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ADVERSE EFFECTS OF LINCOMYCIN AND SPECTINOMYCIN IN RATS

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ABSTRACT

This study was performed to investigate the adverse effects of lincomycin (given orally at 500 mg/kg daily for 21 days) and spectinomycin (given S.C at 250 mg/kg daily for 30 days) on 24 apparently clinically healthy adult male albino rats (175 - 250 gm). Blood, serum and tissues (Liver, kidney and testis) samples were collected for hematological, biochemical and histopathological for investigation. The obtained results revealed that, lincomycin and spectinomycin treated groups showed a significant decrease in total erythrocytic and leucocytic count (especially lymphocytes), hemoglobin values and PCV value. The levels of ALT, AST, cholesterol, triglycerides and LDL revealed a significant increase in lincomycin and spectinomycin treated groups. While the level of HDL showed a significant decrease in both lincomycin and spectinomycin treated groups. The results also showed that, both drugs induced histopathological alterations in the liver, kidney and testis.

INTRODUCTION

The extensive use of antibiotics may lead to a variable drug adverse effect. Some adverse effects are mild, as, reversible discoloration of skin and body fluids with rifampin curing (**Holdiness, 1989**), intestinal colic with erythromycin therapy (**Cantach et al., 1992**), and discoloration of teeth with tetracycline (**Sanchez et al., 2004**). Many other side effects were observed with many antibacterial agents as aplastic anemia with chloramphenicol (**Trevett et al, 1992**), neuromuscular blockage with Lincomycin (**Best et al., 1999**), retinopathy with fluoroquinolones (**Wieb et al., 2002**), ototoxicity and nephrotoxicity with aminoglycosides (**Selimoglu, 2007 and Pannu et al,2008**).

Lincomycin hydrochloride is member of Lincosamides group of antibacterial agents that used for human and veterinary medicine. It is highly effective against G+ve pathogens and has been used for infections of the mouth and upper respiratory tract, as well as skin infections (**Petinaki, et al., 2008**). It is also used against anaerobic pyoderma, but often induces vomition and diarrhea in canines (**Arunvikram., 2014**).

Spectinomycin is an aminocyclitol class, and it closely related to the aminoglycosides, but less toxic (**Debremaeker et al., 2002**). It has some side effects as pain at the site of injection, skin rashes, nausea, trouble sleeping and severe allergiy (**The United States Pharmacopeial Convention, 2004**).

Aim of the work:

The aim of this work was designed to explain the toxic effects; if any; of lincomycin and spectinomycin on white albino rats, through studying the following:

1- Study the effect of the tested drugs on hematological findings.

2- Study the effect of the tested drugs on some biochemical parameters.

3- Histopathology: concerning the liver, kidneys and testis.

MATERIAL AND METHODS

I- Material

1-Tested Drugs:

a-Lincomycin:

Lincomycin hydrochloride (Lincol)^{R} is a product manufactured by Royal Link pharma, Egypt. Lincomycin (Lincol) 468 mg Lincomycin hydrochloride: 1g contains 468 mg Lincomycin hydrochloride.

Dose: A repeated oral dose of lincomycin was given daily for twenty one (21) days in a dose of 500 mg/kg (**Jwad et al., 2015**).

b – Spectinomycin

Spectinomycin dihydrochloride (Spectal Super)^{R} is a product manufactured by ACTO PHARMA for Pharmaceutical Industries, Egypt. Spectinomycin (Spectal Super): 100 g contains 75 mg Spectinomycin dihydrochloride equivalent to 50 g Spectinomycin base.

Dose: A repeated subcutaneous dose of spectinomycin was given daily for thirty (30) days in a dose of 250 mg/Kg bw (**Ulrich et al, 1990**).

2 -Experimental animals:

Twenty four (24) apparently clinically healthy adult male albino rats (175 - 250 g) were used in this study. They were housed in clear plastic cages with wood shavings as bedding and kept under controlled conditions. Rats were fed with unrestricted access to the standard laboratory pelleted diet as food and tap water *ad libitum*. They were accommodated for the laboratory condition for two weeks prior to the commencement of the experiment.

II- Methods

1-Experimental design:

The experiment was conducted over a period of thirty (30) days, after two weeks period of acclimatization; rats were randomly divided into three (3) experimental groups (8 for each).

- The first group was used as control and received distilled water.
- The second group received daily lincomycin (500 mg/kg bw) orally for twenty one (21) days (**Jwad et al., 2015**).
- The third group received daily spectinomycin (250 mg/kg bw) subcutaneously for thirty (30) days (**Ulrich et al, 1990**).

2- Samples collection:

a-Blood samples:

At 24 hours after experimental periods twenty one (21) days for lincomycin group and 30 days for spectinomycin group, all rats from each group were subjected to light anesthesia by ether and fresh blood samples were immediately drown from retro – orbital plexus by using microcapillary tube. Half of blood samples were used for hematological examination (blood samples were collected in

EDETA tubes). While the other half of blood sample was used (for serum separation) were collected in centrifuge tubes, for coagulation. The samples were put in an inclined position for 20 minutes at room temperature, and then put in refrigerator. Then centrifuged at 3000 rpm for 10 minutes and the clear sera were separated carefully, collected and stored in epindorfs tubes at -20 C^o until used for estimation of serum biochemistry parameters .

b-Tissue samples:

For histopathological studies, rats were then sacrificed by decapitation and specimen from liver, kidney and testis were collected excised and immersed in 10% formalin solution (**Ankush et al., 2014**).

3- Experiments

- **Hematological Analysis:**

Blood samples were examined for Erythrocytes and Leucocytes counts (**Feldman et al., (2000**), Hb % **(Drabkin, 1949**), Packed cell volume (**Cole, 1986**). Red cell indices, MCV (FL), MCH (PG) and MCHC (%) were calculated from measured PVC %,Hb concentration and RBCs count according to **Feldman et al., (2000**) . Differential Leucocytic count was done according to **Cole, (1986**).

- **Biochemical analysis:**

Serum samples were analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST) (**Reitman and Frankel,1957)**, urea (**Naito and Kaplan et al., 1984)**, creatinine **(Bartels , et al., (1971)**, Cholesterol (**Naito and Kaplan, 1984)**, Triglyceride **(Buccolo et al., 1973)**, High density lipoprotein **(Friededwald et al., (1972)**, Low density lipoprotein **(Friededwald et al., 1972)**, Urea **(Naito and Kaplan et al., 1984)** and Creatinine **(Bartels , et al., 1971)**.

