

Effect of Cimetidine on Semen Parameters, FSH and LH in Male Rats

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ABSTRACT

Cimetidine is effective drugs on male reproductive system by its effect on semen characteristic or parameters such as sperm motility, sperm morphology and sperm count, and also cimetidine effect on sexual hormones, were effect on testosterone, FSH and LH. In this investigation, 20 male rats were randomly classified into two groups, Control group (G1): This group contain on 10 male rats receiving normal saline and Cimetidine group (G2): This group contain on 10 male rats receiving 100mg/kg. B.W. from cimetidine group, during the period 38days from (20. Novmber.2022 to 28. Desmber.2022), after end from study animals slaughtered, then, seminal samples were taken from the epididymis, as well as blood samples, and converted into serum for the purpose of work hormonal analysis. Group treated with cimetidine showed significantly decrease in sperm motility and increase in immotile sperm and also significantly increase in abnormal sperm morphology and decrease in normal, also this study showed significantly decrease in sperm counts. Also this study showed significantly decrease in level of testosterone and FSH, but increase in LH, it can be concluded that Cimetidine exerted a significant harmful effects on semen characteristics and sexual hormones.

KEYWORDS: Cimetidine effect , semen analysis , Testosterone , FSH, LH

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INTRODUCTION

Cimetidine is a potent competitive H₂ receptor blocker; it is extensively approved for peptic ulcers (1). Cimetidine is a prophylactic drug for colorectal cancer, in addition treatment of Zollinger – Ellison syndrome, heart burn, oesophagitis, upper gastrointestinal bleeding and paracetamol overdose (2,3).

Parker *et al.* (1984)⁴ and Van Theil (1982)⁵ reported the sexual dysfunction after cimetidine treatment. Franca *et al.*, (2000)⁶ and Winters *et al.* (1979)⁷ recorded the antiandrogenic effects of cimetidine in Iraq, like other countries, cimetidine is wildy used usually in clinics and in hospitals, which approved in chronic diseases program without caution to their harmful effects for long-term treatment (8). Moreover, these medications may impair sperm maturation and epididymal function (9).The Food and Drug Administration (USA) has given the drug cimetidine approval to treat stomach acid secretion. It is used to treat hyper secretory disorders such Zollinger-Ellison syndrome, numerous endocrine adenomas, erosive gastroesophageal reflux, and peptic ulcer symptoms (10). The release of

stomach acid brought on by food, histamine, pentagastrin , caffeine, and insulin is considerably reduced by cimetidine. It competes with DHT receptors in the pituitary gland, brain, and other organs that need DHT since it is an H₂ receptor antagonist, in accessory glands, such as the prostate and seminal vesicle gland, DHT, a sterol that is produced when testosterone (T) is converted, performs the role of the so-called true male hormone. The term "weak nonsteroidal anti-androgen" is used to describe it (11).

Cimetidine has been shown to have significant immunoregulatory and anticancer effects, which furthered the therapeutic use of the compound (12, 13). Cimetidine's pharmacological activity is broad since it is extensively dispersed in many types of tissue Male patients on cimetidine have experienced side effects such impotence, reduced sperm count, and libido loss (14). Nevertheless, it has been noted that this medication has negative effects on males that are associated with its antiandrogenic activity, including impotence, gynecomastia, changes in the serum testosterone levels, and a drop in sperm concentration (14,15). Cimetidine lowers blood testosterone levels in animals (16,17), which is

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linked to Leydig cell death and decreased steroidogenesis (16). Loss of germ cells and Sertoli cell death have both been linked to this androgenic dysfunction (17-20). The aim of this study is to find out the extent of the virulence of cimetidine on the male reproductive system.

MATERIALS AND METHODS

Animals

This study was conducted in the department of physiology and pharmacology University of Tikrit College of Veterinary Medicine. Male adult rats in good health were obtained from the Tikrit University College of Veterinary Medicine's animal house.

In this investigation, 20 male rats were, age ranging from 8-10 weeks and weight from (200 to 280) grams. These animals were maintained in an air-conditioned room with a temperature range of (20 - 25) degrees and a 12-hour daily light cycle. The animals were kept in (46*28*13) cm. plastic cage enclosures. Food was provided in the form of freshly made ration pellets. Care was made to avoid any extra stress. Once every week, the cages were cleaned. The rats were housed for at least two weeks before being (adaptation period).

