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Effect of levofloxacin on some body tissues in mice

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Abstract

Levofloxacin is a third generation of fluoroquinolones family. It is commonly used in the treatment of a several bacterial infections. However, misusing antibiotics impose damage to hepatocytes and myocytes. The present study was conducted to access the effect of levofloxacin on tissue histology in mice taking in consideration dose and duration of exposure. 24 matured male Albino mice were divided into 3 groups, Group G1: was considered as a control group. They received normal saline intraperitoneally / day. Group G2: They received 10.7 mg/kg/day of levofloxacin intraperitoneally for 10 days. Group G3: They received 10.7 mg/kg/day of levofloxacin intraperitoneally for 3 weeks. Microscopic examination of liver sections of group G2 revealed severe congestion of blood vessels in the portal area and central veins with inflammatory cells infiltration. While in group G3, Apoptosis, Degeneration and necrosis of hepatocytes with giant cell transformation were noticed. In addition to kupffer's cell activation. Heart sections showed moderate congestion of blood vessels with edema in between the myocytes and inflammatory cells infiltration. Group G3 Necrosis with pyknosis of cardiac muscle nuclei was noticed. We concluded that levofloxacin induces toxic effects on liver and heart according to the dose of administration and duration of treatment.

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Introduction

Fluoroquinolones are now being used for treatment of various bacterial diseases in animals (1). Levofloxacin is a third generation fluoroquinolone that possesses activity against most aerobic gram positive and gram negative organisms and demonstrate moderate activity against anaerobes as well as atypical pathogens, such as mycoplasma and chlamydia (2). Generally, flouroquinolones has been associated with certain adverse effects, and regarding levofloxacin although undergoes limited metabolism in human body being primarily excreted as unchanged drug in the urine (3), but with its wide scale use, has been implicated in many instances of clinically apparent liver injury (4). The mechanism of how fluoroquinolones induce toxic effect on liver is still under research. It has been suggested that the oxidative radical's species (ROS) are generated due to destruction of critical mitochondrial enzymes in addition to those liberated in RNA processing, transcription and inflammation may result in oxidative stress and cellular damage to the liver and kidneys (5-7). With regard its cardiac adverse effects flouroquinolones were reported to increase the risk of fatal arrhythmias and sudden death, Cho and Park 2018 claimed that oral levofloxacin can induce serious ventricular arrhythmia in Korean population (8). Additionally, moxifloxacin and levofloxacin are known to cause higher risk of fatal cardiac arrhythmias (9). The aim of the study was to assess the effects of certain dose of levofloxacin for certain duration on liver and cardiac cells at the histopathological changes level.

Materials and methods

Drug used

Levofloxacin used in this study was obtained from Denk Pharma company, Munch, Germany under traditional name (Levoflox-Denk, 100ml vial, 5 mg/ml).

The approval of the study

The approval of the study protocol by an ethic committee has been obtained from the local health committee of College of Medicine, University of Mosul, Iraq.

Study Design

An Interventional non- randomized opened experimental study design was assumed in the present study.

Animals and administration

Twenty-four male Albino mice were treated in this study. They were eight weeks old and their weights were ranging from 20 to 34gm. They were housed in the animal house of College of Veterinary Medicine, University of Mosul. They were kept in wire mesh cages 12*20*10 cm, eight mice in each cage. At room temperature 25±2ºC, 12-hour light: dark, and had free access to tap water and food ad libitum (10). The treated mice were divided into three groups, eight animals in each group. Group one (G1) was considered as a control group. They received normal saline intraperitoneally/day. Group two (G2) They received 10.7 mg/kg/day of levofloxacin intraperitoneally for 10 days. Group three (G3) They received 10.7 mg/kg/day of levofloxacin intraperitoneally for 3 weeks. Histological sections from liver and heart were stained with hematoxylin and eosin and examined by light microscope.

Results

Group G1

The liver was brown color and smooth surface, and firm in consistency. Sections were taken from this group showing healthy hepatic lobules with normal hepatocytes and sinusoids. The bile ductules were looked normal (Figure 1). The epicardial surface is smooth and glistening. All three layers of the heart (endocardium, myocardium, and pericardium) looked healthy and well distinguished (Figure 2).

