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Histological effect of rifampicin drug in the kidney and liver of tissue of albino mice *Mus Musculus*

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ABSTRACT

The aim of this study is to investigate the histopathological changes induced by the anti-tuberculosis drug (rifampicin) in the tissues of the kidneys and liver of white male mice of *Mus Musculus*. 25 mice were distributed into five groups that included a control group, a therapeutic dose group of 1.25 mg, and a toxic dose group of 2.5 mg. The semi-lethal LD dose group was 150 mg, and the lethal LD dose group was 240 mg.

The results also showed behavioral changes for the treated animals, the intensity of which increased with the increase in concentrations, and the total of these changes was represented by eating less food and drinking water, lack of movement, diarrhea, rapid breathing, and red-orange urine, and these symptoms were more severe in the fatal group and ended with the animal's death.

In the kidneys, the tissue lesions were represented by the occurrence of necrosis in the cells of the urinary tubules in some areas, the infiltration of inflammatory cells clearly, the degeneration of some cells of the urinary tubules, and the swelling of a part of the cells, which led to a narrowing in the lumen of the urinary tubules. The nuclei are necrotic and disintegrated. The glomerulus was some areas enlarged and some areas atrophic. Also, fibrosis of the kidney tissue was observed, which increases with increasing dose.

In the liver, it was represented by the occurrence of necrosis, hemorrhage and congestion, infiltration of inflammatory cells, thickening of the plasma membrane, widening of the sinusoids in some areas and narrowing them in other areas, the onset of fibrosis, and Kupfer cells.

Conclusion: The administration of rifampicin led to pathological changes in the kidneys, represented by necrosis, glomerulosclerosis and fibrosis, as well as pathological changes in the liver represented by rupture of the vessel wall, nuclei enlargement and hemorrhage.

Introduction

At the beginning of the twentieth century, lung diseases such as tuberculosis and pneumonia were the main causes of death, and after a century the main diseases causing death were cancer, stroke and heart disease. The shift in the basic diseases that lead to death from infectious to chronic came as a result of the discovery of many antibacterial drugs, which constituted a turning point in human history, beginning with Alexander Fleming (1881-1955) who discovered [1] penicillin in 1928. After that, attempts were made to discover other types of antibiotics. In 1957, from a sample of sand from pine forests in the

French city of Saint-Raphael, a group of researchers discovered a new bacteria. Immediately, this bacteria showed great importance, as a new class of molecules was produced with antibiotic activity and was given the name rifamycin. [2, 3] After two years of attempts to obtain a more stable semi-synthetic compound, a new molecule was produced with high activity and good tolerability in 1959, and it was called rifampicin.

The drug rifampicin used in the current study joins the class of bactericidal antibiotics (bacteriocidal) [3], which works by inhibiting nucleic acids in the cell [4]

and this drug is mainly used to treat tuberculosis, [5], in addition to other uses such as its use in the treatment of leprosy [6,7]. Rifampicin, like other drugs, has many undesirable side effects as it causes severe inflammation in the liver Kidney failure has also been proven through studies that its use during pregnancy causes many fetal abnormalities [7].

Materials and methods

The study was conducted in the animal house of the College of Veterinary Medicine / Tikrit University.

Experimental animals

The study included an experiment that included 25 male albino mice *Mus Musculus*, their weights ranged from (20-35) g. They were placed in cages designed specifically for breeding mice. They were plastic and with metal mesh lids, and their dimensions were (80 / 15 / 30) cm spread with sawdust, taking care to clean the cages And sterilized twice a week. Throughout the experiment, the animals were placed in standard laboratory conditions in terms of ventilation and temperature, which were within ($25^{\circ}\text{C} \pm 2$) and a photoperiod (12) hours of light and (12) hours of darkness [8] and they were given the ration for feeding them. White mice in addition to sterile water continuously throughout the experiment period in special containers to avoid contamination with sawdust. The ration consists of (wheat 34% barley 20% corn 25% animal protein 10% powdered milk 10% table salt 1%). [9 , 10]

Experimental design

Experimental animals were distributed into five groups and dosed by oral tube feeding as follows.

