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THE EFFECT OF PARACETAMOL ON SOME FUNCTIONS OF THE MALE REPRODUCTIVE SYSTEM IN SWISS ALBINO MICE

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ABSTRACT

The study was conducted in the animal house belonging to the College of Veterinary Medicine / University of Mosul to reveal some of the side effects associated with the administration of paracetamol on male fertility, through the use of (15) male Swiss white mice of the Balb/c strain, aged three months. The animals were randomly allocated to three groups, two of which received 0.40-0.80 mg/kg body weight, while the other was given 0.9% saline solution as their treatment. Animals were weighed before and after treatment and at the time of necropsy, the weight of the testes and the epididymis was measured. The study revealed that there was a significant reduction ($P<0.05$) in the weight of the body, organs following drug administration and also in the number of sperm in the testis, head and tail of the epididymis, percentage of live sperm in the testis, head and tail of the epididymis, and also in the concentration of serum testicular lipoprotein hormone after the treatment with the drug. However, the head and tail of the epididymis showed that significant increases in spermatocytes and abnormalities of the spermatid cells occurred after injection of the same concentration of the drug as was present in the control group. From these results, it can be inferred that the drug had some detrimental and negative effects on fertility parameters of male mice.

Keywords: Paracetamol, Testosterone Concentration, Fertility, Males, White Mice

1 INTRODUCTION

Paracetamol (Acetaminophen), chemically known as N-acetyl-p-aminophen, is a broad-spectrum medication used to treat headaches and various body aches and pains. It is also widely used to treat severe colds and flu, as it is a fever reducer and pain reliever. It is available without a prescription, but its long-term use is considered toxic (1,2). Its chemical structure contains a phenol ring, which is similar to that found in the hormone estradiol, in addition to containing an acyl group similar to that found in the hormone progesterone (3). The primary action of the drug is to inhibit prostaglandins and thus inhibit oxidation enzymes (Cyclooxygenase-1 and 2) through the peroxidase function of these enzymes. These enzymes play a role in reactions that lead to the reduction of glutathione formation and thus the generation of oxidative stress (4). Many studies have shown that taking high doses of the drug for long periods can cause damage to organ cells, including those of the liver, kidneys, testes, and epididymis, etc. However, when using

specific therapeutic doses of the drug, it is rapidly metabolized in the liver by conjugation with glucuronic acid and sulfate. A small portion of it is oxidized by cytochrome P-450 2E-1 to give a highly active intermediate metabolite that is extremely cytotoxic (N-acetyl-P-benzoquinoneimine) (NAPQ). It rapidly binds to hepatic glutathione to form a water-soluble, low-toxicity compound called mercapturic acid. It also binds to some antioxidants, such as vitamins E and C, and other chemical compounds like quercetin (5). Despite its apparent therapeutic efficacy, there is growing evidence of its side effects (6).

Another study showed that injecting male mice with a dose of (0.05) mg/kg of paracetamol for fourteen days caused a significant decrease in serum testosterone levels (7)., Oyedeji et al. (2013) also indicated that administering the drug to male albino mice for 42 days resulted in a decrease in sperm count and motility. However, some studies have shown the toxic effect of the drug on reproductive health, as taking it regularly throughout life leads to a decrease in sperm quality and also affects testicular function (1). Hence, the present study is aimed at investigating the sub-lethal doses of Paracetamol (0.40 and 0.80 mg/kg) on male reproductive performance in Swiss albino mice (Balb/c). This study focuses specifically on the dose-dependent effect of Paracetamol on body and reproductive organs weight (testes, epididymis and seminal vesicle), sperm viability, sperm morphological abnormalities and serum testosterone level after 60 days of treatment.

2 MATERIALS AND WORKING METHODS

2.1 First: Preparation of Laboratory Animals

The study included (15) sexually mature, three-month-old male white mice of the Mus musculus (Balb/c) strain. These mice were placed in the animal house of the College of Veterinary Medicine, University of Mosul, where suitable laboratory conditions were provided, including a 12-hour light/12-hour dark cycle and a temperature of 23-28°C, along with a special animal diet, The males were divided into three groups of (5) males each. The first group was the control group, which was given 0.9% physiological saline solution. The other two groups were used to study the effect of paracetamol, which was administered orally via a mouth tube to all experimental animals every other day for 60 days

2.2 Second: Preparing Paracetamol Drug Concentrations

Two concentrations of the drug were prepared for the current research, including (0.40-0.80) mg/kg, after extracting the LD50 (Lethal Dose Fifty) of 100 mg/kg. Based on this, the drug was obtained from the Samarra Pharmaceutical Factory.