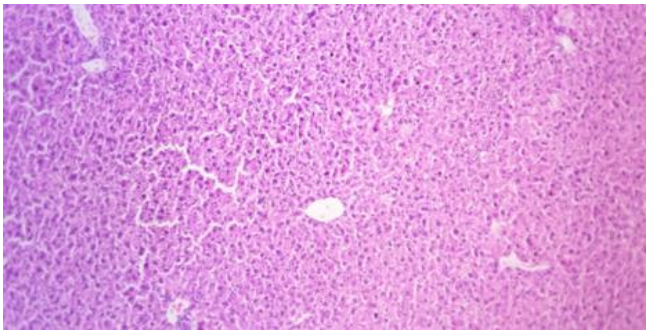

Figure 1: Photomicrograph of liver group G1 showing normal hepatocytes, central vein, and portal area. H&E, 100x.

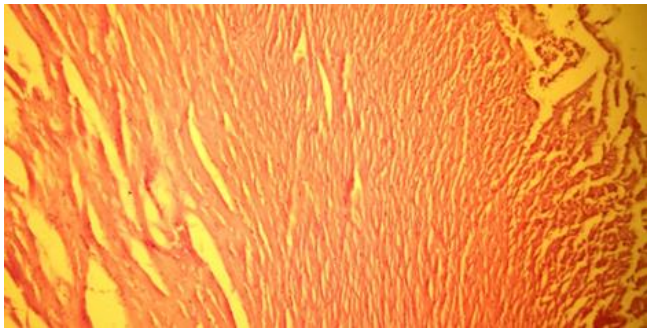

Figure 2: Photomicrograph of heart group G1 showing normal myocytes. H&E, 100x.

Group G2

Microscopic examination of liver sections of this group revealed severe congestion of blood vessels in the portal area and central veins with inflammatory cells infiltration of periportal area and around central veins (Figure 3 and 4). Microscopic examination of heart sections showed moderate congestion of blood vessels. In addition to edema in between the cardiac muscle and infiltration of inflammatory cells within the myocytes (Figure 5 and 6).

Group G3

Microscopic examination of liver sections revealed dilatation and congestion of central veins. Mononuclear and macrophage inflammatory cells infiltration around the central veins, in the sinusoids, and the periportal area (Figure 7). Apoptosis of hepatocytes also was observed (Figure 8). Degeneration and necrosis of hepatocytes with giant cell transformation (Figure 8 and 9). In addition to kupffer cells activation (Figure 10). Microscopic examination of all heart sections showed severe congestion blood vessels with hemorrhage in between cardiac myocytes (Figure 11). Chronic inflammatory cell infiltration between myocytes (Figure 12). Necrosis with pyknosis of cardiac muscle nuclei can be seen (Figure 13).

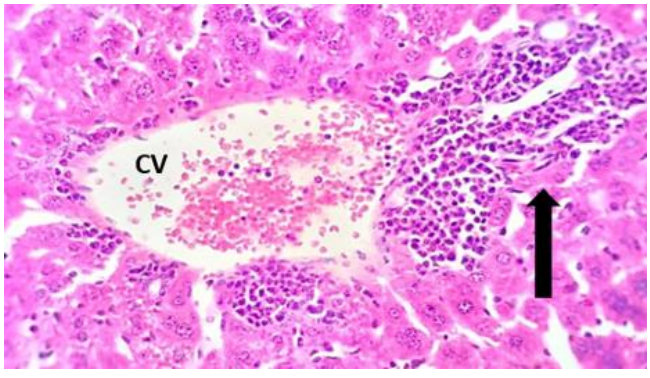

Figure 3: Photomicrograph of liver group G2 showing dilatation and congestion of central vein (CV). Chronic inflammatory cell infiltration (black arrow). H&E, 400x.

