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Physiological and histopathological assessment of the liver and kidney of Rat following administration of a acetaminophen and enrofloxacine

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ABSTRACT

The study included three groups of rats, 5rats for each group each group of five rats. The first group (control) given distill water, the second received I.P 0.01ml acetaminophen and 0.01ml enrofloxacin 1\ml, while the third received I.P 0.01ml of acetaminophen and then after half an hour received 0.01 ml of enrofloxacin for 15 days. Haematological analysis of control and treatment group are presented that all groups no significant in haemoglobin concentration, and packed cell volume. While increased white blood cells in group 2 and 3 counts compared to the control. The results of liver enzyme analysis results indicated that group 2 caused a significant alteration in liver enzymes value compared with group1 and 3, while the results of urea and creatnine analysis there were insignificant alterations in urea and creatnine in both groups 2 and 3 comperes with group1. The histopathological examination (group second) of the liver showed that the thickening wall with fibrosis in the periportal area infiltration of inflammatory cells in the necrotic change of the hepatocytes massive vacuolation of the kupffer cell was the present intensity in the sinusoid. Lymphocyte infiltration in the kidney, congestion with glomerulus and tubular damage. In the third group, the histopathological changes were less when compared to the first group. The present study observed when using drugs at the same time leads to harmful effects on the body.

1. Introduction

Medicines are often used concomitantly with other drugs, and some degree of drug interaction occurs with concomitant use. Although only a small proportion of this interaction is clinically significant, it sometimes causes serious adverse reactions. For example, drug interactions, particularly with drugs having a narrow therapeutic

range, may have serious adverse consequences. Therefore, in the evaluation and clinical application of drugs, appropriate efforts should be made to predict the nature and degree of drug interactions so that patients will not be adversely affected. Humans are genetically diverse, and disease states are likewise diverse. It should, therefore, be kept in mind that drug interactions might readily cause clinically significant changes in blood drug levels (concentration in whole blood, plasma, or serum) in patients having pharmacokinetic parameters markedly deviating from those of the standard population. Drug interactions are classified, based on mechanism, into pharmacokinetic and pharmacodynamic interactions. The former interaction is the phenomenon that is induced by changes in blood levels and tissue distribution of a drug or its active metabolites by the interaction of the drugs in the processes of absorption, distribution, metabolism, and excretion.Since physical and chemical properties, pharmacologic action, pharmacokinetics, and clinical usage differ for each drug lead to harmful effects in the body. therefore, the relative time of administration of the two substances (interactions can be avoided if two drugs are taken at different times [1-3]. The liver is the most important organ for detoxification and deposition of endogenous and exogenous materials [4]. Hepatic injuries are a common sequela of liver diseases such as viral infection, hepatotoxins, xenobiotics, drugs, alcoholism and food poisoning which can devastate liver functions easily [5]. The kidneys provide the final common pathway for the excretion of many drugs and their metabolites and therefore are frequently subjected to high concentrations of potentially toxic substances [6]. Acetaminophen (acetaminophen) is one of the most commonly used analgesic–antipyretic drugs worldwide, and in most countries, it is available without a prescription. Acetaminophen overdose is known to cause hepatotoxicity and numerous studies about acetaminophen-induced hepatotoxicity and its mechanisms are available in the literature. Significant acetaminophen-induced hepatotoxicity usually triggers nephrotoxicity. Renal insufficiency is reported to occur in 1–2% of patients exposed to acetaminophen toxicity. After oral administration, about 63% of acetaminophen is metabolized via glucuronidation and 34% via sulphation primarily in the liver. The water-soluble metabolites consisting of these metabolic pathways are excreted via the kidney. N-Acetyl-p-benzoquinone (NAPQI) is a reactive intermediate that occurs when oxidization of55% percent of acetaminophen takes place by the microsomal P-450 enzyme system. NAPQI is detoxified by intracellular glutathione (GSH) in therapeutic doses. Accordingly, NAPQI has been implicated as a responsible metabolite of acetaminophen toxicity. In acetaminophen over dosing cases, glutathione stores are depleted, and a rapid increase in the concentration of NAPQI causes necrosis. Acetaminophen toxicity creates acute tubular necrosis, which is one of the main causes of acute renal failure. Serum urea and creatinine

