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Research Article

**INVESTIGATING THE METHADONE EFFECTS ON AST, ALT AND ALP
ENZYMES OF SERUM OF MALE WISTAR RATS**Naser Abbasi^{1†}, Ayub Ghorbani^{2†}, Yaser Seifinejad², Mojtaba Mohamadpour³,
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Iran.⁴Department of Clinical Biochemistry, Faculty of Medicine, Ilam University of Medical Sciences,
Ilam, Iran.**Abstract:**

Narcotics abuse and addiction have been turned to a major problem in the communities. Addiction to any type of narcotics is known to be followed by side effects both physically and psychologically. One way to control addiction is the use of another maintenance medication. The current research paper aims at investigating the effect of one such a drug as methadone on the serum levels of Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase enzymes. A total number of 28 male adult Wistar rats were completely haphazardly assigned to four groups (n=7): a control group that received an ordinary daily dietary regime and Experimental groups one, two and three that were administered through oral gavage with 5mg/ml, 20mg/ml and 40mg/ml of methadone syrup, respectively, on a daily basis besides the ordinary dietary regime for eight weeks. Blood samples were collected from the animals at the beginning and at the end of the study for the determination of serum levels of alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase enzymes. In the end, the data were analyzed via taking advantage of one-way variance analysis (one-way ANOVA) and TUKEY Test. The serum levels of all three ALT, AST and ALP enzymes were significantly increased in the groups that had been given different doses of methadone ($P < 0.001$). According to the results obtained herein and the effects that methadone has on the elevation of liver enzymes levels and also due to the fact that this maintenance medication is being increasingly administered on a daily basis for the treatment of addiction to various narcotics, it seems that there is a need for devising better strategies and better planning for the amount and method of methadone use as well as the way this medication has to be distributed within the society.

Keywords: Methadone, Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase, Rats.

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INTRODUCTION:

Nowadays, addiction has its adverse influences on a vast spectrum of the people worldwide and a large number of the families are currently engaged with inauspicious outcomes of addiction that has endangered the safety and security of human communities. Narcotics addiction and drug misuse are the public health major problems followed by an increase in the mortality rates. According to the constant increase in drug abuse tendencies amongst the adolescents, especially through injection, there is required a pervasive program for solving the problem of narcotics addiction and its relevant behaviors [1]. Some 15% of the above-eighteen population of the American society is faced with serious problems in terms of substance misuse prevalence [2]. During the past ten years, in Iran, as well, the substance abuse has grown to over 3% of the population growth rate [3]. Substance misuse is a hygienic, social and economical problem of a crucial importance in the majority of the countries. The studies are suggestive of the idea that narcotics addiction is a multi-faceted problem and various psychological, social, cultural, individual and genetic factors interplay in its occurrence [2]. The extensive nature of addiction has been the cause of offering and examining numerous treatment methods, including drug therapy and psychotherapy [4]. Methadone therapy of addiction is a treatment method that is recommended for assisting the patients and lowering their social and sanitary problems [5]. Methadone is inter alia the industrial substances that are similar in their physiological and analgesic attributes to opium but are not euphoric [6]. This treatment method was first introduced in 1965 by Vansal Dole and Nisvander. The drug is to be taken orally [7]. Methadone is an agonist featuring a long-lasting effect and a half-life ranging from 24 h to 36 h and it is enumerated as the most effective medication for detoxification of heroin addicts [8]. The retention rates of treatment by methadone ranges from 30% to 70% after a one-year period of methadone medication administration. Methadone dosage and the addict's age are the most significant factors contributing to retention rates [9]. Methadone, as well, is known to be accompanied by side effects similar to the other opiates. Methadone consumption negatively influences the memory, information processing and the executive functions [10]. According to the high prevalence of methadone consumption in the society, we have investigated the effect of various oral dosages of methadone on serum levels of AST, ALT and ALP enzymes.

MATERIALS AND METHODS:

In the present study, 28 adult male Wistar rats were randomly assigned to four equal groups each consisting of seven rats. The animals were kept under standard light, temperature and humidity conditions so as to adhere to the principles of handling laboratory animals as well as to get them accustomed to the environment.

