol craving measured by OCDS and VAS (Table 2) at baseline decreased by the end-point in both groups [OCDS, 19.9 ± 9.6 to 11.5 ± 11.1 (A), 22.2 ± 11.7 to 14.9 ± 11.2 (P); VAS, 3.2 ± 3.7 to 2.0 ± 2.6 (A), 3.8 ± 4.0 to 2.7 ± 3.1 (P)], but no significant medication by time interaction [OCDS, $F(1) = 0.316$, $P = 0.575$; VAS, $F(1) = 0.084$, $P = 0.773$] was observed by analysis of variance with repeated measures. The serum GGT level also decreased [87.2 ± 119.5 to 74.0 ± 126.3 (A), 141.4 ± 231.2 to 98.3 ± 157.6 (P)] without producing a significant medication by time interaction [$F(1) = 2.714$, $P = 0.102$] (Table 2).

Relationship between the period of abstinence prior to treatment and the percentage of days abstinent during treatment period

The interval between last drinking and the beginning of medication was significantly correlated with the per cent of days abstinent during the study follow-up period ($r = 0.21$, $P < 0.05$). In particular, there was a significant positive correlation between the interval from last drinking to the beginning of medication and the per cent of days abstinent during the first 2 weeks of the study ($r = 0.19$, $P < 0.05$). However, there was no significant correlation during the remainder of the study period ($r = 0.14$, $P > 0.05$). When ANOVAs were conducted using treatment outcomes as a dependent variable, medication condition as an independent variable and the period of abstinence prior to treatment as covariate, there was no significant effect of medication condition (per cent days abstinent, $F = 0.00$, $P > 0.05$; per cent days without heavy drinking, $F = 0.07$, $P > 0.05$; mean drinking amount per drinking occasion, $F = 0.64$, $P > 0.05$).

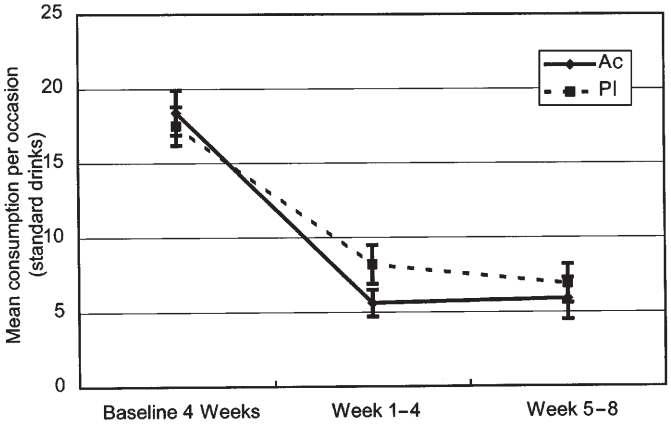

Fig. 4. Mean consumption per drinking occasion over time.
Medication group; $F(1,102) = 0.34$, not significant, time; $F(1,129) = 49.64$, $P < 0.05$, medication group by time interaction; $F(1,102) = 0.62$, not significant in random coefficient regression analysis. Ac, acamprosate, Pl, placebo.

Table 2. Treatment effectiveness

Treatment outcomes	Acamprosate (n = 72)	Placebo (n = 70)	df	t/F	P
Primary outcomes					
% Subjects who abstained continuously in survival analysis	36.9	31.8	1	0.36[a]	ns
% Subjects who never relapsed in survival analysis	40.0	39.4	1	0.02[a]	ns
% Days abstinent during study period (mean ± SD)	81.2 ± 23.7	78.5 ± 27.8	129	0.60	ns
% Days without heavy drinking during study period[b] (mean ± SD)	86.1 ± 20.0	84.9 ± 23.3	129	0.30	ns
Mean drinking amount per drinking occasion during study period (mean ± SD)	7.2 ± 9.8	8.6 ± 9.8	129	0.82	ns
Secondary outcomes					
Change of GGT level[c]					
Baseline (mean ± SD)	87.2 ± 24.3	141.4 ± 23.9			
End-point (mean ± SD)	74.0 ± 18.8	98.3 ± 18.5			
Medication × time interaction			1	2.714	ns
Change of OCDS total score[c]					
Baseline (mean ± SD)	19.9 ± 9.6	22.2 ± 11.7			
End-point (mean ± SD)	11.5 ± 11.1	14.9 ± 11.2			
Medication × time interaction			1	0.316	ns
Change of VAS[c]					
Baseline (mean ± SD)	3.2 ± 3.7	3.8 ± 4.0			
End-point (mean ± SD)	2.0 ± 2.6	2.7 ± 3.1			
Medication × time interaction			1	0.084	ns

