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ORIGINAL ARTICLE

Investigation of the Effect of Acamprosate Treatment on Heart Contractions in Alcohol-Dependent Rats

Alkol Bağımlı Sıçanlarda Akamprosat Tedavisinin Kalp Kasılması Üzerine Etkisinin İncelenmesi

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ABSTRACT

Background/ Aim: Chronic alcohol use leads to impaired heart contraction and also causes a direct toxic effect on myocardial function. Acamprosate, which is widely used in alcohol dependence, is not known to have a pharmacological effect on cardiac contraction. Therefore, this study aimed to investigate the effects of acamprosate on the heart muscle.
Materials and Methods: A total of 32 female Wistar rats were divided four groups as control (10 mg/kg/g saline) group, alcohol (10 mg/kg/g alcohol + 10 mg/kg/g saline) group, acamprosate (200 mg/kg/g) group and alcohol+ acamprosate groups (10 mg/kg/g alcohol + 200 mg/kg/g acamprosate + 10 mg/kg/g saline). Alcoholic rats were scored for alcohol dependence and withdrawal. After that, the rats were sacrificed, respectively and the heart tissue was removed. The amplitude and contraction frequencies of the atrium tissue taken from the heart tissue were measured in the isolated tissue bath.
Results: Alcohol dependence and withdrawal symptoms were observed in the Alcohol group and Alcohol+Acamprosate group (p<0ç05). When atrium contractions were investigated in all groups, a statistically significant difference was found between the tension values (p<0.05).
Conclusion: The use of acamprosate has been found to have negative effects on heart contraction. It would be useful to consider this effect in terms of the treatment protocol.

Key words: Alcohol, Alcohol dependence, acamprosate, heart contraction, isolated tissue bath

ÖZ

Amaç: Kronik alkol kullanımı kalp kasılmasında bozukluklara yol açmakta, aynı zamanda da miyokard fonksiyonları üzerinde direk toksik etkiye neden olmaktadır. Alkol bağımlılığında yaygın olarak kullanılan akamprosat'ın kalp kasılması üzerinde farmakolojik bir etkisi olduğu bilinmemektedir. Bu nedenle bu çalışmada akamprosatın kalp kası üzerindeki etkilerinin araştırılması amaçlanmıştır.
Gereç ve Yöntemler: 32 adet Wistar cinsi rat dört eşit gruba ayrıldı bunlar kontrol grubu (10 mg/kg/g serum fizyolojik), alkol (10 mg/kg/g alkol) grubu, akamprosat (200 mg/kg/g) grubu, alkol+ akamprosat (10 mg/kg/g alkol, 200 mg/kg/g akamprosat, 10 mg/kg/g serum fizyolojik) grubuydu. Alkol bağımlısı sıçanlara alkol bağımlılığı ve yoksunluğu skorlaması yapıldı. Daha sonra sırasıyla sıçanlar sakrifiye edildi ve kalp dokusu çıkarıldı. Kalp dokusundan alınan atriyum dokusunun amplitüdü ve kasılma frekansları izole doku banyosunda ölçüldü.
Bulgular: Alkol grubunda ve Alkol+Akamprosat grubunda alkol bağımlılığı ve yoksunluk belirtileri gözlendi (p<0.05). Tüm gruplarda atriyum kasılmaları incelendiğinde, gerilim değerleri arasında istatistiksel olarak anlamlı fark bulundu (p<0.05).
Sonuçlar: Akamprosat kullanımının kalp kasılması üzerinde olumsuz etkileri olduğu bulunmuştur. Bu etkiyi tedavi protokolü açısından değerlendirmek faydalı olacaktır.

Anahtar Kelimeler: alkol, alkol bağımlılığı, akamprosat, kalp kasılması, izole organ banyosu

Introduction

Dependence is defined as a person's excessive passion, characterized by the desire for the pleasurable effects of substances such as alcohol, cigarettes or drugs and withdrawal crises that develop when these substances are not used (1). Addictive substances have three important features: the development of tolerance to their pleasurable effects of substance, the withdrawal crises and symptoms that occur when the substance is suddenly stopped and the occurence of physical and psychological problems due to long-term use (2-3).

