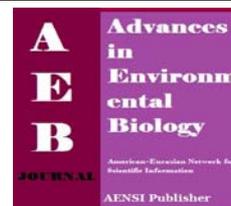




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Investigating the Effect of Imipramine Medication on Enzymes Changes of AST, ALT and ALK in Adult Female Rats

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ABSTRACT

Introduction: Imipramine medication with the generic name of imipramine hydrochloride is a tricyclic antidepressant drug that has different side effects on different body systems. Since the use of this drug has become widespread and importance of liver enzymes and liver function, the main aim of the present study was to investigate the effect of imipramine medication on enzymes changes of AST, ALT and ALK in adult female rats. **Methods and materials:** Female Wistar rats were divided randomly into 5 groups. The first group (control group) did not receive any medication. The second group (sham) received only distilled water. Experimental group 1 received imipramine 6/25 mg/kg, the experimental group 2 received imipramine 12/5 mg/kg and experimental group 3 received imipramine 25 mg/kg intraperitoneally that was based on kilogram of body weight. At the end of day 30, the rats were bled and the serum concentrations of ALT, AST, and ALK were measured. Data were analyzed using SPSS version 18. **Results:** The results showed that the concentration of AST in the experimental groups 2 and 3 had significant increase compared to the control group. ALT concentration in experimental groups 1, 2 and 3 had significant increase compared to the control group. ALK concentration in experimental group 3 had significant increase compared to control group. **Conclusion:** The results showed that imipramine may increase liver enzymes and liver damage, so it should be taken with caution.

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INTRODUCTION

Antidepressant drugs, including Tricyclic Antidepressant (TCAs), Selective serotonin reuptake Inhibitors (SSRIs), Monoamine Oxidase Inhibitors (MAOIs), maprotiline, trazodone, Bupropion and venlafaxine. Tricyclic antidepressants (TCAs) have been used in almost four decades of clinical use. In 1955, a Swiss psychiatrist named Rulandkan who, from early 1950s attempted to get medicines to improve morale, found that G22355 combination made in 1951 by Hafliger and Schneider in the United States had a positive impact on depressed patients with mental retardation [1]. In terms of chemical structure TCAs are very similar to Phenothiazines but in terms of Pharmacology they have fewer similarities. This pharmaceutical group has three Pharmacologic effects: Amine pump inhibitors, sedative and central and peripheral anti-cholinergic. Phenothiazines act on dopamine receptors but tricyclics prevent serotonin reuptake (5 - hydroxy tryptophan) and norepinephrine in the pre-synaptic neuron and thus their effects on neurons increase. Tricyclics are similar to kynidin in that imipramine is one of the indicator drugs [2]. Imipramine drug with the generic name of imipramine hydrochloride (HCL) with the chemical formula of C₁₉H₂₄N₂, has the following chemical structure: Chemical group of this drug is part of amine Trivalent dibenzazepin with the brand name of Tofranil [1]. Tricyclic antidepressants are selective drugs for panic disorder. These drugs in the treatment of anorexia nervosa or particularly, when along with depression are effective. Other uses of these drugs are bulimia, hyperactivity disorder, resistant hiccups, chronic pain (migraine, tension headache), gastric ulcer, sexual

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dysfunction (premature ejaculation), insomnia and premenstrual depression [5,6]. It seems that imipramine applies its antidepressant effect through inhibition of the reuptake of norepinephrine and serotonin in the pre-synaptic nerve terminals in the central nervous system (CNS) and thereby increase the concentration and nerve-mediated activity in the synaptic cleft. Imipramine has anti-cholinergic effects and is used in treatment of enuresis in children older than six years. It is said that through disturbing inhibition and stimulating katcholinergics it has an influence on prolactin secretion [6]. In addition, the drug has a weak effect on dopamine reuptake [7]. Among the tricyclic antidepressants drugs, sedative and anticholinergic effects are common, of which drowsiness, sedation, dizziness, orthostatic hypotension, dry mouth, constipation, blurred vision, urinary retention can be noted [7]. Cardiac conduction disorder and inhibition of bone marrow are important side effects of this drug. This drug also causes headache, metallic taste in the mouth, ear buzzing, hallucinations, confusion, nausea and vomiting, stomach irritation, hypersensitivity, extrapyramidal symptoms, sexual dysfunction, changes in blood glucose concentration, increased appetite and weight, sweating, and tachycardia can also be noted [7]. Further, most of these drugs are excreted through the urine [8]. According to the importance and prevalence of antidepressant medications and the side effects of these drugs on different body systems, the aim of this study was to investigate the effect of imipramine on the liver enzymes.

