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Research Article

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Effect of Moclobemide on Serum Level of Hepatic Transaminases, Blood Biochemical Parameters and Liver Histopathological Changes in Adult Male Rats

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Abstract

Background and aim: Moclobemide (MCB) is an antidepressant that is metabolized in the liver and acts as a monoamine oxidase inhibitor. The aim of this study was to evaluate the effect of MCB on serum levels of hepatic transaminases, blood biochemical parameters and histopathological changes of liver in adult male rats.
Materials and methods: Thirty two adult male Wistar rats were divided into 4 groups of 8. The control group did not receive any treatment, but the experimental groups (Exp) 1, 2 and 3 received doses of 160, 320 and 640 mg/kg MCB as oral gavage for 28 days, respectively. At the end of the study, body weight, liver weight, serum levels of liver transaminases (ALT, AST) and blood biochemical parameters (ALP, total protein, Albumin, total and direct Bilirubin) were measured. Also, liver tissue was removed for histopathological examination.
Results: The results of the study showed that body weight, liver weight and serum levels of total and direct Bilirubin in the experimental groups were not significantly different from the control group ($p<0.05$). Serum levels of ALT, AST and ALP in Exp1 group did not show a significant difference with the control group ($p>0.05$) but in contrast, in Exp2 and Exp3 groups, a significant increase was observed ($p<0.05$). Serum levels of total protein and Albumin in Exp1 and Exp2 groups did not show a significant difference with the control group ($p<0.05$) but in contrast, in Exp3 groups, there was a significant decrease ($p<0.05$). In all 3 Exp groups, some degrees of necrosis and destruction of liver tissue were observed, and the maximum necrosis and destruction was observed at the maximum dose.
Conclusion: Moclobemide causes changes in serum levels of hepatic transaminases, blood biochemical parameters and the destruction of liver tissue, especially at the maximum dose (640 mg/kg) in male rats.

Keywords: *Moclobemide, Liver tissue, Liver enzymes, Depression, Rat*

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Introduction

Depression is one of the most common mental illnesses in the present age. To treat and prevent various complications of this disease, different methods are used and among these methods, drug therapy is one of the most common treatments for depression. Moclobemide (MCB) has been known with the chemical formula $C_{13}H_{17}ClN_2O_2$ and the chemical name 4-chloro-N-[2-(3-oxomorpholin-4-yl) ethyl] benzamide and its lethal dose is 707 mg/kg (Farzin *et al.,* 2008*).* MCB is a white crystalline powder that can be dissolved in 0.4 g/ml in water. MCB is known as a safe antidepressant that acts as a reversible inhibitor of monoamine oxidase A. Many researchers have shown the anti-anxiety properties of MCB in animals and humans (Liebowitz *et al.,* 1993; Nowakowska *et al.,* 1998). The studies conducted in Europe, the United States and Australia have shown that MCB can treat depression. MCB can increase brain metabolism of noradrenaline, dopamine and serotonin. It also has the ability to increase serum prolactin through serotonergic pathways (Papakostas and Fava, 2006; Freeman, 1993).

Moclobemide metabolism is usually done by oxidative pathway. Four main pathways and a large number of metabolic side pathways have been identified for it, and a total of 19 metabolites have been isolated from urine. The major pathways of MCB metabolism include carbon and nitrogen oxidation of the morpholine cycle, which results in the production of two metabolites, Ro-128095 and Ro-125637, in plasma. The compound Ro-125637 remains as an inhibitor of the enzyme monoamine oxidase but in general, its concentration is very low, while the compound Ro-128095, despite having a high concentration, has no medicinal activity (Jauch *et al.,* 1990; Mayersohn & Guentert, 1995). MCB increases the level of noradrenaline as an inhibitor of dopamine and serotonin by affecting nerve cells and synaptic vesicles. It is rapidly absorbed in humans and fully metabolized by the liver. It can bind to proteins such as albumin. The half-life of MCB is very short, about 1 to 3 hours, but the effect of the drug lasts about 16 hours. Moclobemide completely crosses the blood vessel 2 hours after consumption. At the time of oral administration, a time-dependent and dose-dependent state has been observed (Mayersohn & Guentert, 1995; Bonnet, 2002; Guentert *et al.,* 1990).