- **Histopathological studies:**

Specimens from liver, kidney and testis were preserved in 10% formalin for histopathological examination **(Bancroft and Stevens 1996)**.

- **Statistical analysis:**

Data were subjected to statistical analysis using statistical software program (SPSS). Means Differences between means of different groups were carried out using one way ANOVA with Duncan multiple comparison tests, **(Snedecor and Cochran 1981)**.

RESULTS

1-Hematological Analysis:

The results obtained in Table (1) showed that, lincomycin and spectinomycin elicited a significant decrease in total erythrocytic count, total leucocytic count (especially lymphocytes), hemoglobin values and PCV value. While MCV, MCH and MCHC results revealed non significant differences within all compared groups.

2-Serum biochemical analysis:

The results showed that, each of ALT and AST values showed a significant increase in lincomycin and spectinomycin treated groups compared with control group (Table 2).

Table (3) shows that, the levels of cholesterol, Triglycerides and LDL demonstrated a significant increase ($P<0.05$) in lincomycin and spectinomycin treated groups. While the level of HDL showed a significant decrease in both lincomycin and spectinomycin treated groups in comparison with the control group.

The obtained results sowed that, the levels of urea and creatinine revealed a significant increase in spectinomycin treated groups while there was a non significant increase in lincomycin treated group compared with control group (Table 4).

3- Histopathological changes:

The histopathological examination of the liver revealed focal areas of necrosis surrounded by leukocytic cells with presence of leukocytic cells infiltration in portal area, congested hepatic vein, edema and eosinophiles infiltration in portal area and swollen hepatocytes affected with hydropic degeneration in lincomycin treated group **(Fig 1, 2 and 3)** and an individual cell death with more eosinophilic cytoplasm and pyknotic nuclei, fibrous tissue proliferation and biliary epithelium hyperplasia with leukocytic cells infiltration, congested hepatic vein with fibrous tissue proliferation and leukocytic cells infiltration in portal area In spectinomycin treated group **(Fig 4, 5 and 6)**.

The histopathological examination of the kidney revealed a congested renal blood vessel, perivascular edema and dilated renal tubules with tubular hyaline casts in lincomycin treated group (**Fig 7, 8, and 9)** and a congested blood vessel, necrotic renal tubules and edematous renal tubules in spectinomycin treated group **(Fig 10, 11 and 12)**.

The histopathological examination of the testis revealed a eosinophilic edema in between seminiferous tubules, desquamated spermatocytes in lumen of seminiferous tubules, congested blood vessels and interstitial eosinophilic edema in lincomycin treated group **(Fig 13, 14 and 15**) and an irregular outlined seminiferous tubules lined with necrotic spermatocytic cells with arrested spermatogenesis and interstitial eosinophilic edema , vacuolation and necrosis in spermatocytic cells accidently seen in few seminiferous tubules and vacuolated and necrotic spermatocytic cells with arrested spermatogenesis in spectinomycin treated group (**Fig 16, 17 and 18)**.

Table (1): Shows hematological parameters of rats treated with Lincomycin (500 mg/kg) and Spectinomycin (250 mg/kg) after 21 and 30 days, respectively. (Mean ± SE)`n=6

Groups	RBCs 10^6/µL	Hb g/dL	PVC %	MCV Fl	MCH pg	MCHC %	TLC 103/µL	L 103/µL	N 103/µL	M 103/µL
Control	15.31± 0.30^{a}	8.06± 0.10^{a}	45.85± 0.49^{a}	56.93± 0.67^{a}	19.01± 0.39^{a}	33.37± 0.35^{a}	15.88± 0.77^{a}	10.78± 0.76^{a}	4.91± 0.16^{a}	0.19± 0.09^{a}
Lincomycin	13.42± 0.50^{b}	7.20± 0.31^{bc}	41.35± 0.77^{bc}	57.83± 1.86^{a}	18.71± 0.53^{a}	32.43± 0.88^{a}	10.77± 0.94^{b}	6.47± 0.60^{bc}	4.14± 0.44^{ab}	0.16± 0.05^{a}
Spectinomycin	12.90± 0.65^{b}	6.97± 0.34^{c}	40.68± 0.63^{c}	59.17± 3.35^{a}	18.67± 1.10^{a}	31.77± 1.77^{a}	10.57± 0.72^{b}	5.18± 0.36^{c}	5.06± 0.32^{a}	0.33± 0.01^{a}

Means having dissimilar superscript letters in the same column are significant ($P<0.05$).

Table (2): Shows the serum liver function tests of rats treated with Lincomycin, Spectinomycin and Lincospectin after 21, 30 and 21 days respectively (Mean ± SE):

Groups	ALT/UL	AST/UL
Control	20.80 ±.92^{c}	75.29±3.13^{c}
Lincomycin	27.79±.22^{a}	99.66±6.86^{a}
Spectinomycin	25.67 ±.37^{b}	91.01±5.34^{ab}

Means having dissimilar superscript letters in the same column are significant (P<0.05).

Table (3): Showing the serum biochemical parameters tests of rats treated with Lincomycin and Spectinomycin after 21, 30 and 21 days respectively (Mean ± SE):

Groups	Cholesterol /mg/dl	Triglyceride mg/dl	HDL mg/dl	LDL mg/dl
Control	91.15±2.35^{b}	159.63±3.38^{b}	52.20±2.26^{a}	7.01 ±3.32^{c}
Lincomycin	138.62± 7.09^{a}	196.07±3.38^{a}	45.01±.80^{b}	54.39± 7.11^{a}
Spectinomycin	125.80±7.87^{a}	191.89±3.31^{a}	41.61±.84^{bc}	45.83 ±7.79^{a}

Means having dissimilar superscript letters in the same column are significant (P<0.05).

Table (4): Showing the serum kidney function tests of rats treated with Lincomycin and Spectinomycin after 21, 30 and 21 days respectively (Mean ± SE):

Groups	Urea mg/dl	Creatinine mg/dl
Control	51.12± 2.38^{c}	.72±.02^{b}
Lincomycin	55.61±1.32^{c}	.80±.02^{b}
Spectinomycin	81.17 ±3.29^{a}	1.05 ±.04^{a}

Means having dissimilar superscript letters in the same column are significant (P<0.05).