[a]Log rank statistics in Kaplan–Meier survival analysis.
[b]Heavy drinking is defined by a single day of drinking five or more drinks for men or four or more drinks for women.
[c]Analyses of variance with repeated measure from baseline to the end-point carried forward. The effect of interest is the medication group by time interaction.
ns, Not significant.

Adverse events

During the 8-week study period, 37.5% (27/72) of subjects receiving acamprosate reported experiencing one or more symptoms potentially related to the medication. However, the number of subjects reporting one or more symptoms during the treatment period did not differ significantly between the acamprosate- and the placebo-treated group. 'Constipation/diarrhoea' was the most common complaint among the acamprosate group (11.1%, 8/72), and this was significantly greater than in the placebo group (2.9%, 2/70) ($\chi^2 = 2.54$, df = 1, $P < 0.1$ by Fisher's exact test). 'Increased appetite' (11.1%, 8/72), 'decreased libido' (8.3%, 6/72), 'sleeping difficulty' (8.3%, 6/72), 'joint or muscle pain' (8.3%, 6/72) and 'memory impairment' (6.9%, 5/72) were common complaints among the acamprosate group; however, these were not significantly different from complaints received from the placebo group.

DISCUSSION

The efficacy of acamprosate in alcohol dependence has been evaluated by 16 controlled clinical trials conducted across 11 European countries, which have involved more than 4500 alcohol-dependent patients. Can the positive result obtained by European studies [except Roussaux *et al.* (1996) in Belgium and Chick *et al.* (2000) in the UK] be replicated in Korean alcoholics who have a different cultural and genetic background?

The main finding of this study was that acamprosate did not show any better treatment outcomes than placebo in the out-patient treatment of alcohol dependence. Compared with previous European trials that showed positive findings over a relatively short treatment duration (3 months), the treatment efficacy of acamprosate in our study, as represented by the percentage of subjects who abstained completely, was poorer [our study, 37%; Lhuintre *et al.* (1985) in France, 48%; Pelc *et al.* (1997) in Belgium, 51%]. It is possible that this difference may have resulted from the fact that the alcohol dependence of our sample was too severe to respond to acamprosate.

In general, Koreans are very permissive of heavy drinking and the behavioural complications resulting from heavy drinking. For example, 'heavy drinking' in the Korean culture is regarded as an expression of strength and power or an indication of health or virility. 'Loss of control' is also regarded not as a pathological consequence of drinking, but a common result of drinking and even one of the purposes of drinking. The criteria of normal (or social) drinking are dependent not on the amount or the consequence of drinking, but upon its purpose. If someone drinks for business purposes or on social occasions, he is regarded as a social drinker, even though he suffers recurrent physical complications of drinking. Mild to moderate severity of alcohol dependence have been considered as a sort of personal habit, not as a disease warranting treatment (Lee *et al.*, 1995, 1997; Room *et al.*, 1996). Repeatedly, Koreans tend to restrict their concept of disease to the physiological consequences of long-term alcohol use, while Americans accept a definition that is couched largely in social and behavioural terms (Cho and Faulkner, 1993). It thus appears that alcohol consumption in Korea is greater, and that the prevalence of alcoholism by American criteria is higher, than other countries; however, alcoholics are rarely diagnosed and treated. Therefore, only patients with a relatively severe level of alcohol dependence seek treatment.

Actually, 59% of the total sample had previously had treatment and failed. Their mean number of admissions in alcoholism in-patient programmes was 4.6 ± 6.9, 40% of total subjects having, in addition, just been treated as in-patients before entering this trial. Taking into account the higher threshold for the admission of alcohol-dependent patients into a hospital in Korea, our sample seems to have a more severe level of alcoholism than even the UK sample (more than 50% had a history of

treatment failure), which was regarded as being more severe than previous trials (Chick *et al.*, 2000). The mean ADS score during baseline, a quantitative index of the severity of alcohol dependence, of our sample was 22, which also indicates a substantial level of dependence (Skinner and Horn, 1984).