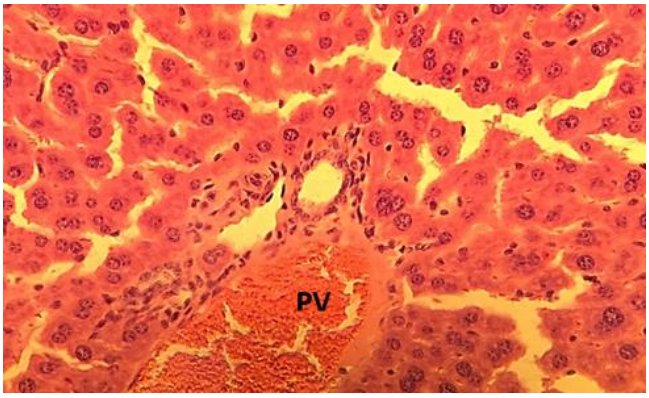

Figure 4: Photomicrograph of liver group G2 showing congestion of portal vein (PV). H&E, 400x.

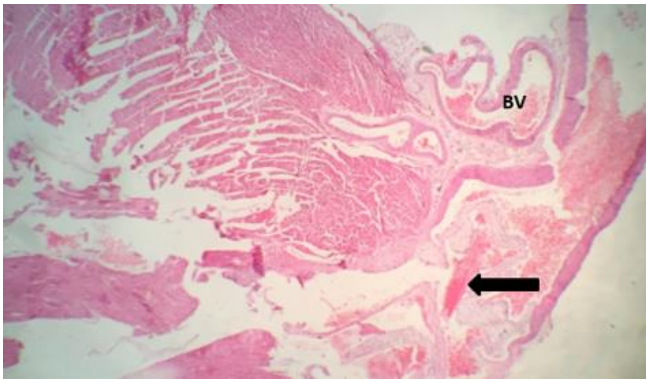

Figure 5: Photomicrograph of heart group G2 showing congestion of blood vessels (BV) and haemorrage between myocytes (black arrow). H&E, 100x.

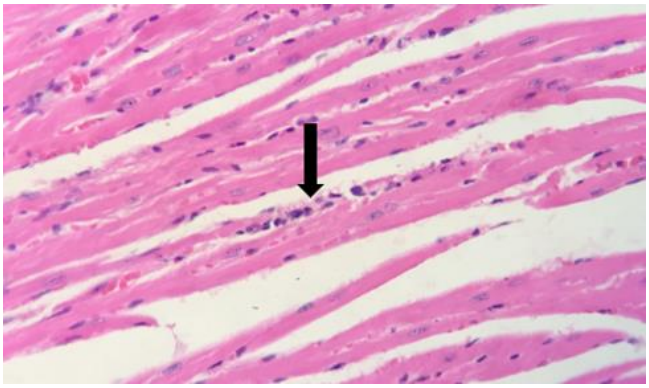

Figure 6: Photomicrograph of heart group G2 showing chronic inflammatory cell infiltration between myocytes (black arrow). H&E, 400x.

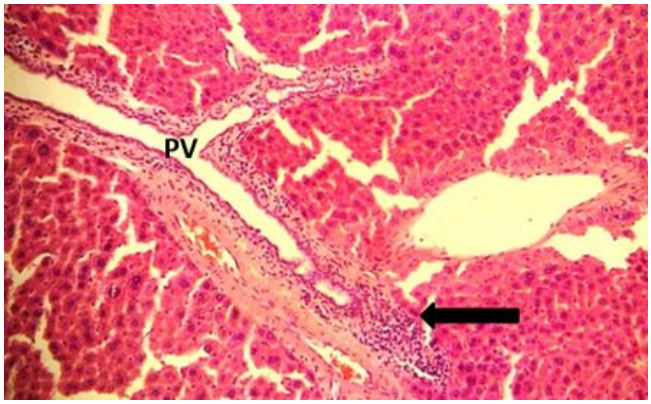

Figure 7: Photomicrograph of liver group G3 showing dilatation and congestion of portal vein with chronic inflammatory cell infiltration in the periportal area (Black arrow). H&E, 200x.