Addiction caused by constant and excessive use of alcohol-containing beverages, which causes behavioral disorders, is called alcoholism (4-5). Alcohol addiction is the state of drinking too much and often enough to impair physical and mental health, work and family life and social harmony and not being able to avoid the alcohol consumption (6). The treatment process in alcohol use disorders requires a multidisciplinary approach using both long-term psychological therapies and pharmacological treatment methods together (7-8).

Acamprosate is the most common pharmacological treatment method used to treat alcohol addiction (9). Acamprosate is a structural analogue of the neurotransmitter taurine, which has an inhibitory effect on the central nervous system (10). Acamprosate, which is in the structure of calcium acetyl-homotaurinate, is also accepted an NMDA (N-methyl-D-aspartate) receptor modulator (10). While antagonizing glutamate, which has an excitatory effect in the brain, stimulates GABA,

which has an inhibitory effect (11). In this way, the balance between the glutamate system and GABA is achieved and alcohol intake is reduced. (12).

Acamprosate reduces alcohol intake by diminishing dopamine hyperexcitability in the nuclei accumbens during alcohol withdrawal (13-14).

Alcohol use disorder is an important problem worldwide because of its negative effects. Excessive alcohol use causes cardiovascular diseases, abnormalities, cirrhosis, neuropsychiatric diseases and many other diseases including some types of cancer (15). Due to chronic alcohol use, alcohol and alcohol metabolite called acetate and acetaldehyde have direct toxic effects on human (16). Dilatation of the sarcoplasmic reticulum and changes in mitochondrial ultrastructure have been observed in the heart after acute alcohol intake (17). Decrease in mitochondrial function in alcohol addicts is associated with impairment of protein synthesis and the development of arrhythmia (17). Chronic alcohol consumption increases the risk of impaired left ventricular function and the development of alcoholic cardiomyopathy (18).

It is emphasized that acamprosate, one of the main pharmacological agents used in alcohol addiction, does not have any significant adverse effects but has side effects such as diarrhea, nervousness and fatigue (19-20).

At the same time, there is not significant interaction of acamprosate with other drugs (21). However, recent research suggests that acamprosate can reduce heart rate, which may be due to an increase in cortisol release during alcohol withdrawal (21-22). This symptom is advocated as the use of acamprosate in individuals with high exposure to alcohol causes autonomic dysregulation (21-23).

As a result of the researches, we can say there is no concrete evidence about the effect of acamprosate treatment used in alcohol addiction on heart contraction.

The aim of this study is to demonstrate the possible effects of acamprosate, which is used in the treatment of alcohol dependence, on heart contraction.

Methods

Animals

This study was approved by Necmettin Erbakan University Animal Experiments Local Ethics Committee's decision no: 2021-007. All experiments complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving animals. In the experiment, 32 adult female Wistar Albino rats between 300-350 gr were used which were obtained from Necmettin Erbakan University KONÜDAM Experimental Medicine Application and Research Center. They randomizedly distributed to 4 groups. Animals were kept under standard laboratory conditions with free access to water and laboratory chow at 21±2˚C with a constant relative humidity of 50% and 12 h-light/12 h-dark cycle.

Experimental Design

Control Group (Group 1), (n=8): Animals were administered 10 mg/kg/g Serum Physiological (0.9% NaCl Solution, Saline) through intragastric tube (oral gavage) for a period of 21 days.

Alcohol Group (Group 2), (n=8): Animals were administered ethanol 10 mg/kg/g and saline 10 mg/kg/g by intragastric tube (oral gavage) for a period of 21 days. At the end of the 21st day, alcohol dependence and withdrawal behaviors of the animals were observed, respectively.