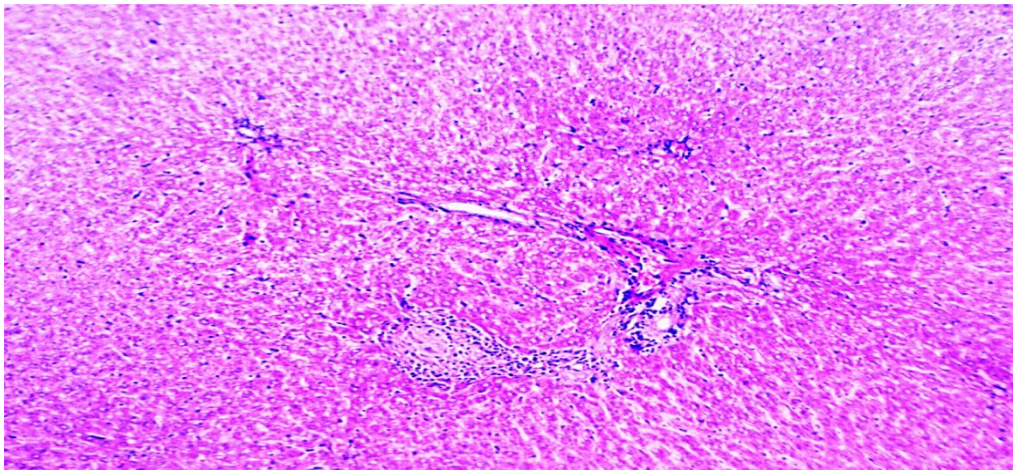

Fig (1): Liver of lincomycin treated rat showing focal area of necrosis surrounded by leukocytic cells with presence of leukocytic cells infiltration in portal area (H&E x 50).

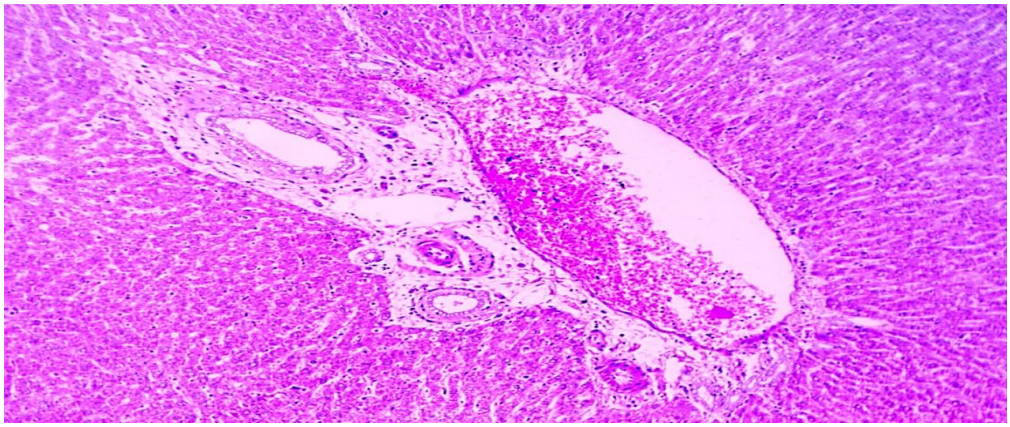

Fig (2): Liver of lincomycin treated rat showing congested hepatic vein, edema and eosinophiles infiltration in portal area (H&E x 50).

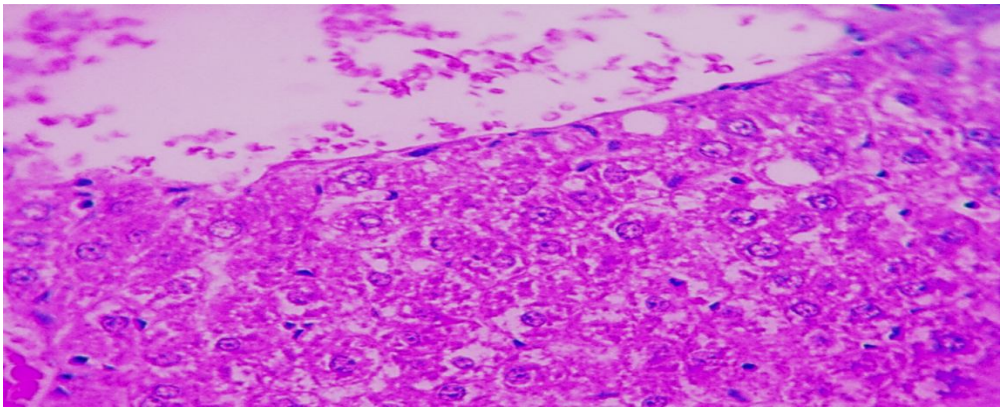

Fig (3): Liver from lincomycin treated rat showing swollen hepatocytes affected with hydropic degeneration (H&E x 100).

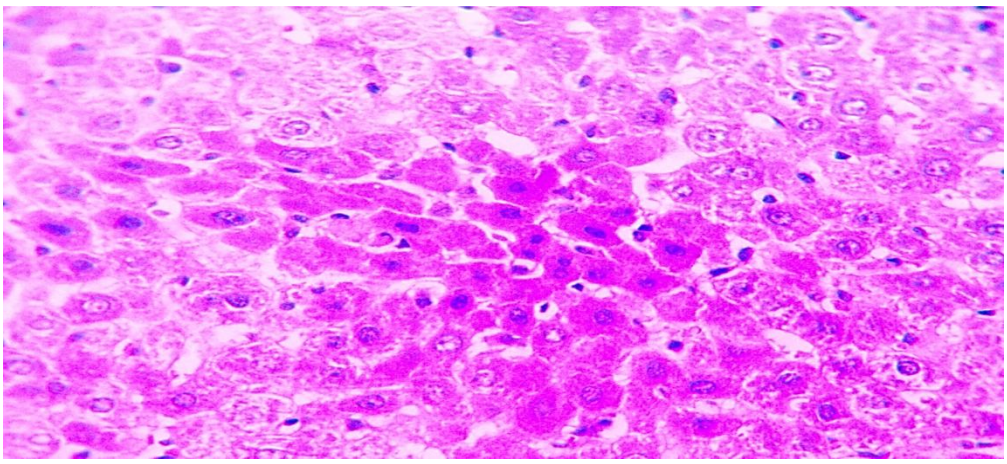

Fig (4): Liver from spectinomycin treated rat showing individual cell death with more eosinophilic cytoplasm and pyknotic nuclei (H&E x 100).