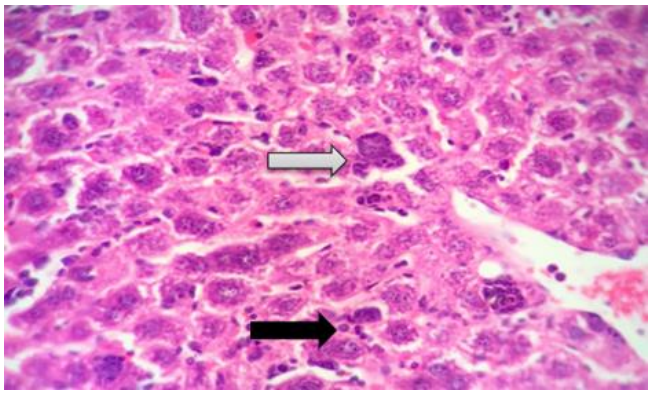

Figure 8: Photomicrograph of liver group G3 showing apoptosis of hepatocyte (black arrow). Giant cell transformation (white arrow) H&E, 400x.

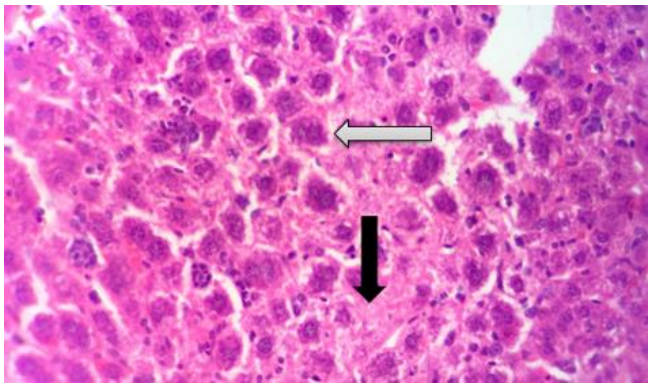

Figure 9: Photomicrograph of liver group G3 revealed necrosis of hepatocytes (black arrow). Giant cell transformation (white arrow). H&E, 400x.

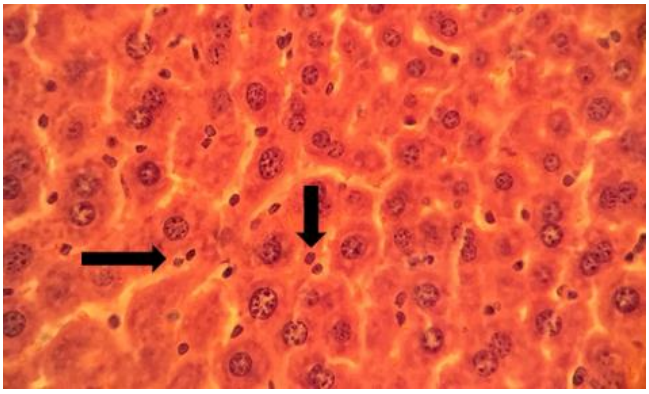

Figure 10: Photomicrograph of liver group G3 showing kupffer's cell activation (black arrows). H&E, 400x.

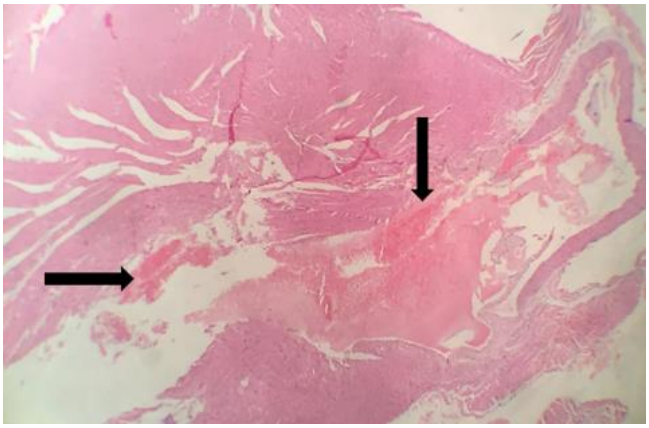

Figure 11: Photomicrograph of heart group G3 showing congestion of blood vessels with haemorrhage in between cardiac myocytes (black arrows). H&E, 100x.

