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The Effect of N-acetylcysteine on Alprazolam Withdrawal Symptoms in Wistar Male Albino Rats

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Abstract:

Introduction: Alprazolam is a benzodiazepine drug that is mainly used to treat generalized anxiety disorder and sleep disorders. Doctors' insistence on prescribing alprazolam due to its long half-life (16 hours) can lead to severe withdrawal complications. The aim of this study was to evaluate the effect of N-acetylcysteine (NAC) as an antioxidant drug on reducing the withdrawal symptoms of alprazolam in male albino rats.

Material and Methods: In this experimental study, 50 albino male Wistar rats were used. 10 rats received normal saline by gavage for 26 days (sham), the rest of the rats received 1 mg / kg of alprazolam daily for 21 days and after drug dependence were randomly divided into 4 groups were divided. The negative control group received normal saline by gavage daily for up to 4 days after the dependence period. The treated groups also received 100, 200, and 400 mg / kg NAC orally for 4 days after the dependence period, after which the anti-anxiety and restless effects of N-acetylcysteine were assessed by behavioral test (Elevated plus-maze test).

Results: The variables OAE (p = 0.18), CAE (p = 0.88), CAT (p = 0.53) and OAT percent (p = 0.29) did not show a significant difference between the 5 treatment groups; But OAT (p = 0.07)

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and OAE_percent (p = 0.001) showed a significant difference between the 5 treatment groups (p <0.05).
Conclusion: Due to the antioxidant properties of NAC and its ability to counteract oxidative stress in the nervous system, it can be used to control the symptoms of withdrawal syndrome in people with a history of alprazolam dependence. In the present study, a dose of 400 mg / kg NAC had the best therapeutic effects in rats. In future studies, it is recommended to obtain an appropriate dose for people who experience symptoms of alprazolam withdrawal syndrome.
Keywords: Alprazolam, N-acetylcysteine, Withdrawal syndrome.

Introduction

Since free radicals are unstable, they have a high tendency to combine with surrounding substances; these radicals can combine in the body or fats, proteins and nucleic acids (1). Due to the harmful nature of oxidative stress, the human body uses many defense mechanisms to fight and protect against it. The defense system against free radicals is called the antioxidant system. Today, in addition to natural antioxidants, synthetic antioxidants are also available, whose effects on the improvement of atherosclerosis, cancer, inflammatory diseases, hypertension, Parkinson's, Alzheimer's, AIDS, diabetes, rheumatoid arthritis, etc. have also been confirmed (2-5).

Benzodiazepines, including alprazolam, are the causes of oxidative stress and cause severe oxidative stress in the liver of rats, resulting in hepatotoxicity. According to the findings of the World Emergency Department, alprazolam is the second most prescribed drug and is the most commonly abused benzodiazepine (6-9). Compared to diazepam, alprazolam has less solubility in fat and its ability to bind to protein is %68, but diazepam's protein binding ability is %98. These differences mean that alprazolam has a higher metabolic rate and a shorter duration of effect than diazepam, and this feature makes stopping alprazolam after a short period of use cause severe withdrawal symptoms (10). The results of several studies indicate the existence of a relationship between oxidative stress and deprivation syndrome, and the use of antioxidants in the treatment of substance abuse has been suggested (11,12).

One of the common problems that can be seen especially in people with withdrawal syndrome is sleep disturbance (10). The relationship between insomnia and oxidative stress has been confirmed in several studies. No study was found on the effect of N-acetylcysteine (NAC) on

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sleep quality, but in several studies, the role of melatonin, which has antioxidant effects, has been investigated in improving sleep quality (11-14). Today, in addition to the natural antioxidants that exist in the body, synthetic antioxidants are also available, which can be referred to as NAC. N-acetylcysteine is a thiol-containing compound that acts as a precursor of reduced glutathione by providing thiol groups. This compound directly removes reactive oxygen species and finally creates a state of balance between oxidation and reduction in cells (15,16). This study was conducted with the aim of determining the effect of NAC on alprazolam withdrawal symptoms in Wistar male albino rats.