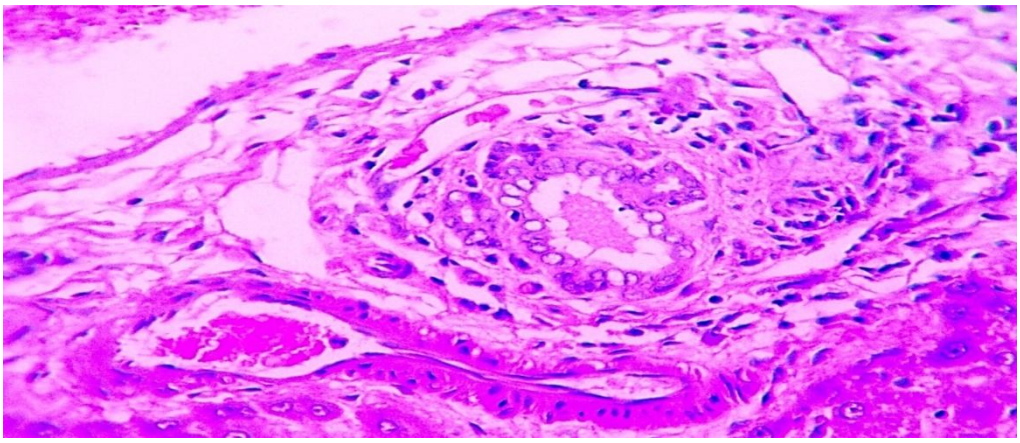

Fig (5): Liver from spectinomycin treated rat showing fibrous tissue proliferation and biliary epithelium hyperplasia with leukocytic cells infiltration (H&E x 100).

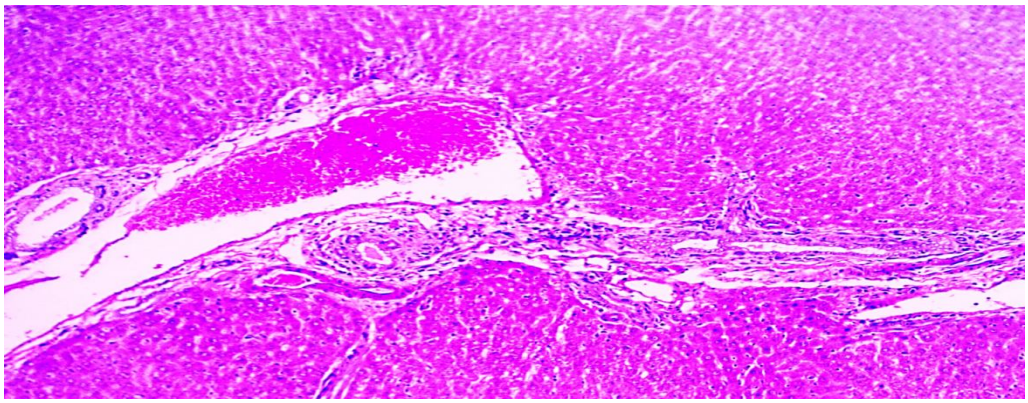

Fig (6): Liver from spectinomycin treated rat showing congested hepatic vein with fibrous tissue proliferation and leukocytic cells infiltration in portal area (H&E x 50).

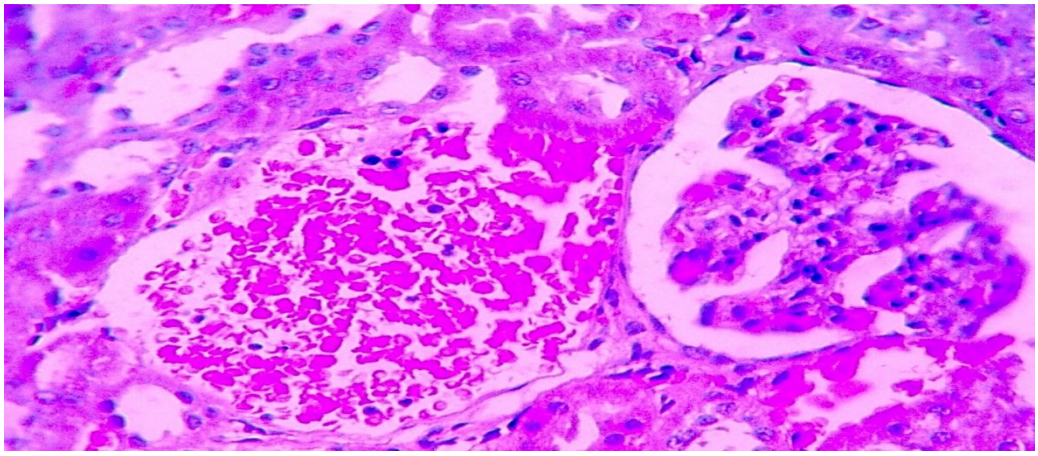

Fig (7): Kidney from lincomycin treated rat show congested renal blood vessel (H&E x 100).

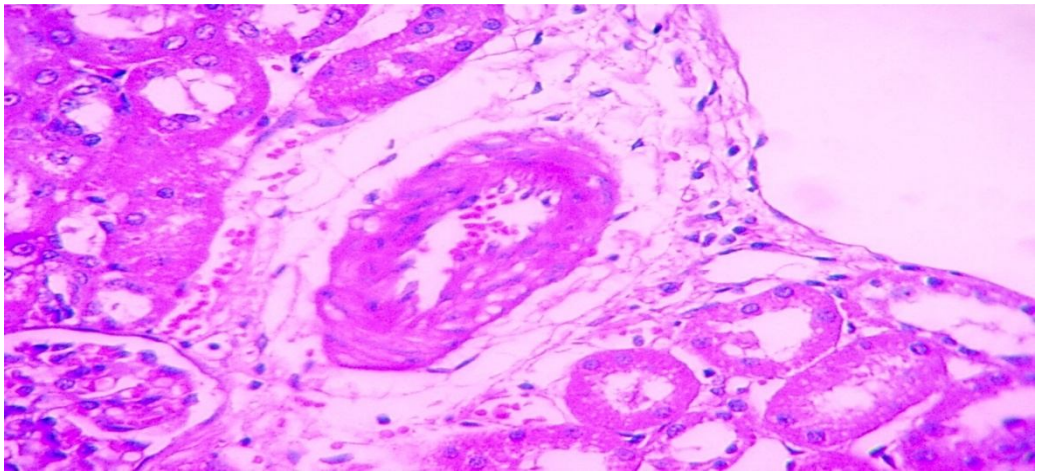

Fig (8): Kidney from lincomycin treated rat showing perivascular edema (H&E x 100).

