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Estimation of the toxic effect of meloxicam on sex hormones in male albino rats *rattus*

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Abstract

The need for anti-steroidal analgesics has garnered increased attention among researchers in the field of pharmacology, particularly Meloxicam, also known commercially as Mobic. It is a typical painkiller. In this investigation, fifty male white rats were employed, which was carried out between September 2023 and October 2023 at the Animal Guest House, College of Science, University of Kufa. Testicular physiological measures were assessed for periods of 15, 30, 45, and 60 days following oral administration of 0.2 mg/kg/day, with the intent of determining how the cumulative dosage altered those parameters. Four groups of six male rats each were created at random from the total population of the rats. Each group was split into two subgroups of three rats each; one was the control group, and the other received 0.2 mg/kg/day. The rats were then euthanized after 15, 30, 45, and 60 days. The physiological and histological parameters of the testis cumulatively decreased with increasing dosage periods (15, 30, 45, and 60 days of Meloxicam 0.2 mg/kg/day) compared to control groups for each period ($p < 0.05$). The doses given were chosen in accordance with the size of the animal, as gradually increasing the dose value led to the appearance of effects on the levels of sex hormones.

Keywords: Anti-steroidal, Meloxicam, Physiological effect, Rat, Sex hormone.

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Contents

Contribution of this paper to the literature
The originality of the research paper includes considering sex hormones as the basis of the study, in addition to extending the dosing period and monitoring the animals for various durations to obtain accurate results.

1. Introduction

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID), antipyretic, and effective painkiller. It is derived from the drug oxicam, which is closely related to piroxicam, and is classified in the enolic acid group of analgesics. It was discovered by Boehringer Ingelheim and is commercially marketed as Mobic, along with other trade names. It is an analgesic from the aspirin family[1].

It is obvious how to manage pain, fever, and inflammation; this may be done by preventing prostaglandin formation and cyclo-oxygenase enzyme activity. Meloxicam prevents the enzyme cyclooxygenase (COX) from prostaglandins at the first stride resulting from converting arachidonic acid into prostaglandin H/2, which is the first move in the formation of prostaglandins, which are mediators of inflammation [2]. It has been demonstrated that meloxicam specifically suppresses COX-1 and COX-2, particularly in instances of rheumatoid arthritis [3].

The immune system causes the chronic inflammatory arthritis known as rheumatoid arthritis (RA) Jena, et al. [4] and Firestein and McInnes [5]. Babaahmadi, et al. [6]. The majority of the time, it parallels both sides of the peripheral synovial joints [7].

This is distinguished by a clinical course that lasts longer than usual, exhibits relapse and progression, and is linked to a systemic illness characteristic. Epidemiology Rheumatoid arthritis now affects 1% of adult population, which is a huge rise. Anti-inflammatory medications and analgesics can be used together to treat the painful condition of arthritis (this is the optimum course of treatment) [8]. Meloxicam is present in synovial fluid at concentrations between 40% and 50% of those seen in plasma. This is as a result of the synovial fluid's reduced albumin level when compared to plasma. It may perform very well in the treatment of osteoarthritis in animal models due to the significance of its penetrance [9, 10].

Pronounced immune response mediators, including T and B leukocytes, which are secreted as immune activity precursors, are suitable for important acute inflammatory disorders and therefore transition to chronic inflammation, like rheumatoid arthritis. meloxicam are thought to have a direct and exclusive impact on a variety of cellular mediators and reaction pathways, which causes osteoporosis, osteoarthritis, and soft tissue inflammation [11].

By suppressing cyclic antioxidant enzymes (such COX-1 and COX-2), this medication has therapeutic benefits as an anticancer and neuroprotective agent [12] indicating risks associated with the gastrointestinal tract and other essential organs within the scope of the speculative study, such as Liver and kidneys, to determine the scope of possible future damage [13].

Several researchers found that in rats, the content of propionic acids such as Mobic in plasma and tissues was higher in liver tissue, as it is metabolized there [14, 15].