Some researchers have reported that the dose of the drug does not cause any particular toxicity and is much safer than tricycle antidepressants (Iwersen & Schmoldt, 1996; Hetzel, 1992). However, there have been reports of deaths from taking MCB alone (Kuisma, 1995; Gaillard & Pepin, 1997) or in combination with other drugs such as Clomipramine (Gaillard & Pepin, 1997; Ferrer-Dufol *et al.,* 1998; Neuvonen *et al.,* 1993; Power *et al.,* 1995; Hernandez *et al.,* 1995), Citalopram (Neuvonen *et al.,* 1993), and Paroxetine (Singer & Jones, 1997). In the present study, the influence of different doses of MCB drug on body weight, liver weight, changes in serum levels of liver enzymes including alanine transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), some blood biochemical factors (total protein, albumin and direct and total bilirubin) and liver tissue were examined to determine the possible side effects of the drug.

Materials and methods

Animals

Adult male Wistar rats weighing 250±10 g were used in n this experimental study. All animals were kept in standard laboratory conditions including 23±2 °C, 50-60% humidity and 12 hours of light/darkness. In order to adapt to the new environment, all animals were kept together for 2 weeks before the start of the study. The experiment was performed for 28 days. The ethical protocol of this study on working with laboratory animals was approved by the ethics committee of the Islamic Azad University, Shiraz branch.

Study Protocol

The animals (n=32) were randomly divided into 4 groups (8 rats/each) including control, experimental 1, 2 and 3 as follows:

1- The control group: did not receive any drug treatment.
2- The experimental group 1(Exp1) received: 160 mg/kg MCB every day at 10 am.
3- The experimental group 2 (Exp2) received: 320 mg/kg MCB every day at 10 am.
4- The experimental group 3 (Exp3) received: 640 mg/kg MCB every day at 10 am (Lotufo-Neto *et al.,* 1999).

The drug was administered as oral gavage for 28 days. At the end of the study, rats were first weighed by a restraint device and then anesthetized using ether (Merck, Germany) and blood samples were taken directly from their hearts. Blood samples were placed in the laboratory at 37 ° C to complete the agglutination process. Blood samples were then centrifuged at 15,000 rpm for 15 minutes to separate serum. The obtained serum was kept at -20 °C until the measurement of liver enzymes and blood parameters. Serum levels of AST, ALT, ALP, Alb and TP were measured with RA-1000 Auto Analyzer

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(Technicon, USA) according to the manufacturer's instructions. Serum levels of ALT (Pars Azmoun, Iran) and AST (Pars Azmoun, Iran) were measured by IFCC method without the addition of pyridoxal-50 phosphate, serum levels of total protein (Meybod Yas, Iran) were measured by photometric method based on Biore method, serum albumin level (Pars Azmoun Company, Iran) was measured by BROMOCRESOL-GREEN method and serum level of total and direct bilirubin was measured by photometric method using Diazo 2 and 4 dichloro aniline (DCA) according to the manufacturer's instructions (Pars Azmon, Iran). For histological study, liver tissue of all animals was removed by opening the abdominal cavity and then weighed immediately. Liver tissues placed in 10% formalin buffer solution for fixation and after tissue passage steps were molded in paraffin. Using a microtome device, successive sections with 6 micron thickness were prepared for histopathological study. Hematoxylin-eosin staining (Merck, Germany) was performed and tissue samples were examined under a light microscope (Nikon, Japan).

Moclobemide

MCB (Aryapharm, Iran) was prepared as a tablet and 20% ethanol (Merck, Germany) was used as its solvent. The oral LD50 of MCB in rat has been reported 730 mg/kg (Hadizadeha *et al.,* 2008), so three doses of 160, 320 and 640 mg/kg were selected for the three groups of minimum, moderate and maximum, respectively.

Statistical Analysis

The data were analyzed by SPSS software version 20 (SPSS Inc, Chicago, IL, USA). Using ANOVA method and Tukey post hoc test, the mean data were compared between control and experimental groups. The obtained values were reported as mean ± SEM and a significant level of $P < 0.05$ was considered. The charts were designed by Ghraphpad software version 6 (GraphPad Prism, Inc., San Diego, CA, USA).

Results

Findings of body weight, liver weight, liver enzymes and blood biochemical parameters

Graph 1 shows a comparison of mean body weight, liver weight and serum levels of ALT, AST, ALP, albumin, total protein, direct and total bilirubin. Body weight and liver weight (Graph 1A and 1B) in Exp1, Exp2 and Exp3 groups were not significantly different from the control group ($p<0.05$). Serum levels of ALT, AST and ALP (Graph 1C, 1D and 1E, respectively) in Exp1 group did not show a significant difference with the control group ($p>0.05$) but in contrast in Exp2 and Exp3 groups, a significant increase was observed ($p<0.05$). Serum levels of albumin and total protein (Graph 1F and 1G) in Exp1 and Exp2 groups did not show a significant difference with the control group ($p>0.05$) but in contrast in Exp3 groups, there was a significant decrease ($p<0.05$). Direct and total bilirubin (Graph 1H and 1I) in Exp1, Exp2 and Exp3 groups were not significantly different from the control group ($p>0.05$).