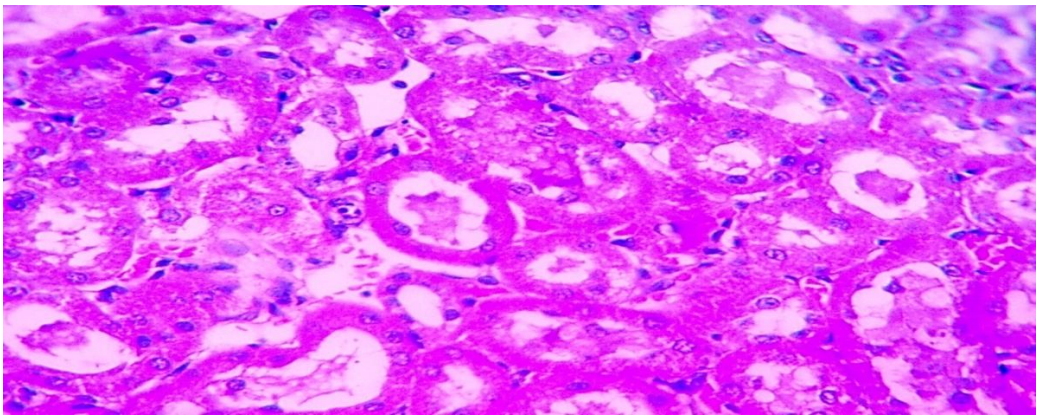

Fig (9): Kidney from lincomycin treated rat showing dilated renal tubules with tubular hyaline casts (H&E x 100).

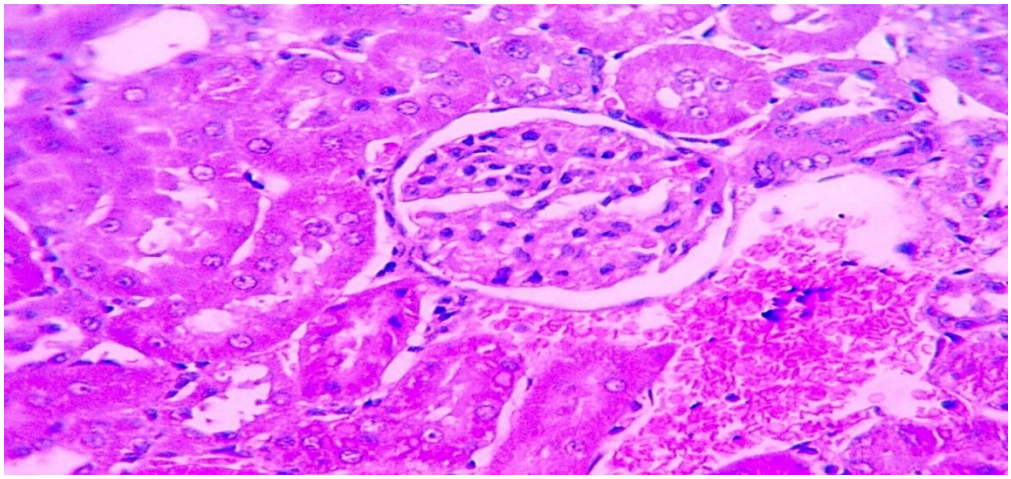

Fig (10): Kidney from Spectinomycin treated rat showing congested blood vessel (H&E x 100).

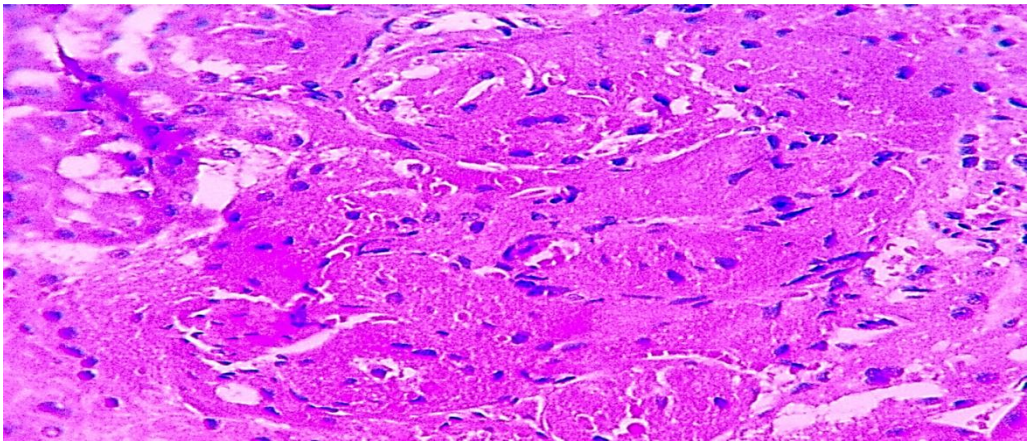

Fig (11): Kidney from Spectinomycin treated rat showing necrotic renal tubules (H&E x 100).

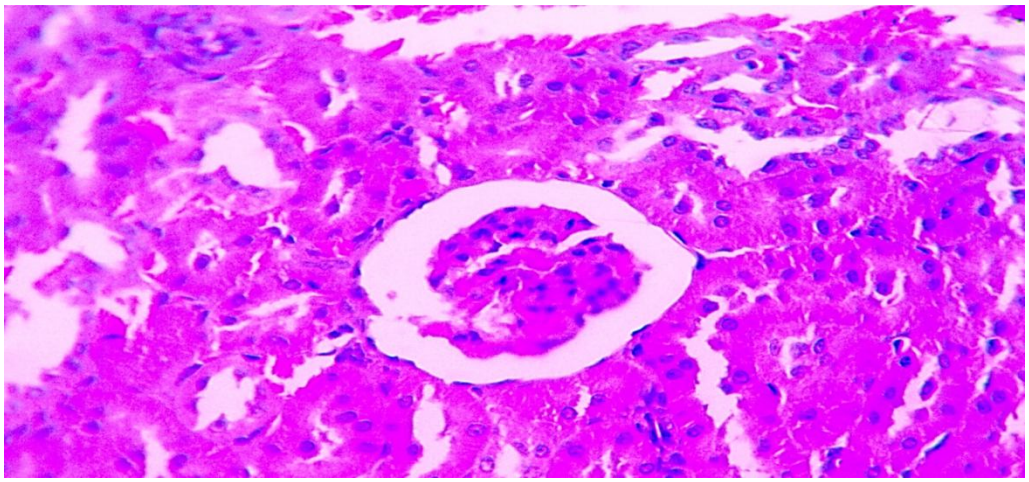

Fig (12): Kidney from Spectinomycin treated rat showing edematous renal tubule (H&E x 100).