2.3 Third: Measuring body and organ weights

Body weight was measured before and after dosing, and the organs targeted for the experiment were weighed after dosing and recorded according to the prescribed intervals, using a medical scale.

2.4 Fourth: Measurement of the level of testosterone in the blood serum.

Chloroform was used to anesthetize the animals and blood was obtained directly from the heart-by-heart puncture. 2ml of blood was drawn and placed in a test tube. It was then centrifuged and the serum was collected and stored at 20-°C. The hormone was then quantified by the method of Mohammed (2010) using Mini Vides device. The Testosterone Kit was supplied by the French company BioMerieus, which is based on the principle of competition between the Enzyme Immune Assay.

2.5 Fifth: Studying the characteristics of sperm

The animals were dissected and the testes, epididymis and seminal vesicles were removed, the fat attached was removed and they dried with filter paper. Then the testes and epididymis were transferred to a physiological salt solution 0.9% to calculate the sperm parameters, head and tail, respectively.

2.6 Count of the living and dead sperms in the testicles:

A sharp syringe was used to remove the sperm from the severed testes and nigrosin-eosin stains were used to stain them. The sperm were then counted at (40x) and the measured percentage of live sperm was derived from the staining of only the dead sperm as per the following equation: (Zeneveld and Polakoski, 1977).

$$\text{Percentage of live sperm} = \frac{\textbf{Number of live sperm}}{\text{Total number of sperm counted}} \times 100$$

2.7 Count the live and dead sperm in the epididymis.

This was previously discussed in the extraction of the percentage of live sperm, as in the testicle.

2.8 The malformations of sperms

Prepared slides containing live and dead sperm were used to study spermatogenic abnormalities, which included, according to the cytoplasmic droplet equation, abnormalities in the head, midpiece, tail, and location of the cytoplasmic droplet(Hinting, 1989):

$$\text{Percentage of live sperm} = \frac{\textbf{Number of abnormal sperm}}{\text{Total number of sperm counted}} \times 100$$

2.9 Measurement of testosterone hormone concentration in the serum

The concentration of testicular fat hormone was measured using the Enzyme-Immunosorbent Assay (ELISA) method, using a measurement kit with a wavelength of 450 nanometers.

2.10 Statistical analysis

The results were statistically analyzed using the SPSS test with the ready-made statistical program to find the rates and significant differences, Analysis of Variance (ANOVA) Least significant differences (LSD) for the criteria included in the study. (11).

3 RESULTS

3.1 The effect of paracetamol on body weight, testicular, head and tail of the epididymis, and seminal vesicle

The results of the current study shown in Table (1) showed a significant decrease (P< 0.05) in body weight, testis, head and tail of the epididymis and seminal vesicle with the effect of oral dosing with the second concentration of paracetamol drug, higher than the first concentration, compared to the control group.

Table 1: The effect of paracetamol on the weights of: body, testis, epididymis, and seminal vesicle

	Control group,	**Dosage group (0.40 mg/kg)**	**Dosage group (0.80 mg/kg)**
Body weight /g	26,07± 1,80	24,03±2,51	19,58± 1,82
Testicular weight mg/100g	286,8± 7,78	273,4 ±8,44	228,23±9,42
Head of epididymis weight mg/100g	65,37± 2,02	63,16±2,11	50,6±2,14
Tail of epididymis weight mg/100g	44,29±1,36	37,06±1,11	31,00±1,37
seminal vesicle weight mg/100g	252,73±7,54	245,7±6,81	178,27±2,60

3.2 The effect of paracetamol on the percentage of live sperm in the testis and the head and tail of the epididymis

The statistical results obtained from the present study revealed that after administration of 2nd concentration of paracetamol a significant decrease in live sperm was observed in the testis and in the head and tail of the epididymis compared with the control group more than the 1st concentration of paracetamol. There was a slight effect on the first concentration compared to the control group.