Histopathological Findings

Figure 1 shows the histopathological findings of the liver in control and Exp groups. In the control group, the hepatocytes were next to each other regularly and without any damage, and the liver tissue was completely normal (Figure 1A). In Exp1 group, compared to the control group, histopathological changes were minor, so that a slight necrosis was observed (Figure 1B). In Exp2 group, necrosis and destruction of liver tissue was moderate compared to the control group (Figure 1C). In Exp3 group, compared with the control group, liver tissue destruction, local inflammation and the rate of necrosis was severe (Figure 1D).

Discussion

MCB is an antidepressant that selectively inhibits the monoamine oxidase enzyme. Research has shown that this drug has anti-Parkinson's effects and has also a neuroprotective effect by inhibiting monoamine oxidase (Youdim *et al.,* 2006; Song *et al.,* 2013).

Depression is the second most common cause of life-threatening illnesses in the world (Vos *et al.,* 2012) and it has been found that depressed people have a lower quality of life compared to sick people who are not depressed (Baumeister *et al.,* 2011; Diez-Quevedo *et al.,* 2013). In this study, the pharmacological effect of different doses (low, medium and high) of MCB on ALT and AST hepatic transaminases was investigated. Also, the effect of this drug on blood biochemical factors related to liver function such as ALP, total protein and albumin was investigated and finally liver tissue was evaluated pathologically.

These enzymes are commonly tested in liver diseases. Liver diseases are the most important factor in increasing the activity of transaminases in serum. Serum activity of both ALT and AST enzymes increases under the influence of drugs and liver diseases (Burtis *et al.,* 2011). According to the results

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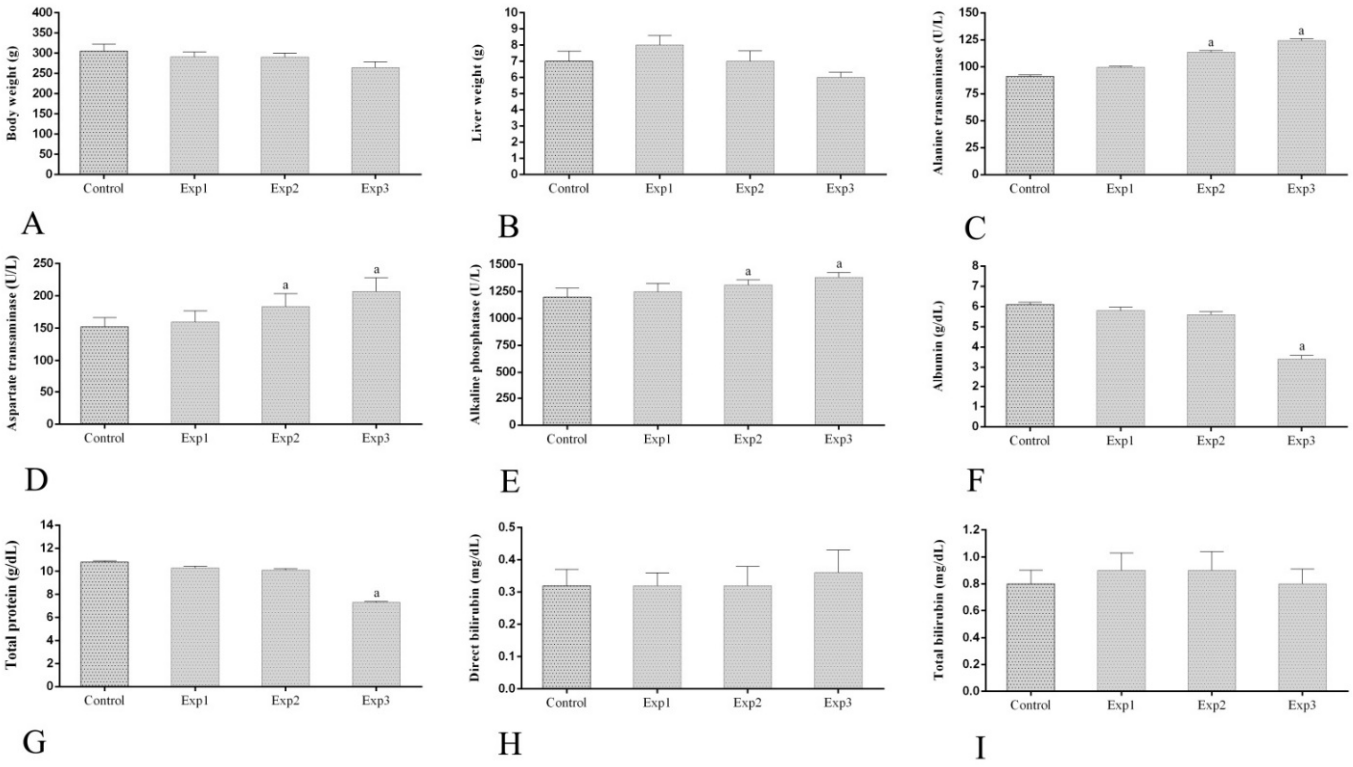