Acamprosate Group, (Group 3), (n=8): Animals were given acamprosate (Sigma- Aldrich) 200 mg/kg/g and saline 10 mg/kg/g by intragastric tube for a period of 21 days.

Alcohol + Acamprosate Group, (Group 4), (n=8): Animals were administered both ethanol 10 mg/kg/g, acamprosate 200 mg/kg/g and saline 10 mg/kg/g via an intragastric tube (oral gavage) over a 21-day period. As a result of the literature review, alcohol and acamprosate do not react with each other.

The animals were weighed in the first phase of the experiment, 10 days after the start of the experiment, and on the 20th day of the experiment, respectively. Weight measurements were made between 08:00 and 09:00 hours just before intragastric tube administration to all animals.

Evaluation of alcohol dependence and withdrawal symptoms of animals was scored manually and recorded with the help of video recording system at the end of the 21st day of the experiment.

After alcohol administration, the animals were placed in plexiglass transparent cylindrical cages with a diameter of 25 cm and a height of 65 cm and each animal was observed in turn for 20 minutes.

These observations were made 4 times in total, in the first 30 minutes after alcohol administration, after 2 hours, after 4 hours and after 6 hours.

Atrium removal from all the animals in the experimental groups was carried out between 08.00-10.00 in the morning. A mixture of ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg) was administered intraperitoneally (i.p.) to the animals. After the animals were under the effect of anesthesia, cervical dislocation was performed. Afterwards, the heart tissue taken from the animals was placed in the Krebs-Henseleit solution. (Krebs-Henseleit Solution; NaCl;118 mM/L, KCl;4,7 mM/L, MgSO4;1,2 mM/L, Glukoz;11,5 mM/L, CaCl2;2,4 mM/L, KH2PO4;1,18 mM/L, NaHCO3;15,8 mM/L, EDTA;0,0016 mM/L).

Tissue and blood residues in the heart were completely cleaned before being taken into the isolated tissue bath and then 3 milimeter sections taken from the atrium were placed on the lower and upper hooks inside the chambers of the isolated organ bath with Krebs-Henseleit solution in continuously gassed (95% O2 and 5% CO2) at 37˚C. The tension is set at 1000 mg. Isometric tensions in atrium sections recorded by transducer. After the tissues were placed in the isolated organ bath, each atrial tissue was monitored for 75 minutes. Krebs solution was renewed at 15-minute periods. Atrial contraction data were recorded every 15 minutes. 30 minutes after the tissue was placed in the isolated organ bath, contractions were induced with a 0.001 M adrenaline solution. Krebs-Henseleit solution was renewed 30 minutes after adrenaline administration. Afterwards, 10-6 M acetylcholine (Ach) was given. Atrial contractions continued to observed for another 30 minutes. The contractions were recorded with a physiological power convertor (FDT05, Commat Ltd.) and with MP150WS Windows (Biopac Systems Inc).

Statistical Analysis

Statistical calculations were performed for variable data from alcohol withdrawal syndrome scores, weight changes of animals throughout the experiment and contraction-relaxation responses of heart tissues. Frequency and percentage values for categorical assessments were included in the statistical calculation.

A mixed-effects model was used to calculate the tension values of heart contractions between groups and over time.

As a result of using the mixed effect model, the changes in the group-time values were analyzed in detail. Poisson mixed effects model was used in the statistical evaluation of alcohol withdrawal syndrome scoring.

Jamovi Version 2.0 and R. Core Team Version 4.0 programs were used for all statistical evaluations. As a result of the statistical calculations; $p<0.05$ was considered significant.

Results

Weight Change Results

Animals were weighed regularly on the first day, 10th and 20th days of the experiment. There was no significant difference in the comparison of the weights of the animals between groups at the beginning of the experiment. On the 10th day of the experiment, a comparison was made between the control group and the other groups in the weighing process. A significant difference was obtained as a result of comparing the weights of the control group (Group 1) and Alcohol group (Group 2) ($p<0.05$). There was no significant difference between the control group (Group 1) and the Acamprosate group (Group 3). There was a significant difference in weight change between the Control group (Group 1) and the Alcohol + Acamprosate group (Group 4) ($p<0.05$).