2. Lab Animals

The current study will investigate by treating 24 male albino rats (Rattus rattus) with an age of more than eight weeks and weights ranging from (230-250) grams obtained from the animal house of the College of Science, University of Kufa. After that, their health was examined, as well as ensuring that the aggregates were distributed in proportion to the research line, and the mice were placed in plastic cages, and plastic cages were provided with metal covers, 48 cm long and 15 cm wide. and 7 cm high [16].

Adding and replacing sawdust three times a week to ensure a suitable environment for the cage floor and to ensure moisture control. Therefore, taking care of them is by cleaning the hatchlings and giving them a special diet. Plastic bottles can be used to make watering difficult with a cork fitted with metal tubes.

Mice are placed in appropriate laboratory conditions in terms of temperature 20-25°C, light/dark cycle 10/14, ventilation rate/hour 10-15, and relative humidity (30-70) %.

The doses of Meloxicam 0.2 mg/kg that are supposed to be given are obtained as follows:

1. The first group consisted of 6 rats, 3 of which were given 1 ml of saline per day as a control group.
   3 Give 0.2 mg/kg Meloxicam daily for 15 days
2. The first group consisted of 6 rats, 3 of which were given 1 ml of saline per day as a control group.
   3 Give 0.2 mg/kg meloxicam daily for 30 days
3. The first group consisted of 6 rats, 3 of which were given 1 ml of saline per day as a control group.
   3 Give 0.2 mg/kg meloxicam daily for 45 days
4. The first group consisted of 6 rats, 3 of which were given 1 ml of saline per day as a control group.
   3 Give 0.2 mg/kg meloxicam daily for 60 days

3. Statistical Analysis

Consider the t-test as the function that shows the relationship between values. Consider the SPSS program for conducting statistical analyses (version: Statistical Package for the Social Sciences, version 23.0, SPSS Inc., Chicago, Illinois, USA). 0.05 was considered statistically significant to express the P value.

4. Result

4.1. Testis Function Test

4.1.1. Effect of Interactions of Oral Administration of Different Concentrations of Mobic on Testosterone, LH and FSH (ng/ml) in Male Rats

The results displayed a significant increase ($p<0.05$) in FSH (Follicle-Stimulating Hormone) levels (360±0.29, 523.00±0.32, 539.50±0.22, 634.2±0.29) ng/ml while the LH (Luteinizing hormone) levels significant decrease (99.5±0.32, 160.35±0.22, 158.00±0.32, 138.1±0.32) ng/ml concentrations respectively, whereas; the testosterone levels showed a significant increase ($p<0.05$) (0.48±0.29, 0.76±0.4, 1.44±0.32 and 1.69± 0.19) ng/ml after oral

administration of concentrations 50,100,150 and 200 mg/kg/day of aspirin compared with control groups (500.2±0.32, 431.66±0.4, 500.5±0.29, 569.4±0.32) (163.5±0.22, 145.6±0.29, 122.25±0.29, 140.4±0.22) and (0.51 ±0.3, 1.01±0.22, 2.95±0.39, 3.11±0.1) ng/ml. Table 1 shows the effect of meloxicam on the levels of testosterone, LH and FSH in the blood plasma.

Table 1. The effect of meloxicam on the levels of testosterone, LH and FSH in the blood plasma.

Groups		FSH nglml	LH nglml	Testosterone nglml
I	Control	500.2±0.32	163.5±0.22	0.51± 0.3
	Experiment	360±0.29	99.5±0.32	0.48±0.29
II	Control	431.66±0.4	145.6±0.29	1.01±0.22
	Experiment	523.00±0.32	160.35±0.22	0.76±0.4
III	Control	500.5±0.29	122.25±0.29	2.95±0.39
	Experiment	539.50±0.22	158.00±0.32	1.44±0.32
IV	Control	569.4±0.32	140.4±0.22	3.11±0.1
	Experiment	634.2±0.29	138.1±0.32	1.69±0.19

Figure 1 shows the effect of interactions of oral administration of different concentrations of Mobic on testosterone with different periods.