The control group: consisted of (5) males, they were dosed with distillal water for a month, in addition to diet.

Therapeutic group This group includes (5) males who were treated with rifampicin at a concentration of 1.25 mg / kg of animal weight for a month, once a day[11].

Toxicological group This group includes (5) males that were treated with rifampicin at a concentration of 2.5 mg / kg of animal weight for a month, once a day.

Semi lethal LD50 group. This group includes (5) males that were treated with rifampicin at a concentration of 150 mg/kg of animal weight orally twice a day, and the result was 50% death after 24 hours.

A lethal LD group that includes this group (5) males were treated with rifampicin at a concentration of 240 mg for 24 hours, and the result was 100% death.

After the end of the experiment period the animals were fasted for 12hours, and then the animals were anesthetized and dissected, and the required organs were removed

Preparation of tissue microscopic sections

The microscopic tissue sections were prepared according to the method mentioned in [4] from fixation, washing, Dehydration, Clearing, infiltration to get wax molds they were then cut using the microtome to obtain tissue sections with a thickness

of 5-7 micrometers. The slides were loaded onto clean glass slides marked with a diamond pen and left to dry. Finally, the tissue sections were stained with hematoxylin-eosin and loaded with DPX and cover glass. Then the slides were placed on a clean surface to dry.

Examination and microscopic imaging of tissue sections

The microscopic examination of the tissue sections prepared from the samples prepared for the study was carried out using the imaging light microscope in the Department of Biology / College of Science, and then photographs of the sections were taken using a compound microscope equipped with a Novel type camera.

Results

Kidneys results

Control group

The kidney is composed of the cortex and includes the glomerulus. It is a tuft-like network of capillaries located in the front of the renal tubular unit, and it performs the function of the first station for the process of filtering blood, which is assumed by the renal tubular unit during the urine formation process. The glomerulus is structurally supported by the mesangial (the space between blood vessels), which consists of mesangial cells within the glomerulus. Blood filters through the walls of the blood vessels through the glomerular filtration septum, which passes water and dissolved substances into a cup-like sac called "Bowman's capsule", to enter Then the glomerular filtrate the proximal renal tubule. The pulp is composed of urinary tubes(Image1).

Mouse kidneys therapeutic dose group

The samples taken from the first group with a therapeutic dose, which were treated for a month with rifampicin at a concentration of 1.25 mg / kg of body weight, showed hemorrhage, as well as the occurrence of fibrosis in the walls of most of the blood vessels, fibrocystic infiltration Inflammatory cell, and the presence of cast (Image No.2.).

toxicity Group

The samples taken from the second group with a toxic dose, which were treated for a month with rifampicin at a concentration of 2.5 mg / kg of body weight, showed absence of lumen of the tubules, fibroblast, and hypertrophy of the cell tubules (Image No.3).

LD50 group

The histological examination of the group of mice treated with the LD50 dose, which lasted for 24 hours, and the dose was 150 mg / kg of body weight, and the fatality percentage was 50% shrinkage of the glumula, as well as an increase in the thickening of the nuclei of piknosis and changes in the nature of the structure of the tubes. Necrosis of the epithelium lining the urinary tubules, karyolysis and cell disintegration (Image No 4).

Mouse kidneys lethal group

The histological examination of the group of mice treated with the lethal dose, which lasted 24 hours, the dose was at a concentration of 240 mg / kg of body weight, and the death rate was 100%, showed

swelling in the cells of the tubules, fibrocyte fibrosis, rupture of Bowman's capsule and disintegration of the glomerulus. glumula and inflammatory cell infiltration Infiltration (Image No 5).