In addition, the higher unemployment rate (40%) of our subjects than in previous positive studies (Paille *et al.*, 1995: 21%; Sass *et al.*, 1996: 26%; Tempesta *et al.*, 2000: 32%), might be another factor that influenced the negative result of the present study. This possibility is supported by the other negative studies, which also comprised subjects with high unemployment (Roussaux *et al.*, 1996: 60%; Chick *et al.*, 2000: 48%).

The comparatively short interval between last drinking and the first medication may also have contributed to this negative finding. Compared to previous studies in which all subjects maintained abstinence for at least 5 days (except Chick *et al*., 2000), the mean interval of our sample was merely 3.8 ± 6.4 days and 68.3% of subjects started taking study medication within 2 days of their last drinking. Actually, as mentioned above, the period of abstinence prior to treatment was significantly correlated with the per cent of days abstinent during the entire study period ($r = 0.21$, $P < 0.05$).

There is a dosage issue of acamprosate, which must also be considered. It is common knowledge that genetic factors are significant determinants of a patient's response to psychotropic medication, and that dosage requirements and the potential for toxic reactions might differ among racial and ethnic groups (Lin *et al.*, 1986). Medication administration should be also determined by the patient's environmental and cultural background, in addition to the patient's genetic predisposition, because these also influence drug response (Kudzma, 1999). Increasingly, studies have confirmed that ethnicity affects how people react to drugs. For example, Korean–American patients achieved significantly lower clozapine concentrations than Caucasians, even after controlling for differences in daily doses (Matsuda *et al.*, 1996). In contrast to Korean–American patients, Chinese patients were reported to have 30–50% higher concentrations than those reported for Caucasians (Chang *et al.*, 1997). Therefore, a person of Asian descent is more likely to experience a lack of effectiveness or an adverse outcome to pharmacotherapy if the drug hasn't been properly adjusted from some Caucasian optimum (Potkin *et al.*, 1984). Moreover, because a multitude of factors might interact during the development, diagnosis and treatment of alcohol dependence, rigorous and carefully designed studies to optimize dosages are necessary to confirm the efficacy of a drug treatment for alcohol dependence across ethnic groups. Actually, a daily schedule of 3 g of acamprosate has recently been tried in an American acamprosate trial (Mason *et al.*, 1997).

Finally, studies have shown a high prevalence of alcohol dependence in the Korean population, despite the high frequency of variant aldehyde dehydrogenase allele (ALDH2*2), known to be a protective factor against alcohol dependence (Helzer *et al.*, 1990; Lee *et al.*, 1990). This suggests that a large portion of the alcohol dependence among Koreans might have been determined socio-culturally, rather than biologically or genetically. This may be another reason for our subjects' resistance to treatment with acamprosate.

Several limitations of the present study should be addressed. First, in the light of a previous finding that the difference in the rate of abstinence, between acamprosate and placebo, generally emerged within the first 30–90 days of treatment (Mason, 2001), the 8-week study duration might have been too short to evaluate the efficacy of acamprosate on the prevention of relapse. Secondly, the diverse type and dosage of concomitant psychosocial intervention provided by different centres may have increased the possibility of a type II error in our study. Actually, a few centres provided 12-step facilitation or cognitive behavioural therapy for 60 min at least twice per week, while other centres provided only a medication prescription with minimal psychosocial intervention at each patient's visit. A number of recent studies have demonstrated that proper psychosocial intervention can increase the likelihood of a significant difference between medication and placebo in pharmacological trial upon alcohol dependence, by increasing patient retention, enhancing medication compliance, and fostering the acquisition of new skills that reinforce the effects of medication (O'Malley and Carrol, 1996). Therefore, an increased intensity of psychosocial intervention may obscure medication effects by improving treatment outcome in a placebo condition. Conversely, a relatively low intensive psychosocial approach might even minimize the efficacy of active medication.