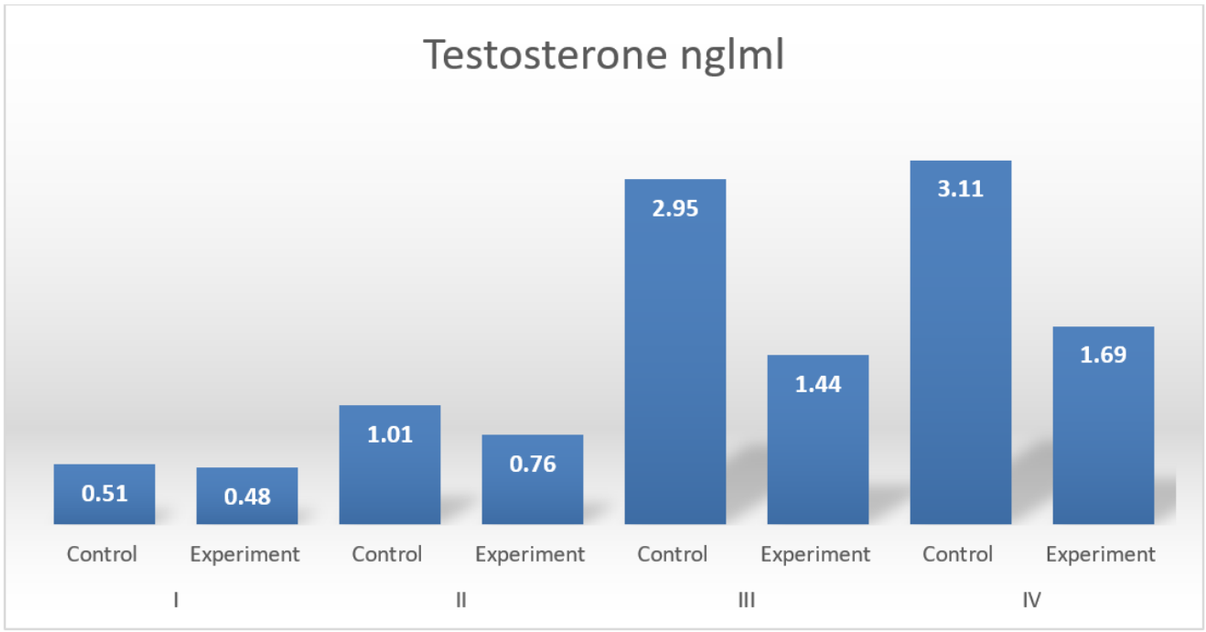

Figure 1. The effect of interactions of oral administration of different concentrations of Mobic on testosterone with different periods.

Figure 2 shows the effect of interactions of oral administration of different concentrations of Mobic on LH with different periods.

