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Effect of Bupropion on Liver Function Tests in Male Rats

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ABSTRACT

Introduction &objectives: Depression is a wide range of mental health problem that appears with positive impact reduction (loss of interest and pleasure), feelings of guilt, helplessness or worthlessness and disappointment. It seems that depression in addition to hereditary reasons, is related to chemical changes in the brain that will disorder the relation between nerve cells with each other. Of course using some drugs and drug abuse or other diseases can also be a cause of depression. Bupropion is one of the new drugs that are potent inhibitor of the reuptake of dopamine and epinephrine at the end of pre-synaptic central nervous system and other catecholamine and antagonist nicotine. This drug acts selectively on Noradrenergic and dopaminergic systems. This drug causes antidepressant effects and reduces the dependence on nicotine through acetylcholine receptors.
Materials & methods: In the present study 40 male Wistar rate, each weighting 200±20 g in 5 groups of 8 were used as follow: The control group which did not receive any materials during the experiments, the witness group received only water and alcohol as solvent. Minimum, average and maximum experimental groups received orderly amount of 160,320,640 mg Bupropion drug solution orally. Prescription lasted for 28 days and after the end of this period, the heart blood was given to determine the level of liver enzymes such as ALT, AST, ALP and also the serum protein. Obtained results were analyzed by ANOVA , T test and Tukey test. Based on the obtained result the level of AST and ALT enzymes serum, indicate significant increase at the level of $P \leq 0.05$ compare to control group and no significant changes was observed in ALP plasma concentration, albumin, protein compare to control group. Also the liver was collected for studying of histological changes and its changes among experimental groups compare to control group were determined for preparation of tissue sections and staining.
Results: Accordingly we can say that this drug effects on cells and liver tissue and leads to hepatic necrosis that itself justifies an increase in AST and ALT enzymes. Because in drug maximum group, acute necrosis has been occurred, it will compensate the increase of protein.
Conclusion: So in general we can say that this drug has a negative impact on hepatocytes cells and causes disorder of liver function and changes the concentration of some enzymes and blood biochemical factors.
KEY WORLD: Bupropion, LFT, Liver, Rat

INTRODUCTION

The liver is the largest gland in the body with a central role in metabolism; and as a distributor, providea good mix for all body organs through the bloodstream. Liver is the main and most important place for converting drugs to an active metabolite. Therefore, these important functions has clear physiological significance, and made research on liver invaluable [1,2]. According to previous studies, some medications have hepatotoxicity effects that detrimental to liver functions. Anti-depressant drugs fall in this group of medication [5, 8]. One of common anti-depressant drugs, bupropion has hepatotoxicity and exert its antidepressant effects as follows:

1. This drug is a potent inhibitor of pre-synaptic reuptake of dopamine and norepinephrine in the central nervous system (CNS) and other catecholamines and it is a nicotine antagonists which affects nor-adrenergic and dopaminergic systems selectively [3].
2. It is demonstrate the antidepressant effects and also reduction of dependence on nicotine through acetylcholine receptors, therefore, it uses as smoking quitting drug [11].
3. Bupropion is a norepinephrine and serotonin reuptake inhibitor antidepressants and belong to polycyclic anti-depressant drugs. These drugs work by inhibiting the reuptake pumps of amines (norepinephrine or serotonin), which is increases the serotonin and norepinephrine levels in the brain pre-synaptic neurons [3, 5].

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MATERIAL AND METHODS

Bupropion is available as 75, 100, 150, and 300 mg tablets. We used 150 mg tablets in the current study. First, the drug was powdered by mortar and pestle, then a uniform solution was prepared using 20% alcohol as solvent and stored for administration to each experimental groups.

Grouping and other procedures in the 28 days period of study

As preparation phase, 40 wild adult male rat were weighted. The rats were Wistar strain with approximate weight of 200 ± 20 gram and 2.5-3 month old. Then, they randomly divided in 5 group of 8 animals as follow:

- The control group: consisted of 8 animals that didn't receive any drug treatment.
- The placebo group: consisted of 8 animals that received 2 ml of distilled water (as a placebo) orally.
- Experimental group 1: consisted of 8 animals that was given daily dose of 160 mg/kg dissolved bupropion orally.
- Experimental group 2: consisted of 8 animals that was given daily dose of 320 mg/kg dissolved bupropion orally.
- Experimental Group 3: consisted of 8 animals that was given daily dose of 640 mg/kg dissolved bupropion orally.

The study period was 30 full day, all groups has similar condition regarding to food, water, environmental conditions. The gavages was done every day at 8 am using oral feeder device. After the completion of the study period, they were sacrificed under general anesthesia with ether. The blood sample was collected from heart for evaluation of liver function enzymes and some biochemical tests. Specimens were centrifuged promptly and plasma was separated and sent to laboratory for desired tests. Their liver was dissected and then tissue slices was prepared and slide fixed.

