December 30, 2020

PharmacologyOnLine

Archives • 2020 • vol.3 • 134-141

The Safety of Clinically Equivalent Therapeutic Dose of Oxandrolone Administration on Rat livers

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Abstract

Oxandrolone is a testosterone derivative with a weak androgenic properties. There are previous controversial results regarding the safety of using oxandrolone in human and animal models.

Aim: The present study aimed to find out the safety of using clinical therapeutic dose of oxandrolone on rats liver.

Fourteen rats were divided into 2 groups, which was administrated oxandrolone in a dose equivalent to that used for human treatment (0.28 mg/kg), for continuous 14 days. Subsequently, liver and blood samples were isolated from the rats for morphological, biochemical and histological examination.

The results showed no significant differences (p value > 0.05, t-test) in the levels of hepatic transaminase enzymes, ALT, AST, in the blood. The relative liver weights of oxandrolone-treated rats were in comparable values (p value>0.05) to those of the control animals. In addition, the histological examination revealed that oxandrolone had no harmful effect on the liver tissue of rats. In conclusion, this preliminary study found that clinically equivalent therapeutic dose of oxandrolone is safe for the rat livers, which might indicate that oxandrolone is not hepato-toxic to human livers. Further clinical studies are needed to confirm these findings.

Keywords: *aminotransferase enzymes, Liver, oxandrolone, rats, hepatotoxicity*

Introduction

Anabolic-Androgenic Steroids (AASs) represent a huge group of testosterone derivatives, which have both the anabolic and androgenic properties that testosterone owns [1].

Oxandrolone is a testosterone derivative with a weak androgenic properties [2]. It belongs to AASs with a high ratio of anabolic to androgen activity [3]. It was discovered in 1964 and marketing under the trade name Anavar, Oxandrin, Lonavar, and Lipidex [4]. It was approved by the Food and Drug Administration as an oral medicine used to restore weight after illness that leads to weight loss.

Oxandrolone is safe when used to treat different conditions associated with wasting poor weight gain, or short stature [5]. Otherwise, consuming of oxandrolone has begun to rise between athletes and bodybuilders, as well as, teenagers who plan to increase their muscle mass for prettiness or athletic purposes. Nevertheless, The World Anti-Doping Agency (WADA) has evaluated AASs as the greatest group used as a doping agent [6].

Oxandrolone has various side effects which have been observed among bodybuilders and professional athletes [7]. It is associated with sexual dysfunction, headache, menstrual irregularities, and mood depression [8,9].

It was found that there was an increase in the levels of liver transaminase enzymes, ALT, AST, and a decreasing in HDL level associated with the use of therapeutic dose of Oxandrolone [10]. Conversely, some studies had shown that oxandrolone does not alter the level of liver transaminase enzymes [11, 12].

There is a wide controversy surrounding the safety of oxandrolone on the liver. Therefore, the present study aimed to find out the influence of clinically equivalent dose of oxandrolone on the liver rats.

Methods

Drugs

Oxandrolone was bought from Pharmacom Labs (Chișinău, Moldova). Dimethyl sulfoxide (DMSO) >99.9% solvent was obtained from Sigma-Aldrich (St. Louis, USA).

Experimental animals

Fourteen Sprague-Dawley (Rattus norvegicus) rats with average weight of 200±30g and similar age (7 to 8 weeks) where obtained from laboratory animal facility of Al-Zaytoonah University (Amman, Jordan). All the rats were treated according to the ethics of the guideline of Canadian Animal Laboratory Care [13]. All rats were placed in an environment with a temperature of 23 +-1 ℃, and 12 hours light-12 hours dark cycle. The rats were given water and food at *ad libitum*. This study has been permitted from the ethical committee of Al-Zaytoonah University with reference number of 2020-2019/06/17.

Before the drug administration, the rats were stabilized for 7 days period. Then, the animals were divided into two groups. Each group contained 7 rats, as followings:

i. First group was the control group: The animals received only DMSO, where it was used as a vehicle to dissolve the drug.

ii. Second group received 0.28 mg/kg Oxandrolone, which it was dissolved in DMSO.

All rats were injected with the drug every day up to 14 days by intra-peritoneal route (IP) with an injection volume of 1ml. The dose of the drug used in this research were according to the human equivalent dose [14].

Consequently, the rats were sacrificed through anesthetization. Then, liver were isolated from the rats for morphological and histological examination. Moreover, 2 ml blood samples were collected from the rats for the biochemical examination.

Physical observation

Daily follow-up to check the status of the animals and record whether there was any deaths or any other changes that occurred.

The weight of the rats were recorded three times in this study: The first weight measurement was before drug administration, while the second weight was measured on the seventh day from the

beginning, and the last one was on the 14th day from the beginning of drug administration.

Relative weight measurement

Relative weight was calculated for the liver of the treated rats. The determination was done after animal scarification, where the weight of the whole liver, of each rat, was divided by the whole weight of the rat and multiplied by 100.