The rats were grouped as stated below:

Group One (Control) received daily ordinary diets. Group Two, Three and Four (Experimental Group One, Group Two and Group Three) were fed on an ordinary dietary regime plus 5, 20 and 40 mg/kg body weight per day methadone syrup through gavage intubation. Methadone syrup was purchased from Iran Drug Distribution Company. In order to provide the control group with the same conditions as the other groups, 2cc of the drug was gavage-fed to this group on a daily basis. The treatment period lasted eight weeks and the blood samples were collected from all the rats to measure ALP, ALT and AST enzymes levels: once on the first day of the treatment onset and a second time at the end of the treatment period, i.e. week eight. The acquired blood samples were kept under laboratory conditions for 20 minutes and then centrifuged in 2000 rpm for ten minutes. Autoanalyzer Device (Technico RA-1000) was utilized to measure the intended enzymes. The data were evaluated by means of one-way variance analysis (one-way ANOVA) and TUKEY test. The results are presented in the Mean \pm SEM format and $P < 0.05$ was considered as the statistical inference threshold. The present study has been granted an ethic code (ir.medilam.rec.1395.77) by the ethics committee of Ilam University of Medical Sciences.

RESULTS:

Based on the results obtained from variance analysis, the AST enzyme levels of all three groups receiving methadone in different dosages underwent a significant increase in contrast to the control group ($P < 0.001$). This increase was also found statistically significant regarding ALT enzyme in the groups that had received methadone medication as compared to the control group ($P < 0.001$). Moreover, a significant increase was also confirmed for ALP enzyme levels of all three groups that had been administered with methadone medication ($P < 0.001$) in respect to control group (Figure 1-3).

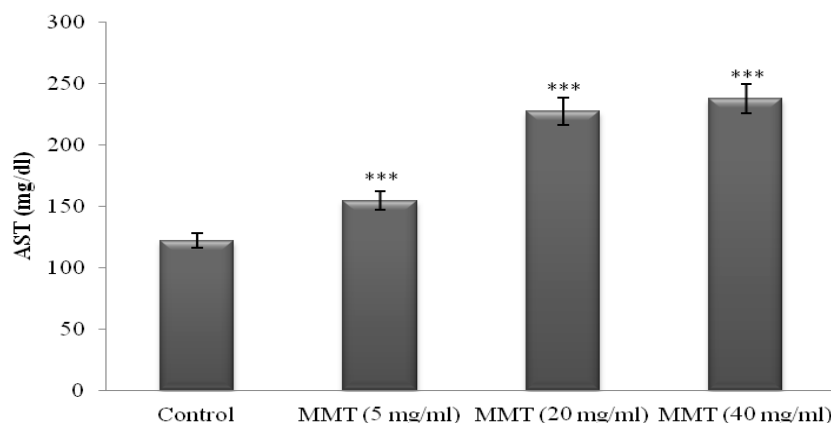


Fig 1: Comparison of aspartate aminotransferase serum levels in control group with the groups receiving methadone medication (for dosages of 5, 20 and 40 mg/kg body weight per day). The given values are mean \pm standard error of the Wistar Rats; * indicates the significance of the values obtained for experimental groups as compared to the control group (***: P<0.001).

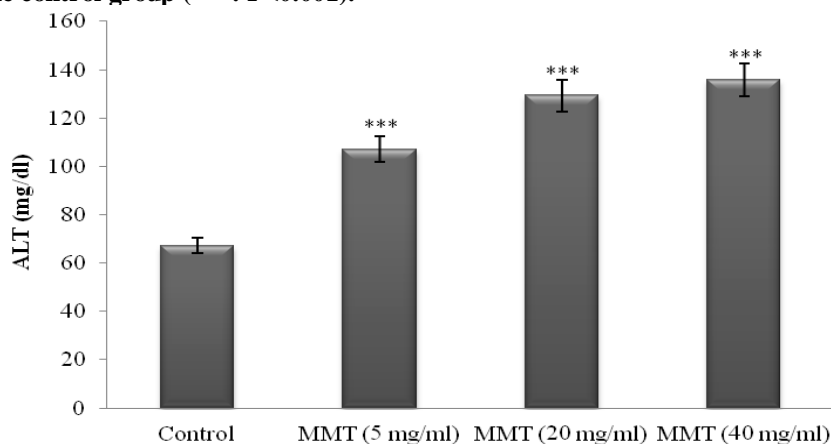


Fig 2: Comparison of alanine aminotransferase serum levels in control group with the groups receiving methadone medication (for dosages of 5, 20 and 40 mg/kg body weight per day). The given values are mean \pm standard error of the Wistar Rats; * indicates the significance of the values obtained for experimental groups as compared to the control group (***: P<0.001).