In conclusion, our study did not show any treatment benefit in terms of outcome of acamprosate treatment. The findings of this study differ from those of most European clinical trials, which found that acamprosate helps to maintain abstinence and prevent relapse in abstinent out-patient alcoholics, over a 3–12-month treatment period following withdrawal. However, the findings of our study are consistent with those of a Belgium study by Roussaux *et al.* (1996) and a UK study by Chick *et al*. (2000). This negative finding might be explained by our sample's characteristics (i.e. a more severe form of alcohol dependence, a lower level of social support, a short interval between the last drink and the first medication), the dosage issue of acamprosate, as outlined above, the short study period, and the variable concomitant psychosocial treatment. We recommend that optimal treatment dose and concomitant psychosocial intervention suitable for the treatment of Korean alcoholics need to be further investigated.

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REFERENCES

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association, Washington DC.

Anton, R. F., Moak, D. H. and Latham, P. (1995) The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcoholism: Clinical and Experimental Research* **19**, 92–99.

Anton, R. F., Moak, D. H. and Latham, P. K. (1996) The obsessive compulsive drinking scale: a new method of assessing outcome in alcoholism treatment studies. *Archives of General Psychiatry* **53**, 225–231.

Barrias, J. A., Chabac, S., Ferreira, L., Fonte, A., Potgieter, A. S. and Teixeira de Sousa, E. (1997) Acamprosate: multicenter Portuguese