Weight measurements on the 20th day of the experiment were also carried out between the control group and the other groups. A significant decrease was found between the weight changes of the control group (Group 1) and the alcohol group (Group 2) ($p<0.01$). A significant increase was found between the weight changes of the control group (Group 1) and the acamprosate group (Group 3) ($p<0.05$). There was significant decrease between the weight changes of the control group (Group 1) and the alcohol+acamprosate group (Group 4) ($p<0.05$).

Alcohol Withdrawal Symptom Results

Evaluation of withdrawal symptoms in alcohol dependence was scored manually at the end of the 21st day of the experiment.

As a result of continued alcohol application for 21 days; Withdrawal symptoms were analyzed in the alcohol group and alcohol+ acamprosate group. The evaluation was carried out in the first half hour, 2, 4 and 6 hours after alcohol administration.

As a result of the evaluations, no withdrawal and addiction symptoms were observed between all time periods of the control group (Group 1) ($p>0.05$). There was a significant increase in total withdrawal and dependence symptoms in the alcohol group (Group 2) in the 2nd, 4th and 6th hours after administration ($p<0.01$). No symptoms were observed during all time periods in the acamprosate group (Group 3). A significant increase in withdrawal symptoms was observed in the alcohol + acamprosate group (Group 4) in the first 2nd, 4th and 6th hours after the administration ($p<0.01$).

Observations at all time periods compared with the control group; When the withdrawal symptoms were compared between the control group and the alcohol group, a significant increase was found ($p<0.05$). When the control group and acamprosate group were compared, no significant difference was found ($p>0.05$). Control group (Group 1) and alcohol + acamprosate group (Group 4) were compared and a significant increase was found in withdrawal symptoms ($p<0.05$).

Isolated Tissue Bath Results

Spontaneous contractions of the tissue were recorded between 15th-30th minutes. 0.001 M adrenaline was administered to the isolated organ bath chamber to induce atrial contractions.

Between the 30th and 45th minutes, contractions of the atria were recorded after administration 0.001 M adrenaline. In the 45th-60th minutes, the krebs-henseleit solution was renewed and 10-6 M of acetylcholine was added to the chamber. Contractions were observed for 30th minutes. At the 60th-75th minutes, the krebs-

henseleit solution was renewed and spontaneous contractions were observed. In comparison of the control group (Group 1) and alcohol group (Group 2) in the first 15th minute after placing the atrium tissue in the isolated organ bath; An increase was observed in the contraction data of the Alcohol group and a significant increase was obtained between the data (n=8, p<0.05).

When the control group (Group 1) and acamprosate group (Group 3) were compared, a decrease was observed in the contraction data of the acamprosate group and a significant result was obtained (n=8, p<0.05). A significant decrease was found between the control group (Group 1) and alcohol + acamprosate group (Group 4) (n=8, p<0.05).

As a result of the comparison of the tension values in the 15th minute after adrenaline administration to the atria with the tension values in the 15th minute before adrenaline administration, the control and alcohol groups (n=8, p<0.05) there was significant increase between.

As a result of the comparison of the tension values in the 15th minute after adrenaline administration to the atria with the tension values in the 15th minute before adrenaline administration, there was significant decrease between the acamprosate group (n=8, p<0.05) and in the alcohol+ acamprosate group (n=8, p<0.01).

