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Some Pharmacological Studies of Ciprofloxacin and Levofloxacin in Rats

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Abstract

This study was conducted to investigate some pharmacological effects of ciprofloxacin and levofloxacin in their therapeutic and double therapeutic doses on healthy male albino rats. Forty five rats were divided into 5 groups, each of 9 rats, 1st was left as a control, 2nd and 3rd groups received 100 mg/kg BW ciprofloxacin and levofloxacin respectively, orally for 10 successive days (therapeutic dose). The 4th and 5th groups were administrated 200 mg/kg ciprofloxacin and levofloxacin respectively, orally for 10 successive days (double therapeutic doses). Urine analysis and serum biochemical parameters were estimated in addition to histopathological examination of liver and kidneys. The urine analysis revealed that levofloxacin at its therapeutic and double therapeutic doses produced a significant increase in urinary proteins, blood, bilirubin, urobilinogen and urinary ketones while ciprofloxacin doses produced less damage. However, serum biochemical parameters disclosed that levofloxacin is a safer fluoroquinolone than ciprofloxacin; these results were confirmed by histopathological examination of liver and kidneys. Urine analysis despite widely used in human laboratories, it is not a reliable technique; blood biochemical parameters examination and histopathological examination are more dependable.

Keywords: Ciprofloxacin, Levofloxacin, Urinalysis, Liver and Kidney Functions.

Introduction

An increasing interest in fluoroquinolones, a new class of potent orally absorbed antimicrobial agents, the first analogue was nalidixic acid, a non-fluoronated agent that was used for treatment of urinary tract pathogens, new fluoroquinolones, also called quinolones or 4-quinolones had been developed and include many agents like norfloxacin, enrofloxacin, ciprofloxacin, ofloxacin, tosufloxacin, lomifloxacin, among others [1]. The principle target of quinolones is DNA gyrase [2], an essential bacterial enzyme. This enzyme is a member of the class of type II topoisomerase and composed of two A subunits encoded by the gyr A gene and two B subunits encoded by the gyr B gene. Gotter and Klostermeier [3] suggested that each topoisomerase II and IV represent a different solution to the complex reaction sequence in DNA supercoiling and both were inhibited by fluoroquinolones. Ciprofloxacin is the most famous second generation fluoroquinolones with demonstrated efficacy; furthermore, levofloxacin is one of the most recognizable third generation fluoroquinolones which is widely used and extensively studied in human medicine [4]**.** They are used medically in a variety of infections as uncomplicated and complicated urinary tract infections, pyelonephritis, sexually transmitted diseases, prostitis, skin and soft tissue infections plus acute exacerbations of chronic bronchitis and community acquired pneumonia [5].

Several reports had discussed adverse effects of ciprofloxacin and levofloxacin despite the frequency of these adverse events is too low, but they already exist as anaphylaxis, hemolytic anemia, renal failure, hypoglycemia and hepatic failure [6, 7]. Animal urine collection is an important part of veterinary practice for ascertaining animal physical condition and in specific investigations for assessing the results of experimental manipulations [8].

The present study aimed to inspect some pharmacological effects of ciprofloxacin and levofloxacin based on urine analysis, some serum biochemical parameters and histopathological changes in liver and kidneys.

Material and Methods

Drugs

Ciprofloxacin is available as 500 mg tablets (Bayer pharmaceutical company, Germany). Its dose for rats after conversion the dose for human according to Paget and Barnes [9] was 100 mg/kg twice daily as therapeutic dose and

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200 mg/kg as double therapeutic dose. While, levofloxacin (500 mg) was obtained from Sanofi Aventis Pharmaceutical Co at recommended dose for rats is 100 mg/kg once daily as therapeutic dose and 200 mg/kg as double therapeutic dose after converting the dose of human to rats [9].

Experimental animals and protocol

A total of 45 male albino rats were used in the present study. They were obtained from laboratory Animal Research Unit, Faculty of Veterinary Medicine Zagazig University, weighting 150-170 g. They were housed under standard conditions in at metabolic cages, constant temperature (25±2)^{o}C, 12 hour light-dark rhythm and had a free access to standard diet of food billets and tap water *ad-libitum* during the study period. After one weak of acclimatization, rats were divided equally into five groups as follows: First group: control group, received only saline solution. The Second group: Ciprofloxacin (100 mg/kg BW) administered group, it was orally administered twice daily. Third group: Levofloxacin (100 mg/kg BW)- once daily , Fourth group: Ciprofloxacin (200 mg/kg BW). as double therapeutic dose) twice daily , and the Fifth group: Levofloxacin (200 mg/kg BW) as double therapeutic dose) once daily . All administrations were for 10 successive days.