Materials and Methods

In this experimental study, after obtaining the code of ethics, IR.SSU.MEDICINE.REC.1396.243, 50 adult male Wistar rats weighing about 20±200 grams were obtained from the Infertility Center of Sadougi University of Medical Sciences, Yazd. These rats were kept for one week in the animal house of Yazd Infertility Clinic at a temperature of 25-20 degrees Celsius and in a light-dark cycle of 12 hours day and 12 hours night. During this period, four rats were kept in each cage without restrictions on the use of water and food.

The studied animals were randomly divided into five groups of ten, and the animals belonging to different groups were housed separately, and the animals of each group were kept individually in special cages.

10 rats received 10 ml/kg of normal saline by gavage daily for 26 days (Sham group), the rest of the animals (negative control group and treated groups 1, 2 and 3) also received daily for 21 days. They received 1 mg/kg of Alprazolam (Xanax) with a gavage volume of 2.5 ml/kg. Alprazolam used daily was first powdered in a mortar and then dissolved in 20 ml of distilled water with two drops of Tween 80 (as a solvent) and given to animals with a volume of 2.5 ml/kg using a gavage tube. It was eaten. These steps were repeated for 21 days (dependency period). On the 22nd day, when the drug was discontinued, the development of drug dependence in animals was confirmed by checking the amount of daily food consumed (minimum %8 reduction in the amount of daily food consumed). The animals whose drug dependence was determined were randomly divided

into 4 groups (3 treated groups and one negative control group) and other animals that did not show signs of drug dependence were excluded from the experiment.

The negative control group received 2.5 ml per kilogram of normal saline by gavage up to 4 days after the dependence period, and treated groups 1, 2 and 3 also received 100, 200 and 400 mg daily after the dependence period. They received NAC per kilogram orally for 4 days with a volume of 2.5 ml per kilogram. Finally, Elevated plus-maze test was used to investigate the effect of NAC on alprazolam withdrawal symptoms.

Analyzes were performed using spss 23software and at an error level of %5from Repeated Measures tests: for time comparisons and One-way ANOVA: for inter-group comparisons. used.

Results

Elevated plus-maze test:

This device is made of black wood and has four arms in the shape of a positive sign (+). The dimensions of the open and closed corridor are 10x 50cm, and two sides and the end of the closed corridor have a 40cm high wall, and to prevent animals from falling, a 1cm high edge of glass was installed on both sides and the end of the open corridor. Four corridors lead to a central area measuring 10x 10cm. The maze was placed by a base at a height of 50cm from the ground. Adequate light was provided by a 100-watt lamp located at a height of 120cm from the center of the maze. Each animal was placed within the central boundary of the maze, so that it faced an open corridor. During the 10minutes that the animal was moving freely in different parts of the maze, for each animal, the number of times it entered the open and closed arms was counted, and the time the animal was in the open and closed arms was recorded using a cornometer. Open Arm Entr percent) and Open Arm Time were calculated. The amount of movement activities, which was the total number of times entering the open and closed arms of the maze, was measured by direct observation. The meaning of entering an open or closed corridor is when all four animals are placed in the considered corridor and the time spent in each corridor was also calculated based on this (Figure 1).

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Figure 1: Elevated plus-maze test

In the following, each of the Open Arm Enter, Close Arm Enter, Open Arm Time, Close Arm Time, Open Arm Enter_percent and Close Arm Enter_percent variables have been examined.

