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Original Research Article

Ciprofloxacin and levofloxacin adversely affect male infertility indicated by pharmacological, andrological and pathological evidence

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ABSTRACT

Background: Drug-induced reproductive organs toxicities is an important aetiology in investigation of male infertility. The aim is to study levofloxacin effect on male reproductive system in comparison to ciprofloxacin.
Methods: Twenty-five male wister rats weighted 230±20 gm and aged 8 weeks were randomly divided into five groups of five. The first group received ciprofloxacin with dose 78.23 mg/kg/day in 2 doses (therapeutic dose). The second group received the double dose of the first group ciprofloxacin. The third group received levofloxacin with dose 39.11 mg/kg/day once daily (OD) (therapeutic dose). The Fourth group received the double dose of the third group levofloxacin. However, the fifth group served as a control and received normal saline with carboxymethylcellulose OD. All treatments were administered orally for 14 days. On the 15th day, blood samples and reproductive organs were obtained from all rats. Testicular tissues were prepared for genetic testing and chemical and microscopical examination.
Results: Ciprofloxacin and levofloxacin negatively altered reproductive organ weights, sperm parameters and serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) level ($p<0.05$). Additionally, serum testosterone level was significantly deceased in ciprofloxacin-treated group (the double dose) ($p<0.05$) relative to control. The difference between ciprofloxacin and levofloxacin was significant in seminal vesicle weight and serum LH and FSH level ($p<0.05$). Testicular histopathological changes were also found with the two drugs with different degrees. Effects of levofloxacin and ciprofloxacin were dose-dependent.
Conclusions: Both ciprofloxacin and levofloxacin adversely affect andrological function that should be monitored and controlled during application of these drugs.

Keywords: Ciprofloxacin, Levofloxacin, Oxidative, Testis, Sperm, Reproduction, Fertility

INTRODUCTION

Ciprofloxacin is a second-generation fluroquinolone antibiotic which is the most potent quinolone against *Pseudomonas aeruginosa* and it has stronger activity against Gram negative bacteria compared with Gram positive.[1,2] Ciprofloxacin is commonly prescribed for urinary tract infection, orchitis and prostatitis, although bacterial resistance is increasing and gonadotoxicity was reported in human.[3-7] Levofloxacin is a third generation fluroquinolone antibiotics that has more activity toward Gram positive bacteria.[1] It is commonly used in respiratory tract infection, urinary tract infection, prostatitis and orchitis.[8-12]

Ciprofloxacin and levofloxacin are lower in side effects compared with ofloxacin specially CNS effects.[13] However, levofloxacin has more QTc prolongation effect

on the heart and less effect on hepatic cytochrome enzymes compared with ciprofloxacin.[14,15] Additionally, levofloxacin has higher oral bioavailability that reached 100% when compared with ciprofloxacin which equal 69%.[16,17] On the contrary to ciprofloxacin, human studies regarding levofloxacin effect on male reproductive system are scarce. However, animal studies are conflicting; some found it was safe and others found it wasn't.[18-20] Direct comparison between ciprofloxacin and levofloxacin regarding their effects on male reproductive system histopathology, physiology and biochemistry is required to address the relative risk of both drugs on male fertility.

Therefore, the aim of the present study is to asses and evaluate the possible side effects of ciprofloxacin and levofloxacin on testicular function. The aim of the study was effect of ciprofloxacin and levofloxacin on reproductive organs weight (testis, epididymis, prostate and seminal vesicles), effect of ciprofloxacin and levofloxacin on sperm parameters (morphology, motility, mutation), effect of ciprofloxacin and levofloxacin on reproductive hormones (gonadotropins and testosterone) and effect of ciprofloxacin and levofloxacin on histological structure of testis.

