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RESEARCH ARTICLE

Study the Effect of Ribavirin Drug on the histological structure of the testes in Albino mice (*Mus musculus*)

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Abstract

The results have gotten from this study was showed that all animals of two experiment groups that inoculated with Ribavirin drug appeared change in the thickness of seminiferous tubule wall of the testes and contraction in them where its appearance became irregularly and crooked as well as observed emergence of Vaculation. Also some sections of the sperm tubules Seminiferous tubule revealed increased in the widening of the distance between the germ cells and ecdysis of the epithelial tissue and aggregation in the cavity of some Seminiferous tubule also the occurrence of degeneration and raised the distance between neighboring Sertoli cells.

Keywords: *Testes, Sertoli cells, Ribavirin, Seminiferous tubules, Leydig cells, Mus musculus.*

Introduction

Recently, humans have been exposed to many pathogens, contaminants and different chemicals, such as food additives or medicines used to treat a particular disease. These drugs are analogues of chemicals naturally present in Biosynthetic pathways. Ribavirin, a synthetic nucleoside is synthesized in its composition as guanosine, with a modification in the base and d-ribose sugar, both of which are so necessary for antiviral activity. Ribavirin contains three mono-, bilateral-, and triple-phosphate metabolic forms these metabolic forms are more effective against many RNA and DNA viruses [1].

Ribafrine is an effective inhibitor of inosine monophosphate dehydrogenase (IMPd), which promotes the conversion of inosinate into xanthylate and has been detected by synthesizing isotopes of compounds involved in pathways of nucleotide Bio-synthesis [2]. Ribavirin has multiple biological features favorable to remedy viral diseases that can directly prevent the recurrence of many deoxyribonucleic acid and RNA viruses. More currently, studies have shown that it can also act as an immune modifier, thereby enhancing T-cell immunity from viral infections [3]. The nucleoside compounds are important groups in the medication of various viral diseases [4]. Isotopes of nucleosides and nucleotides can be used in therapeutic drugs, which include a range of antiviral products used to prevent virus replication in infected cells, after they are phosphorylated and become similar enough to fuse into DNA or RNA strands it can end the chain and stop its elongation, which is not specific to viral DNA.

It also affects mitochondrial DNA [5]. Ribavirin is usually indicated in the treatment of many viral cases in general and for patients with liver disease in particular, including the treatment of viral hepatitis C HCV [6]. It is also referred to in the treatment of viral infections belonging to the

family Flafivirus, a family of viral DNA of races single-stranded and cause widespread spread of viruses transmitted by mosquitoes and ticks and from the races of this viral family and treated with ribavirin, hemorrhagic fever, yellow fever, and viral hepatitis C HCV [7]. The toxic effects of ribavirin have been documented in numerous scientific researches where it has been observed that ribavirin treatment creates a variety of damages in humans and animals, such as respiratory damage [8].

Moreover this compound has damage to the histological and functional structure of the nasal epithelium in human's Nasal epithelium and trachea of monkeys [9]. Ribavirin also causes renal impairment as well as glomerulonephritis associated with viral hepatitis C HCV, mesenteric glomerulonephritis, Mesangioproliferative glomerulonephritis and MPGN Membranoproliferative glomerulonephritis [10].

It is known that drugs stimulate many kinds of side effects in different organs of the body and to protect organs from damage and destruction caused by drug treatments, the study of these effects is very important as the data from the studies have opened new horizons to restore some concepts of chemical compounds involved in the synthesis drugs by studying histological changes in the tissues of organs after taking these medicines [11]. The aim of the present study is to investigate the effect of Ribavirin on the histological structure of testes in white mouse males *Mus musculus*.