levels may be indicators of acute tubular necrosis induced by acetaminophen. Free radicals are produced by exposure to drug toxicity in an organism, and oxidative damage plays an important role in acetaminophen-induced hepatorenal injuries [7-9]. Enrofloxacin is a member of the family of 6-fluoro-7-piperazinyl-4-quinolones.1 This antibiotic is highly lipophilic, and the addition of a carboxic acid and a tertiary amine contributes to the amphoteric properties of enrofloxacin.2 Enrofloxacin is bactericidal and has excellent activity against both Gram-positive and Gram-negative pathogens. This antibiotic has also been used to control certain intracellular pathogens. Modification of the 4-quinolone ring has enhanced the antimicrobial activity of this compound. The oral bioavailability of enrofloxacin is excellent in monogastric mammals and preruminant calves, with up to 80% of the ingested dose being absorbed into the systemic circulation.Enrofloxacin alters the action of bacterial DNA gyrase, a type II topoisomerase. This enzyme is involved in unwinding, cutting, and resealing DNA. There are two subunits to DNA gyrase: subunit A and subunit B. Enrofloxacin acts on the nalA locus of subunit A. Inhibition of the gyrase leads to rapid cell death in bacteria. The concentration of fluoroquinolones required to alter the DNA of mammalian cells is two orders of magnitude higher than the concentration against bacterial DNA. [6,7]. The adverse effects associated with fluoroquinolones are primarily associated with abnormal development of immature cartilage, the urinary and gastrointestinal tracts, and the central nervous system. Arthropathies have been reported in immature rats, beagles, guinea pigs, and foals. The cartilaginous surfaces of the femur, humerus and tibial tarsal bone are the primary sites where fluoroquinolone induced arthropathies occurred in beagle pups [10-13].

2. Materials and Methods

2.1Study design

Wistar rats [9] weeks old, 180-200 g body weight) used in these trials were divided into three groups of 15 animals each (control group and 2experimental group). and the rats were maintained and acclimatized in the college of veterinary medicine –Tikrit university under laboratory conditions in group cages. The rats were fed standard diet pellets and water was provided at the lab. The rats were allocated randomly into three groups 5for each; group(A) was kept as control, group(B) 5Rats were given an intraperitoneal (IP) injection acetaminophen 0.01 ml\body weight and enrofloxacine. Treatment was last for 15 days. The blood was withdrawn from the Rats heart. Each blood sample was collected and then. The animals were killed on the day after the last dose under an intensive dose of chloroform. Kidneys and livers of the animals were rapidly removed and micro dissected to obtain tissue samples for histological examination. Blocks of tissues were immediately fixed in 10% neutral buffered formalin, dehydrated with graded series of ethyl alcohol and embedded in paraffin. Sections of 5 microns were cut and stained with eosin and hematoxylin according to [16].

Photomicrographs of the slides were taken using a digital camera attached to a light microscope. The whole photomicrographs were compared with those of the liver and kidneys of the control group.

2.2 Chemicals compounds

Acetaminophen powder was purchased from Enrofloxacine

2.3 Experimental design

After a period of adaptation for one week prior to the experiment, animals were randomly divided into three groups (n = 3 per group) and treated as follows

Group 1: Control received amount of distilled water equivalent to that given in treatment solution for experimental rats.

Group 2: Acetaminophen, treated in a dose of 0.01ml WB/day I/P. and Enrofloxacine 0.01ml WB\day at the same time

Group 3: Acetaminophen treated in a dose of 0.01ml WB/day I/P. after half-hour treated in a dose enroflxacine 0.01 ml WB\day I/P.

2.4 Blood sampling

Blood samples were collected between 8 and 10 a.m. to avoid circadian rhythm induced changes. The blood samples were collected in tubes using K-EDTA as anticoagulant for haematological analysis and in tubes without anticoagulants for the other analysis. Biochemical parameters were measured on the day of sacrifice.

2.5 Haematological methods

EDTA-added whole blood samples were used for haematological examination. Haematological parameters included number of white blood cell (WBC), Packed cell volume (PVC), haemoglobin (Hb) concentrat values weredetermined by standard methods on an automated haematology analyzer (Horiba Medical ABXMicros 60, Japan).