METHODS

Drug preparation

Ciprofloxacin was purchased as a generic pharmaceutical preparation Serviflox® with concentration 750 mg of ciprofloxacin in one tablet manufactured by Novartis pharma-Cairo, under license of Sandoz GmbH- Australia. The tablets were crushed and diluted with carboxymethylcellulose (CMC) in normal saline (NS) to a final volume 1 ml per one rat. levofloxacin was purchased as a brand pharmaceutical preparation Tavanic® with concentration 500 mg of levofloxacin in one tablet produced by: Sanofi-Aventis Egypt SAE. Under license of: Sanofi-Aventis, Germany. The tablets were crushed and diluted with CMC in NS to a final volume 1 ml per one rat. Ciprofloxacin and levofloxacin were administered orally with 18-gauge soft gavage tubes.

Animals

Twenty-five adult Wistar albino male rats were 8 weeks old and weighting 230±20 g. They were obtained from animal house of Faculty of Veterinary Medicine, Benha University. Male rats were housed in normal room temperature with humidity (40-60%) and 12h/12h light or dark cycle prior to use in experimental protocols. The animals were fed laboratory formula and tap water ad libitum.

Study design

After two weeks of adaptation to a standard diet, the 25 rats were randomly divided into five groups with five rats in each group. Rats in group 1 and 2 received PO ciprofloxacin in two divided daily doses of 78.23 and 156.46 mg/kg respectively. Rats in group 3 and 4 received PO levofloxacin OD in daily doses of 39.11 and 78.22 mg/kg respectively. Group 5 served as control and received PO 1 ml CMC in NS OD. All treatments were administered for 14 days. On the fifteenth day, the five animals in each group were sacrificed by cervical dislocation under anaesthesia after blood sampling. Immediately after dissection, testis, epididymis, prostate, and seminal vesicle were removed and weighted (absolute and relative to body weight). Relative organ weight was expressed as organ weight (mg) or body weight. The experiment was carried out in the Departments of Pharmacology and Theriogenology, Faculty of Veterinary Medicine, Benha University.

Blood sample collection

Blood samples were collected from the retro-orbital venous plexus located at the medial canthus of the eye by means of heparinized capillary tubes. The collected blood was kept in heparinized test tubes and centrifuged at 1500 xg for 15 minutes then collected in sterile Eppendorf tubes using automatic pipettes. Plasma samples were kept frozen (-20 °C) till analysis of the following biochemical parameters: testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) using rat ELISA kits (Elabscience®, Taxus, USA).

Tissue sample collection

About 80% of the right testis was homogenated with phosphate buffer solution (PBS) at PH 7.4 and centrifuged at 10000 rpm for 10 minutes at 4 C. the supernatant was removed and kept at -20 C till used in analysis. The separated homogenate was used for the estimation of the following parameters: catalase enzyme, superoxide dismutase, malondialdehyde and total antioxidant capacity using universal kits under commercial name of biodiagnostic kits. The rest 20% of the right testis was used in gene expression analysis. All biochemical analysis was performed in the central lab of the faculty.

Sperm parameter assessment

Sperms were obtained from the tail of the two epididymis by cutting the epididymis into small pieces in petri dish containing 2 ml of saline (0.9% NaCl).

For evaluation of sperm motility, immediately after collection of a semen sample, a small drop was taken with a micropipette and placed on a warm clean glass slide. A cover slip was placed onto the semen drop and the percentage of progressively motile sperms was estimated microscopically at 400x magnification.

For evaluation of sperm morphology and viability, two types of seminal smear slides were obtained from each

animal. One of them was stained with eosin and nigrosine and the other was fixed in Carnoy's solution then examined with light microscope under magnifications of 400X and 1000X to determine sperm head and tail abnormalities and sperm viability.

For evaluation of sperm count, the epididymal contents extracted in 2 ml normal saline were diluted to 10 ml normal saline and kept for 24 hours to let sperms distribute in the solution. To stain sperms heads to be easily counted, a few drops of eosin 2% solution were added to the solution before examination. According to the method described previously, the number of sperm in five large squares was multiplied by 5 to obtain sperm count in one chamber that contains 25 large squares (one chamber volume =100 ml).[21] To obtain sperm count in 1 ml, the number was multiplied by 10000. Because we diluted semen in 10 ml and used two epididymis, the number was multiplied by 10 and divided by 2 as the following:

Number of sperms per 1 ml =

$$\frac{\text{No. of sperms in 5 large squares} \times 5 \times 100000}{2}$$

Histopathology of the testis

The left testis was fixed in 10% formalin and embedded in paraffin. Five-micron thick sections were prepared and stained with hematoxylin and eosin (H&E). The specimens were examined under Olympus or 3H light microscope under power of 200X and 400X. the examination was carried out in the department of pathology of the faculty.