3.3 The effect of paracetamol on the percentage of malformed sperm in the head and tail of the epididymis

The findings of the study revealed that there was a significant increase (P<0.05) in the percentage of malformed sperm in the head and tail of the epididymis of the male mice after they were administered with the second dose of paracetamol. These percentages, however, did not differ significantly between the first concentration and the control group or between the second concentration compared to the control group. Significant differences were also observed.

Table 2: The effect of paracetamol on the percentages of live sperm in the testes, head and tail of the epididymis, and malformed sperm from the head and tail of the epididymis

	Control group,	Dosage group (0.40 mg/kg)	Dosage group (0.80 mg/kg)
Percentage of live sperm in the testes	95,62 ± 0,81	82,86 ±1,82	75,94 ± 3,60
Percentage of live sperm from the head of the epididymis	95,2 ± 0,80	84,63 ± 1,85	82,86 ± 1,86
Percentage of malformed sperm from the head of the epididymis	9,41± 0,54	15,16± 1,08	16,18±1,04
Percentage of live sperm from the tail of the epididymis	96,93± 0,55	86,4±2,07	84,53±1,95
Percentage of malformed sperm from the tail of the epididymis	9,2± 0, 48	13,64± 0,97	15,61±1,08

3.4 The effect of paracetamol on the concentration of testicular fat hormone in the serum

The results of administering paracetamol at two concentrations showed a significant decrease ($p < 0.05$) in serum testosterone levels in mice compared to the control group. The second concentration of the drug resulted in a greater decrease than the first.

Table 3: Effect of paracetamol on the concentration of testicular fat hormone in the serum

	Control group,	Dosage group (0.40 mg/kg)	Dosage group (0.80 mg/kg)
Testicular fat hormone concentration ng/ml	0,59 ± 0,054	44,39 ±1,37	0,19 ± 0,03

4 DISCUSSION

4.1 The effect of paracetamol on the weights of: body, testis, head and tail of the epididymis, and seminal vesicle

The results of the current study showed a decrease in body weight in the drug-injected groups compared to the control group. The recorded decrease in body weight was consistent with what was indicated by (12), which showed that there are several possible variables that could explain the decrease in body and organ weight when injected with the drug, The reason may be due to disturbances in the digestive tract, resulting in a decrease in the rate of feed consumption, which causes indigestion or loss of appetite.

In the study (13), male mice were used, and some studies have demonstrated the potential for high doses of paracetamol to cause upper digestive tract disorders and stomach bleeding. Our study is consistent with what Tuan (2021) indicated, that the observed decrease in testicular and epididymis weights may explain the treatment of male mice with the drug, which causes a disruption in the basic building block (structural and functional unit) of both the testis and epididymis. This can lead to the diameters of the seminiferous tubules in the testis becoming smaller and the diameters of the epididymis tubules becoming smaller, and lead to increased number of epithelial cells in the head of the epididymis. The decrease in testicle weights in male mice treated with the drug may be explained by the activity of the anterior lobe of the pituitary gland, which may inhibit (ICSH and FSH) the drug to suppress the secretion of gonad nutrients, causing testicular atrophy and a significant decrease in its weight. A subsequent study added that the use of high doses of the drug may hinder or negatively affect normal reproductive performance due to its anti-gonadal nutrients action and that it inhibits biosynthesis. In the case of prostaglandins, the fat in testicles has been shown to have some effect on the growth of the seminal vesicles, vas and epididymis in male embryos, while testicular fat, testicle, scrotum and penis growth are influenced by dihydrotestosterone (15;16).