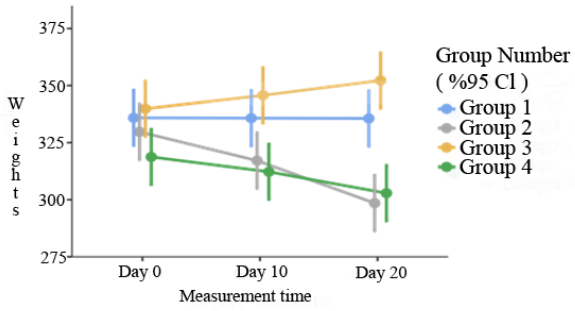
A significant increase was observed between the control group (Group 1) and the alcohol group (Group 2) at the 15th minute after acetylcholine administration (n=8, p<0.01). When the contraction values of the control group (Group 1) and acamprosate group (Group 3) were compared, a significant decrease was obtained (n=8, p<0.05).

A significant decrease was also observed when the control group (Group 1) and alcohol + acamprosate group (Group 4) were compared (n=8, p<0.05).

Table 1: Result of time- group comparative analysis of alcohol withdrawal syndrome data evaluated using the rats spesific alcohol withdrawal syndrome behavioral scoring test

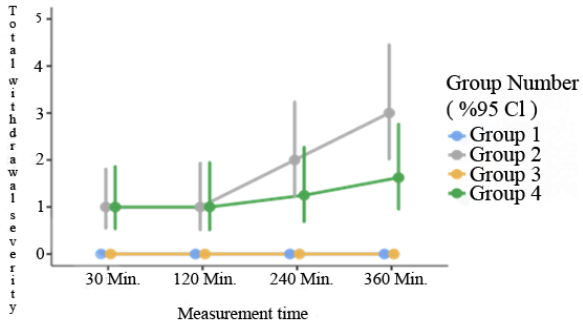
Moderator Levels		**95% Exp(B) Confidence Interval**
Time	Contrast Groups	p
30. Minute	Alcohol – Control Groups	<0.01
	Alcohol +Acamprosate – Control Groups	<0.01
	Acamprosate – Control Groups	>0.05
120. Minute	Alcohol – Control Groups	<0.01
	Alcohol +Acamprosate – Control Groups	<0.01
	Acamprosate – Control Groups	>0.05
240. Minute	Alcohol – Control Groups	<0.01
	Alcohol +Acamprosate – Control Groups	<0.01
	Acamprosate – Control Groups	>0.05
360. Minute	Alcohol – Control Groups	<0.01
	Alcohol +Acamprosate – Control Groups	<0.01
	Acamprosate – Control Groups	>0.05

Figure 1- Time- Weight Changes



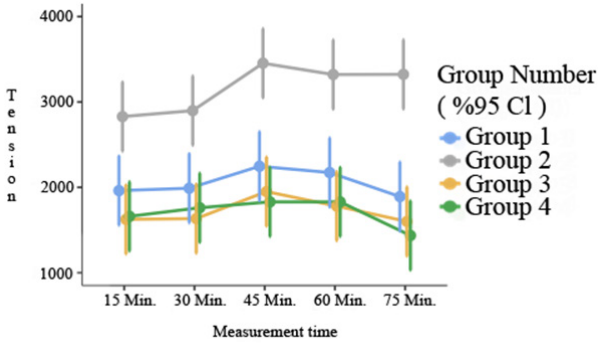
Distribution of Weight (Gram) Changes in Rat Groups by Days

Figure 2 – Total Witdrawal Severity



Time-Dependent Change of Total Alcohol Withdrawal Severity of Rat Groups

Figure 3- Time- Tension Values



Time-Varied Tension (Contraction-Relaxation) Data of Rat Groups

Discussion

Alcohol is one of the substances that is widely consumed and causes the development of addiction. It is easier to access legally than other addictive substances (24-25). During the alcohol dependence and withdrawal phases it causes changes in the functions of the GABA and glutamate systems in the

brain, damage to the dopaminergic system and an difference in the serotonin level. These changes lead to an increase in alcohol craving, anxiety, stress and the development of neurodegeneration (26).