The results of one-way analysis of variance showed that the variables OAE (p=0.18), CAE (p=0.88), CAT (p=0.53) and OAT_percent (p=0.29) did not show significant differences between the 5treatment groups; But OAT (p=0.07) at %10level and OAE_percent (p=0.001) at %5level showed a significant difference as follows (Table 1, figure 2,3):

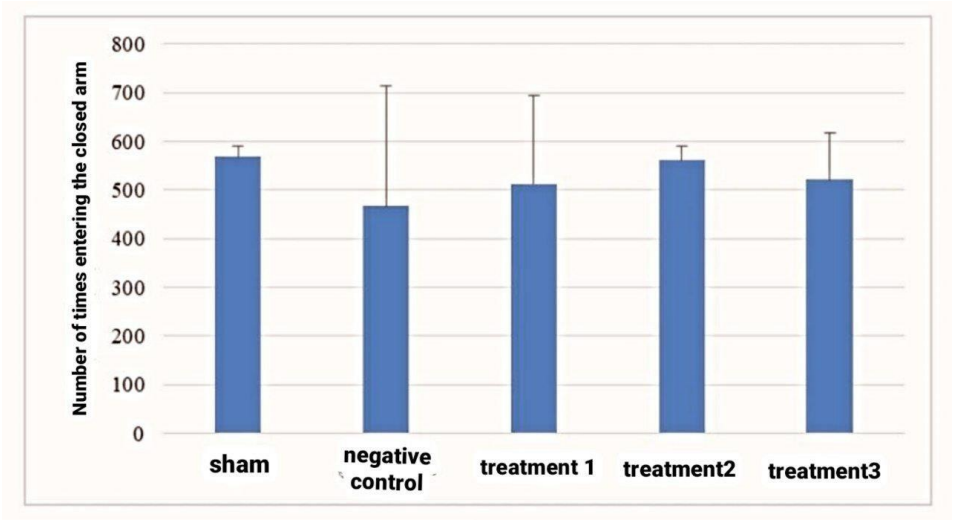

Figure 2: Column chart of mean CAT by treatment group

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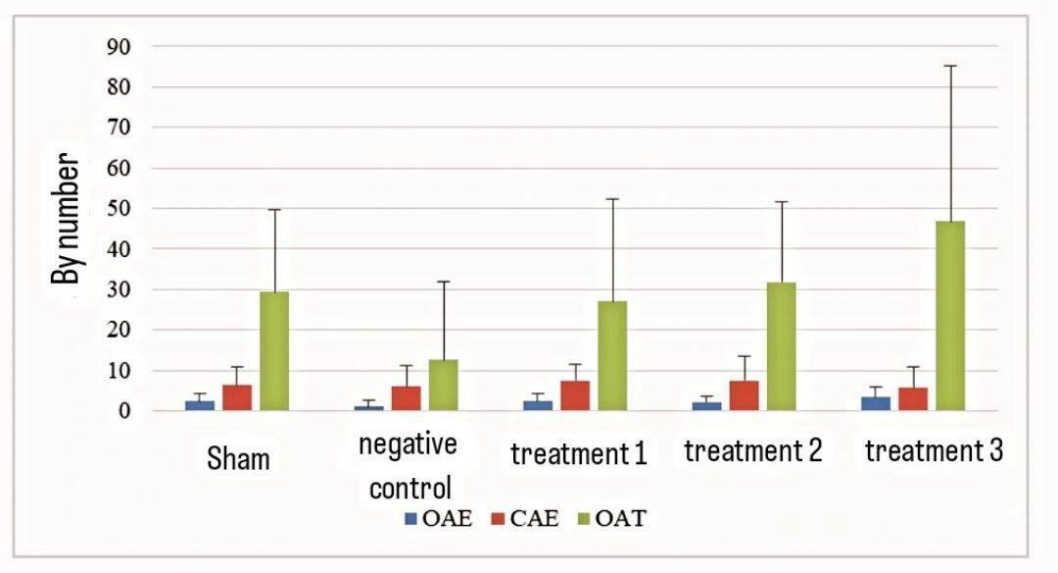

Figure 3: Average OAE, CAE, OAT by treatment group

According to Tukey's post hoc test, OAT had a statistically significant difference between the first and fifth groups (P=0.03). Also, based on Tukey's post hoc test, OAE_percent between the second and first groups at the %5level (P=0.04) and the second and fifth groups at the %5level (P<0.001), the second and fourth groups at the ten percent level (P=0.06) and the The third and fifth were significant at the ten percent level (P=0.07).