Methods:

It's a completely randomized experimental study. All works about animals comply with the ethical principles. 40 adult female Wistar rats weighing $200 \pm 5\%$ g and aged 100-120 days were obtained from the research center of Jahrom city. Rats were maintained in the animal house of Islamic Azad University of Jahrom for 21 days in laboratory conditions, including a temperature of 21 ± 2 °C and a cycle of 12 hours light and 12 hours dark. Standard rat food (pellet) was used. Also, water by special glass bottles was given to them. The cage was disinfected with 70% alcohol three times a week. Lethal dose of the drug was 40 mg. On this basis, dose rate of minimum, average and maximum were determined. In this way maximum dose was half of the lethal dose, medium-dose was half of maximum dose, and minimum dose was half of medium dose. Imipramine is a water-soluble drug. In this study, distilled water was used as solvent. All solutions were prepared fresh every morning and the injection was performed for 30 days. The rats were divided into five groups of eight:

The control group (A): did not receive any medication and all conditions of maintenance and nutrition were similar to other groups.

The control group (B): received distilled water daily based on body weight.

Experimental group 1: Received daily 25 mg tablet dissolved in 4 mL of distilled water based on body weight.

Experimental group 2: Received daily 25 mg tablet dissolved in 2 mL of distilled water based on body weight.

Experimental group 3: Received daily 25 mg tablet dissolved in 1 mL of distilled water based on body weight (Table 1).

Table 1: Method of drug prescription.

Blood sample time	Amount of drug	Grouping
End of 30 days	Control
End of 30 days	Physiological serum 1mg/kg	Sham
End of 30 days	Imipramine 6/25 mg/kg	Experimental 1
End of 30 days	Imipramine 12/5 mg/kg	Experimental 2
End of 30 days	Imipramine 25 mg/kg	Experimental 3

After a 21 day period, rats of all groups after weighing were anesthetized by ether and blood samples were collected from their heart by syringe 5 cc and after separation of blood serum concentrations of OT, PT and ALP were measured in the laboratory of Medical Sciences of Jahrom. One-way ANOVA for comparison between treatments (ANOVA) followed by t-test and Duncan test were used for multiple comparisons between groups. ($P < 0.05$) was considered as significant level. Data analysis and statistical testing was performed using SPSS, version 18.

Results:

Results showed that concentration of AST in the experimental groups 2 and 3 has a significant increase compared to the control group (Table 1). ALT concentrations in experimental groups 1, 2 and 3 have a significant increase compared to the control group (Figure 2). ALK concentration in experimental group 3 has a significant increase compared to control group (Figure 3).

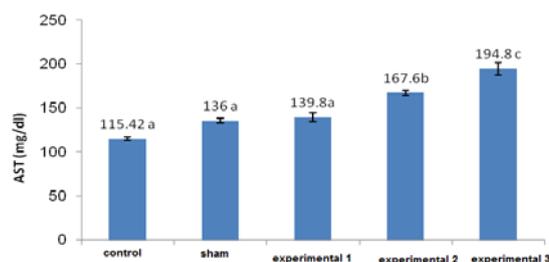


Table 1: Changes about AST in different groups.

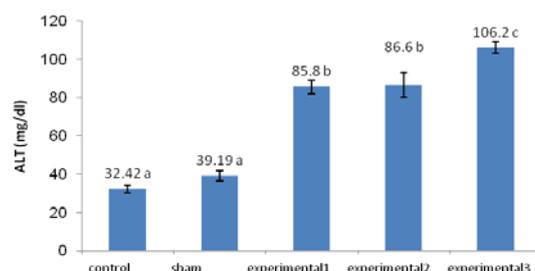


Table 2: Changes about Concentration of AST in different groups.