Ethical approve OR data collection permit

Trials, including laboratory rats, in animal house of the College were followed-up by the academic board of the Department of Physiology, Biochemistry, and Pharmacology at the University of Tikrit Veterinary Medicine College

Study design

The study was worked in the animal house of the Veterinary Medicine College\ Tikrit University during the period 38 days from (20. November.2022 to 28. Desmber.2022), 20 male rats were randomly classified into two group 10 male rats to each group.

1. Control group (G1): This group contain on 10 male rats receiving normal saline for 38 day.

2. Cimetidine group (2): This group contain on 10 male rats receiving 100mg/kg. B.W. from cimetidine

Preparation of cimetidine solution: -

Cimetidine stock solution was made by dissolving 100% pure cimetidine product in distilled water. This solution was then administered to rats through stomach tube one time daily at a dose of 100 mg/kg B.W (20). Individual adjustments were made to the dosage of the provided solution based on body weight.

Sperm function test. (sperm motility, sperm morphology and sperm count):-

Semen collection: -

Animals were slaughtered after the course of therapy, and an abdominal incision was made. The testis and epididymis are removed, cleaned from the accessory connective and adipose tissues, the analyses were achieved in

diagnostic lab in animal house in collage of veterinary medicine/Tikrit university.

A. Sperm motility and immotility: -

For analysis of sperm motion, collect samples from cauda epididymitis, (21) then making slicing by surgical blade to diffusion with a solution and making mix, then take drop of the sample and placed on the slide and then cover slide, to be examined under microscope on power(10X and 40X). The percentage motile sperm, which is defined as the number of motile sperm/total number of sperm x 100.

B. Sperm morphology: -

The aberrant sperm morphology was assessed using Siegmund's approach from 1979. Two smears of each sample were created on microscope slides by first preparing a drop of sperm suspension, placing it over the edge of the slide, and adding a drop of Eosin-Nigrosin stain. Examining the smears for unusual morphology Abnormal sperm morphology was calculated as in the following equation:

Percentage of morphologically abnormal sperms = (No. of morphologically abnormal sperms/Total sperms no.)×100. According to the sperm abnormalities, such as tapering head, tailless head, coiled tail, bifurcate tail, and broken tail, the morphologically abnormal sperms were calculated (20).

C. Sperm count: -

According to (Yuxin Ma, *et al.*, 2011)²², sperm count was performed. Use a Haemocytometer (Neubauer Type). Sperms were counted in 25 tiny squares of the chamber that were divided into 5 l of a sperm suspension and covered by a cover slide in the Haemocytometer.

The following formula was used to estimate the amount of sperm:

Sperm concentration = Number of sperm X 1000.

Estimation of Sex Hormones (Testosterone, FSH and LH): -

Blood collection: -

After the end of the experiment, animals were anesthetized by chloroform, blood samples were obtained via eye puncture and heart after anatomy from each anesthetized animal using disposable syringes. Samples were centrifuged at (2500 rpm) for 15 minutes, and then serum samples were stored in freezer at (-18c) untill use.

Hormonal assessment (Testosterone, FSH & LH): -

Sex hormones were measured by Enzyme Linked Immunosorbent Assay (ELISA) (Bio Check Company, USA).

Statistical analysis:

The statistical analysis made use of the ANOVA Analysis of Variance. The significant differences were discovered at a significant level ($P \leq 0.05$) in accordance with Duncan's multiple ranges. (23).

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RESULTS

This study showed significantly decrease ($p \leq 0.05$) in sperm motility, normal sperm morphology and sperm count in group

treated with cimetidine after 38 days from give drug compare with control group, but also showed increase ($p \leq 0.05$) in immotile sperm, abnormal sperm morphology.

Table 1: - Effect of Cimetidine 100mg/kg B.W. on sperm motility in adult male rats.

Parameters Groups	Motility (%)	Immotility (%)
G1(Control)	89.0000000 ± 1.7320508 A	11.0000000 ± 1.7320508 D
G2(Cimetidine 100mg/kg B.W)	58.0000000 ± 2.0000000 D	42.0000000 ± 2.0000000 A

A statistically significant difference appears in the same row at a significant level at $P \leq 0.05$

Table 2: - Effect of Cimetidine 100mg/kg B.W. on sperm morphology in adult male rats.