2.6 Biochemical methods

Blood samples in non-anticoagulant tubes were centrifuged at 4000 rpm for 15 min at +4 °C, and serum was used. Measurement of biochemical parameters for serum liver enzyme and kidney function (GPT)(glutamate-pyruvic transaminase) and (GOT)(glutamate oxaloacetatic transaminase), Urea and Creatnine.

2.7 Histopathological examination

The stored livers and kidney were used to prepare sections using a rotary microtome at 5 µm, then were stained with hematoxylin and eosin (H&E). The sections were examined under a light microscope. The various changes in histological features were graded[18].

2.8 Biochemical laboratory test

The measurement of plasma enzyme activity is a helpful diagnostic tool in mammalian pathological, toxicological and general clinical testing. Recently there have been some attempts to utilize

these techniques in aquatic toxicology studies, In mammalian toxicology, the identification of altered plasma enzyme patterns can be used to evaluate the functional status of the damaged organ(s) or tissue(s), the measurements of glutamate exaloacetate transaminasen (GOT) and glutamate pyruvate transaminase (GPT) in grey mullet.) and Urea and Creatnine [14].

Haematology tests include laboratory assessments of blood formation and blood disorders. Some examples of these tests are Full blood count - A count of the total number of red blood cells, white blood cells, PCV, and platelets present in the blood .

2.8.1 White Blood Cells (WBC) Testing

White blood cells are responsible for assisting the body's defences in fighting illnesses and disease. Knowing how many white cells are within the blood can prove invaluable for diagnosing and treating a range of conditions. Increased white blood cells are common in people fighting infection or suffering from anaemia.

2.8.2 Red Blood Cells (RBC) Testing

The number of red blood cells in the body can increase through dehydration, stress and anxiety, or failure of the bone marrow, to name a few conditions. Decreased blood cells can be the result of receiving chemotherapy treatments, chronic inflammatory diseases, blood loss and some types of cancer.

2.8.3 Haemoglobin Testing

Without hemoglobin, oxygen would not be able to travel around the body. This oxygen-rich protein is essential to life, but it can increase or decrease due to a number of conditions. Dehydration, congestive heart failure and chronic obstructive pulmonary disease can all cause an increase in hemoglobin levels, while blood loss, anemia, liver disease and lymphoma can result in a decrease.

2.8.4 PCV packed cell volume test

The amount of the volume of the packed cell is accurate suitable value haematological parameter of diagnosis also essential for quality control database in the haematology laboratory.

2.9 Statistical analysis

All the group data were statistically evaluated with SPSS program. The results were expressed as mean ± S.E.M. and analyzed by factorial analysis of variance (ANOVA) the level of statistical significant was set at where $p<0.05$

3.Results and Discussion:

3.1 Effect of acetaminophen and enrofloxacine on Haematological parmeters.

The results of haematological analysis of rats in the control and treatment groups are presented in Table1. Results indicated that all groups no a significant difference at $p\leq5\%$ in Hb concentration, and PCV. while increased WBCs in group2 and 3 count compared to the control, the higher of WBCs is a problem in the body considering WBCs as a defense. The results of liver enzyme with the study groups.

Table (1). Effects of treatments on haematological parameters.

Parameters Treatment	Hb	WBC	PCV
Group1	12.12±0.45	4.09±0.07	34.67±1.50
Group2	11.10±0.16	5.18±0.26	38.17±0.75
Group3	12.00±0.83	4.30±0.15	37.00±1.13

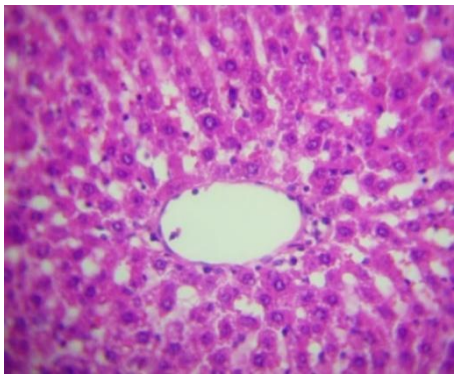
3.2 Effect of acetaminophen and enrofloxacine on biochemical parameters

Analysis of rats in the control and treatment groups are presented in Table 2. Results indicated that group 2 caused a significant at p≤5% alteration in liver enzymes to value, where it caused damage to liver cells causing increase liver enzyme in blood serum, while that group 3 less effect on liver cells through the results. The results of urea and creatnine analysis of rats in the control and treatment groups are presented in Table 2 there were insignificant alterations in urea and creatnine in both groups 2 and 3 compere with group1, may be the treatments led to a defect in kidney cells.