At the end of these processes, urine samples were collected from each group on individual basis after drug withdrawal by 24 hours. Animals were then sacrificed; blood was collected and then centrifuged at 3000 rpm for 15 minutes to separate the serum and stored at -20^{o}C for estimating some serum biochemical parameters. Meanwhile, both the kidneys and liver were collected and were immediately kept in 10% neutral buffered formalin then were embedded in paraffin and used for histopathological assay.

Urine analysis

Urine collection was done as described by Arda and Mehmet, [10]. Urine analysis was performed by field test using diagnostic combur-10 test strips (Roche-Switzerland). A qualitative urine analyses including pH, specific gravity (SG), blood, protein, ketones, bilirubin and urobilinogen, nitrites and leucocyte esterase was done .

Biochemical parameters

Aspartate and alanine amino-transferases activities (AST and ALT) were measured according to Tietz [11], serum alkaline phosphatase (ALP) was estimated colorimetrically [12], serum total, direct and indirect bilirubin [13]. Assessment of total proteins were performed according to Henry [14], serum albumin according to method described by Doumas and Gigg [15], serum globulin was calculated as difference between total proteins and albumin. Creatinine and blood urea nitrogen (BUN) levels were analyzed according to Husdan and Rapoport [16], and Talke and Sehubert [17], respectively. Determination of serum triglycerides according to Fossati and prencipel [18], meanwhile, estimation of serum total cholesterol was performed after Allian *et al*., [19].

Histopathological examination

Histopathological examinations of liver and kidney specimens were performed by the method described by Lillie and Fulman, [20].

Statistical analysis

Statistical analysis was done by one way analysis of variance (ANOVA) using computerized SPSS program version 16. Results are presented as mean ± S.E. The data were analyzed by one way ANOVA followed by Duncan's test. $P < 0.05$ was considered significant [21].

Results and Discussion

Both of ciprofloxacin and levofloxacin shared the property of being highly effective, broad spectrum fluoroquinolone antimicrobial agents, widely used for the treatment of infections caused by bacteria that are resistant to other antibiotics including aminoglycosides and β-lactams. There is no antimicrobial agent has 100% safety profile. An unexpected medical problem could happen during treatment course with a drug or any other therapy, and what worsens the situation is the presence of already existed disease in the organ that has involved with the unexpected problem.

This study had focused on the effect of ciprofloxacin and levofloxacin with their therapeutic and double therapeutic doses on

urine analysis, some serum biochemical parameters plus throwing the light on the histopathological changes in liver and kidneys.

Collection of urine from experimental animals is a basic requirement in a variety of kidneys biochemical, urological, nutritional, metabolic toxicological and physiological studies, the most recognizable features of experimental animal urine collection are (1) ease of collection, (2) quality of sample, (3) prevention of contamination, (4) severity of procedure used, (5) levels of pain caused to the laboratory animal, and (6) refinement of the methods to reduce stress, pain or distress [22].

To our knowledge, there is no available data regarding the estimation of ciprofloxacin or levofloxacin in urine of rats using urine test strips. There was no significant change in mean indicator of urinary pH, it means that kidneys do normal regularity function of acid-alkali balance. As well, no significant changes in specific gravity of all tested animals normal range was between 1.000 and 1.030 indicating normal glomerular filtration rate (Table 1).