Histological examination

Liver samples were obtained from rats, as they were cut up and immediately retained in 10% formalin solution. Tissue samples were dehydrated by ascending alcohol grades. After that, the tissues were washed three times with xylene, one hour each time. Next tissue impregnated in oven to dissolve paraffin wax at 60 ° C, for one hour. Then, the tissue was inserted with melted solid paraffin, and then left to even solidify at room temperature to form hard masses. Sections were stained with hematoxylin and eosin pigment (H and E). Investigation of the sections was under the optical microscopy (original magnification is 400 ×s) [15].

Transaminase level measurement in the blood

The blood samples were drawn from the rats at the last day of the experiment. Subsequently, the samples were sent to Vital Lab (Amman, Jordan) for analysis. ALT and AST levels were measured by the cobas c 311 analyzer (photometric assay).

Statistical analysis

All the obtained data were expressed as mean ± standard deviation. The biochemistry and morphological results were analyzed by students T test. The seventh version of the GraphPad prism program was used in analyzing the results. The difference between the treated and control group was considered significant when the *p* value was less than 0.05.

Results

Total body weight

After 14 day treatment, the data showed non-significant differences in final (14day) body weight observed in rats treated with vehicle (DMSO) (181 ±15g), Oxandrolone alone (158.6 ±38.6g) when compared with initial total body weight (173 ±11.9, 131.5±13.5g, respectively: *P* >0.05) ***(Figure 1).***

Liver relative weight

We found that there was no significant difference in the relative liver weight of oxandrolone treated group (3.1± 0.6g) in comparison with control group (3.5 ± 0.3g) (*P* >0.05) (**Figure2**

Aspartate Aminotransferase level (AST)

Data obtained from Bio lab of blood sample measurement revealed that there was no significant differences in the level of AST liver enzyme of Oxandrolone treated group (1207 U/l) in comparison with control group (1869 U/l) (*P* > 0.05) **(Figure 3).**

Alanine Aminotransferase level (ALT)

The results of this study showed a non-significant different in the level of ALT liver enzyme of group treated with oxandrolone alone (447.3 U/l) in comparison with control group (689.3 U/l) (**P**> 0.05) **(Figure 4).**

Histological alterations in the liver

The histological results of liver tissues showed normal morphology of liver of the control group **(Figure 5A).** In addition, the results showed non-significant changes in the morphology liver tissues of rats treated with Oxandrolone **(Figure 5B**).

Discussion

Different studies have shown that there is a close relationship between the use of AASs and the occurrence of harmful changes in the liver [16]. In addition, studies conducted on some adolescents indicated that liver damage is one of the common side effects associated with the use of AASs [17]. It is suggested that the mechanism of how AASs cause liver injury is through increasing the oxidative stress and dropping the antioxidant system in the liver 19. However, it was reported that oxandrolone is safer than other AASs, regarding its hepatotoxicity [18].

In this study, we found that human equivalent dose of oxandrolone did not cause a significant hepatic alterations to the treated rats. The histological examination showed no effect of Oxandrolone on the hepatic tissues and biochemical

analysis showed no alterations in the blood liver enzymes of ALT and AST after sub-acute oxandrolone treatment. Accordingly, these findings are in line with what was reported previously that oxandrolone is safe to the hepatic tissues [18-20].

We choice in this study oxandrolone rather than other AAS drugs; since oxandrolone is orally absorbed, while other AASs are administrated parentally [5]. Therefore, oxandrolone is conveniently be administrated and hence it is the most commonly used as AASs, especially among athletes and bodybuilders.

Regarding the period of oxandrolone administration, it is recommended that oxandrolone is administrated clinically in cycles, each cycle is around 2 weeks [21]. In this study, we treated the rats in a period that mimics clinically one cycle of oxandrolone administration.

The mechanism of how oxandrolone is relatively safer than other AASs, regarding their influence on the liver, is still not clarified. It might be due to that the lipophility of oxandrolone, is less than other AASs. Decreased drug lipophilicity can decrease the distribution of oxandrolne to the hepatic tissues and hence the hepatotoxicity.

In conclusion, this study found out that oxandrolone, in clinically equivalent dose, is no a hepato-toxic to the liver. Further clinical studies are needed to confirm these findings.

Acknowledgments

This work has been funded by Al-Zaytoonah University of Jordan with fund number 29/12/2019-2020.

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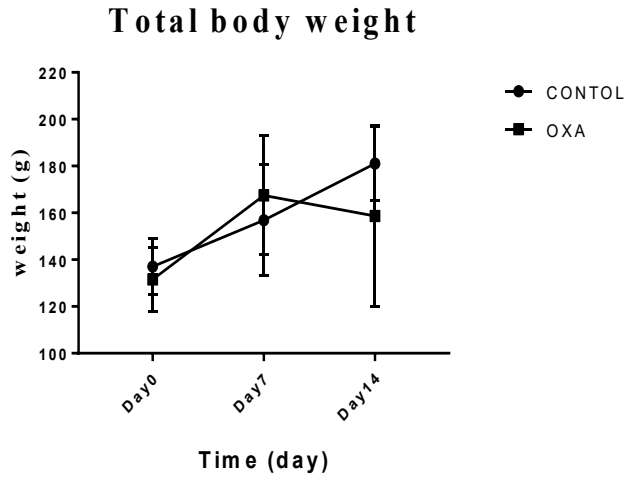

Figure 1. The changes in total body weight of the experimental rats.