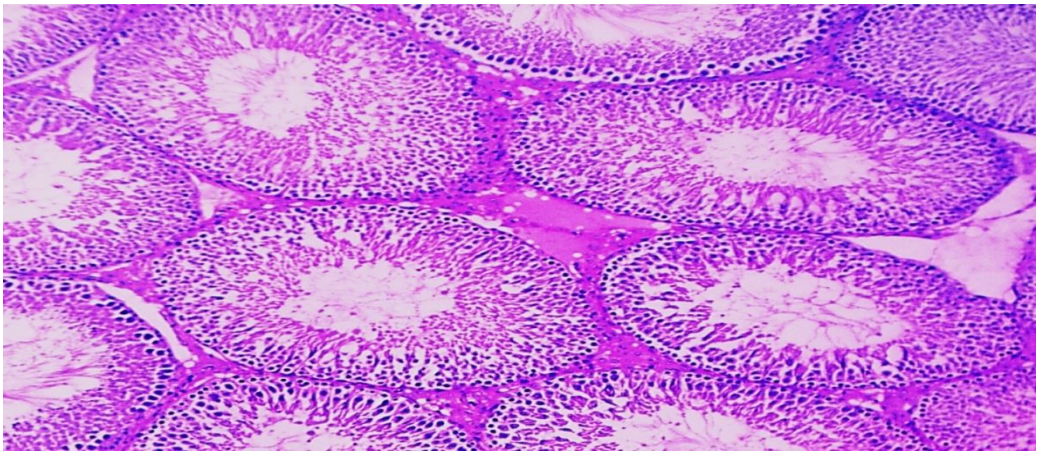

Fig (13): Testis from lincomycin treated rat showing interstitial eosinophilic edema in between seminiferous tubules (H&E x 100).

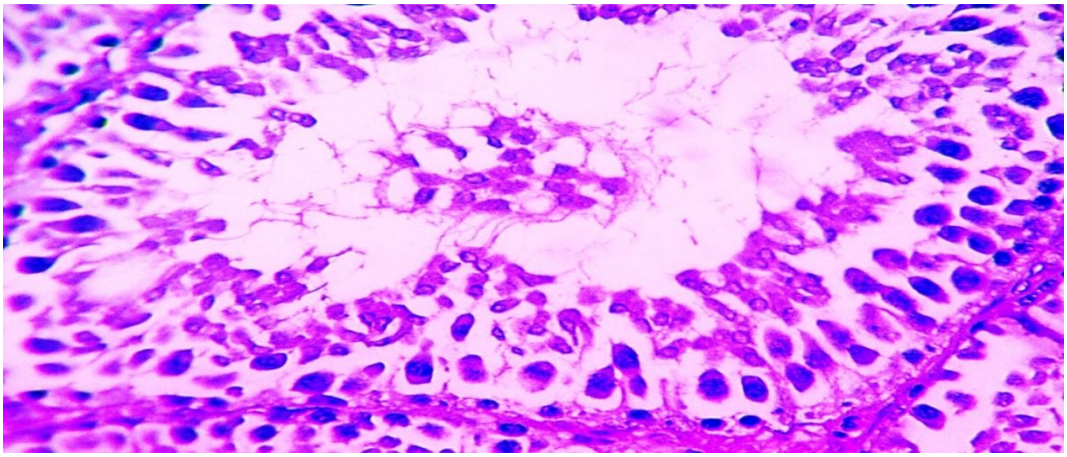

Fig (14): Testis from lincomycin treated rat showing desquamated spermatocytes in lumen of seminiferous tubules (H&E x 200).

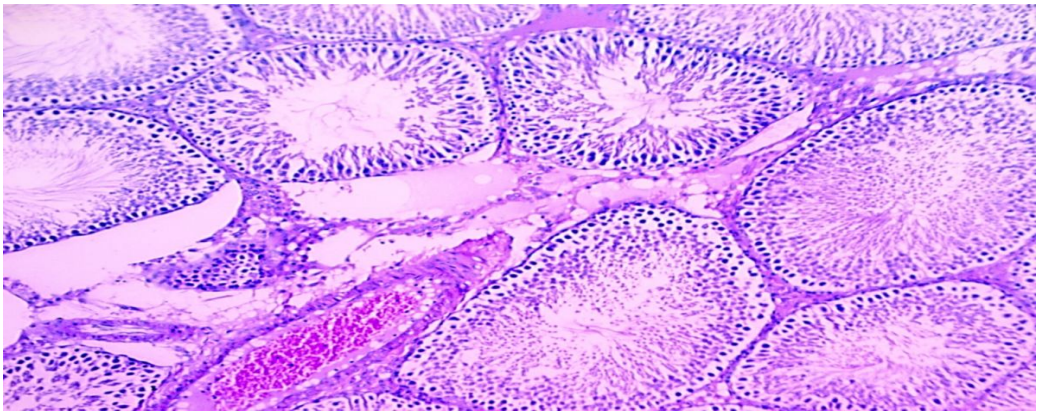

Fig (15): Testis from lincomycin treated rat showing congested blood vessel and interstitial eosinophilic edema (H&E x 100).

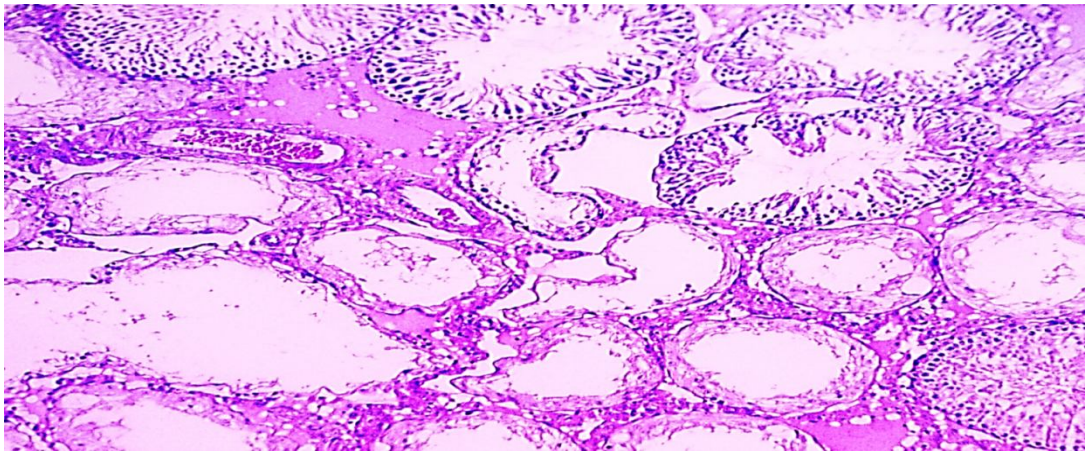

Fig (16): Testis from Spectinomycin treated rat showing irregular outlined seminiferous tubules lined with necrotic spermatocytic cells with arrested spermatogenesis and interstitial eosinophilic edema (H&E x 50).