Graph 1. Comparison of mean body weight (A), liver weight (B) and serum levels of ALT (C), AST (D), ALP (E), albumin (F), total protein (G), direct bilirubin (H) and total bilirubin (I) In control and experimental groups. a ($p < 0.05$): Compared with the control group.

of this study, it was found that drug doses of 160 mg/kg, 320 mg/kg, and 640 mg/kg of MCB did not have a significant effect on the body weight of rats, such that the weight of rats did not show a significant difference with the control group in the three experimental groups from the beginning to the end of the experiment. Many antidepressants increase body weight by increasing appetite, including tricyclic antidepressants. Monoamine oxidase inhibitors, which are irreversibly classified, usually cause weight gain in individuals in short-term (less than 6 months) and long-term (more than 1 year) doses. But, in monoamine oxidase inhibitor antidepressants, which are classified in the reversible category and MCB belongs to this category, it does not cause weight change, which is consistent with the results of this study (Deshmukh & Franco, 2003).

In this study, in addition to body weight and liver, liver enzymes were analyzed to evaluate the effect of MCB. In the case of liver damage, ALT and AST activities are increased and these enzymes are released into the plasma (Larson *et al.,* 2005; Bajt *et al.,* 2004). It is difficult to quantify the level of damage to liver tissue, and liver function tests such as ALT and AST activity are measured (Suttner *et al.* 2000). The results of the present study showed that the activity of ALT and AST in the control and Exp1 groups did not increase significantly, but the activity of these enzymes increased in Exp2 and Exp3 groups, which received moderate and maximum doses of MCB, and showed significant differences with the control group. AST and ALT are enzymes released from liver parenchymal cells and are among the most reliable markers in significant liver diseases due to chronic liver cell damage and necrosis (Giboney, 2005). ALT is a more specific marker of hepatitis than AST due to its presence in the hepatic cytosol (Adias *et al.,* 2013; Giboney, 2005). AST increases in acute liver injury. ALP is another enzyme that is used to check the condition of the liver. In addition to secretion from the bile ducts, this enzyme is also released from bone cells, and its increase indicates damage to the bile ducts. However, this enzyme is not specific to the liver (Adias *et al.,* 2013), but liver is the only place that contains the highest concentration of the alkaline phosphatase enzyme, and damage to the liver cells causes it to be released and increased in the blood (Fattahi *et al.,* 2012). In the present study, the amount of this enzyme has increased in the second and third Exp. groups and showed a significant difference with other groups. Increased