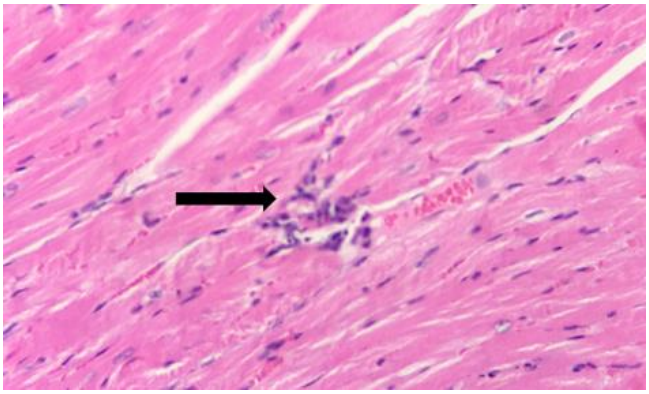

Figure 12: Photomicrograph of heart group G3 showing chronic inflammatory cell infiltration between myocytes (black arrow). H&E, 100x.

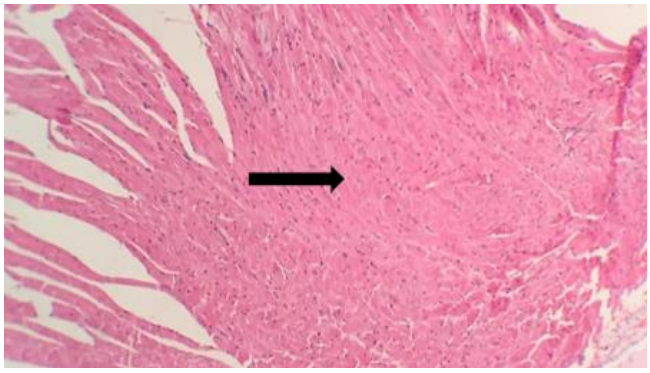

Figure 13: Photomicrograph of heart group G3 showing necrosis and pyknosis of cardiac myocytes (black arrow). H&E, 100x.

Discussion

Liver is the main organ responsible for the metabolism of drugs, chemicals and toxic agents. This makes liver target for reactive metabolites of drugs and more liable to necrosis and hepatitis (11).

Liver sections in group G2 showed mononuclear inflammatory cell infiltration around central vein and in the portal area. But in group G3 which received the same dose of levofloxacin but for a longer duration, sections showed coagulative necrosis and apoptosis of hepatocytes.

Although the mechanism of how the levofloxacin causing liver injury is not well understood, but reseaches suggested that the hepatic injury induced by flouroquinolones is mainly due to mitochondrial damage (12). Necrotic changes, inflammatory reaction and apoptosis are the most important and common outcomes in drug induced liver injury (13). Apoptosis is programmed cell death and regular cell turnover that occurs under body control (14). It occurs due to exposure to heat (15), chemicals, and drugs (16).

There are two pathways to apoptosis, the extrinsic and the intrinsic (mitochondrial) pathways. In both cases, there will be activation of caspase 3 and 7 results in a histological picture of apoptosis (proteolysis, pyknosis and karyorrhexis) (17).

These results were coincided with the results of Gulen *et al.* (6) reported a case of women presented with toxic hepatitis after 10 days of treatment with levofloxacin (750 mg/day). Biopsies of the patient revealed extensive necrosis of hepatocytes and pyknosis of nucleus. inflammatory cell infiltration in the portal area were noticed. They suggested that flouroquinolones cause direct damage to DNA gyrase of the microorganism but it also affects the mitochondria in mammalian DNA.

Schloss *et al.* (18) reported a case of hepatitis and high transaminases levels after 5 days of levofloxacin administration.

Olayinka *et al.* (19) used variant doses of levofloxacin, they found that after 7 days of administration there were high AST and ALT. They concluded that these changes were due to its effect on the antioxidant defense system by stimulating the oxidative stress. Schwalm and Lee (20) reported a case of hepatotoxicity in 73 old women after levofloxacin oral administration and they recognized the reversible effect after cessation of treatment. Exogenous sources like drugs, chemical agents, and environmental pollutants when metabolized in the body can lead to liberation of free radicals and direct damage of lipids peroxidation, proteins and DNA of the cell (21). Fluoroquinolones are identified to encourage the production of singlet oxygen and superoxide anion that are responsible for the toxic histological picture of the fluoroquinolones family (22).