Methodology

Animals used in the Laboratory Experiments and Histological Study

In the current study has included 20 male mice were obtained from the Animal House of the Department of biology, College of Education for Pure Sciences, University of Diyala (7-10) weeks. These mice were randomly divided into two groups whose details were as follows: The first group is the control group has involved 5 mice and the second group is the test group and it was included 18 mice, the test group in turn was divided equally into two subgroups (9 mice for each group). Mice of the two subgroups were injected with ribavirin at a concentration of (100 and 200 mg / kg body weight) daily for 45 days. At the end of the experiment, the mice were anesthetized with chloroform, then the animals were explained and the testes were removed from their site. After that samples were then stabilized with formalin solution for 24 hours and then washed with tap water and transferred to 70% alcohol for preservation. Next textures have according to Bancroft and Gamble [12].

The prototypes passed through an ascending series of ethyl alcohol and then placed with xylene for dissolution, then buried with paraffin wax and cut wax molds prepared using a 7 micron rotary microtome. The extracted glass sections were stained using Haemotoxylin and Eosin (H&E) dyes according to [13]. The glass-colored sections of Canada carried a balsam and then the samples were examined and photographed using a digital microscope.

Results and Discussion

There are many different drugs that affect the histological structure of the testes and the spermatogenesis [14]. The results of the our study have shown that the mice that were dosed with a concentration of (100 and 200 mg / kg) of the drug ribavirin for 45 days showed a distinct histological changes represented by increasing the thickness of the walls of the Seminiferous tubule It shrank significantly as its general shape became irregular, as well as irregular germ epithelium as observed in the Figure 1. This finding is consistent with [15] in which they showed that the base plate plays an important role in maintaining the transfer of substances between interstitial tissues and Spermatogonic epithelium, as well as maintaining the structure and function of these tissues.

While [16] indicated that the thickening of the sperm tubing walls may be due to the secretion of Sertoli cells Collagen Fibers IV, thus causing poor spermatogenesis development, While the researchers reported [17] that the weak relationship between the epithelium Spermatogonic and interstitial tissue may be due to the increase in the thickness of the wall Seminiferous tubule and with this increase shows a lot of changes within the testicle, especially in Sertoli cells that directly affect the differentiation and The development of germ cells. The results of present study also showed the emergence of

Vaculation and in some sections of the sperm tubules Seminiferous tubule as well as the widening of the distance between the germ cells, and ecdysis of the epithelial tissue and aggregation in the cavity of some Seminiferous tubule as well as the occurrence of degeneration and increase the distance between neighboring Sertoli cells as shown in the Figures (1, 2, 3). Large macrophage cells were also observed within the tubular cavity as shown in Figure 4.

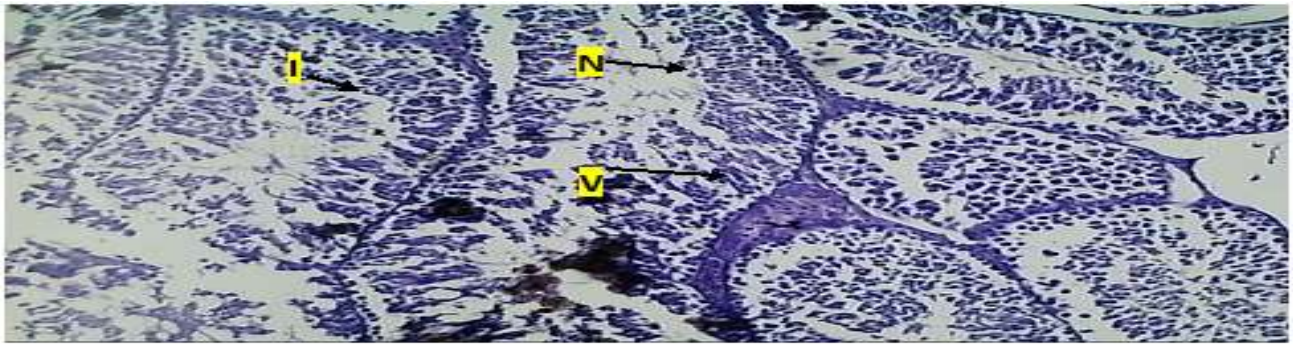

Figure 1: Parasagittal section of the Testes of mice receiving with 100 mg/kg ribavirin drug for 45 days showing (I) irregularity of the semeniferous epithelium, (V) Vaculation, (N) necrosis of the seminiferous epithelium. H&E, 40×