Table 1: Effect of oral administration of ciprofloxacin (100 and 200 mg/kg BW) and levofloxacin (100 and 200 mg/kg BW) on urine analysis in healthy male albino rats. (Mean ± S.E.) (n=9)

Group / Color indicator for	Control	Ciprofloxacin (100 mg/kgBW)	Levofloxacin (100 mg/kg BW)	Ciprofloxacin (200 mg/kg BW)	Levofloxacin (200 mg/kg BW)
pH	5	5	5	5	5
SG	1.000	1.020	1.025	1.030	1.030
Blood	-ve	40	90	70	177
Protein (mg/dl)	-ve	200	350	225	500
Ketones (mg/dl)	-ve	22.5	33	22.5	45
Bilirubin (mg/dl)	-ve	3	9	7.5	9
urobilinogen (mg/dl)	-ve	3.5	10	10	26
Nitrite (µmol/L)	-ve	0.75	1.00	0.75	1.00
Leucocyte esterase (Lec/µL)	-ve	1.25	1.75	1.26	1.76

SG: specific gravity

Significant increase in blood values were observed in urine analysis in all administrated groups and it was more pronounced in levofloxacin (200 mg/kg BW) treated animals; it may be attributed to urinary tract specific problem following the drug administration. The most detectable observation was the significant increase in urinary protein levels Administration of levofloxacin at its therapeutic and double therapeutic doses evoked a significant increase in protein levels in urinalysis. The most pronounced proteinuria being observed in nephrosis and glomerulonephritis as protein excretion is usually 200-300 mg/dl [23].

Bilirubin is a highly pigmented metabolite that is a by-product of hemoglobin degradation. Kidneys are unable to filter the unconjugated bilirubin because of its binding to albumin, however, it is conjugated with glucuronic acid in liver forming what is called water-soluble conjugated bilirubin, and it does not normally appear in urine as it is directly excreted from intestine to bile. Intestinal bacteria reduce bilirubin to urobilinogen that in later oxidized to be excreted in feces as stercobilin or in urine as urobilin [24]. The conjugated bilirubin appears in urine when normal degradation cycle is altered due to obstruction of biliary duct or when kidney's functional integrity is damaged, this occurs as in hepatitis or hepatic cirrhosis.

The findings of the present investigation showed that administration of levofloxacin (100 and 200 mg/kg BW.) significantly increased urinary bilirubin of examined rats compared to control group that showed negative results as shown in Table (1). The treatment with ciprofloxacin with its therapeutic and double therapeutic doses evoked a slight increase in urinary bilirubin. The detection of bilirubin in urine is considered an early indication of liver disease and its presence or absence can be used to determine jaundice using serum biochemical analysis as a confirmative measure.

Any deterioration in liver function reduces its ability to process the recirculated urobilinogen [25]. The excess that remains in blood is filtered out by glomerular filtration system and appears in urine. Levofloxacin administered groups either with therapeutic or double therapeutic doses elicited a significant increase in urinary urobilinogen which was a result of increased urinary bilirubin. When hemolytic disorder occurs, the amount of unconjugated bilirubin that is present in blood increases which in turn leads to increase hepatic excretion of conjugated bilirubin, results in increasing amounts of urobilinogen that causes an increase in its renal excretion.

Elevated concentrations of ketones are not generally found in urine as metabolites such as fatty acids, acetone and acetoacetic acid are completely metabolized, producing energy, carbon dioxide and water. Ketone bodies were significantly increased in urine following treatment with both ciprofloxacin and levofloxacin either with therapeutic or double therapeutic doses (Table 1). The increase in urinary ketones was more pronounced with levofloxacin treated animals indicated an alteration in carbohydrate metabolism. Further biochemical studies are needed to ensure these results.

The current investigation revealed that administration of ciprofloxacin and levofloxacin either with their therapeutic or double therapeutic doses slightly increased urinary nitrites and these slight elevations may indicate a systemic disorder. Urinary leucocyte esterase was within normal limits in this study as administration of both antibiotics with their therapeutic or double therapeutic doses evoked no significant changes compared to the control animals. Put our heads together, the urine test strip is a basic diagnostic tool, used to determine pathological changes in the subject's urine in standard urinalysis, several false positive results may occur because of a variety of reasons.

Effect of oral administration of ciprofloxacin (100 and 200 mg BW) and levofloxacin (100 and 200 mg/kg BW) on AST, ALT, ALP, total bilirubin, direct and indirect bilirubin in healthy male albino rats were evaluated (Table 2). It was apparent that ciprofloxacin (200 mg/kg BW.) displayed the most significant increase ($P < 0.05$) in serum transaminases, serum ALP, total, direct and indirect bilirubin when compared to the control animals.