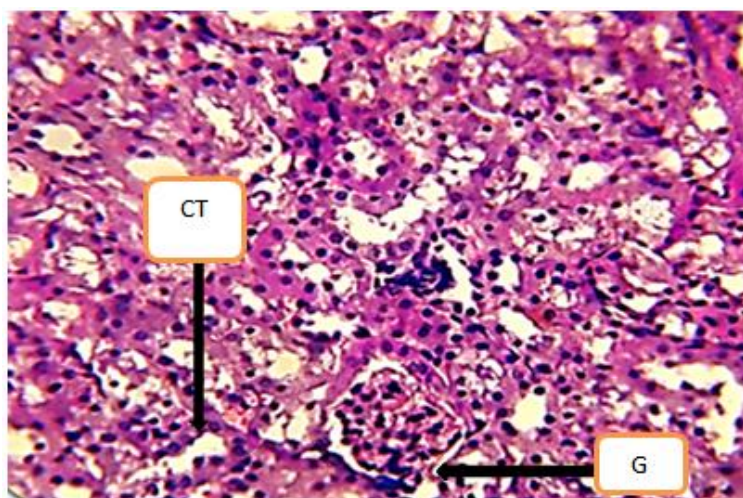


Image 1: a Section of the kidneys of mice from the control group showing Glomerulus (G) and convoluted tubule (CT)(X400,H&E)

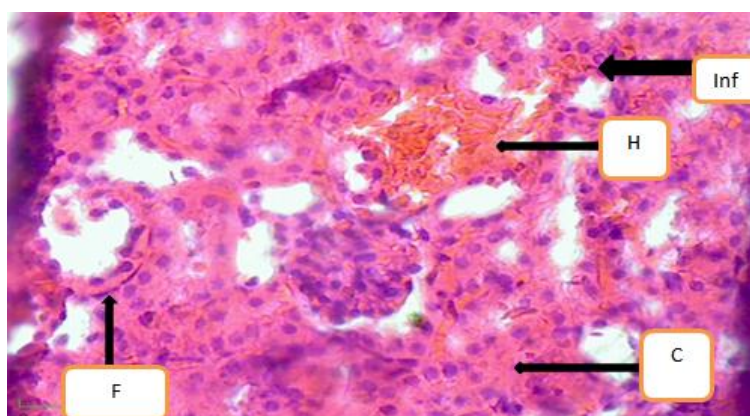


Image 2: asection of the kidney of a mouse from the group treated with rifampicin at a concentration of 1.25 mg l, rifampicin, showing (Hemorrhage (H) as well as most of Fibroblast (F), Inf Inflammatory cell infiltration(Inf) , and the presence of cast(C) (X400, H & E)

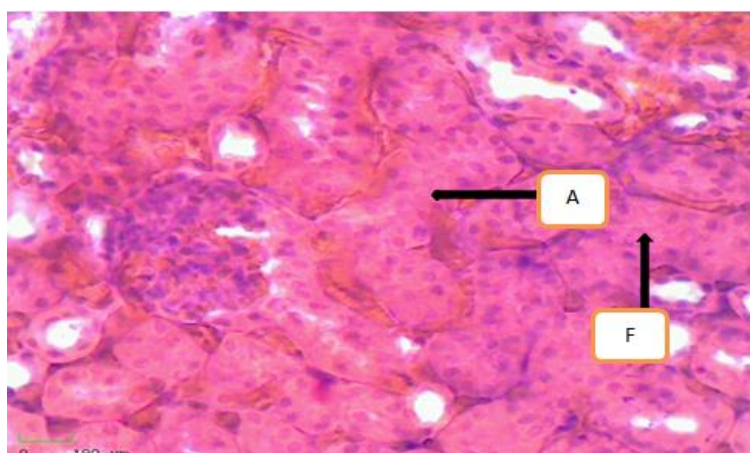


Image 3: a section of the kidneys of mice from the toxic group treated with rifampicin at a concentration of 2.5 mg showing absent of lumen of the tubules(A) and the presence of fibroblast(F) (X400, H&E)