Many mechanisms are detected to eliminate ROS or inhibit their production, like the elimination of superoxide and hydrogen peroxide to prevent the liberation of hydroxyl radicals, which are the most reactive species within the ROS clan (23).

Giant cell transformation was noticed in group G3 which received the drug for 3 weeks. It can occur in response to viral and autoimmune hepatitis, drugs or toxins exposure. It is formed due to merging of the injured liver cell or division of cells without mitosis (24). These results were coincided with the results of Orman *et al.* (25) who studied the features and patterns of Fluoroquinolone-induced liver injury. They found that liver biopsies of the patients revealed severe coagulative necrosis.

The results of the present study were coinciding with the study of Aba delrady *et al.* (26) they reported a loss of striation of cardiac muscles with edema between myocytes after long duration treatment with levofloxacin and ciprofloxacin in addition to harmful effects on the electrocardiograph (ECG) of the treated rats (26). These results were coincided with the results of Ravikumar *et al.* (27) they noticed congestion, hemorrhages in cardiac muscle and inflammatory cells infiltration between myocytes after administration of 10 mg/kg bw and 20 mg/kg b.wt of levofloxacin for 4 weeks in chicken. Absi *et al.* (28) noticed elongation of QT interval and ventricular fibrillation in addition to Dysglycaemia after intraperitoneal administration of levofloxacin to rats for 14 days. The findings of the present study are in accordance with Lin *et al.* (9) study, they described that a mild degree of congestion, perivascular of mononuclear inflammatory cell infiltration in the myocytes was detected.

Conclusion

Levofloxacin at this particular dose for long duration carry histopathological changes in the liver and cardiac cells of male albino mice.

Acknowledgments

The authors would like to express their deep thanks to the College of Medicine, University of Mosul.

Conflict of interest

The authors have no conflict of interest by any mean.

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تأثير عقار ليفوفلوكساسين على بعض انسجة الجسم في الفئران

رند عبد اللطيف عبد الله[١]، فاتن ذنون عبد الرحمن الطائي[١] و عماد عبد الجبار ذنون[٢]

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الخلاصة

الفلوكساسين هو الجيل الثالث للمضاد الحيوي الفلوروكوينولون ويستخدم على نطاق واسع في علاج عدد من الإصابات البكتيرية. سوء استخدام المضادات الحيوية يسبب ضررا على خلايا الكبد والقلب. وقد أجريت هذه الدراسة لمعرفة تاثير الفلوكساسين على انسجه الكبد والقلب لدى الفئران مع الأخذ بنظر الاعتبار الجرعة ومدة التعرض للعقار. أربعه وعشرون من ذكور الفئران البيضاء البالغة قسمت إلى ثلاثة مجاميع: المجموعة الأولى حقنت يوميا داخل الصفاق بالمحلول الملحي النظامي، المجموعة الثانية حقنت يوميا داخل االصفاق بعقار الفلوكساسين ١٠,٧ ملغم/كغم يوميا لمدة ١٠ أيام، المجموعة الثالثة حقنت يوميا داخل االصفاق بعقار الفلوكساسين ١٠,٧ ملغم /كغم لمدة ٣ أسابيع. الفحص المجهري لشرائح الكبد للمجموعة الثانية توضح احتقان شديد في الأوعية الدموية في منطقة البوابة والوريد المركزي مع تراكم خلايا التهابية. ولكن في المجموعة الثالثة، موت الخلايا المبرمج مع الانتكاس والتنخر كان ملحوظا. إضافة الى نشاط خلايا كبفر. شرائح القلب تظهر احتقان متوسط للأوعية الدموية مع حدوث وذمة وخلايا التهابية بين خلايا القلب. المجموعة الثالثة فقد لوحظ تنخر مع تغلظ في انوية خلايا القلب. نستنتج من هذا ان عقار الفلوكساسين له تأثيرات سمية على الكبد والقلب اعتمادا على الجرعة ومدة التعرض للعقار.

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