Measuring biochemical parameters

As biochemical parameters, ALP, ALT, AST, protein and albumin levels were measured using standard IFCC technique at pH=7.4 and with RA1000 biochemical auto-analyzer (US made) and also kits purchased from Pars Azmoon Company (Iran).

Data analysis

The mean of measured blood biochemical factors and liver enzymatic activities form each groups was statistically analyzed using ANOVA, t-test, and Tukey test. The inferential base of the statistics were F-test and level of significance ($p \leq 0.05$) (all values were means).

RESULTS

Comparison of statistical results shown that the enzyme alanine amino transfrase (ALT) and aspartate amino transferase (AST) were increase significantly in the experimental group whom received mean and maximum drug dosecompared to the control group ($P \leq 0.05$). In the case of alkaline phosphatase, none of the groups receiving the drug showed any significant difference compared to control group (Table 1).

The comparison of plasma protein and albumin levels in the group receiving the drug compared to the control group, shown a significant differences ($P \leq 0.05$) (Table 2). Microscopic observations shown that liver tissue in rats receiving average and maximum dose of the drug lead to increase the amount of hepatic necrosis compared to control group (Figs 1,2,3).

Table 1. comparison of AST, ALT, ALP serum concentration of treatment and control groups

Groups	No	Mean ± SD of AST serum level (U/L)	Mean ± SD of ALT serum level (U/L)	Mean ± SD of ALP serum level (U/L)
Control	8	172.00 ± 14.3	52.00 ± 1.3	915.40 ± 85.2
Placebo	8	253.00 ± 7.4	61.00 ± 4.0	773.13 ± 86.7
Treatment 1	8	212.50 ± 17.8	58.20 ± 1.2	868.30 ± 76.2
Treatment 2	8	269.70 ± 20.0*	69.00 ± 1.7*	849.40 ± 46.0
Treatment 3	8	341.10 ± 22.2*	78.13 ± 2.0*	763.80 ± 46.1

Values are presented as mean ± standard deviation $(\overline{X} \pm \mathrm{SEM})$.

* The differences are statistically significant between treatment and control group ($P \leq 0.05$).

Table 2. comparison of serum concentration of protein and albumin in the treatment and control groups

Groups	No	Mean ± SD of serum protein level (U/L)	Mean ± SD of serum albumin level (U/L)
Control	8	7.5 ± 0.12	4.1 ± 0.11
Placebo	8	7.8 ± 0.16	4.1 ± 0.11
Treatment 1	8	7.5 ± 0.23	3.9 ± 0.17
Treatment 2	8	8.0 ± 0.08	4.1 ± 0.12
Treatment 3	8	7.9 ± 0.09	4.1 ± 0.11

Values are presented as mean ± standard deviation $(\overline{X} \pm \mathrm{SEM})$.

* $P \leq 0.05$ was considered statistically significant.

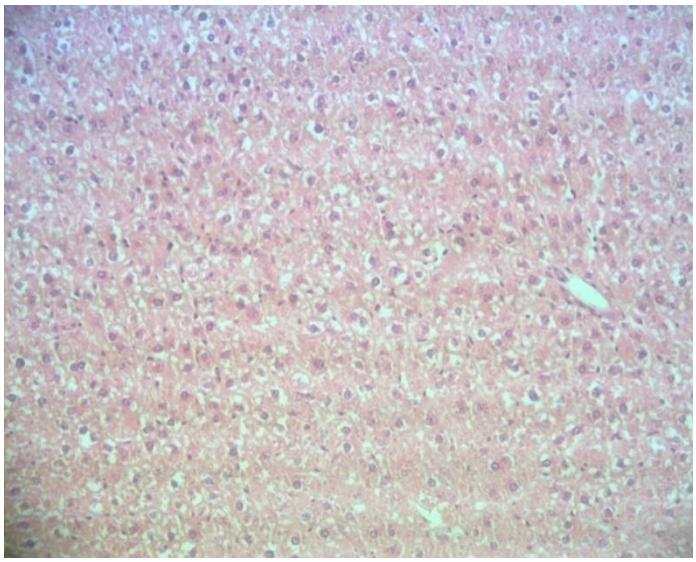

Fig 1. The photo micrograph of liver tissue in the treatment group with minimum dose (magnification of 10x)