Statistical analysis

Statistical analysis was performed by using GraphPad Prism 8.0.2 software. Numerical data in this study were expressed as mean±standard deviation (M±SD) and categorical data as percentages. Analysis of variance (ANOVA) and a post hoc Tukey test were used. The difference between groups was defined to be statistically significant when a p value ≤0.05.

Ethics statement

This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health 8th edition and adhered to principles published by International Council for Laboratory Animal Science (ICLAS) and those of Benha University Animal Care and Use Committee.

RESULTS

Body and reproductive organ weights

After 14 days of treatment, weights of the total body and ventral prostate didn't differ significantly among groups (p>0.05). Weights of testis, epididymis and seminal vesicle were significantly lower in animals treated with ciprofloxacin and levofloxacin relative to control (p<0.05). A significant dose dependent effect was observed with testis and epididymis weights in all treated groups (p<0.05) and seminal vesicle in levofloxacin-treated groups (p<0.05). A significant difference between the two antibiotics was seen with seminal vesicle at the therapeutic dose level (p<0.05) (Table 1).

Table 1: Total body weight, absolute and relative reproductive organ weights of male rats after administration of ciprofloxacin and levofloxacin with therapeutic and double dose for 14 days compared with control.

	Control	Ciprofloxacin (mg/kg)		Levofloxacin (mg/kg)	
Weight		78.23	156.46	39.11	78.22
Total body weight (g)	274±2.9	266.4±3.1	273±2.7	270.2±3.2	276±3.3
Testis (g)	1.522±.032	1.098±0.042 *	0.87±0.01*	1.2±0.041*	0.83±0.03*
Epididymis (mg)	556±16	429±13*	383±8*	455±9.5*	382±7.4*
Seminal vesicle (mg)	572±14	427±11.7*	389±18*	501±23*	404±11.6*
Ventral prostate (mg)	486±18	508±26.3	464±12	490±22.1	496±24.1
Relative (R) testis (mg)	554±11.5	412±13.3*	321±7.8*	444±19.2*	302±11.1*
R epididymis (mg)	202.2±4.5	161.2±6.1*	140.3±3.2*	168.6±4.6*	138.5±3.6*
R seminal vesicle (mg)	208.7±7.3	160±4.6*	144.7±8.6*	182.3±8.6	156.8±8.7*
R ventral prostate (mg)	177.13±8.3	190.6±9.05	170±4	181.6±9.4	177.13±8.3

Values expressed as mean±SE of 5 observations, *: significant difference at p<0.05 compared with control. One-way ANOVA and post hoc Tukey test were used.

Sperm parameters

Administration of therapeutic and double dose of both ciprofloxacin and levofloxacin significantly decreased sperm count and progressive motility relative to control (p<0.05) in a non-significant dose dependent manner (p>0.05) with nonsignificant differences between the two drugs at the two dose levels (p>0.05) except for levofloxacin with the double dose that showed higher effect on sperm motility compared with the therapeutic dose (p<0.05). Viability and head normality were significantly decreased with the double dose of

ciprofloxacin and the two doses level of levofloxacin relative to control ($p<0.05$) with nonsignificant difference between the antibiotics at the two doses level ($p>0.05$). Tail abnormalities were seen with higher significant percentages in the treated groups compared to control ($p<0.05$) with nonsignificant dose related effect and significant differences between the two drugs at the two dose levels ($p<0.05$) (Table 2).

Table 2: Sperms count, motility, viability and morphology of male rats after administration of ciprofloxacin and levofloxacin with therapeutic and double dose for 14 days compared with control.