Table 2: Effect of oral administration of ciprofloxacin (100 and 200 mg/kg BW) and levofloxacin (100 and 200 mg/kg BW) on some serum biochemical parameters in healthy male albino rats. (Mean ± S.E.) (n=9)

Parameter / Group	AST (U/L)	ALT (U/L)	ALP (U/L)	Total bilirubin (mg/dl)	Direct bilirubin (mg/dl)	Indirect bilirubin (mg/dl)
Control	21.26 ±1.48 ^{c}	12.41 ±0.69 ^{d}	17.76 ±1.27 ^{d}	1.07 ±0.03 ^{d}	0.34 ±0.04 ^{c}	0.73 ±0.07 ^{d}
Ciprofloxacin (100 mg/kg BW)	48.72 ±0.84 ^{b}	57.67 ±2.14 ^{b}	60.49 ±3.77 ^{bc}	2.71 ±0.19 ^{c}	0.97 ±0.04 ^{b}	1.74 ±0.14 ^{bc}
Levofloxacin (100 mg/kg BW)	34.44 ±3.30 ^{b}	41.93 ±1.68 ^{c}	40.23 ±3.97 ^{c}	1.71 ±0.18 ^{d}	0.78 ±0.08 ^{b}	0.93 ±0.10 ^{cd}
Ciprofloxacin (200 mg/kg BW)	68.1 ±2.51 ^{a}	90.27 ±5.39 ^{a}	136.64 ±25.05 ^{a}	6.05 ±0.37 ^{a}	1.5 ±0.18 ^{a}	4.54 ±0.55 ^{a}
Levofloxacin (200 mg/kg BW)	54.48 ±1.68 ^{ab}	60.44 ±8.16 ^{b}	100.79 ±15.93 ^{ab}	4.04 ±0.12 ^{b}	1.54 ±0.18 ^{a}	2.5 ±0.08 ^{b}

All data have different letters are different significantly at $P < 0.05$.

Levofloxacin (100 mg/kg BW) administered group showed the least elevation in the aforementioned parameters with serum total bilirubin and indirect bilirubin showed no difference when compared to control group. Studies were conducted by Yagaw, [26], and Liu, [27] mentioned that levofloxacin has a very low photo-toxicity inducing potential and a very low incidence of hepatic effect. In contrast to our results regarding urinalysis, levofloxacin with its therapeutic dose had showed high safety profile about liver function tests with minimal or negligible increase in serum biochemical parameters, these results agree with the previous findings mentioned before [26, 27].

Ciprofloxacin on the other hand produced a significant increase in serum biochemical

parameters with its therapeutic and double therapeutic doses indicating its hepatotoxic effects. Many studies had augmented our results, potential of liver failure and hepatitis from ciprofloxacin were observed as adverse effects [28- 30].

The liver synthesizes not only the protein it needs, but also produces a variety of export proteins. Among the later, serum albumin is the most important protein to be synthesized. Export proteins are created on polyribosomes bound to rough endoplasmic reticulum of hepatocytes; in contrast, proteins destined for intracellular use are synthesized on free rather bound polyribosomes [31]. Albumin considered as the most abundant protein in animal serum, transporting hormones, fatty acids and other compounds, buffers pH among other functions and hypoalbuminemia in hepatocellular disorders, appearing as inflammatory reaction of liver. In this study, the administration of ciprofloxacin at 200mg/kg b.wt. evoked a significant decrease in serum total proteins and albumin when compared with the control animals (Table 3). There was a significant decrease in the aforementioned parameters with all tested doses and the more hypoalbuminemia produced was observed in ciprofloxacin double dose treated animals.

Table 3: Effect of oral administration of ciprofloxacin (100 and 200 mg/kg BW) and levofloxacin (100 and 200 mg/kg BW) on serum total proteins, albumin and globulin in healthy male albino rats. (Mean ± S.E.) (n=9).

Parameter / Group	Total protein (gm/dL)	Albumin (gm/dL)	Globulin (gm/dL)
Control	9.00±0.18 [a]	5.01±0.11 [a]	3.99±0.07 [a]
Ciprofloxacin (100 mg/kg b.wt.)	7.13±0.02 [b]	4.13±0.15 [b]	3.00±0.14 [ab]
Levofloxacin (100 mg/kg b.wt.)	7.49±0.03 [b]	4.39±0.20 [b]	3.10±0.10 [a]
Ciprofloxacin (200 mg/kg b.wt.)	5.02±0.30 [d]	2.6±0.18 [d]	2.42±0.55 [b]
Levofloxacin (200 mg/kg b.wt.)	6.43±0.21 [c]	3.66±0.18 [c]	2.77±0.08 [b]

All data having different letters are differing significantly at P<0.05.