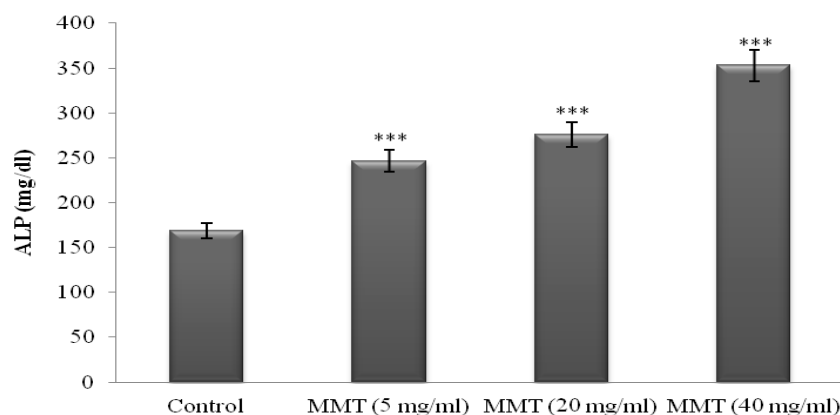


Fig 3: Comparison of alkaline phosphatase serum levels in control group with the groups receiving methadone medication (for dosages of 5, 20 and 40 mg/kg body weight per day). The given values are mean \pm standard error of the Wistar Rats; * indicates the significance of the values obtained for experimental groups as compared to the control group (***: P<0.001).

DISCUSSION:

The obtained results indicated that the ALT, AST and ALP enzymes levels have undergone a significant increase in all the three groups that had been administered with different dosages of methadone in comparison to the control group. Methadone, as well, is recounted as a narcotic substance; it is an analgesic agonist and it causes an elevation in the effects pertinent to the use of similar narcotics [6]. Methadone possesses physiological and analgesic effects similar to opium and heroin but it is not toxic [11]. Methadone is administered as a maintenance medication to reduce the use of narcotics and it is known for bringing about stability in the addict's life. Also, it inhibits the dangerous and risky behaviors such as injection that is followed by the probable transferring of diseases like AIDs and hepatitis. Although, methadone use can also be envisioned as a sort of drug dependency but its characteristics are not consistent with addiction [12]. The results of the studies on the effects of methadone maintenance on the addicts' psychological health are contradictory. It has been made clear in some of the researches that the addicts receiving methadone exhibit a high level of problems related to psychological health in contrast to the general population and a great many of the addicts treated with methadone experience behavioral and affective disorders such as anxiety and depression [13]. In a study undertaken by Raisi et al, 72 addicts were subjected to depression before being treated by methadone. The results demonstrated that the number of the addicts with persistent depression symptoms had been reduced to 46 individuals one month after treatment which means that the depression level had been decreased post-methadone administration and the quality of life had been considerable improved. The results of another study that dealt with the systematic examination of methadone maintenance effects, it was claimed that methadone use has a considerable effect on psychological and physical health improvement [14, 15]. Methadone can elevate the quality of life and performance of addicts, their psychiatric status and the patients treated with methadone can enjoy a long-lasting behavioral regulation [16-20]. The effect of methadone on testosterone levels was also explored and, of course, the results are suggestive of a large deal of contradictory and conflicting findings. Some studies have presented a normal appraisal of testosterone level in methadone users [21-23], while others have reported a significant reduction in testosterone levels as a result of methadone maintenance medication [24, 25]. According to the effective mechanisms employed by methadone as a weakened narcotic substance and based on the effects it has on opioid

neuron circuits as well as limbic system as its major locus of influence, methadone use is most likely to be continued which might be possibly accompanied by the emergence of more symptoms [26, 27].

CONCLUSION:

The results of the present study showed that methadone brings about a significant increase in the liver enzymes. According to the daily increasing use of this maintenance medication, precise supervision on the dosage and method of methadone use seems necessary.

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