Table (2): Effects of treatments on the liver enzyme, Urea and Creatnine.

Parameters Treatments	**GPT**	**GOT**	**Urea**	**Creatnine**
Group1	**28.00±1.18**	**32.67±2.43**	**39.03±1.07**	**0.90±0.10**
Group2	**39.33±1.26**	**43.17±1.49**	**45.50±2.28**	**1.32±0.17**
Group3	**30.67±1.09**	**40.17±1.76**	**40.67±1.76**	**0.95±0.14**

3.3 Effects of acetaminophen and enrofloxacine on organ & tissues



Fig(1): Showed liver (group1) liver lobule, central vein, columen of liver cells and blood sinusoid (H&EX40). The liver parenchyme are containing many lobule, each lobule has central vein and surrounded by many columns of hepatocytes, each liver cells is polygonal in shape with central, spherical nucleus in between liver cells ,kupffer cells with blood sinusoid

Kidney (Control group1)

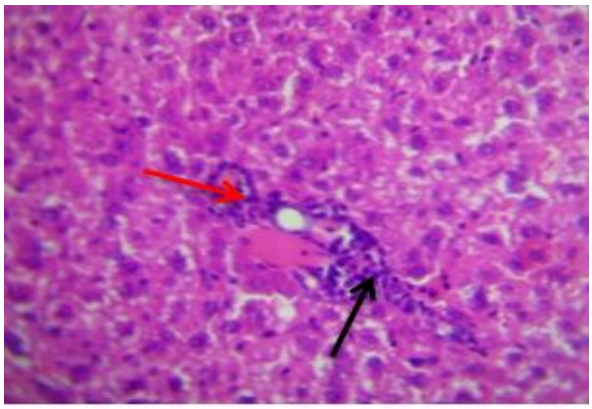


Fig (2): Showed liver (group1) portal of liver, portal vein (black arrow), hepatic artery (red arrow), bile ducts (blue arrow), and lymphocyte aggregation(H&EX40). The liver parenchyma also have portal area of the periphery of liver lobules, the portal area have branch of hepatic artery and bile ductless surrounded by number of lymphocytes

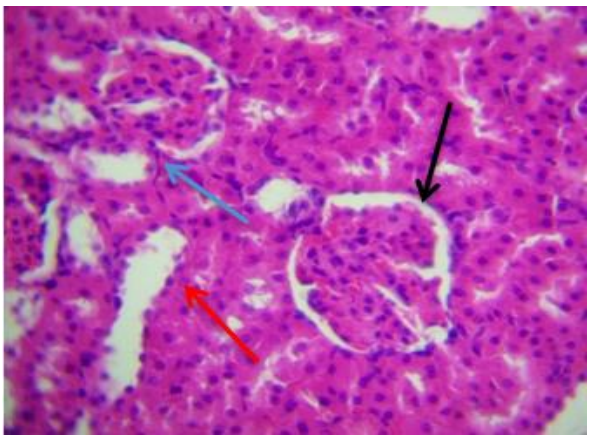


Fig (3): kidney (group1) showed renal cortex, the glomeruli (black arrow), proximal convoluted (red arrow), distal convoluted tubule (blue arrow) (H&EX40). The renal cortex was containing the glomeruli which are forward afferent and efferent arterial to form a tuft of capillary inside Bowman's capsule. this surrounded by proximal and distal convoluted tubule cells lined by pyramidal cells with deep an acidophilic stain. while the distal tubule was lined by simple cuboidal cells with wide lumens.