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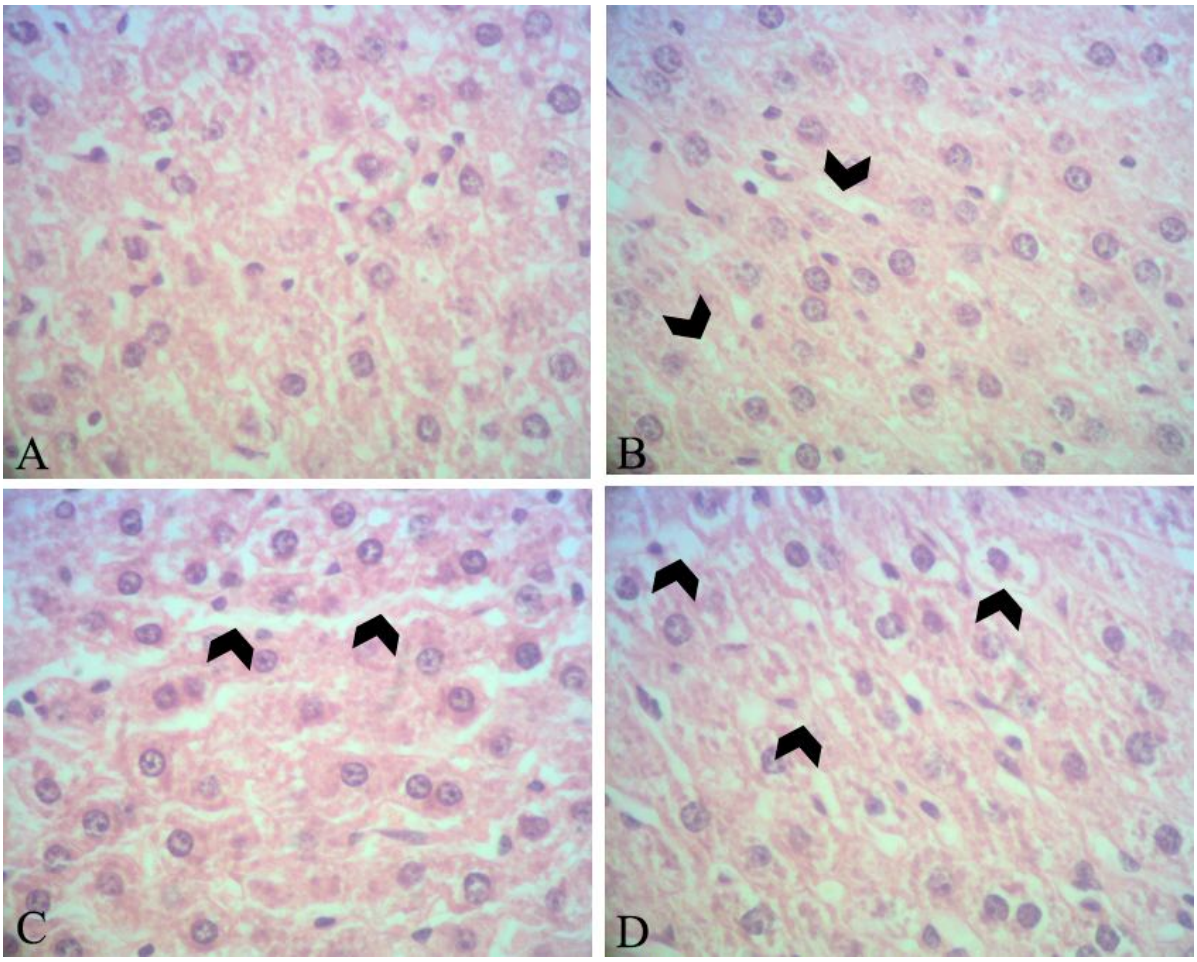

Figure 1. Optical photomicrograph of liver tissue in control and experimental groups. (A) In the control group, the normal structure of liver tissue is observed. (B) In Exp1 group, necrosis (arrowheads) and mild local inflammation are observed. Liver tissue destruction is minor. (C) In Exp2 group, the rate of necrosis (arrowheads) is more severe than in Exp1 group and the destruction of liver tissue is moderate. (D) In the Exp3 group, severe necrosis (arrowheads) is observed and the structural changes of liver tissue are severe. Liver tissue is destroyed. (E&H staining, 40X)

alkaline phosphatase can increase lipid peroxidation resulting in membrane destruction (Fattahi *et al.,* 2012).

Albumin is the most important plasma protein and is synthesized exclusively in the liver, so it is considered as evidence for the function of hepatocytes and its changes indicate damage to liver tissue and its function. In this study, albumin and plasma protein were measured. The results showed that only Exp3 group, which received the highest dose of MCB, showed a significant decrease in albumin and plasma protein levels, which had a statistically significant difference with other groups, especially the control group. Following hepatocellular damage, albumin synthesis by hepatocytes decreases, resulting in decreased serum albumin levels. Chronic liver diseases also lower albumin. In these patients, the liver cannot produce albumin. Of course, it is also important to note that due to the short half-life of albumin and its low production and degradation, serum levels of this protein are not a good indicator of mild or acute liver dysfunction and in acute liver diseases such as viral hepatitis and drug-induced hepatotoxicity, albumin levels change slightly (Kreinin *et al.,* 2009).