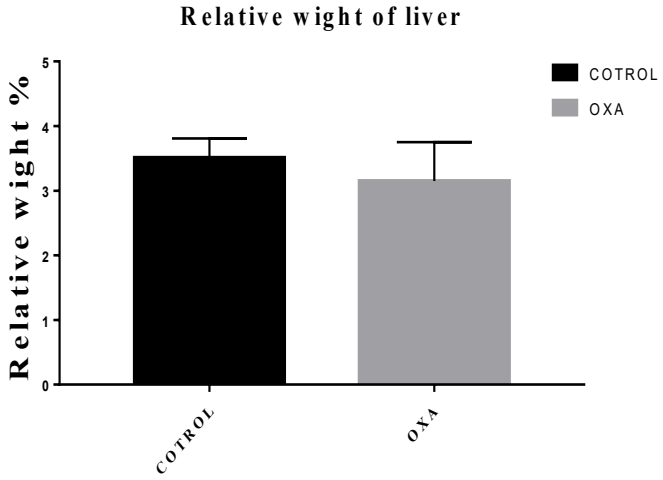

Figure 2. Relative liver weights index of experimental rats.

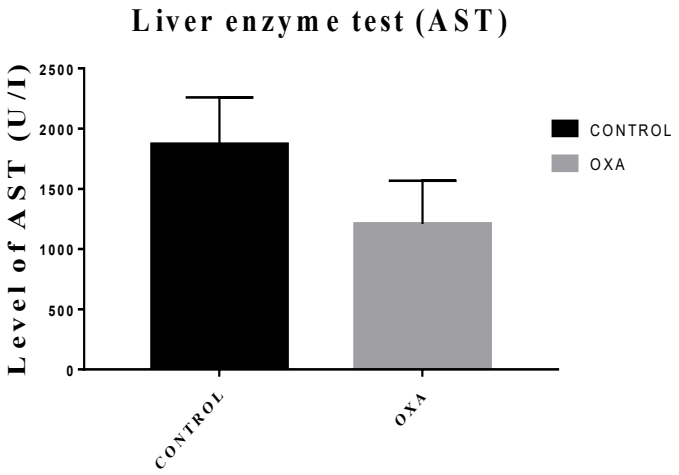

Figure 3. The blood level of AST in different experimental groups. AST is the abbreviation of Aspartate Aminotransferase.

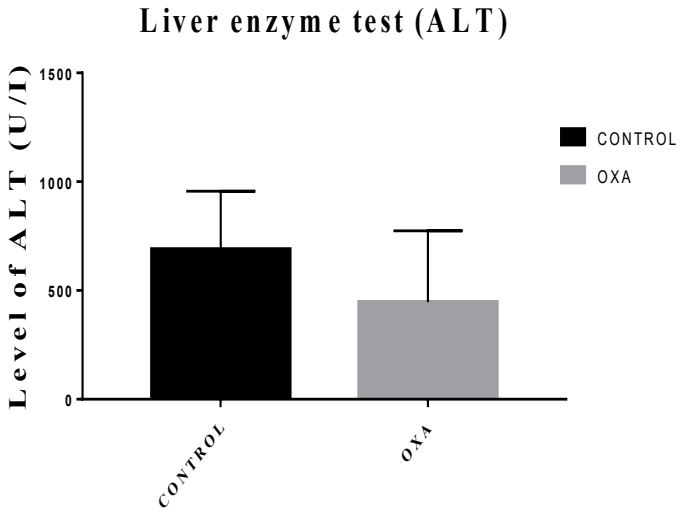

Figure 4. The blood level of ALT in different experimental groups. ALT is the abbreviation of Alanine Aminotransferase.

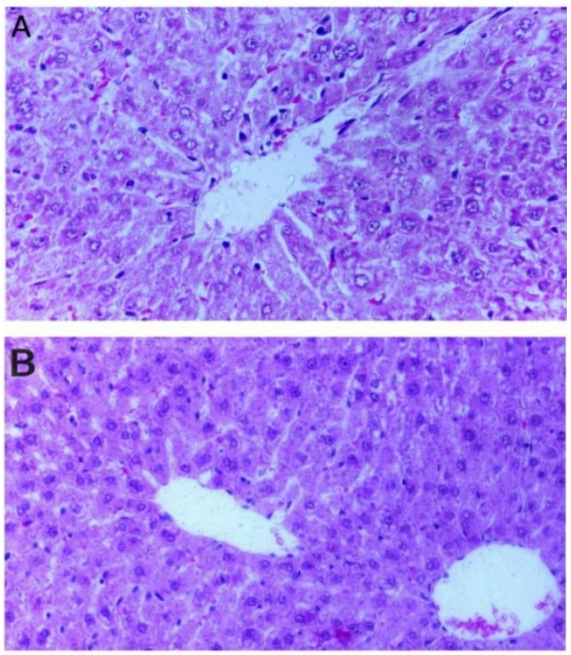

Figure 5. Liver tissue under histological examination. The original magnification is 400 ×s.