Discussion

Opioids are one of the causes that cause oxidative stress. This has been confirmed in studies conducted on laboratory animals in recent years. For example, it has been found that apple morphine causes severe oxidative stress in the liver of rats, resulting in hepatotoxicity. Heroin also leads to an increase in ROS by raising the level of dopamine and increasing its oxidative metabolism. The results of several studies point to the existence of a relationship between oxidative stress and deprivation syndrome. In recent studies, the use of antioxidants in the treatment of substance abuse has been suggested.

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In the study of Votava et al., it is mentioned that benzodiazepines are widely used as therapeutic agents with sedative, anti-anxiety, anticonvulsant and muscle relaxant effects in humans and animals. The use of these agents is limited due to the risk of developing tolerance to their effects and the risk of developing dependence. Dependence on benzodiazepines can also appear with deprivation syndrome, which may include symptoms such as tremors, sweating, sleep disorders, reduced threshold, seizures, increased tension and anxiety, irritability, difficulty concentrating, etc. (6).

Behavioral studies of benzodiazepine withdrawal in animal models are mostly focused on detecting symptoms of increased anxiety. For example, decreased open-arm exploration in the elevated plus-maze test, decreased social behavior in the social interaction test, or increased ultrasonic "distress" vocalizations were reported in rats or mice after withdrawal from benzodiazepines. In the present study, we investigated the effects of NAC on withdrawal syndrome symptoms caused by alprazolam (7, 8).

Our results showed that the use of NAC in all three therapeutic doses used did not cause side effects, and none of the drug side effects reported in the intervention with NAC were reported in our studied samples. The results of the alprazolam addiction study have been established in the target groups and the current results showed that there was a significant difference between the negative control group and Sham with another. It was also found that the dose of 400 mg/kg NAC reduced the neurological complications caused by alprazolam withdrawal syndrome and The results of social incompatibility tests are effective. In the present study, it was observed that alprazolam withdrawal syndrome in rats is associated with a decrease in social activities, an increase in aggressive activities, an increase in defensive activities and a decrease in motor activity, and the dose of 400 mg/kg NAC and in some cases the dose of 200 mg/kg significantly improved The symptoms are effective.

In a study, Lieber et al. stated that chronic consumption of ethanol increases the level of acetaldehyde and has harmful effects on the central nervous system (CNS) and the peripheral system. In fact, chronic ethanol consumption affects the oxidative status through the production of ROS and increases the expression level of CYP2E1 mRNA and protein, which leads to the

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increase of peroxide radical formation and lipid peroxidation. Therefore, ethanol oxidation in the brain may lead to the formation of ROS and oxidative stress, which may contribute to withdrawal symptoms, especially in frequent ethanol users (9). Huang et al. and Haorah et al. showed that the use of antioxidants such as glutathione enhancing agents can partially reduce the effects and clinical symptoms caused by oxidative stress and withdrawal syndrome (10,11).

In a 2017 study, Schneider et al concluded that NAC prevents the increase of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, IL-18, IL-10 in the frontal cortex and hippocampus of the brain. It reduces the result of alcohol poisoning and the desire to consume alcohol and its withdrawal effects (12). In a study, Froeliger et al showed that NAC may help treat the pathology of nicotine addiction and may prevent relapse, theoretically through changes in the functional connections between top-down control centers and striatal centers. shows (13). In a study, Schmaal et al concluded that NAC does not have a role in reducing the desire to use nicotine, but it reduces the withdrawal symptoms caused by sudden cessation of its use, so NAC may be a suitable treatment option to prevent the relapse of nicotine addiction (14).