Sperm parameters	Control	Ciprofloxacin (mg/kg)		Levofloxacin (mg/kg)	
		78.23	156.46	39.11	78.22
Sperm count (10^6/ml)	29.45±0.72	18.35±1.05*	16.95±0.6*	17±0.9*	16.5±1.4*
Progressive motility%	73±4.2	34±3.2*	23±2.2*	42±3.6*	23±2.2*
Viability%	75±1.7	70±1.6	55±3.9*	60±1.7*	56±3.3*
Head abnormality%	3±0.6	6.4±1.7	9±2.1*	17±1.03*	17±1.05*
Tail abnormality%	20.6±2.6	71.6±3.6*	76±2.5*	55.8±1.8*	65.8±1.7*

Values expressed as mean±SE of 5 observations, *: significant difference at $p<0.05$ compared with control. One-way ANOVA and post hoc Tukey test were used.

Table 3: Plasma hormones level of male rats after administration of ciprofloxacin and levofloxacin with therapeutic and double dose for 14 days compared with control.

Hormones level	Control	Ciprofloxacin (mg/kg)		Levofloxacin (mg/kg)	
		78.23	156.46	39.11	78.22 mg/kg
Testosterone (ng/ml)	0.954±0.07	0.89±0.07	0.69±0.06*	0.99±0.08	0.77±0.018
FSH (ng/ml)	1.23±0.05	2.14±0.1*	4.4±0.06*	2.4±0.05*	2.9±0.06*
LH (mIU/ml)	0.65±0.05	1.45±0.013*	2.6±0.02*	1.34±0.02*	1.74±0.04*

Values expressed as mean±SE of 5 observations, *:significant difference at $p<0.05$ compared with control. One-way ANOVA and post hoc Tukey test were used.

Testosterone, FSH and LH

Only double dose ciprofloxacin significantly reduced testosterone level ($p<0.05$). On the other hand, the two doses of each drug significantly increased FSH and LH levels relative to control ($p<0.05$). A significant dose dependent effect was seen with FSH and LH in all treated groups ($p<0.05$). A significant difference was found between the two drugs in FSH level with all doses ($p<0.05$) and LH with the double doses only ($p<0.05$). (Table 3).

Histopathological findings

The testes of the treated rats with therapeutic dose ciprofloxacin for 2 weeks revealed congestion of the sub-capsular and interstitial blood vessels. Increase in the thickness of tunica albuginea with numerous degrees of degeneration of the lining epithelial cells of most seminiferous tubules was detected (Figure 1a) and occasionally accompanied by reduced spermatogenesis and absence of spermatozoa in the lumen of these degenerated tubules. Meanwhile, swollen, pale and vacuolated cytoplasm of the lining epithelium of some seminiferous tubules with accumulation of necrotic eosinophilic debris in the lumen of some seminiferous tubules was seen as well as incomplete spermatogenesis and absence of spermatozoa in the lumen of these degenerated tubules (Figure 1b). The testicular interstitium was expanded by homogenous eosinophilic material (edema) admixed with interstitial cells (Leydig cells) and few mononuclear leukocytic cellular infiltration (Figure 1c). Multifocally, the lining epithelial cells of some seminiferous tubules exhibited degeneration characterized by swollen pale discrete large vacuoles, usually replaced the cytoplasm. Rarely, degenerated tubules showed exfoliated epithelial cells in their lumen (Figure 1).

However, these histopathological changes were more pronounced in rats treated with double dose ciprofloxacin for 2 weeks. The testes of these animals showed marked congestion and thrombosis of the testicular blood vessels with obvious sub-capsular and inter-tubular edema (Figure 1d). The seminiferous tubules were more affected with extensive testicular degeneration of great numbers of seminiferous tubules was observed (Figure 1e). Marked reduction in the number of the germinal epithelium of seminiferous tubules with complete inhibition of spermatogenesis in most tubules. Extensive necrosis of germinal epithelium of seminiferous tubules with stop of spermatogenesis was also detected (Figure 1f). Additionally, dead and hyalinized sperms were demonstrated in the lumen of some seminiferous tubules (Figure 1g). Moreover, destruction of the basement membrane of some seminiferous tubules with distension of its lumen with desquamated germinal cells was also noticed. In the meantime, multiple areas of lytic necrosis of the germinal epithelium of seminiferous tubules that characterized by complete loss of spermatogenic cells in some seminiferous tubules was also demonstrated.