4.2 The effect of paracetamol on the percentage of live sperm in the testis and the head and tail of the epididymis

Administering varying and high doses of paracetamol to male mice resulted in a decrease in the percentage of live sperm in the testis and the head and tail of the epididymis, as well as a reduction in the activity of the remaining sperm. Our study is consistent with the findings of Sulaimon et al. (2019), They found that high doses of the drug, when administered to mice , led to a reduction in the number of sperm and a decrease in the motility of many of them. This also agreed with (Banihani) (2018) regarding the significant decrease observed in motility (living to dead), However, I disagreed with them that the percentage of live sperm did not change significantly. This may be due to the decrease in the ICSH and FSH levels, resulting from the effect of a concentration of (0.65) mg/kg of the drug in inhibiting the anterior pituitary secretion and subsequently inhibiting the production of testicular fat from interstitial cells (Leydick cells), These effects may have been accompanied by the destruction of testicular tissue due to oxidative stress caused by injection at that concentration of the drug, which may have been able to penetrate the testis through the blood-testicular barrier that ensures a relatively stable environment for the complex mitotic processes in the seminiferous tubules, thus leading to changes in the microscopic internal environment of those tubules. Bin-Meferij & El-Kott (2015) stated that the decrease in sperm motility results from the use of chemical drugs that have the ability to diffuse across the blood-testicular barrier, resulting in subtle differences in the environment of the inner parts of the seminiferous tubules compared to the outer parts of the tubules. added (William, 2000) that paracetamol caused a significant increase in the percentage of abnormal sperm cells and a significant decrease in sperm motility.

He attributed this to the drug's effect on spermatogenesis within the seminiferous tubules of the testis, or to its effect on the functional performance of the epididymis, which was also reflected in spermatogenesis.

4.3 The effect of paracetamol on the percentage of malformed sperm in the head and tail of the epididymis

The results of our study confirmed a significant increase in the percentages of deformed sperm, and this was consistent with what Oyediji et al (2013) indicated, This also agrees with Luangpirm et al. (2012), who indicated that there was a significant increase in the percentage of malformed sperm. These malformations included the presence of cytoplasmic droplets on the midpiece, twisted and coiled midpieces, detached heads, and twisted tails, which were also recorded in the current study. Other malformations were also observed, such as asymmetrical heads, broken midpieces, broken tails, and tail loss, Researchers have indicated that these abnormalities occur during the sperm maturation stage, specifically within the epididymal tubules. The increased percentage of malformed sperm may be attributed to impaired epididymal function resulting from a significant decrease in testicular lipid levels in the serum of male mice treated with the drug. Klein et al (2020) also noted a significant increase in the occurrence of sperm abnormalities, This is due to the epididymis deviating from its normal functions, which are to secrete many substances necessary to protect sperm, mature it, and increase its efficiency and ability to fertilize. These functions are regulated by androgens secreted from Leydeck cells, especially testicular fat. Since the level of the latter has decreased significantly under the inhibitory effect on the secretion of gonadal nutrients resulting from the injection of the drug, the percentages of deformed sperm will increase significantly.

4.4 The effect of paracetamol on serum testosterone levels

Our study agrees with what Naznin et al (2022) indicated: that dosing animals with the drug led to a decrease in testicular fat concentration, and this decrease may be attributed to negative effects. This decrease was achieved through three mechanisms, the first being an indirect effect through its physiological action on the anterior lobe of the pituitary gland to inhibit the secretion of reproductive nutrients and thus reduce the level of biosynthesis of testicular fat. The second of these mechanisms is the destruction of Leydeck cells under the direct influence resulting from the metabolic oxidation of the drug and the reduction of their numbers in testicular tissues, which negatively affected the hormone level in the serum (NAPQ) of the compound, as it is the main source of its production. The third mechanism is the potential for the drug to directly inhibit the activity of two essential enzymes involved in the synthesis and production of testicular fat: P450 17α-hydroxylase and C17,20 lyase (23).

5 CONCLUSION

The current study concludes that the use of current doses of paracetamol has several negative effects on the male reproductive system, and that the decrease in male fertility may have resulted from its inhibitory effect on the secretion of gonadal nutrients, thus reducing the level of testicular fat production. This, in turn, is associated with oxidative stress and the resulting damage to testicular tissue through a reduction in the diameter of seminiferous tubules, which negatively impacts sperm concentration and increases the percentage of dead and malformed sperm. Therefore, we recommend avoiding the use of high doses of the drug and conducting further studies on its effects on different body tissues, as well as female fertility.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The author declares no conflicts of interest regarding this manuscript.

Statement of ethical approval

The Ethics Committee of the Department of Biology, College of Education for Pure Science, University of Mosul, Mosul, Iraq, reviewed and approved all animal procedures and experimental protocols. All the national and institutional guidelines for care and use of animals were followed.

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