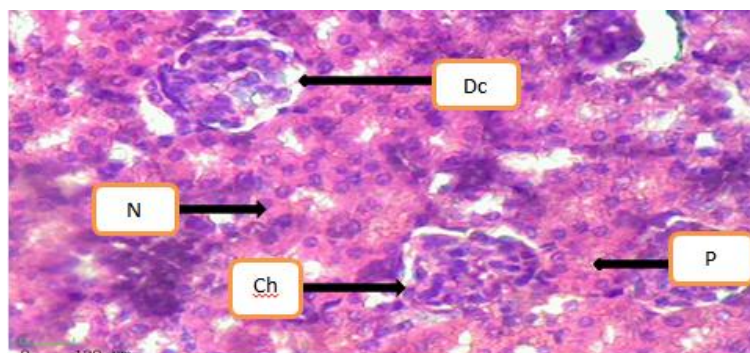


Image 4: asection of the kidney of mice of the LD50 group treated with rifampicin at a concentration of 150 mg showing (shrinkage of glumuahe (ShG) as well as occurrence of pyknosis and change of normal architecture of tubules (Ch), necrosis(N), and cell disintegration (Dc) (X400,H&E)

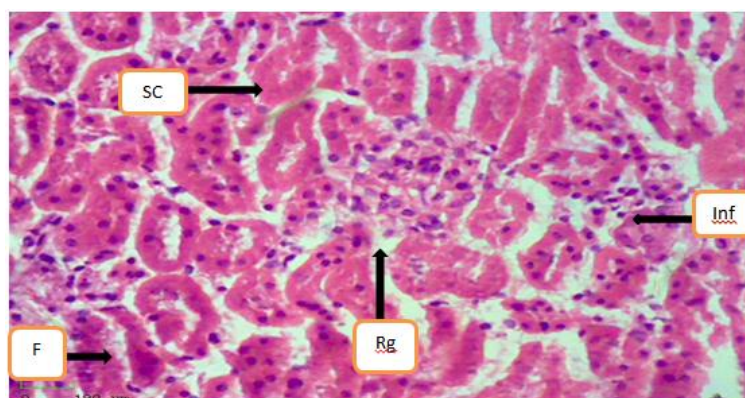


Image 5: a section of the kidney of mice from the lethal group treated with rifampicin at a concentration of 240 mg showing the occurrence of swelling in the cells of tubules(SC), fibroblast (F), rupting bowman capsules and disintegration of glumula(Rg) and Inflammatory cell infiltration (Inf) (X400, H& E)

Control group

The liver represents one of the appendices of the digestive system and the largest of the body glands surrounded by a capsule extending from it barriers called interlobular barriers that divide the liver into several lobules. We note the middle of each lobule central vein. These hepatic plates extend from the central vein to the periphery of the lobule. The hepatocytes are characterized by being polygonal in shape and have a central nucleus and acidic cytoplasm between the hepatic plates. We notice spaces or pockets called the sinusoids, which open into the central vein at the interlobular septa and line the sinuses with two types of cells, the first is the endothelial epithelium and the second is the Kupffer-mediated cells. There are hepatic artery, portal vein, bile duct and lymphatic vessels (Image6).

Mouse liver therapeutic group

The histological examination of the group of mice treated with a therapeutic dose that lasted for a month and at a concentration of 1.25 mg / kg of body weight showed hemorrhage, deposition of collagen in the cytoplasm, desquamation and rupture in the wall of the central vein. vein and necrosis of some hepatocytes (Image No.7

Toxicity group

The histological examination of the group of mice treated with a toxic dose that lasted for a month at a concentration of 2.5 mg / kg of body weight showed deposition of collagen in the cytoplasm and fibrocytes, as well as the occurrence of necrosis of hepatocytes and the appearance of kupffer cell cells (Image No 8

LD50 group

The histological examination of the group of mice treated with a semi-lethal LD50 dose that lasted for 48 and at a concentration of 150 mg / kg body weight showed hemorrhage, deposition of collagen in the cytoplasm, hepatocyte necrosis, rupting of central vein, appearance of kupffer cell and Inflammatory cell infiltration. (Image No.9

Mouse liver group lethal

The histological examination of the group of mice treated with a lethal dose that lasted for 48 and at a concentration of 240 mg / kg of body weight showed hemorrhage, deposition of collagen in the cytoplasm, necrosis, wall rupting of central vein, and change in the structural structure of hepatocytes chang of architecture of the hepatocyte band and the occurrence of thickening of the nuclei of some hepatocytes (Image No10.