The obtained results showed that there was a significant increase (P<0.05) in serum creatinine, serum blood urea nitrogen (BUN) an urea levels in all treated groups when compared to control group, the increase was more pronounced in rats treated with ciprofloxacin (200 mg/kg BW) (Table 4). Administration of levofloxacin with its therapeutic dose evoked a non-significant increase in serum BUN and serum urea levels when compared to the control animals.

The impairment in kidney function markers following ciprofloxacin administration had been documented in Hafiz *et al.* [32] who mentioned that ciprofloxacin treatment was an offending agent causing an increase in serum lactate dehydrogenase and serum creatinine among other adverse effects. Moreover, Shaki *et al*., [33] reported that ciprofloxacin showed an oxidative damage and inflammation with marked nephrotoxicity, represented by increase in serum BUN and creatinine with histopathological changes.

Regarding the effect of ciprofloxacin (100 and 200 mg/kg BW) and levofloxacin (100 and 200 mg/kg BW) on serum triglycerides and cholesterol, Table (4), there were no significant changes in all tested groups when compared with control one. This indicates drugs safety either in their therapeutic or double therapeutic doses in cases of hyperlipidemia or hypercholesterolemia. Our findings were in disagreement with Ebenzer *et al*., [34], they found an increase in serum HDL-Cholesterol, LDL-cholesterol, total cholesterol and triglycerides following levofloxacin treatment at different doses.

Table 4: Effect of oral administration of ciprofloxacin (100 and 200 mg/kg BW) and levofloxacin (100 and 200 mg/kg BW) on serum BUN, urea, creatinine, triglycerides and cholesterol in healthy male albino rats. (Mean ± S.E.) (n=9).

Parameters / Groups	BUN (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	Triglycerides (mg/dl)	Cholesterol (mg/dl)
Control	7.09 ±1.42 [d]	15.12 ±3.06 [d]	2.71 ±0.67 [d]	162.78 ±6.21 [a]	41.40 ±3.29 [a]
Ciprofloxacin (100 mg/kg BW)	22.05 ±0.62 [c]	47.29 ±1.36 [c]	5.21 ±0.26 [c]	166.91 ±8.07 [a]	43.67 ±4.55 [a]
Levofloxacin (100 mg/kg BW)	12.24 ±0.87 [cd]	26.24 ±1.87 [cd]	4.38 ±0.19 [c]	164.44 ±5.19 [a]	45.93 ±2.26 [a]
Ciprofloxacin (200 mg/kg BW)	71.82 ±7.21 [a]	153.96 ±15.39 [a]	8.67 ±0.03 [a]	163.87 ±13.26 [a]	47.60 ±6.04 [a]
Levofloxacin (200 mg/kg BW)	39.45 ±3.83 [b]	84.68 ±8.22 [b]	7.26 ±0.33 [b]	171.32 ±5.93 [a]	48.79 ±7.62 [a]

All data have different letters are different significantly at $P < 0.05$.

Histopathological examinations following administration of ciprofloxacin (100 and 200 mg/kg BW) and levofloxacin (100 and 200 mg/kg BW) for 10 consecutive days were recorded, Fig. (1a and 1b), representing the liver and kidney tissues of ciprofloxacin (100mg/kg BW) administered groups. It was apparent that the majority of liver showed acute cell swelling, dilated hepatic sinusoids and portal edema. The renal parenchyma revealed interstitial round cell infiltration, dilated inters renal capillaries and cloudy swelling of some renal tubules in ciprofloxacin treated animals, similar results were observed liver of pregnant female rats and their fetuses following ciprofloxacin administration [35]. Regarding levofloxacin treated animals, Fig. (1c and 1d), the majority of the hepatic parenchyma was apparently normal and few rats showed mild reversible changes. The renal parenchyma was apparently normal, A few rats revealed mild revisable nephrotic changes.