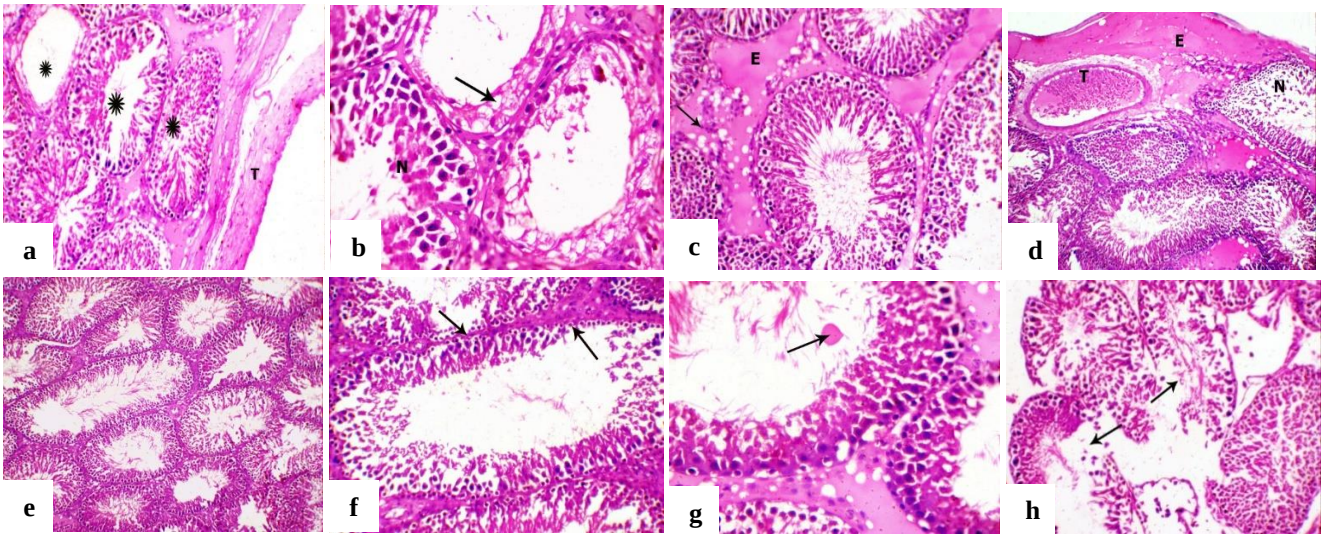

Figure 1: H&E stained section of testes obtained from rat treated with therapeutic dose ciprofloxacin (a-c) and double dose ciprofloxacin (d-h) for 2 weeks showing (a) increase in the thickness of tunica albuginea (T) with variable degree of degeneration of the lining epithelium of some seminiferous tubules (asterisk, X200), (b) loss of spermatids with severe degenerative changes with vacuolated (arrow) and necrosis (N) of the lining epithelium of some seminiferous tubules (X400), (c) inter-tubular edema (E) admixed with leydig cells and few leukocytic infiltration (arrow, X400), (d) thrombosis of the testicular blood vessels (T) with sub-capsular and inter-tubular edema and necrosis (N) of the lining epithelium of some seminiferous tubules (X400), (e) variable degree of degenerative changes of the lining epithelium of seminiferous tubules (X200), (f) Extensive necrosis of spermatogenic cells of seminiferous tubules with stop of spermatogenesis (arrow, X400), (g) dead and hyalinized sperm in the lumen of some seminiferous tubules (arrow) with inter-tubular edema (X400), (h) destruction of the basement membrane of some seminiferous tubules with complete absence of germinal cells (arrow) and distension of its lumen with desquamated epithelial cells (X200).