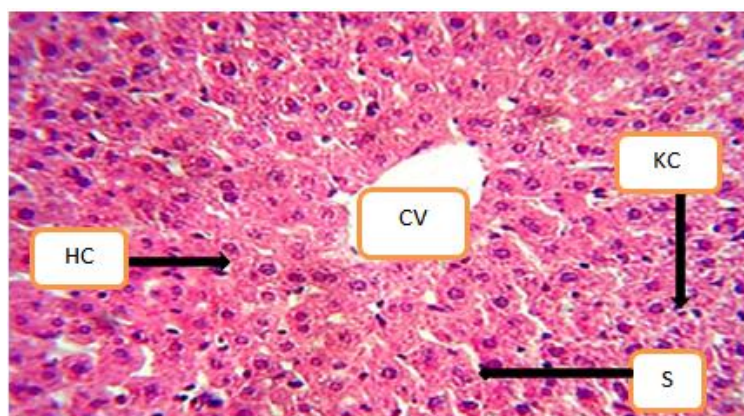


Image 6: a section of the liver of mice from the control group showing central vein(CV) and sinusoids (S) and, Kupffer cell(KC) (Hepatic cell (HC) (X400, H&E)

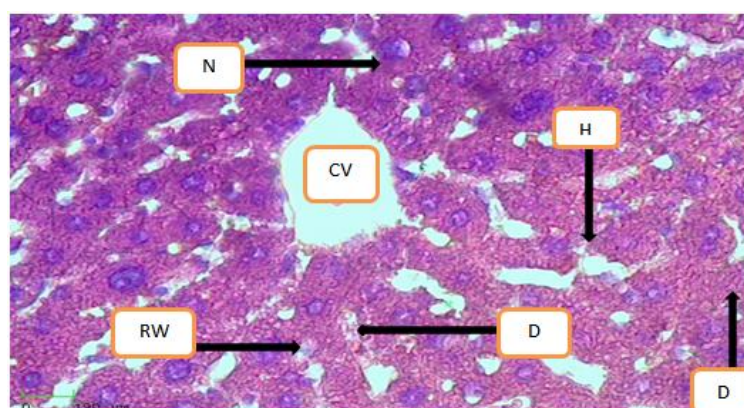


Image 7: a section of a mouse liver from a treatment group treated with rifampicin at a concentration of 1.25 mg showing the occurrence of Hemorrhage(H), deposition of collagen in the cytoplasm (D), desquamation (D) and rupture in the wall of center vein(RW). necrosis(N),(X400,H&E)

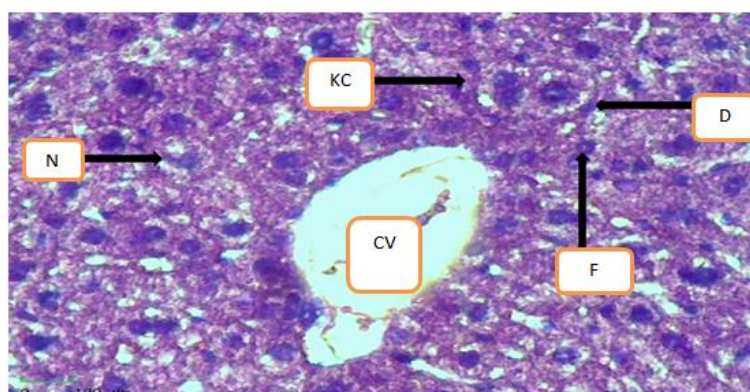


Image 8: a section of the liver of mice from a group treated with rifampicin at a concentration of 2.5 mg, showing the occurrence of deposition of collagen in the cytoplasm and(D)fibroblast (F), as well as the occurrence of Necrosis(N) and kupffer cell(KC) (X400, H&E)