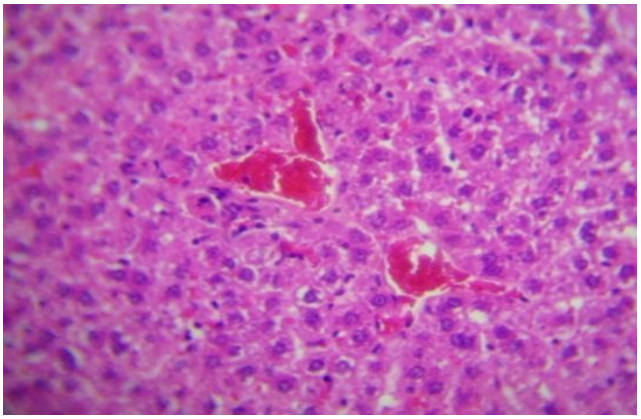


Fig (4): Kidney (group1) showed renal medulla renal tubule (H&EX40). The renal medulla was containing a renal tubule and collecting ducts these are lined by simple cuboidal cells and surrounded by interstitial C.T with the presence of blood capillaries.

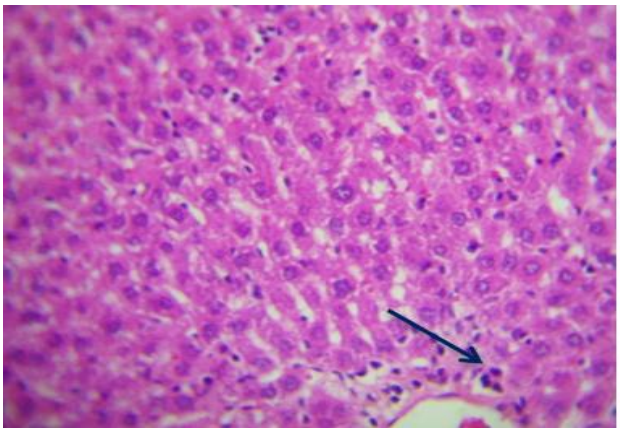


Fig (6): Liver (group2) showed WBC infiltration around the central vein (black arrow), hypertrophy of Kupffer cells

(H&EX40). There were many WBC cells infiltration around the central vein with hypertrophy of Kupffer cells in blood sinusoid.

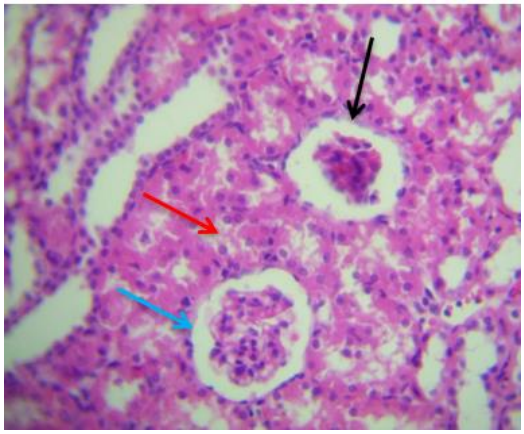


Fig (7): Kidney (group 2) showed cortex of the kidney, atrophy of glomeruli (black arrow), degeneration proximal tubule (blue arrow) filtration of glomerular (red arrow) (H&E X40). The renal cortex was containing atrophied glomeruli and the capsule pale wide the cells of proximal convoluted tubule were present most of intact, but others were degenerated and sloughed toward the lumen of these tubules also glomerulus filtrate was seen in the lumen of the tubules.

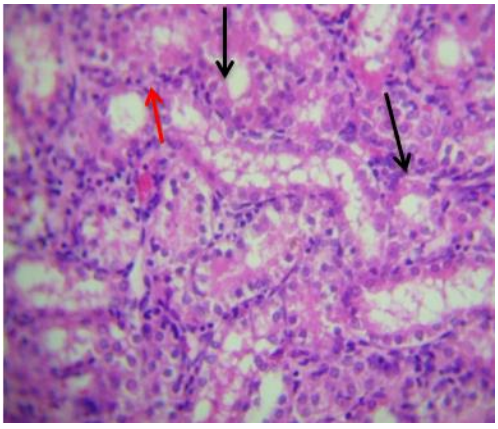


Fig (8): Kidney (group 2) showed renal medulla, renal infiltration in the lumen (black arrow) and lymphocyte infiltration (red arrow) (H&EX40). The renal medulla was containing the renal tubules and collecting ducts which are filled its lumens with renal filtrate and oedema, the interstitial C.T. was heavily infiltration with lymphocytes