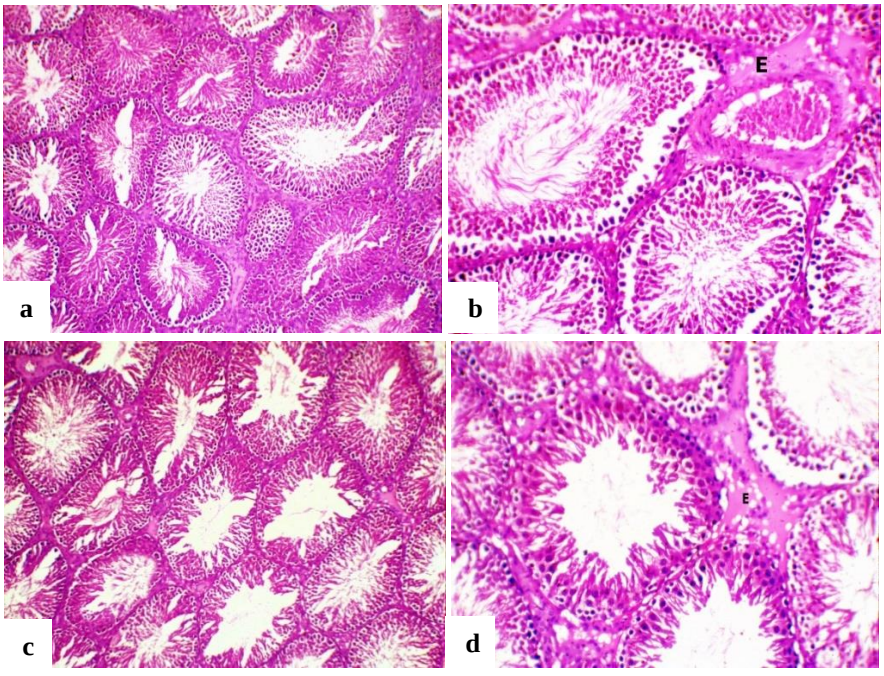

Figure 2: H&E stained section of testes obtained from rat treated with therapeutic dose levofloxacin (a-b) and double dose levofloxacin (c-d) for 2 weeks showing (a) most of the seminiferous tubules were compact with each other with normal spermatogenic layers (X100), (b) mild degeneration of the germinal epithelium of some seminiferous tubules with mild inter-tubular edema (E, X200), (c) degeneration of germinal epithelium with incomplete of spermatogenesis (X100), (d) severe degenerative changes with and loss of spermatids and inhibition of spermatogenesis as well as marked inter-tubular edema (E, X200).

However, the microscopical examination of testes of animals treated for 2 weeks with therapeutic dose of levofloxacin revealed less obvious histopathological changes when compared with the group treated with therapeutic dose ciprofloxacin for the same period. Most of the seminiferous tubules were compact with each other and the spermatogenic layers appeared normal in most examined animals (Figure 2a), consequently, most of the seminiferous tubules restored its normal histological architecture except mild congestion of testicular blood vessels, with mild degeneration of the germinal epithelium of some seminiferous tubules with mild inter-tubular edema (Figure 2b) and hyperplasia of Leydig cells was demonstrated only in two examined cases.

On the other side, the testes treated with double dose levofloxacin revealed more advanced pathological changes in comparison to the testes treated with therapeutic dose of levofloxacin. Meanwhile, these pathological alterations were less prominent when compared with the testes of animals treated with the double dose ciprofoxacin. The testes of the treated rats revealed congestion of the testicular blood vessels with degeneration of its wall. Multifocally, the lining epithelial cells of large numbers of seminiferous tubules exhibited variable degenerative changes (Figure 2c) characterized by reduction in the number of germ cells and inhibition of spermatogenesis with accumulation of inter-tubular edematous fluid admixed with leydig cells was detected in most investigated rats (Figure 2d).

On the other side, normal histological structure of tunica albuginea, seminiferous tubules and interstitial tissue was detected during the histopathological examination of the testes taken from rats received control. (group 1).