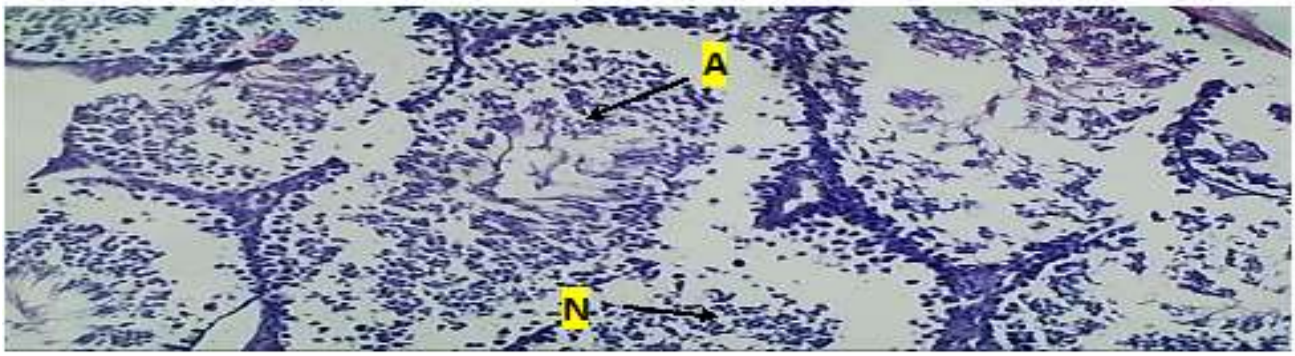

Figure 2: Parasagittal section of the Testes of mice have injected with 100 mg/kg ribavirin for 45 days showing (A) aggregate the germinal cells in the lumen of Seminiferous tubules, (N) necrosis of the seminiferous epithelium . H&E, 40×

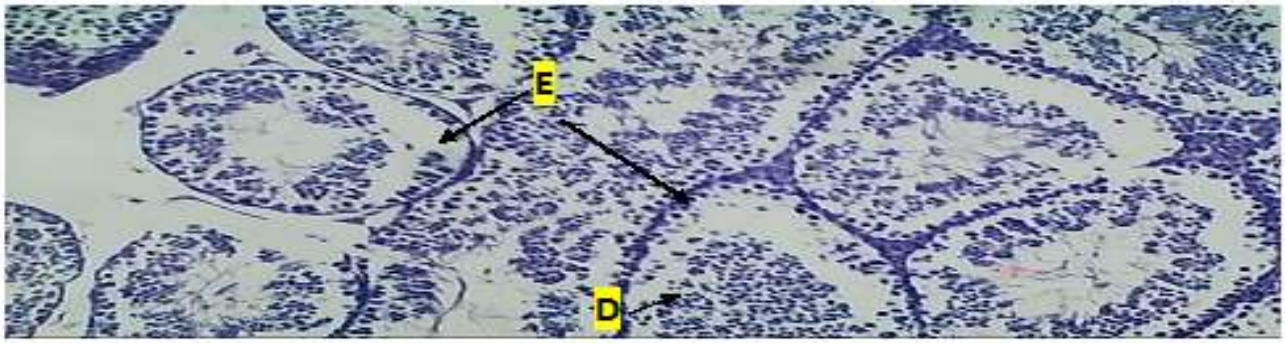

Figure 3: Parasagittal section of the Testes of mice receiving with 100 mg/kg ribavirin for 45 days showing (E) ecdysis of the epithelial tissue and aggregation in the cavity of some seminiferous tubule (D) degeneration in Sertoli cells