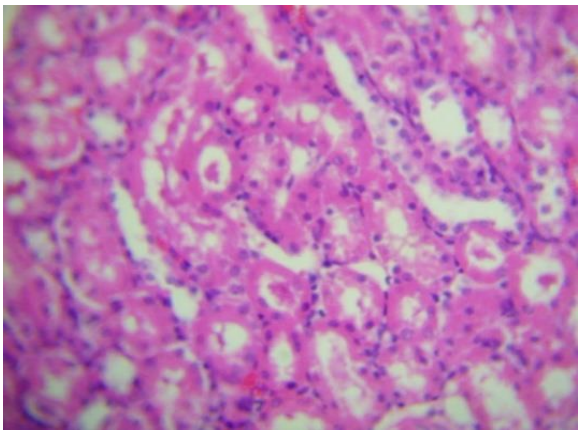


Fig (9): showed hyaline casts in the renal lumen of the renal tubule (H&EX40). The renal tubule containing hyaline casts appeared homogenized red masses in the lumen of the tubules

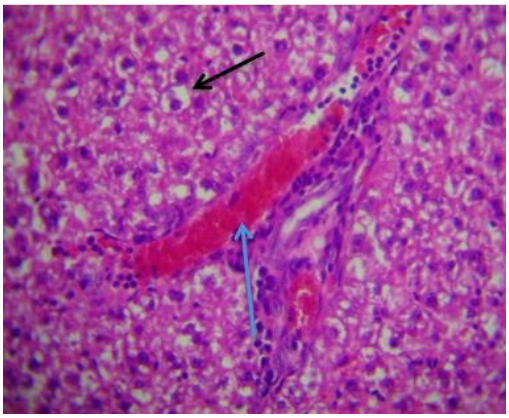


Fig (10): Liver (group3) showed hypertrophy of liver cells with vacuolation (black arrow), congestion of portal vein (blue arrow) (H&EX40). the parenchyma of the liver was occupied by hypertrophy of liver cells which appeared its cytoplasm vacuolated with the disappearance from any stain also pyknotic nuclei were present the branch of the portal vein was congested with blood and surrounded by heavy infiltration of lymphocytes.

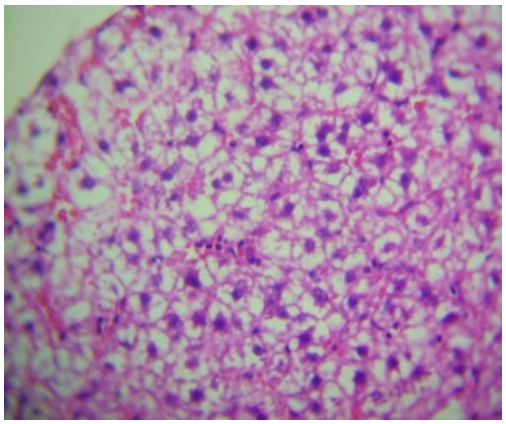


Fig (11): Liver (group 3) showed degeneration of liver cells (H&EX40). The periphery of liver tissues was containing degenerated liver cells pyknosis of nuclei with koryohexsis and koryolysis of nuclei

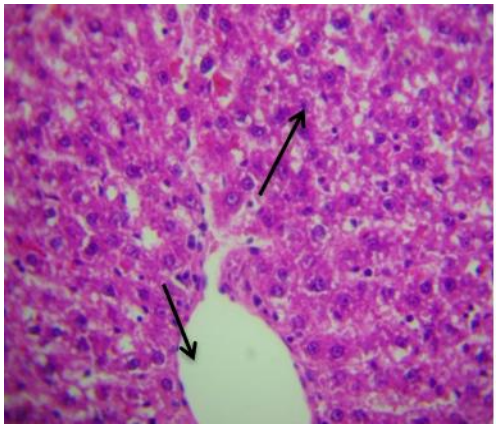


Fig (12): Liver (group 3) showed hypertrophy of Kupffer cells (black arrow) (H&EX40). The hypertrophy of Kupffer cells was present along the blood sinusoid and around the central vein present of a myeloid mass in between the liver cells.