Parameters Groups	Normal (%)	Abnormal (%)
G1(Control)	89.0000000 ± 1.7320508 A	11.0000000 ± 1.7320508 D
G2(Cimetidine 100mg/kg B.W)	43.3333333 ± 2.8867513 E	56.6666667 ± 2.8867513 A

A statistically significant difference appears in the same row at a significant level at $P \leq 0.05$

Table 3: - Effect of Cimetidine 100mg/kg B.W. on sperm counts in adult male rats.

Parameters Groups	Sperm count (%)
G1(Control)	8.2666667 ± 0.3605551 A
G2(Cimetidine 100mg/kg B.W)	5.9000000 ± 0.3605551 D

A statistically significant difference appears in the same row at a significant level at $P \leq 0.05$

Estimation of Sex Hormones

This study showed significant decrease ($p \leq 0.01$) in level of testosterone and FSH in group treated with cimetidine

compared to control group, but also showed increase in LH level .

Table 4: - Effect of Cimetidine 100mg/kg B.W. on testosterone level in adult male rats.

Parameters Groups	Testosterone (ng/ml)	FSH (mIU/ml)	LH (mIU/ml)
G1(Control)	4.650 ± 0.572 A	42.07 ± 3.79 A	24.92 ± 0.320 D
G2(Cimetidine 100mg/kg B.W)	2.160 ± 1.80 C	25.61 ± 4.76 C	69.53 ± 0.363 A

A statistically significant difference appears in the same row at a significant level at $P \leq 0.01$

DISCUSSION

Cimetidine showed to has side effect on semen quality especially when used at high concentration and effect on sperm parameters (24). This study demonstrated a decrease

in motile sperm and an increase in immotile sperm in the cimetidine-treated group compared to the control group. It is possible that this is because cimetidine inhibits c.AMP, which in turn causes the adenylyl cyclase c.AMP dependent protein

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kinase-C to reduce the amplitude of flagellar waves and the frequency of flagellum beats by reducing the number of (25). In spermatozoa of CMTG, there was a noticeable rise in flagellum anomalies, particularly tail looping or bending. These alterations have been noted in spermatozoa with absent or very little motility (26). This study showed decrease in number of sperm in group treated with cimetidine compared with control group, this result is agreement to (11). the result agree with (27,28) mentioned that cimetidine had an inhibitory effect for LDC4 enzyme and lead to delay the spermatogenesis, spermiogenesis and finally reduce sperm concentration. Conti et al. (1981)²⁸ and Hoie et al. (1994)²⁹ reported the ability of cimetidine to inhibit DNA synthesis, and lead to cessation of spermatogonial development and delay spermatogenesis Cimetidine inhibits testicular structure and steroidogenesis, as shown in earlier research (30), leading to poor testosterone bioavailability and dysfunctional androgenic epididymis (17). This research revealed Similar to(14), who noted that cimetidine therapy raises GnRH levels, which were linked to the involvement of LH negative feed back mechanism impairment in the response of LH to luteinizing releasing hormone, was the decrease in testosterone and FSH levels (LH-RH). Moreover, the disruption of the LH negative feedback system results in increased LH production, which alters LH testosterone secretion (31,32). According to Luiz et al. (2000)³³, using cimetidine causes the growth of the adrenal glands. Nonetheless, this study also revealed a gradual, substantially higher level of FSH and testosterone in the groups treated with OLE; this outcome is comparable to (34, 35).

CONCLUSION

According to this study, administering Cimetidine has harmful on male reproductive system in rats, at a dose of **100mg/kg B.W** for 38 days through its influence on sperm parameters(sperm motility, morphology and counts) and sex hormones (testosterone, FSH and LH).


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Conflicts of interests: The authors declare that there is no conflict of interest in the publication of this paper.

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Article Highlights:

- I. cimetidine on the reproductive system of male rats comparison between 2 groups.
- II. This paper attempts to study the effect of cimetidine on semen parameters of male rats.
- III. This paper attempts to study the effect of cimetidine on the sex hormones of male rats