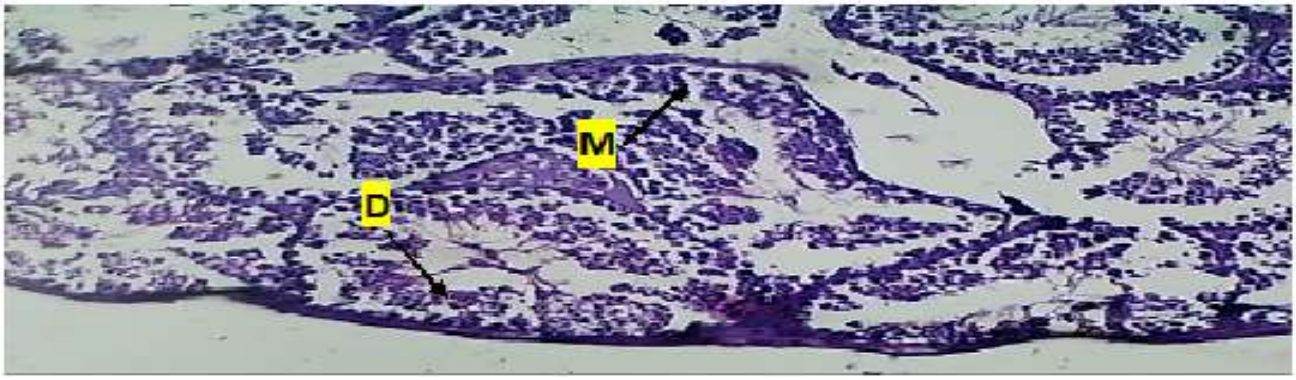

Figure 4: Parasagittal section of the Testis of mice injecting with 100 mg/kg ribavirin for 45 days showing, (M) The emergence of Large macrophage cells within the cavity semeniferous, (D) degeneration in Sertoli cells. H&E, 40×

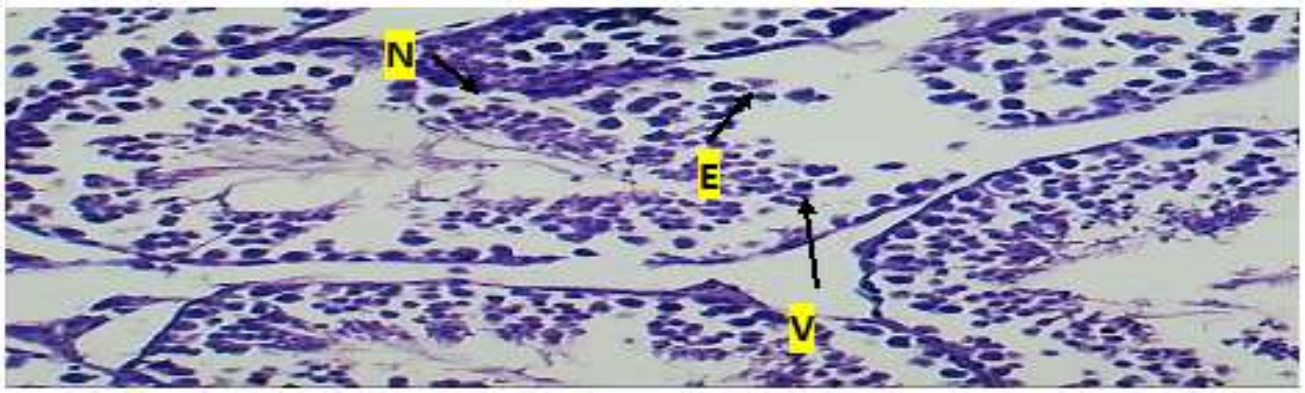

Figure 5: Parasagittal section of the Testis of mice receiving with 200 mg/kg ribavirin for 45 days showing (V) Vaculation (N) necrosis of the seminiferous epithelium (E) ecdysis of the epithelial tissue and aggregation in the cavity of some Seminiferous tubule . H&E, 40×

An imbalance in Sertoli cells will lead to histological changes in the testes and germ cells [18, 19].Pointed to the role of Sertoli cells in differentiating germ cells by forming a testicular barrier that protects germ cells, as well as transporting nutrients and hormones into the testes. These signs may be caused by a defect in the structure and function of Sertoli cells.