Bile duct hyperplasia and peri-ductular fibrosis and acute cell swelling of the adjacent hepatic cells were common (Fig. 1e). Hyperplastic kupffer cells and focal interstitial lymphocytic aggregation were encountered in ciprofloxacin (200mg/kg) treated group. The renal parenchyma exhibited shrunken glomerular tuft, dilated glomerular space and a few extravasated erythrocytes in the interstitial space (Fig. 1f). The levofloxacin treated animals with the double therapeutic dose revealed acute cell swelling or focal necrotic changes accompanied with hyalinized wall of hepatic arteriole, proliferative bile ductules and portal fibrosis (Fig. 1g). The renal parenchyma exhibited degenerative or necrotic changes in tubular epithelium, necrosis in glomerular tuft and dilated glomerular space (Fig. 1h). A study by Vahidi *et al.* [36], they observed a dilated blood vessels and some inflammatory cells, hepatic sinusoids appeared as dilated irregular spaces with degenerative appearance within hepatocytes following a treatment with levofloxacin.

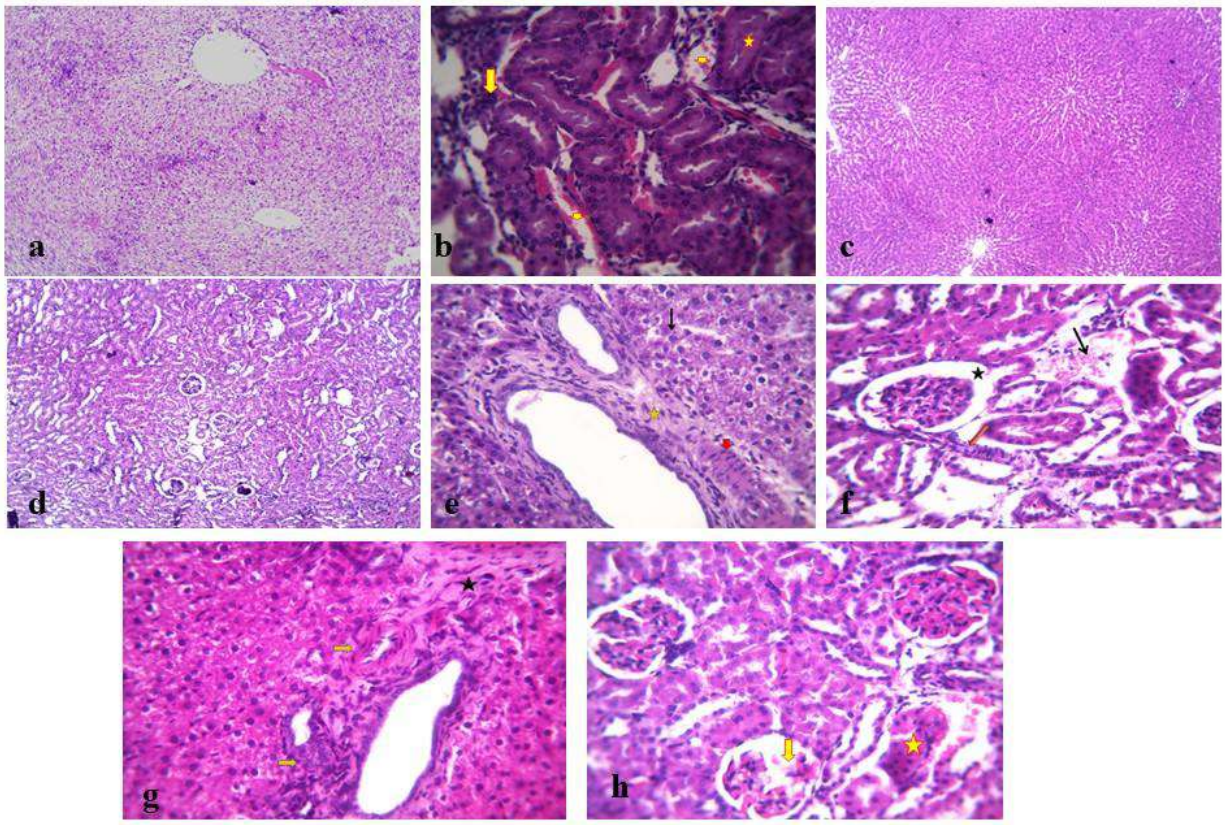

Figure 1: 1a) Liver section of rat (ciprofloxacin100mg/kg) H&E X200 showing acute cell swelling, dilated hepatic sinusoids and portal edema, Proliferated bile duct epithelium surrounded by a few lymphocytes could be seen. 1b) Kidney section (ciprofloxacin100mg/kg) H&E X400 showing the renal parenchyma revealed interstitial round cell infiltration, dilated inters renal capillaries and cloudy swelling of some renal tubules. 1c) Liver section of rat (levoofloxacin100mg/kg) H&E X200 showing that majority of the hepatic parenchyma was apparently normal. 1d) Kidney section of rat (levoofloxacin100mg/kg) H&E X200 showing normal renal parenchyma. 1e) Liver section of rat (ciprofloxacin200mg/kg) H&E X400 showing bile duct hyperplasia and peri-ductular fibrosis and acute cell swelling of the adjacent hepatic cells were common. 1f) Kidney section of rat (ciprofloxacin200mg/kg) H&E X400 showing renal parenchyma exhibited shrunken glomerular tuft, dilated glomerular space. 1g) Liver section of rat (levoofloxacin200mg/kg) H&E X400 showing hepatic cells that exhibited acute cell swelling and focal necrotic changes. 1h) Kidney section of rat (levoofloxacin200mg/kg) H&E X400 showing renal parenchyma exhibited degenerative or necrotic changes in tubular epithelium, necrosed glomerular tuft and dilated glomerular space.