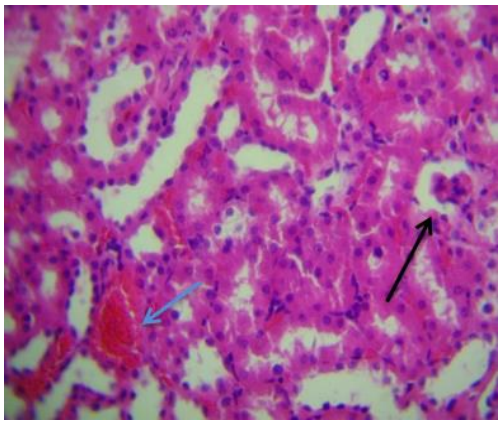


Fig (13): Kidney (group 3) showed atrophy of glomeruli of the kidney (black arrow), and blood congestion (blue arrow) (H&EX40).The cortex of the kidney was containing atrophied and degenerated glomeruli with the winding of the capsule space of Bowman, capsule were congested in between the proximal and distal convoluted tubules.

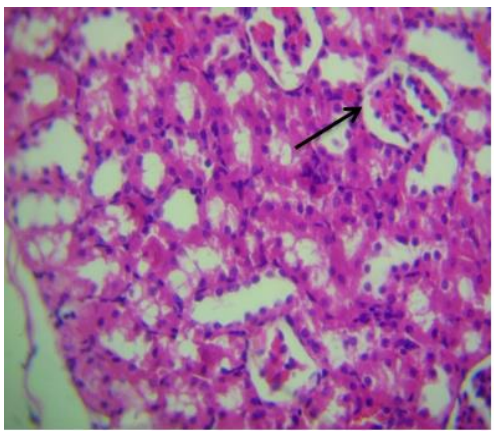


Fig (14): kidney (group 3) showed glomeruli filterate (black arrow) (H&EX40). The capsule of the kidney was sloughed from the cortex the lumen of the many convoluted tubules were filled with glomerular filtrate

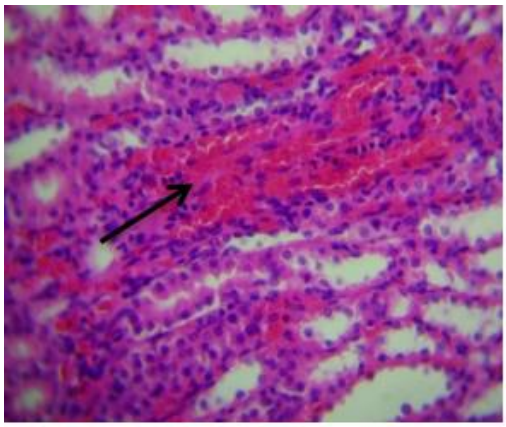


Fig (15): Showed congestion of blood vessels (black arrow) (H&EX40). The medulla of the kidney was containing congested blood haemorrhage in between the renal tubule and a certain number of epithelial cells were desquamated inside the lumen of these tubules

4. Discussion

The results of this research show that acetaminophen and enrofloxacin treatment induces oxidative stress and study the histological examination in group second, we showed in the liver the thickening wall with minimal fibrosis in the periportal area infiltration of inflammatory cells in the necrotic change of the hepatocytes massive vacuolation of the hepatocyte, kupffer cell were present intensity in the sinusoid. While the histopathological examination of the kidney revealed lymphocyte infiltration, congestion, glomerulus and tubular damage. while in the third group the histological changes were less when compared to the first group. In the present study, we observed when using drugs at the same time leads to harmful effects on the body. In the present study we observed when two or more drugs are taken concurrently, they may influence one another in a manner that results in either an enhanced or diminished intensity of effect produced by any of the drugs taken alone. suggesting that the acetaminophen-induced haematotoxicity. In this study we observed when giving the drugs at the same time have more harmful effects when compared to the second group and the first group as described in the results. At therapeutic doses, acetaminophen is considered a safe drug. However, when taken for a long time, it can cause hepatic necrosis, nephrotoxicity, extrahepatic lesions, and even death in experimental animals and humans [19]. In recent years there has been growing interest in understanding the role of antioxidants in the management of many diseases, including clinically useful drug-induced toxicities [20]. Suggesting that the acetaminophen. induced haematotoxicity. These findings were in agreement with other studies that found that after administration of high doses or acute poisoning with acetaminophen heavy damage of the liver and kidneys was developed [21,22]. The fluoroquinolones have been widely used because of their long elimination halflives, excellent antibacterial activity and wide antibacterial spectrum. Although there is knowledge about the side-effects of fluoroquinolones related to blood and biochemical parameters. Biochemical and haematological side-effects of fluoroquinolones are anaemia, thrombocytopenia, leukopenia, neutropenia, reversible decreases in haemoglobin, haematocrit levels and blood glucose concentration, reversible increases in serum concentrations of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), c-glutamyltransferase and bilirubin