The results of the present study also showed that ribavirin has an effect on the Leydig Cells and the interstitial tissue due to the appearance of decomposition and necrosis as well as an vaculation in the interstitial tissue As shown in Figure 2. The finding of this study agree with the results of the researchers [20] who pointed out that Ledge cells are a center for regulating fertility because they secrete testosterone Hormone. The results of the study revealed that the injection of mice at a concentration of 200 mg / kg of the drug leads to increased shrinkage of Seminiferous tubules in some sections and also caused the occurrence of Vaculation and degeneration, and necromet cells in primary sperm cells and spermatids and mature sperm and return of spermatids and sperm differentiated to within the germ epithelium as in Figures 5 and 6.

This may be due to deformation or destruction to Sertoli cells and this damage will affect the proteins necessary in the process of formation and differentiation of germ cells. These proteins have released during the stage of spermatids differentiation. This finding is consistent with the researchers' study [21]. The resilience of spermatids may have been caused by sensitivity to testicular toxicity by ribavirin. This result is agreed with the Foley study [22].

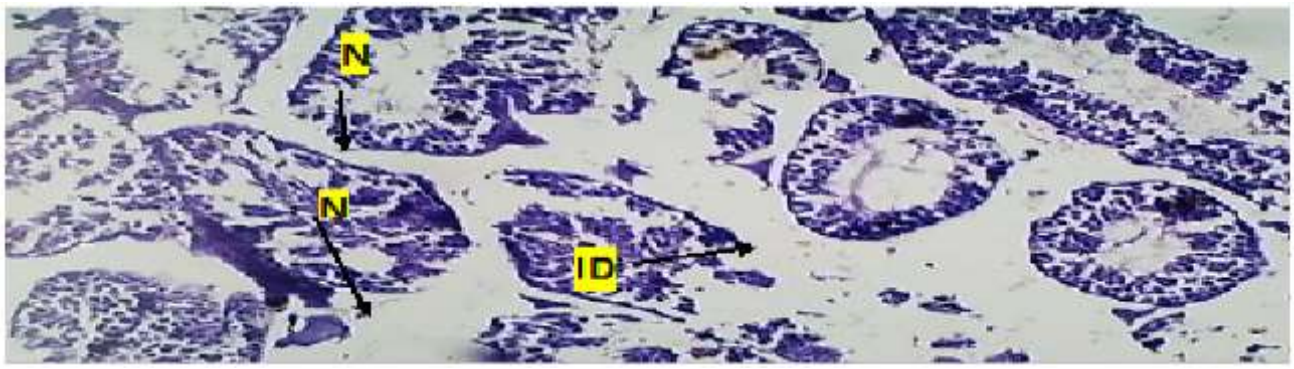

Figure6: Parasagittal section of the Testis of mice receiving with 200 mg/kg ribavirin for 45 days showing (N) necrosis of the seminiferous epithelium) ,(ID) Increase the distance between Seminiferous tubule A) aggregate the germinal cells in the lumen of Seminiferous tubules, . H&E, 10×

References

1. Acosta EP, Flexner C (2011) "Antiviral Agents (Non-retroviral) (Chapter 54)", In: Goodman & Gilman's: The Pharmacological Basis of Therapeutics Pharmacology, 12th Edition. McGraw Hill.
2. Montero C, Duley JA, Fairbanks LD, McBridge MB, Micheli V, Cant AJ, Morgan G (1995) "Demonstration of induction of erythrocyte inosine monophosphate dehydrogenase activity in Ribavirin-treated patients using a high

performance liquid chromatography linked method", Clinica Chimica Acta, 238 (2): 169-178. https://doi.org/10.1016/0009-8981 (95)06088-U.