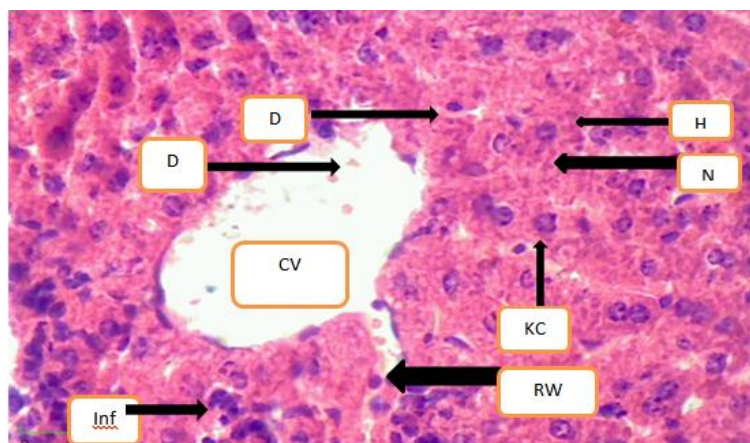


Image 9: a section of the liver of mice from a semi-lethal group treated with rifampicin at a concentration of 150 mg showing the occurrence of hemorrhage(H), desquamation(D), deposited of collagen in the cytoplasm (D), necrosis(N) and rupting of center vein wall (RW) and Inflammatory infiltration cell(Inf) and kupffercell (KC) (X400, H&E)

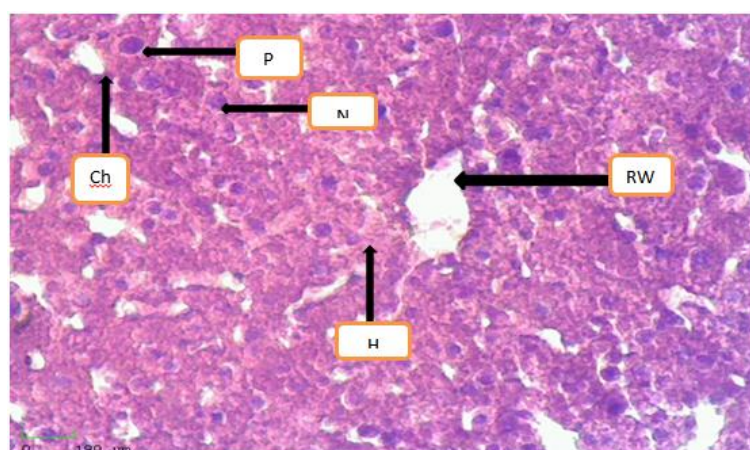


Image 10: section of the liver of mice from a lethal group treated with rifampicin at a concentration of 240 mg showing hemorrhage (H), deposition of collagen in the cytoplasm, necrosis(N), rupting of wall central vein(RW) and the chang of architect of the hepatocyte band(Ch) peknosis(p),(X400,H&E)

Discussion

The current study, it was found that many tissue damages occurred, the severity of which increased with the increase in the dose and the duration of the dose. These damages were generally represented by damage to the tubules. It was also noted that nuclei necrosis and lysis and Inflammatory cell infiltration appeared. It was also noted that fibrosis in the kidney tissue increases with increasing dose. It was also noted that hemorrhage and congestion spread in the stroma of tissue and their intensity is directly proportional to the dose. These results agree with the findings of [13], where the researcher noticed the same damage to the kidneys when mice were dosed with diclofenac sodium. As for the damage to the tubules, it is caused by stimulating the immune system in response to the toxicity resulting from the drug, so large amounts of antibodies accumulate in blood vessels and tissues. The interstitium of the kidney causes an increase in the thickness of the endothelial tissue of the glomerulus, which results in damage to the tubules.[14, 15] Also, the accumulation of antibodies in the blood stimulates an