efficacy and tolerance evaluation study. *Psiquiatria Clinica* **18**, 149–160.
Chang, W. H., Lin, S. K., Lane, H. Y., Hu, W. H., Jann, M. W. and Lin, H. N. (1997) Clozapine dosages and plasma drug concentrations. *Journal of Formosa Medical Association* **96**, 599–605.
Chick, J., Howlett, H., Morgan, M. Y. and Ritson, B. (2000) United Kingdom multicentre acamprosate study (UKMAS): a 6 month prospective study of acamprosate vs placebo in preventing relapse after withdrawal from alcohol. *Alcohol and Alcoholism* **35**, 176–187.
Cho, Y. I. and Faulkner, W. R. (1993) Conceptions of alcoholism among Koreans and Americans. *International Journal of the Addictions* **28**, 681–694.
Geerlings, P. J, Ansoms, C. and van den Brink, W. (1997) Acamprosate and prevention of relapse in alcoholics. *European Addiction Research* **3**, 129–137.
Goedde, H. W., Benkmann, H. G., Kriese, L., Bogdanski, P., Agarwal, D. P., Du, R. F., Chen, L. Z., Cui, M. Y., Yuan, Y. D. and Xu, J. J. (1984) Aldehyde dehydrogenase isozyme deficiency and alcohol sensitivity in four different Chinese populations. *Human Heredity* **34**, 183–186.
Helzer, J. E., Canino, G. J., Yeh, E. K., Bland, R. C., Lee, C. K., Hwu, H. G. and Newman, S. (1990) Alcoholism—North America and Asia. A comparison of population surveys with the Diagnostic Interview Schedule. *Archives of General Psychiatry* **47**, 313–319.
Kudzma, E. C. (1999) Culturally competent drug administration. *American Journal of Nursing* **99**, 46–51.
Ladewig, D., Knecht, T., Leher, P. and Fendl, A. (1993) Acamprosate — a stabilizing factor in the long-term treatment of alcoholics. *Therapeutische Umschau* **50**, 182–188.
Lee, C. K., Kwak, Y. S., Yamamoto, J., Rhee, H., Kim, Y. S., Han, J. H., Choi, J. O. and Lee, Y. H. (1990) Psychiatric epidemiology in Korea. Part I: Gender and age differences in Seoul. *Journal of Nervous and Mental Disease* **178**, 242–246.
Lee, H. Y., Namkoong, K., Lee, M. H., Hyun, Y. H. and Cho, E. Y. (1995) Ethnographic study on concept of alcoholism in Korea (I) — Key Informant Interview Study (KIIS). *Psychopathology* **4**, 24–37.
Lee, M. H., Namkoong, K., Lee, H. Y., Yoo, S. W. and Cho, E. Y. (1997) Ethnographic study on concept of alcoholism in Korea (II) — Focus Group Study (FGS). *Journal of Korean Neuropsychiatric Association* **36**, 1022–1032.
Levine, J. and Schooler, N. (1986) SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacology Bulletin* **22**, 343–381.
Lhuintre, J. P., Daoust, M., Moore, N. D., Chretien, P., Saligaut, C., Tran, G., Bosimare, F. and Hillemand, B. (1985) Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. *Lancet* **i**, 1014–1016.
Lin, K. M., Poland, R. E. and Lesser, I. M. (1986) Ethnicity and psychopharmacology. *Culture, Medicine and Psychiatry* **10**, 151–165.
Mason, B. J. (2001) Treatment of alcohol-dependent outpatients with acamprosate: a clinical review. *Journal of Clinical Psychiatry* **62** (Suppl. 20), 42–48.
Mason, B. J., Goodman, A. M. and Koob, G. F. (1997) Methodology of the US multicenter study of acamprosate in alcohol dependence. Presented at the American College of Neuropsychopharmacology (ACNP) Annual Meeting, Kamuela, Hawaii.
Matsuda, K. T., Cho, M. C., Lin, K. M., Smith, M. W., Young, A. S. and Adams, J. A. (1996) Clozapine dosage, serum levels, efficacy, and side-effect profiles: a comparison of Korean-American and Caucasian patients. *Psychopharmacology Bulletin* **32**, 253–257.
Namkoong, K., Lee, H. Y., Lee, M. H., Lee, B. Y. and Lee, D. G. (1990) Cross-cultural study of alcoholism: comparison between Kangwha, Korea and Yanbian, China. *Yonsei Medical Journal* **32**, 319–325.
O'Malley, S. S. and Carroll, K. M. (1996) Psychotherapeutic considerations in pharmacological trials. *Alcoholism: Clinical and Experimental Research* **20** (Suppl. 7), 17A–22A.
Paille, F., Guelfi, J. D., Perkins, A. C., Royer, R. J., Steru, L. and Parot, P. (1995) Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol and Alcoholism* **30**, 239–247.
Pelc, I., Le Bon, O., Verbanck, P., Lehert, P. H. and Opsomer, L. (1992) Calcium acetyl homotaurinate for maintaining abstinence in weaned alcoholic patients; a placebo controlled double-blind multi-centre study. In *Novel Pharmacological Interventions for Alcoholism*, Naranjo, C. and Sellers, E. eds, pp. 348–352. Springer Verlag, New York.
Pelc, I., Verbanck, P., Le Bon, M., Gavrilovic, M., Lion, K. and Lehert P. (1997) Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients: a 90-day dose finding study. *British Journal of Psychiatry* **171**, 73–77.
Poldrugo, F. (1997) Acamprosate treatment in a long-term community based alcohol rehabilitation programme. *Addiction* **92**, 1537–1546.
Potkin, S. G., Shen, Y., Pardes, H., Phelps, B. H., Zhou, D., Shu, L., Korpi, E. and Wyatt R. J. (1984) Haloperidol concentrations elevated in Chinese patients. *Psychiatry Research* **12**, 167–172.
Room, R., Janca, A., Bennett, L. A., Schmidt, L. and Sartorius, N. (1996) WHO cross-cultural applicability research on diagnosis and assessment of substance use disorders: an overview of methods and selected results. *Addiction* **91**, 199–220.
Roussaux, J. P., Hers, D. and Ferauge, M. (1996) Does acamprosate diminish the appetite for alcohol in weaned alcoholics? *Journal de Pharmacie de Belgique* **51**, 65–68.
Sass, H., Soyka, M., Mann, K. and Zieglgansberger, W. (1996) Relapse prevention by acamprosate: results from a placebo controlled study on alcohol dependence. *Archives of General Psychiatry* **53**, 673–680.
Skinner, H. A. and Horn, J. L. (1984) *Alcohol Dependence Scale (ADS) User's Guide*. Addiction Research Foundation, Toronto.
Sobell, L. C. and Sobell, M. B. (1992) Timeline follow back: a technique for assessing self-reported ethanol consumption. In *Measuring Alcohol Consumption: Psychosocial and Biological Methods*, Allen, J. and Litten, R. Z. eds, pp. 41–72. Humana Press, New Jersey.
Tempesta, E., Janiri, L., Bignamini, A., Chabac, S. and Potgieter, A. (2000) Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. *Alcohol and Alcoholism* **35**, 202–209.
Whitworth, A. B., Fischer, F., Lesch, O., Nimmerrichter, A., Oberauer, H., Platz, T., Potgieter, A., Walter, H. and Fleischhacker, W. W. (1996) Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet* **347**, 1438–1442.
World Medical Association (1997) Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *Journal of the American Medical Association* **227**, 925–926.