Chronic use of alcohol causes adverse effects on many organs and systems. One of these systems is the heart and circulatory system (27). Chronic ethanol use leads to impairment of the functions of the sarcolemma membrane, sarcoplasmic reticulum, mitochondria and contractile proteins and it causes cardiac contraction and deterioration of mitochondrial oxidative phosphorylation (27-28). In addition, ethanol metabolites such as acetate and acetaldehyde have toxic effects on myocardial functions (29). Being dependent on chronic alcohol use, deficiencies in some vitamins, trace elements and various electrolytes may cause adverse effects on myocardial functions (29).

As a result of chronic ethanol use, one of the systems most affected is the cardiovascular system (29). High doses and chronic use of ethanol increase cerebral, coronary and peripheral vascular involvement (30).

It also increases the risk of developing atherosclerosis. At the same time, it increases arterial hypertension and causes progressive myocardial damage (30).

On the other hand, there are studies showing that low doses of alcohol consumption may have a positive effect on the cardiovascular system (29, 30). However, it is also known that moderate and high doses of alcohol can cause adverse effects in case of consumption (30). Pathologically, ethanol in the heart; in myocytes; increases myocytolysis, apoptosis and necrosis formation (30, 31).

Commonly used pharmacological treatment methods in alcohol dependence are naltrexone, disulfiram and acamprosate (10). The main neurochemical function of acamprosate is to antagonise the NMDA and glutamate system in brain (10). As a result of a magnetic resonance study; evidence has been obtained that acamprosate treatment reduces the excitatory activity of brain regions rich in N-acetylaspartate and glutamate in humans, thereby regulating glutamate transmission (31). It is to rearrange the balance of neurotransmitter transmission of the excitatory and inhibitory mechanism of acamprosate, which is an antagonism of the NMDA-Glutamate receptor, as a result of chronic alcohol use (31-32).

Acamprosate has been shown to reduce dopamine hyperexcitability in the nucleus accumbens and neuronal excitability in general during alcohol withdrawal (31).

There is no effect on stimulant reactivity or the rewarding or sedating effects of initial alcohol use of acamprosate treatment (31). As a result, it is thought that the therapeutic effect of acamprosate use in alcohol dependents is a potential mechanism by significantly reducing the desire to drink following alcohol use (31). In addition to these, as a result of a study in which alcohol addicts were exposed to various stimuli; In patients treated with acamprosate, a significant decrease in physiological activities has been observed due to stimuli (31).

When acamprosate stimulates GABA-A receptors in the central nervous system, it may follow cardiovascular dysfunction. Stimulation of central GABA-A receptors may cause significant deterioration of the autonomic neurocardial balance (32). Acamprosate slows down the functioning of voltage-gated calcium channels in the brain. As a result of this slowdown, it causes a decrease in alcohol intake (31-32).

Conclusion

In this study, an alcohol addiction model was created by intragastric intubation for 21 days. At the end of the study, the alcohol withdrawal syndrome scale was evaluated to determine alcohol dependence in the relevant groups. As a result of the evaluation; Alcohol withdrawal and dependence symptoms were observed in the alcohol group (Group 2) and alcohol+acamprosate group (Group 4) and were considered statistically significant increase.

It has been proven by the data obtained that acamprosate has a significant negative effect on the contraction feature of the heart muscle.

It was observed that acamprosate, one of the most frequently used pharmacological drugs in alcohol dependence, adversely affected the contractile function of myocardium. It was concluded that acamprosate, which is used in alcohol-dependent individuals, is important in the cardiovascular evaluation of the patients regularly and at certain intervals during the treatment and performing the necessary tests.

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Conflict Of Interest

There is no conflict of interest between the authors.

Credit authorship contribution statement

Behiye Nur Karakuş: Concepttualization of main research questions, literature review, data analysis and results interpretation, data management and curation, manuscript preparation and writing.

Faik Özdengül: Concepttualization of main research questions, literature review, data analysis and results interpretation.

Aysu Şen: Data management and curation, manuscript preparation and writing and literature review.

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