Histological results showed that due to damage to the liver tissue, an empty space was created between the cells. The amount of empty space had been increased with increasing the dose of the consumed drug, and it can be assumed that the amount of cell damage in the liver tissue is directly related to the dose of drug. The studies conducted on the effect of MCB on the liver are very limited, however, no severe liver damage has been observed in people taking moderate doses of the drug (Stoeckel *et al.,* 1990). The mechanism of action of MCB is probably

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similar to that of phenelzine, which is an antidepressant with the ability to inhibit the monoamine oxidase. By acting on cytochrome P450, this drug inhibits oxidation in liver microsomes and in high doses can cause liver tissue necrosis (Baker *et al.,* 1992). It is possible that MCB also has followed this pathway in tissue necrosis.

Conclusion

This study represented that the administration of MCB for 28 days alters serum levels of hepatic transaminases, blood biochemical parameters, and has a pathologic effect on the liver tissue in adult male rats, in a dose-dependent manner. Maximum dose (640 mg/kg) has the greatest effect on the destruction of liver tissue and changes in serum levels of hepatic transaminases and blood biochemical parameters. Therefore, according to the results of this study, since this drug is administered as one of the most common antidepressants, long-term use should be limited or be administered with more cautions and even it is better to prescribe alternative drugs for patients with liver diseases.

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Conflict of interest

None

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مقاله پژوهشی

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بررسی تاثیر داروی موکلوبماید بر سطح سرمی ترانس آمینازهای کبدی، پارامترهای بیوشیمیایی خون و تغییرات هیستوپاتولوژیک کبد در موشهای صحرایی نر بالغ

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چکیده

زمینه و هدف: موکلوبماید یک داروی ضدافسردگی است که در کبد متابولیزه می‌شود و به عنوان مهار کننده مونوآمین اکسیداز عمل می‌کند. این پژوهش با هدف بررسی تاثیر داروی موکلوبماید بر سطوح سرمی ترانس آمینازهای کبدی، پارامترهای بیوشیمیایی خون و تغییرات هیستوپاتولوژیک کبد در موش صحرایی نر بالغ انجام گردید.

مواد و روشها: ۴۰ موش صحرایی نر از نژاد ویستار در ۵ گروه ۸تایی تقسیم‌بندی شدند. گروه کنترل هیچگونه تیماری دریافت نکرد، اما گروههای تجربی ۱، ۲ و ۳ به ترتیب دوزهای ۱۶۰، ۳۲۰ و ۶۴۰ میلی‌گرم بر کیلوگرم موکلوبماید را بصورت گاواژ دهانی به مدت ۲۸ روز دریافت نمودند. در انتهای مطالعه وزن بدن، وزن کبد، سطوح سرمی ترانس آمینازهای کبدی (ALT و AST) و پارامترهای بیوشیمیایی خون (ALP، پروتیین تام، آلبومین، بیلی روبین تام و مستقیم) اندازه‌گیری شدند. همچنین، بافت کبد برای بررسی های هیستوپاتولوژیک خارج گردید.

یافته‌ها: نتایج حاصل از مطالعه نشان داد که وزن بدن، وزن کبد و سطوح سرمی بیلی روبین تام و مستقیم در گروههای تجربی تفاوت معناداری با گروه کنترل نداشتند ($p>۰/۰۵$). سطوح سرمی ALT و AST در گروه تجربی ۱ تفاوت معناداری را با گروه کنترل نشان ندادند ($p>۰/۰۵$) اما در مقابل در گروههای تجربی ۲ و ۳ افزایش معنادار مشاهده گردید ($p<۰/۰۵$). سطوح سرمی پروتیین تام و آلبومین در گروه تجربی ۱ و ۲ تفاوت معناداری را با گروه کنترل نشان ندادند ($p>۰/۰۵$) اما در مقابل در گروههای تجربی ۳ کاهش معنادار مشاهده گردید ($p<۰/۰۵$). در هر ۳ گروه تجربی درجاتی از نکروز و تخریب بافت کبدی مشاهده گردید که در دوز حداکثر بیشترین نکروز و تخریب مشاهده گردید.

نتیجه‌گیری: موکلوبماید باعث تغییر در سطوح سرمی ترانس آمینازهای کبدی، پارامترهای بیوشیمیایی خون و تخریب بافت کبد بویژه در دوز حداکثر (۶۴۰ میلی‌گرم بر کیلوگرم) در موشهای صحرایی نر می‌گردد.

واژه‌های کلیدی: *موکلوبماید، بافت کبد، آنزیم‌های کبدی، افسردگی، موش صحرایی*

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