There are thesis that NAC can be used as the first line of smoking cessation treatment because it is very effective on systemic inflammation and reduces symptoms of withdrawal syndrome (15, 16). McKetin et al. concluded that NAC can be effective in the treatment of addiction to methamphetamines due to its antioxidant effects and ability to balance brain glutamate systems but reports emphasize the dual role of ROS in cancer development and progression. The possible beneficial effect of NAC treatment in triple-negative breast cancer was attributed to the attenuation of ROS in the tumor microenvironment (17-19). In particular, treatment with the antioxidant N-acetylcysteine (NAC) significantly reduces upregulation of the DNA damage marker γH2AX, subsequent ATM activation and cell death (20,21). The presence of NAC during ex vivo T cell expansion improves the persistence of adoptively transferred cells, reduces tumor growth and increases survival (22,23). Also, It is necessary to check the patient's condition, medications and underlying disease before prescribing. Abuse of benzodiazepines usually involves co-administration with other drugs, alcohol, and/or other illicit substances, which

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increases the likelihood of serious adverse outcomes. Before prescribing alprazolam and during treatment, assess the risk of abuse and addiction in each patient (24-27).

Patients who visit medical professionals do not always report their past medical history, either because they do not consider it important or because they do not consider it relevant to their problem (28-30). Adequate medical training and taking a detailed medical history, which should include the patient's past medical and drug history and checking the general health status, are necessary to identify patients with related medical conditions and prevent the resulting risks in choosing treatment (31,32).

Always, this point should be in focus that the ultimate goal of all the advances made in medical sciences is to provide, maintain and promote health for patient (33). Thus, the client/patient as a human being is the center of all activities of the health group (34-36). This centrality should be at the top of all the activities of this group (37); Because the experience of illness and the necessity of compliance and follow-up of the treatment and care process increases the vulnerability of patients and increases their need for comprehensive support (38,39); Although the change in social conditions has already increased their expectations of their rights (40-42).

Many experts have emphasized respecting the rights of patients as the main duty of all people in the health group (43); But at the same time, the role of doctors and nurses is very prominent in this regard, due to their continuous and close relationship with patients and their sense of commitment to them, and they are among the best professional groups to recognize the needs and support the rights of patients (44,45). At times, there is a need for devices that integrate both motion and image processing capabilities, as seen in certain medical devices (46,47).

It should be noted that usually after long-term administration of benzodiazepines, symptoms of withdrawal syndrome are observed in humans, but in animal samples, it has been reported in studies that only two weeks of treatment with benzodiazepines is enough to develop dependence and check the symptoms of withdrawal syndrome after it. be In the present study, 21 days of alprazolam were used.

Conclusion

In this study, we came to the conclusion that due to the antioxidant properties of N-acetylcysteine and its ability to deal with oxidative stress in the nervous system, as well as the proven effects of this drug on the glutamate receptor, it can be used to control withdrawal symptoms in people. He used alprazolam with a history of addiction. In the present study, the dose of 400mg/kg NAC had the best therapeutic effects in rats, it is recommended to obtain the appropriate dose for people who experience the symptoms of alprazolam withdrawal syndrome in the next studies.

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Group		OAE	CAE	OAT	OAT	%OAE	%OAT
Sham	Mean	4.2	3.6	3.29	5.568	5.30	7.8
	SD	8.1	3.4	4.20	57.21	4.20	59.12
Negative control	Mean	1.1	6	5.12	4.467	4.9	59.2
	SD	59.1	24.5	4.19	247	4.10	5.3
Treatment 1	Mean	4.2	5.7	27	513	6.22	4.4
	SD	2	9.3	3.25	7.181	8.16	2.4
Treatment 2	Mean	2.2	5.7	9.31	561	29	4.5
	SD	39.1	6	7.19	8.29	9.14	5.3
Treatment 3	Mean	3.3	7.5	8.46	522	42	7.7
	SD	58.2	5	5.38	5.94	3.16	3.6
P4		18.0	8.0	07.0	53.0	001.0	29.0

Table 1: Examining the average variables of OAE, CAE, OAT, CAT, OAE_percent and OAT_percent according to the investigated groups