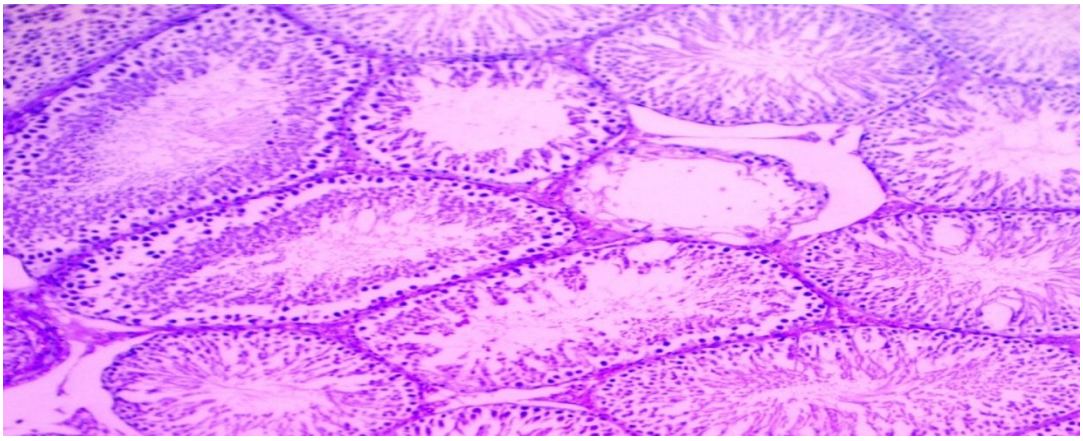

Fig (17): Testis from Spectinomycin treated rat showing vacuolation and necrosis in spermatocytic cells accidently seen in few seminiferous tubules (H&E x 100).

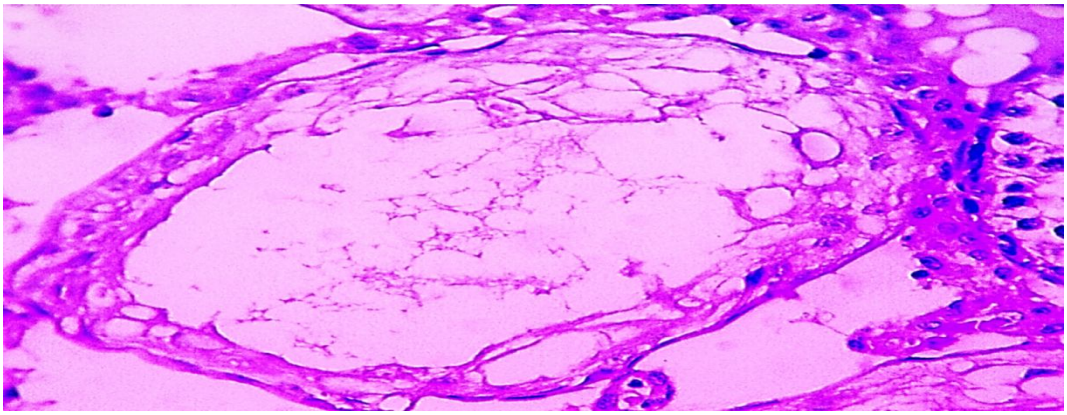

Fig (18): Testis from Spectinomycin treated rat high power to show vacuolated and necrotic spermatocytic cells with arrested spermatogenesis (H&E x 200).

DISCUSSION

In this study, the hematological parameters of rats treated orally with lincomycin for 21 days showed a significant decrease in RBCs count, Hb, PVC and TLC count. These results may reflect the adverse effect induced in the haemopoietic organs. The decreased RBCs count may be related to inhibition of erythropoiesis or decreased flow rate of RBCs from the spleen, while the reduction of Hb value may be the result of drug action. These results agreed with **Wade et al, (1977)** who stated that, prolonged administration of lincomycin induced granulocytosis, leucopenia, and thrombocytopenia, and with **Jwad et al, (2015)** who mentioned that, lincomycin elicited a significant decrease in hemoglobin concentration, packed cell volume and white blood cell.

Our study revealed a significant reduction in RBCs count, Hb, PVC and TLC count in spectinomycin treated group. These results were in agreement with those of **Ray and Ceru (1969)** who reported that spectinomycin given to the rat at highest subcutaneous dose for three months decreased RBCs, PVC and Hb. **Novack et al, (1974)** and **Wade et al., (1977)** also mentioned that the repeated dose of spectinomycin evoked a decrease in hemoglobin and blood count. Similarly **Toncho et al, (2007**) reported that, healthy goats received spectinomycin (20mg/kg) showed some hematological changes (reduction in erythrocytes, leukocytes counts, hematocrit percentage, hemoglobin concentration, and differential leucocytic counts).

The increased levels ALT and AST activities may be due to the damage of hepatocytes. This elevation may be attributed to the release of these enzymes from the cytoplasm into the blood circulation after rupture of the plasma membrane and cellular damage.

Regarding the effect on enzymatic markers of liver function test, ALT and AST our results revealed a significant increase after 21 days post oral administration of lincomycin, and 30 days post subcutaneous spectinomycin administration. These results were in accordance with those of **Gray and Purmalis, (1964**) who found that administration of lincomycin at higher doses (three times a day for 90 day) to beagles increases serum alanine aminotransferase activity, but the level had returned to the normal level by the end of the experimental study. Moreover, **Ulrich et al, (1990**) and **Jwad et al, (2015**) mentioned that hight does of trospectomycin sulfate when given intravenously or subcutaneously to laboratory animals, evoked a significant increase in serum levels of alanine and aspartate transaminase activities.