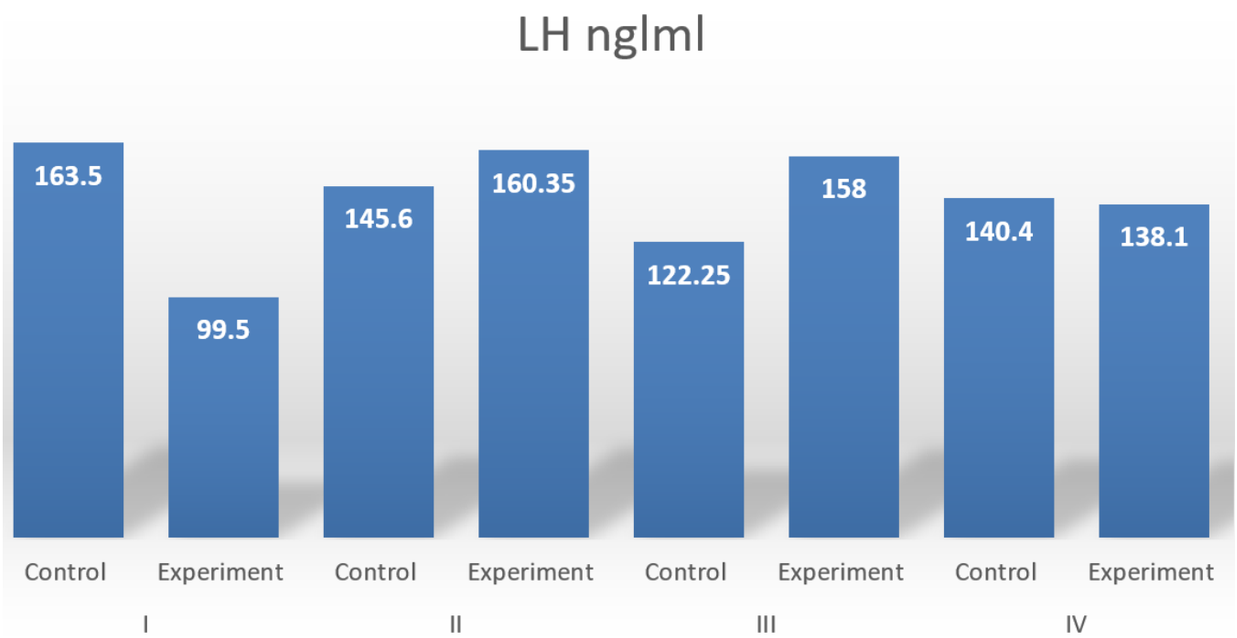

Figure 2. The effect of interactions of oral administration of different concentrations of Mobic on LH with different periods.

Figure 3 shows the effect of interactions of oral administration of different concentrations of Mobic on FSH with different periods.

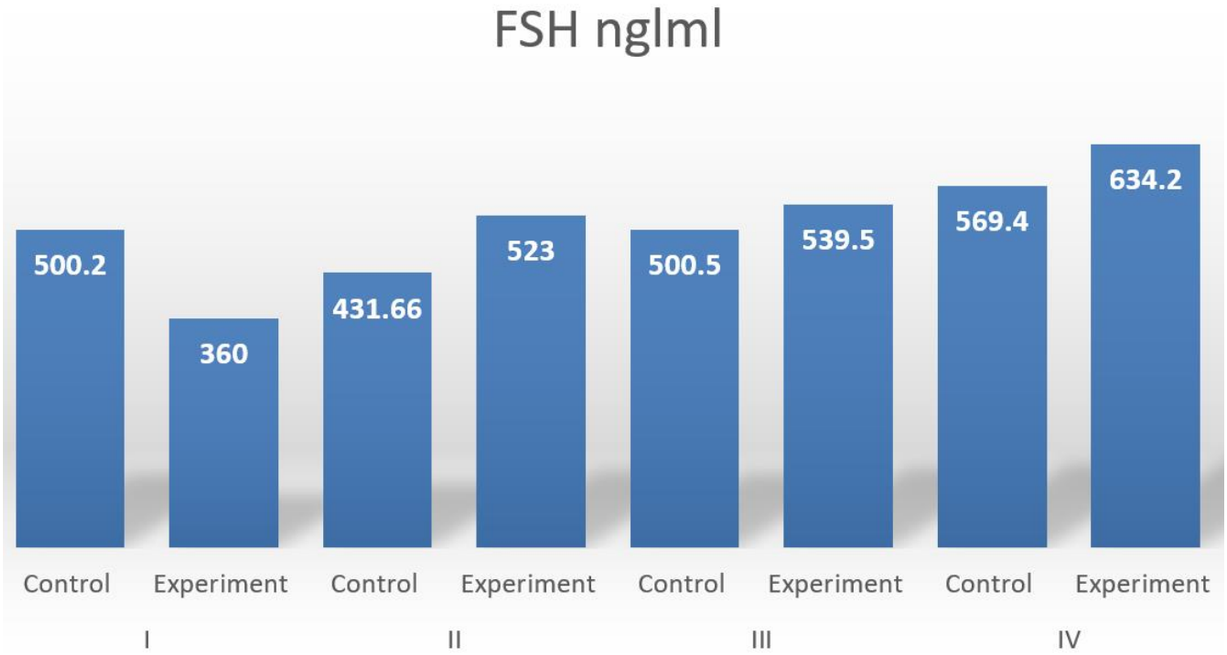

Figure 3. The effect of interactions of oral administration of different concentrations of Mobic on FSH with different periods.