Conclusion:

The present study showed that levofloxacin at a dose of (100mg/kg BW) was the safest dose to be administered among other tested doses that were confirmed with serum biochemical parameters analysis alongside histopathological examination of liver and kidney tissues. Ciprofloxacin administration at its therapeutic and double therapeutic doses evoked marked enzymatic elevation, jaundice, nephrotoxicity among significant changes in histological picture of liver and kidney architectures. Urinalysis technique using urine test strips was not a reliable procedure and its level of accuracy was questionable.

Conflict of interest

The authors declare that they have no conflict of interest.

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الملخص العربي

بعض الدراسات الدوائية علي السيبروفلوكساسين و الليفوفلوكساسين في الفئران

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قسم الفارماكولوجي، كلية الطب البيطرى، جامعة الزقازيق، الزقازيق ٤٤٥١١، الشرقية، مصر

قد أجريت هذه الدراسة للتحقيق في بعض التأثيرات الدوائية للسيبروفلوكساسين و ليفوفلوكساسين بالجرعات العلاجية والجرعات العلاجية المزدوجة على ذكور الفئران البيضاء الصحيحة .تم تقسيم خمسة وأربعين الفئران إلى ٥ مجموعات، كل من ٩ الفئران تم تقسيم عدد خمس وأربعون جرذاً (٤٥ جرذاً) الى خمس مجموعات ، بكل مجموعة عدد ٩ من الجرذان. تركت المجموعة الأولى كضابطة وتلقت فقط محلول ملحى. المجموعة الثانية والثالثة تلقت ١٠٠ مجم/كجم من وزن الحيوان من عقارى السيبروفلوكساسين والليفوفلوكساسين على التوالى وهى الجرعة العلاجية أما المجموعة الرابعة والخامسة فتلقت كلاً منهما ٢٠٠ مجم/كجم من وزن الحيوان لنفس العقارين السالف ذكرهما على التوالى وهى الجرعة العلاجية المضاعفة. .وقد تحليل البول والمعلمات الكيميائية الحيوية في مصل الدم بالإضافة إلى الفحص الهستوباثولوجى للكبد والكلى .وكشف تحليل البول أن الليفوفلوكساسين في الجرعات العلاجية والعلاجية المزدوجة لها أنتجت زيادة كبيرة في البروتينات البولية والدم والبيليروبين، يوروبيلينوجين والكيتونات البولية في حين أن جرعات سيبروفلوكساسين تنتج أقل الضرر .ومع ذلك، كشفت لمعلمات البيوكيميائية المصل أن الليفوفلوكساسين هو الفلوروكينولون أكثر أمنا من سيبروفلوكساسين .تم تأكيد هذه النتائج عن طريق الفحص الهستوباثولوجى للكبد والكلى وعلى الرغم من استخدام .تحليل البول على نطاق واسع في المختبرات البشرية، الا أنها ليست تقنية موثوقة . بينما يعتبر فحص المعلمات الكيميائية الحيوية والهستوباثولوجى هما اللذان يمكن الاعتماد عليهما.