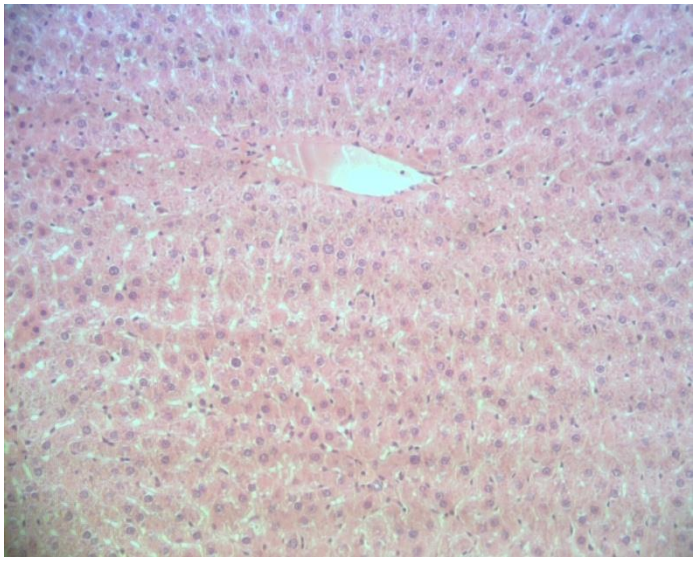

Fig 2. The photo micrograph of liver tissue in the treatment group with medium dose (magnification of 10x)

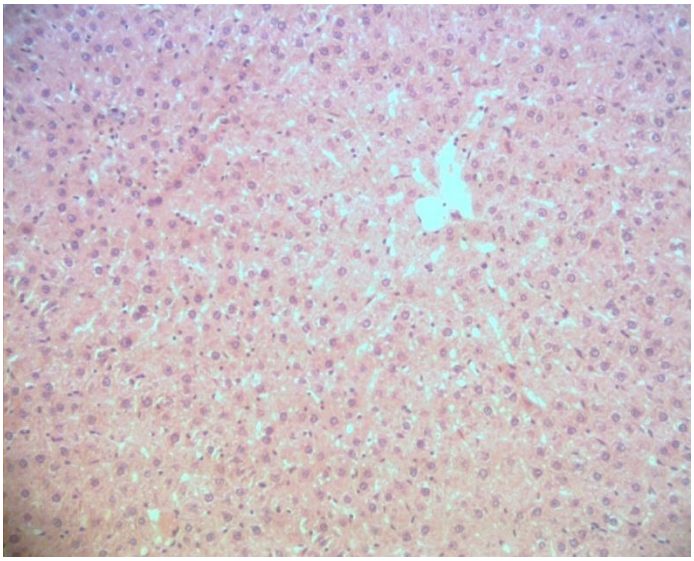

Fig 3. The photo micrograph of liver tissue in the treatment group with maximum dose (magnification of 10x)

DISCUSSION

Bupropion is a drug used for depression treatment and quitting smoking, which belong to polycyclic anti-depressant group and similar to three-cyclic antidepressant drugs from pharmacokinetic point of view; exert its effects through strong inhibitory effects on the dopamine (about 2-fold) and nor epinephrine reuptake at the pre-synaptic sections in the central nervous system (CNS) and also other catecholamines. This empower the post-synaptic effects of these neurotransmitters [4, 6]. Because bupropion is a nicotine antagonist and an antidepressant with selective effects on nor-adrenergic and dopaminergic systems, causing the release of dopamine and norepinephrine in the hypothalamus, nucleus accumbens and the frontal cortex [12].This drug affects the liver function, and causes liver toxicity and liver failure resulting in liver enzymes changes; thus, there are possibility that this drug is one of the liver toxicity causes [7, 8].

Since bupropion has a similar effects with paroxetine and both are CYP_2D_6 inhibitors (cytochrome P_2D_6 are involved in drugs metabolism), it is likely that thecytochromeP_2D_6inhibition and lack of drug metabolism lead to increased toxicity in cells which is an explanation for the necrosis [13, 14].

Because bupropion is converted to epoxide hydrolase, its active metabolite by cytochrome P2B6 in the liver; the covalent binding of the drug's active metabolite with wall-bound macromolecules resulting in liver cell damage and necrosis [8]. Thus, there are possibility that bupropion can used this mechanism in the creation of hepatic necrosis. Well as active metabolites of bupropion may cause decreased mitochondrial activity and energy production in the cells, which causes necrosis of liver cells.

Because bupropion is also functionally similar to Fluoxetine, it is likely that the production of free radicals cause damage to cell's nucleus and membrane, resulting in necrosis [12].

ALT and AST are mainly found in the liver cells and to lesser extent in kidney, heart and skeletal muscle [9, 10]. Any illness or injury that affects the liver parenchyma can cause the release of ALT and AST enzymes from liver cells into the blood stream; therefore, we can say that because of the hepatic metabolism of bupropion, there are possibility that the drug caused the necrosis of liver cells and increases in serum ALT and AST levels. As in mammals, mild to moderate elevations of liver enzymes such as ALT and AST are confirmation for liver dysfunction, but the concentration of ALP could be normal. Because the concentrations of these enzymes in hepatocellular are several times higher than the extracellular fluid [10]. However, for definitive conclusions, more qualitative and quantitative work is needed in this area.

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