In this study the levels of serum cholesterol, triglycerides and LDL were increased significantly, while the level of HDL was significantly decreased in lincomycin and spectinomycin treated groups. These results agree with **Jwad et al, (2015**) who proved a significant increase in cholesterol, triglycerides, low density lipoprotein and decrease in high density lipoprotein in male albino rats received daily dose of 500 mg /Kg bw lincomycin. **Malamo et al, (2004**) showed a significant increase in serum cholesterol concentration in rats injected subcutaneously with 50 mg /Kg/day bw of Spectinomycin combined with 70 mg /Kg /day bw of ethanol subcutaneously for seven days.

The elevated serum cholesterol, triglycerides and LDL levels and decreased HDL may be attributed to liver or kidney

damage or even heart. As, serum cholesterol concentration has been reported to be an indicator of degenerative renal epithelial cells usually in nephritic condition (**Marsh, (1985**).

An elevated level of serum cholesterol is positively related to the risk of coronary disease (atherosclerosis) characterized by an increase in serum high-density lipoproteins (HDL) and decrease in serum low-density lipoproteins (LDL) in patients with cardiovascular disease (**Gordon et al, 1977**).

The present study demonstrates an increase in the level of triglycerides and cholesterol and decrease in serum HDL level of lincomycin and spectinomycin treated rats. **Cheik et al., (2008**) reported that hypercholesterolemia and hypertriglyceridemia are risk factor for predicting coronary heart disease, as well as HDL may plays an essential role in the transport of cholesterol to the liver for excretion into bile. Furthermore, impaired hepatic function may also have affected cholesterol metabolism.

The histopathology examination showed many lesions in liver, kidney and testis of lincomycin and spectinomycin treated groups. **Bell et all., (1980**) demonstrated that following lincomycin therapy, renal biopsy showed acute interstitial nephritis characterized by infiltration of neutrophils, plasma cells and lymphocytes in the medulla, edema, degenerative tubules, dilated endoplasmic reticulum and swollen and disrupted mitochondria. Moreover, **Anufrieva et al, (1990**) mentioned that, the intoxication picture after a single inhalation of lincomycin was characterized by renal dysfunction. In addition, **Roger et al, (1994**) reported that following spectinomycin treatment in cattle, the histopathological analysis revealed congestion, and hemorrhage in several organs.

CONCLUSION

It could be concluded that both tested drugs evoked some adverse effects on some hematological and biochemical parameters in treated rats., Regarding to the above mentioned parameters we can also conclude that spectinomycin has more effect on kidney than lincomycin, while lincomycin has more effect on liver than spectinomycin.

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الملخص العربي

الآثار السلبية للينكومايسين والإسبكتينومايسين في الفئران

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أجريت هذه الدراسة على عدد ٢٤ من ذكور الفئران (١٧٥ – ٢٥٠ جم) السليمة إكلينيكيا لتقييم الآثار السلبية عند استخدام كل من اللينكومايسين (٥٠٠ مجم/كجم) المعطى بالفم مرة واحدة فى اليوم لمدة ٢١ يوما متتاليا، والاسبيكتينومايسين (٢٥٠مجم/كجم) المعطى بالحقن تحت الجلد مرة واحدة فى اليوم لمدة ٣٠ يوما متتاليا .على صور الدم، وظائف كل من الكبد و الكلى، و كذلك دراسة التغيرات الهستولوجية للعقاقير المستخدمة على كل من الكبد،الكلية و الخصية.

تم تقسيم الفئران إلى ٣ مجموعات (بواقع ٨ فئران لكل مجموعة) على النحو التالي :

- المجموعة الأولى : استخدمت كمجموعة ضابطة.
- المجموعة الثانية : أعطيت عقار اللينكومايسين (٥٠٠ مجم/كجم) عن طريق الفم مرة واحدة فى اليوم لمدة ٢١ يوما متتاليا.
- المجموعة الثالثة : أعطيت عقار والاسبيكتينومايسين (٢٥٠مجم/كجم) عن طريق الحقن تحت الجلد .

تم أخذ عينات للدم من كل مجموعة (بواقع ٦ فئران) ٢٤ ساعة بعد انتهاء العلاج و ذلك لقياس صور الدم و للحصول أيضا على مصل الدم لقياس مستوى كل من الإنزيمات الدالة على وظائف كل من الكبد و الكلى بالإضافة الى بعض القياسات البيوكيميائية للمصل. وقد تم تشريح الفئران لأخذ عينات من الكبد، الكلية و الخصية لدراسة التغيرات الهستولوجية للعقاقير التى استخدمت.

هذا و قد أظهرت النتائج ما يلى :

١- إن كل من عقار اللينكومايسين و الاسبيكتينومايسين قد احدثا تغيرات سلبية فى صور الدم بالمقارنة مع المجموعة ا لضابطة متمثلة فى انخفاض ملحوظ فى العدد الكلى لخلايا كريات ا لدم الحمراء، تركيز الهيموجلوبين و حجم الدم المضغوط. كما أظهرت النتائج إن عقار اللينكومايسين و الاسبيكتينومايسين أحدثا انخفاضا ملحوظا فى العدد الكلى لخلايا كريات ا لدم البيضاء و عدد الليمفوسايت.

٢- بدراسة تأثير اللينكومايسين و الاسبيكتينومايسين على مستوى انزيمى الاسبرتات أمينو ترانسفيراز و الألانين أمينو ترانسفيراز،مستوى تركيز اليوريا و الكرياتنين ، الترايجليسرايد و ال LDL فى مصل الفئران المستخدمة وجد أن هذه العقارات أحدثت زيادة معنوية فى تلك القياسات بالمقارنة مع المجموعة ا لضابطة. وقد أحدثت أيضا هذه العقاقير ا انخفاضا ملحوظا فى ال LDL بالمقارنة مع المجموعة ا لضابطة.

٣- ان اللينكومايسين و الاسبيكتينومايسين قد احدثا بعض التغيرات الهستوباثولوجية على كل من كبد، كلى و خصية الفئران المستخدمة.

الخلاصة

يستخلص من هذه الدراسة أن كل من عقاري اللينكومايسين و الاسبيكتينومايسين أظهرا تأثيرا سلبيا على صور الدم، و بعض القياسات البيوكيميائية بمصل الفئران المعالجة، بالإضافة إلى بعض التغيرات الهستوباثولوجية التى ظهرت على كل من كبد، كلى و خصية الفئران المستخدمة.