3. Robert CTAM, Ramasamy K, Bard J, Pai B, Lim C, Averett DR (2000) "The Ribavirin Analog ICN 17261 Demonstrates Reduced Toxicity and Antiviral Effects with Retention of both Immunomodulatory Activity and Reduction of Hepatitis-Induced Serum Alanine Aminotransferase Levels", American Society for Microbiology, 44: 1276-1283.
4. Parker WB (2005) "Metabolism and antiviral activity of ribavirin". Virus Res.; 107: 165-171.
5. Golan DE, Tashjian AH (2016) "Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy", 2nd Edition, ISBN: 1451191006, 9781451191004
6. Holbrook MR (2017) "Historical Perspectives on Flavivirus Research", Viruses, 9 (5): 97. http://doi.org/10.3390/v9050097
7. Ahrens CL, Manno EM (2014) "Chapter 46 - Neurotoxicity of commonly used hepatic drugs", in Neurologic Aspects of Systemic Disease Part II-Handbook of Clinical Neurology.
8. Kronen MR (2008) "Flaviviridae", online lecture, Stanford University. Available online at: https://web.stanford.edu/group/virus/flavi/2008/flavi.html
9. Lindsay H, Nelsen B (1975) "Effect of ribavirin on replication of influenza viruses in Rhesus monkey tracheal organ cultures", In: Annual meeting of the American Society for Microbiology: abstract A28.
10. Sabry AA, Sobh MA, Sheaashaa HA, Kudesia G, Wild G, Fox S, Wagner BE, Irving WL, Grabowska A, El-Nahas A-M (2002) "Effect of combination therapy (ribavirin and interferon) in HCV-related glomerulopathy", Nephrol. Dial. Transplant, 17: 1924-1930.
11. Altaf M, Hasnain S, Khan MR-U Khan MW (2015) "Study of drug mediated effects in mice: Histology based findings", Advancements in Life Science, 2 (3): 119-124.
12. Bancroft JD, Gamble M (2008) "Theory and Practices of Histological Technique", 6th edition. Churchill Livingstone, Elsevier, Philadelphia.
13. Yano CL, Dolder H (2002) "Rat testicular structure and ultra structure after paracetamol treatment", Contraception, 66 (6): 463-467.
14. Carreau S, Bourguiba S, Lambard S, Galeraud-Denis I, Genissel C, Levallet J (2002) "Reproductive system: aromatase and estrogens", Molecular and Cellular Endocrinology, 193 (1-2): 31: 137-143.
15. Richardson LL, Kleinman HK, Dym M (1998) "Altered basement membrane synthesis in the testis after tissue injury", Journal of Andrology, 19 (2): 145-155.
16. Winters SJ (2004) "Male Hypogonadism: Basic, Clinical, and Therapeutic Principles", Humana Press Inc., Totowa, NJ. Chapter 2: Leydig Cell Function in Man by Dong Q. and Hardy M. P., 23-43.
17. Zheng Y, Zhang X, Zhon J, Cheng F, Rao T, Yao Y (2002) "Expression of extracellular matrix proteins and vimentin in testes of azoospermic man: an immunohistochemical and morphometric study", Asian Journal of Andrology, 4 (1):55-60.
18. Monsees TK, Franz M, Gebhardt S, Winterstein U, Schill WB, Hayatpour J (2000) "Sertoli cells as a target for reproductive hazards", Androlgia, 32 (4-5): 239-246.
19. Reis MM, Moreira AC, Sousa M, Mathur PP, Oliveira PF, Alves MG (2015) "Sertoli cell as a model in male reproductive toxicology: Advantages and disadvantages", Journal of Applied Toxicology, 35 (8): 870-883.
20. Kaur G, Thompson L A, Dufour JM (2014) "Sertoli cells--immunological sentinels of spermatogenesis", Seminars in Cell & Developmental Biology, 30, June 36-44.
21. Manivannan B, Mittal R, Goyal S, Ansari AS, Lohiya NK (2009) "Sperm characteristics and ultra structure of testes of rats after long-term treatment with the methanol sub fraction of Carica papaya seeds", Asian Journal of Andrology, 11 (5): 583-599.
22. Foley GL (2001) "Mechanisms of Male Reproductive Organ Toxicity", Toxicological Pathology, 29 (1): 49-63.