concentration and metabolic acidosis (23,24). Suggesting that the liver is the major organ of metabolism and excretion and possesses the function of detoxifying xenobiotic, environmental pollutants and chemotherapeutic agents; these substances alongside oxidative stress are responsible for the occurrence of liver injury (hepatotoxicity) which is a major clinical concern [25]. The measurement of some nitrogenous compounds in the blood (urea and creatinine) is an indication of the efficiency of the college in performing its function of removing these compounds from the blood by filtering and putting them out using release and increasing the nitrogen compounds means the presence of kidney deficiency [26]. Age-related chronic diseases or severe infection usually require the use of multiple drugs, a state known as polypharmacy. This refers to the use of multiple medications and/ or more medications than clinically indicated. [27]. lead to the occurrence of medication errors, drug-drug interactions, adverse reactions, and poor quality of life. It increases morbidity, mortality, and complexity of care. It also imposes a huge financial burden on both older adults and the health system. The potential for interactions with medications should always be considered when administering or prescribing any drug [28,29]. The renal tubular changes which has been found in this research was agreed with results of other researches which found that The acetaminophen induced renal damage results from a mechanism similar to that which is responsible for hepatotoxicity [30,31]. Drug interactions might readily cause clinically significant changes in blood drug levels (concentration in whole blood, plasma, or serum).

Conclusion

The research concluded that there are physiological and histological effects when using two forms of drugs and at different times.

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دراسة بعض التغيرات الفسيولوجية والنسيجية عند اعطاء الأدوية في أوقات مختلفة (الاسيتامينوفين والإنروفلوكساسين) في الجرذان

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الملخص

اشتملت الدراسة على ثلاث مجموعات من الجرذان، كل مجموعة مكونة من خمسة فئران. المجموعة الأولى (المجموعة السيطرة) أعطيت الماء المقطر، والثانية اعطيت 0.01 مل من الأسيتامينوفين عن طريق الصفاق و 0.01 مل من الإينروفلوكساسين 1 \ مل ، بينما تلقت المجموعة الثالثة 0.01 مل من الاسيتامينوفين ثم بعد نصف ساعة تلقت 0.01 مل من الإينروفلوكساسين لمدة 15 يومًا. لوحظ التحليل الدموي للجرذان في مجموعتي السيطرة والمعالجة بأن جميع المجموعات ليس لها معنوية في تركيز الهيموغلوبين، وحجم خلايا الدم الحمراء المكدسة. بينما زاد عدد كرات الدم البيضاء في المجموعة 2 و3 مقارنة بمجموعة السيطرة. كما وأشارت نتائج تحليل إنزيمات الكبد إلى أن المجموعة الثانية تسببت في تغير كبير في قيمة أنزيمات الكبد مقارنة بالمجموعة 1 و 3، بينما أظهرت نتائج تحليل اليوريا والكرياتينين تغيرات طفيفة في اليوريا والكرياتينين في كلا المجموعتين 2 و 3 مع المجموعة 1. أظهر الفحص التشريحي المرضي للكبد (المجموعة الثانية) تثخن في الجدار مع التليف في المنطقة المحيطة بالبوابة وارتشاح في الخلايا الالتهابية مع النخر لخلايا الكبد ووجود العدد الهائل لخلية كوبفر كانت الشدة الحالية في الجيوب الجيبانية. ارتشاح الخلايا اللمفية في الكلى، واحتقان

الاوعية الدموية الشعرية مع الكبيبات وتلف في الانابيب الكلوية. في المجموعة الثالثة، كانت التغيرات النسيجية المرضية أقل بالمقارنة مع المجموعة الأولى. الدراسة الحالية التي لوحظت عند استخدام الأدوية في نفس الوقت يؤدي إلى آثار ضارة على الكبد والكلى