increase in renin secretion, which leads to constriction of the glomerular arterioles and thus a decrease in blood flow to the renal tubules, which results in damage to these tubules [16]. Also, the swelling of the cells of the urinary tubules leading to blockage of the lumen of these tubules in some concentrations is due to the fact that toxic substances lead to swelling of the renal tubules, as the cells are large in size and swelling is large, leading to convergence of cells and obstruction of the lumen of the renal tubules and thus leads to necrosis of cells and this is the result of a deficiency Oxygen, which impedes the work of mitochondria to produce ATP energy to work on balancing osmotic pressure, and there is a defect in the presence of sodium, which leads to pressure imbalance and fluid accumulation in cells, as well as tubule necrosis resulting from the presence of materials with affinity towards calcium, and it is believed that phosphoric acid and fatty acids have a role in Calcification in the vicinity of kidney cells [17]. The results showed the occurrence of necrosis of the renal tubules due to poisoning, where the tubular epithelial cells die as a result of not

obtaining sufficient oxygen, as their metabolic activity depends on the oxygen supplied by the blood vessels, and any damage that occurs to the blood vessels from necrosis and narrowing of the renal artery leads to slow blood flow. And then the lack of oxygen supply to cells [18]. The occurrence of bleeding and congestion in the treated kidney tissues is attributed to the direct destruction of the epithelium lining the blood vessels, which caused the leakage of red blood cells into the renal tissue.

It was also observed that fibrosis in the kidneys occurred, especially in the lethal and sub-lethal doses for rifampicin. This is consistent with the study conducted by [19], where the researcher noted.

Occurrence of fibrosis in rat kidneys when treated with dexamethasone. It also agrees with when he treated mice with zinc sulfate, where he also noticed the occurrence of fibrosis in the kidney tissue.

The results also indicated the occurrence of atrophy of the glomeruli with high doses, and this result is consistent with the findings of [20] (which showed that the increase in the concentration of the drug in the blood entering the glomerulus leads to a defect in the filtration process of the glomerulus as a result of a decrease in the amount of blood entering the kidney consistent with Also with [21], who also noted the occurrence of glomerular atrophy when mice were treated with piroxicam.

Studies have shown that rifampicin, like other anti-tuberculosis drugs, has a toxic effect on the liver [22]. Toxic metabolic reaction is generated during the liver biotransformation of some anti-TB drugs into compounds that are covalently bound with large molecules. For cellular macro-molecule cells, free radicals are generated, which in turn cause cell damage, as the oxidative activation of these metabolites in the liver by cytochrome p450 generates interfering electrolytes and free radicals, which in turn are responsible for liver toxicity and damage to its cells [23,24]. In the current study with regard to rifampicin, it was found that many tissue lesions of the liver that vary in severity vary with the concentration of the dose. These damages were generally represented by the occurrence of necrosis, hemorrhage, infiltration inflammatory cell, thickening of the plasma membrane, lysis of red blood cells, the onset of fibrosis, enlargement of Cover cells, nucleolysis, , degeneration and proliferation of vacuoles. This is consistent with [25] when they tried to use rifampicin to treat itching caused by cholestasis, where they noticed many tissue damages to the liver, represented by fatty degeneration, lymphocyte infiltration and necrosis to a large extent. Liver of rats when treated with paracetamol. The reason for bleeding in the tissues is due to the increase in pressure inside the blood vessels, which leads to a breakdown in the wall of the blood vessels and the expulsion of red blood cells. As for the reason for the breakdown of red blood cells, the interactions between toxic compounds and glutathione form

compounds that lead to the dissolution of blood cells [26,27] pointed out that the cause of the decomposition of red blood cells is mediated by macrophages due to local hemorrhage, and this lysis leads to the formation of globin and heme, as the globin is reduced by dissolving it in body fluids and heme cleaves to give hematin and hemosiderin, hematin is deposited at the site of the bleeding golden yellow granules. The color is oily or yellowish-red at the bleeding site, while hemosiderin is deposited in macrophages.