5. Discussion

The results of the current study showed a significant decrease ($p \leq 0.05$) in the level of testosterone, LH, and FSH in the serum of rats treated with MOBIC for different periods, and this effect increases with increasing the exposure period, and this result is consistent with many studies indicating the ability of this drug to have this effect.

Studies have shown that this drug causes an abundance of smooth endoplasmic reticulum in the cytoplasm of Leydig cells, developed Golgi complexes, and many mitochondria. Where they undergo beta oxidation, which leads to the generation of metabolic energy in the form of ATP (Adenosine triphosphate) that cells need to perform their functions, which affects the measurement of testicular shape and the function of both Sertoli and Leydig cells [17, 18]. presents ultrastructural changes and various maturation defects in the process of spermatogenesis from germ cells. Varicocele histology shows that all cell types and testicular compartments can share the effects of varicocele on Leydig cells indicative of hyperplasia [19].

Importantly, in this study, the increase in the number of potential Leydig cells is relative to a reduction in the size of the seminiferous tubules causing impairment of spermatogenesis and this may result in a decrease in the size of the tubules. Another explanation is that the function of the Leydig cell in testosterone production is impaired. Reducing testosterone may then increase LH levels and this may cause true Leydig cell hyperplasia [20].

In addition, a fundamental enzyme in the biosynthesis of prostaglandins (PGs) is cyclooxygenase-2 (COX-2), which is primarily found in testicular interstitial cells (Leydig cells) [21]. PGF2α is hypothesized to act through the PGF2α receptor present in Leydig cells and a negative feedback mechanism involving the down-regulation of StAR (a transporting protein involved in regulating cholesterol transport into the inner mitochondrial membrane) and 17β-HSD (an enzyme that converts androstenedione to testosterone), leading to the inhibition of LH-stimulated testosterone production [19].

The harmony of acting in testicular α-PGF2 system with the prime upshot of gonado-tropins on the axis of hypothalamic-pituitary has the vote of local inhibitory control of steroidogenesis in the rat [22] actually during diagnoses no alterations morphological or obvious abnormality along with no COX-2 was detected in human testicular biopsies, it is referred in the testes of men with weakened spermatogenesis and infertility cases. COX is also causing inducing in testicular cancer. Furthermore, COX-2 referred to potential weighty factor in the slimming age-related testosterone production Because increased COX-2 expression in rats during aging, concomitantly with decreased testicular fabrication of testosterone was recently described. In this context, inhibition of COX-2 enhances steroidogenesis and StAR. gene expression in mouse Leydig MA-10 cells, whereas the Over-expression leads to opposite side [23].

the current of vanquishing of testosterone and finally a severe progressively worse and in the process of spermatogenesis were observed due to the significant drop in the Leydig cells number [24]. This decreasing in the number of Leydig cells leads to a marked inhibition of COX-2 expression and elevated production of PGF2α leading to meloxicam treatment of mice and according to previous histological studies documented a significant decrease in the number of Leydig cells compared to animals administrated with saline [25].

Therefore, such a significant decrease in the number of Leydig cells results in marked inhibition of COX-2 expression and no increased production of PGF2α which leads to inhibition of testosterone and finally deterioration of spermatogenesis. Also, the decrease in testosterone restores the negative effect of testosterone on the pituitary gland relative to the normal level gradually, which eventually leads to an increase in the production of LH from the pituitary gland, and this may in turn reduce the hyperplasia of Leydig cells, because the decrease in testosterone due to a defect in Leydig cells in the testis may cause an increase in LH levels may cause true Leydig cell hyperplasia [26].

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