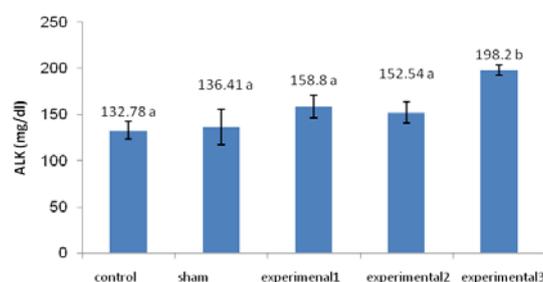


Table 3: Changes about AST in different groups.

Discussion:

Hepatocytes are complex cells of metabolic liver containing large amounts of the liver enzyme. These enzymes due to liver damage leak into the plasma, and can be useful for the detection and determination of liver damage. AST is a microsomes enzyme that is found in the liver in large amounts and in addition to damaging liver tissue, is released in large amounts in blood [9]. ALT is a liver-specific enzyme that is present in the cytosol and has been determined as an indicator of liver cells, and it is a more sensitive and specific criteria for liver cell damage [10]. Alkaline phosphatase is present in most tissues of liver and due to liver diseases would increase. Depending on the type of liver disease the amount of these enzymes vary [11]. Both liver-specific enzymes ALT and AST are enzymes that, in addition to liver toxicity and histopathologic changes are more sensitive than other enzymes and are evaluated in a shorter time [12]. Enzymes as biological catalysts control all of the enzyme reactions of the body and therefore changes in the quality and quantity of various enzymes are reflect in health and disease [13]. ALT catalyzes the conversion of alanine to pyruvate and glutamate, and are more specific for the liver and as a biomarker for the quantification of liver cells determines the amount [14]. Further, it has been shown that increased levels of liver enzymes AST, ALT and ALK are indicative a cell leak and indicattive of damage to the cell membrane structure and function in the liver [15,16]. Probably damaged liver cells cause leakage of these enzymes from the liver cytosol into the blood stream. In other words, in the early stages of liver damage hepatocytes cytoplasmic enzyme most likely leak from the cells into the blood flow and increase the membrane permeability [17]. Serum total alkaline phosphatase activity depends on the activity of various tissues generating these enzymes of which bone tissue, kidney, intestine and liver could be named. The disorder in total alkaline phosphatase activity can be associated with increase of one isoenzymes and decrease of another [18]. It has also been stated that the increase in serum ALK could be due to increased production of bile in the presence of increasing pressure [19]. Alkaline phosphatase is a hydrolytic enzyme whose optimal activity is at alkaline PH and has in different shapes in blood, and is released in bone and liver in large amounts. Although increased serum alkaline phosphatase levels along the bile ducts, hepatitis, cirrhosis, and the accumulation of fatty deposits in the liver has been observed and chemical factors and different drugs

have an effect on its level, they are not indicators of liver damage and pathologically increase in cardiac and bone defects [20,21,22]. Sometimes increase of ALK without any liver or bone damage has been observed. Considering that the drug enters the bloodstream and may affect other tissues, increasing it is fully justified in all treatment groups. In the present study, concentration of AST in experimental groups 2 and 3 have a significant increase compared to control group. Also, the concentration of ALT levels in experimental groups 1, 2 and 3 have a significant increase compared to the control group. In past studies in which the imipramine toxicity rate on liver was done, it was stated that imipramine causes damage to the liver, and in severe conditions requires transplant [23]. The study stated that mechanisms by which imipramine causes an increase of serum aminotransferases is unknown but it is likely that damage to the liver tissue can cause elevated liver enzymes [24]. It has been previously stated that imipramine can cause DNA damage [25]. It is likely that imipramine with impaired DNA production causes liver tissue damage resulting in elevated liver enzymes.

Conclusion:

According to this study it could be stated that imipramine, Probably by impairment of DNA production and also the damage to the liver tissue, causes increase of enzymes ALT, AST and ALK. Therefore, use of this drug should be with more caution, but further testing and histopathological studies are recommended.

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