As for the inflammatory cell infiltration, it calls to say that there are degenerative changes in the tissue that stimulate the secretion of chemical attractions, and then the infiltration of the area with lymphocytes, as the cells affected by the action of toxic substances secrete chemical attracting factors that attract white cells such as neutrophil cells and monocytes for defense about the body.

where [28] indicated the role of damaged cells in secreting attracting factors to attract inflammatory cells to areas of damage for the purpose of defending the body, and removing dead cells and their debris [29]. The enlargement of Cover cells to their defensive role in the body against foreign bodies and by virtue of their phagocytic function, which leads to their enlargement [18]. The results of the histological examination showed that some hepatocytes suffer from hypertrophy, which leads to the narrowing of some of the sinusoids, and this phenomenon occurs as a result of the adaptation that occurs when any physiological defect occurs, as the cells prepare to divide to compensate for the damaged cells, and on the contrary, an expansion of the sinusoids resulting from degeneration was observed in other areas. hepatocytes; This is consistent with the study conducted, where he observed when giving rabbits a dose of alcoholic extract of fenugreek seeds that hepatocytes necrosis occurred on one occasion and the disappearance of the radial arrangement of the liver and swelling of the hepatocytes on another time. While [30] attributed the cause of hepatocyte swelling to a defect in the permeability of its plasma membrane due to the toxicity resulting from the drug, which leads to the entry or exit of substances severely, leading to cell swelling or contraction according to the direction of the imbalance between the existing elements and their salts, and this affects the cellular structures. The internal cells, including the mitochondria, cause the cell to go through stages of programmed death or degeneration. Hence, the swelling of hepatocytes in turn led to the narrowing of the sinusoids. On the one hand, the expansion of the sinusoids is due to the shrinkage and degeneration of hepatocytes [29]. The degeneration of hepatocytes results from a disturbance in the metabolic processes of the hepatocytes, and the exposure of the nuclei of the cells to degeneration indicates that the hepatocytes are vulnerable to harm, because they are

the first cells to receive substances through the hepatic portal cycle [27]

[31] mentioned that drug-induced hepatitis is the most common type of hepatitis. With regard to rifampin, studies have shown that it causes acute hepatitis [25]. It is noticeable that the inflammation increases with increasing the amount of the dose, causing chronic active hepatitis, which is

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التأثير النسيجي لعقار الريفامبيسين في أنسجة كلى وكبد الفئران البيضاء

منى صلاح رشيد ، اسراء عبد المنعم محمد

قسم علوم الحياة ، كلية العلوم ، جامعة تكريت ، تكريت ، العراق

الملخص

الهدف من هذه الدراسة هو فحص التغيرات النسيجية المرضية التي يسببها مضاد السل (ريفامبيسين) في أنسجة الكلى والكبد لدى ذكور الفئران البيضاء. تم توزيع 25 فأراً على خمس مجموعات تضمنت مجموعة ضابطة ومجموعة جرعة علاجية 1.25 ملغم ومجموعة جرعة سامة 2.5 ملغم. كانت مجموعة جرعة LD شبه المميتة 150 ملغم ، ومجموعة جرعة LD المميتة 240 ملغم.

كما أظهرت النتائج تغيرات سلوكية للحيوانات المعالجة زادت شدتها مع زيادة التركيزات، وتمثل مجموع هذه التغيرات بتناول كميات أقل من الطعام ومياه الشرب، وقلة الحركة ، والإسهال ، وسرعة التنفس ، واحمرار الجسم. البول البرتقالي ، وكانت هذه الأعراض أكثر حدة في المجموعة القاتلة وانتهت بموت الحيوان

في الكلى، تمثلت الآفات النسيجية في حدوث نخر في خلايا الأنابيب البولية في بعض المناطق، وارتشاح الخلايا الالتهابية بوضوح ، وتنكس بعض خلايا الأنابيب البولية ، وانفخاخ جزء من الخلايا. مما أدى إلى تضيق تجويف الأنابيب البولية. النوى نخرية ومتفككة. كانت الكبيبة متضخمة في بعض المناطق وضمور بعض المناطق. كما لوحظ تليف أنسجة الكلى يزداد مع زيادة الجرعة

في الكبد، تم تمثيله بحدوث نخر ، نزيف واحتقان ، ارتشاح الخلية الالتهابية سماكة غشاء البلازما ، اتساع الجيبانيات في بعض المناطق وتضييقها في مناطق أخرى.