DISCUSSION

Medications are important aetiology of male infertility and should be investigated carefully when diagnose male infertility.[22,23] Ciprofloxacin and to a lesser extent, levofloxacin have been studied in rats regarding their effect on male reproductive system. The present study calculated the therapeutic doses based on the average doses of Kg-based dosing that equal 21.5 and 10.71 mg/kg/day in ciprofloxacin and levofloxacin respectively and body surface area-based dosing that equal 135 and 67.5 mg/kg/day in ciprofloxacin and levofloxacin respectively.[31] So, the therapeutic doses are 78.23 and 39.11 mg/kg/day and the double doses are 156.45 and 78.23 mg/kg/day in ciprofloxacin and levofloxacin respectively that fall in the previous dosing ranges. Different doses and durations were used in the previous reproductive animal studies and it ranged from 12.5 mg/kg ciprofloxacin daily for 60 days, 150 mg/kg for 10 days and 135 mg/kg for 15 days and 12 weeks to 206 and 412 mg/kg for 45 days and ranged from 0.03, 0.06 and 0.08 mg/kg levofloxacin for 60 days to 37.5 and 75 mg/kg for 14 and 28 days.[20,24-30] The present study showed that the testis, epididymis and seminal vesicle weight were negatively affected by the ciprofloxacin and levofloxacin with the therapeutic and double doses ($p<0.05$). Similar findings were observed and it was found that testis, epididymis and seminal vesicle weight were significantly reduced ($p<0.05$) after 60 days treatment with ciprofloxacin 12.5 mg/kg/day.[24] Testis weight depends on germ cell content and loss of these cells decreases the testis weight.[32] Consistent with this, histopathological findings of the present study reported testicular cells loss including germ cells and other cells. In the present study, both levofloxacin and ciprofloxacin significantly impaired sperm parameters ($p<0.05$). Previous studies reported that sperm count was decreased after 10 days treatment with 150 mg/kg ciprofloxacin; sperm motility count and viability were also reduced after 60 days treatment with 12.5 mg/kg ciprofloxacin and daily sperm production, motility and total sperm count were decreased after 15 days treatment with 135 mg/kg ciprofloxacin.[24,26,27] On the other hand, sperm parameters weren't affected significantly with either 37.5 or 75 mg/kg levofloxacin for 14 days, but they were significantly reduced after 28 days treatment.[20] Testosterone is important hormone in maintaining testis weight through maintenance of the spermatogenic process and inhibition of germ cell apoptosis.[33] However, testosterone was reduced only with double dose ciprofloxacin ($p<0.05$) which is similar to the effect of 135 mg/kg ciprofloxacin after 14 days treatment that significantly reduced serum testosterone.[28] Testosterone was also reduced after 45 days treatment with 206 and 412 mg/kg ciprofloxacin ($p<0.05$).[29] On the other hand, levofloxacin in the present study didn't have a significant effect on serum testosterone ($p>0.05$). Consistent with our findings, levofloxacin with dose 75 mg/kg for 28 days didn't affect testosterone level.[20] Meanwhile, low doses of levofloxacin with 0.03, 0.06 and 0.08 mg/kg didn't affect testosterone level, but increased FSH and LH levels.[30] This study found a significant effect of ciprofloxacin and levofloxacin on FSH and LH that were increased relative to control ($p<0.05$) which is different from the effect of 416 mg/kg ciprofloxacin that significantly reduced FSH and LH, but 206 mg/kg ciprofloxacin didn't have a significant effect.[29] This discrepancy may be related to different animal ages or species. One possible mechanism of ciprofloxacin and levofloxacin-induced testicular cell damage is oxidative stress where it was found that ciprofloxacin increased testicular oxidative stress and levofloxacin increased oxidative stress in other organs such as plasma.[34,35] Direct effect of levofloxacin on testicular oxidative stress in comparison with ciprofloxacin will be presented in a separate investigation by our team. It might give some explanations for the small difference between the two drugs regarding their negative effects on male reproductive system. Another possible explanation is the blood-testis barrier; a tight junction between Sertoli cells that protect germ cells from substances penetration and there is a good correlation between lipophilicity of the drug and its permeability through blood-tissue barriers.[36,37] Levofloxacin is more lipophilic than ciprofloxacin.[38] So, it is predicted that levofloxacin

achieved higher testicular concentration relative to blood than ciprofloxacin. The present study showed histopathological alterations in seminiferous tubules and interstitial tissues with ciprofloxacin and to a lesser extent levofloxacin. Similar findings were reported with levofloxacin and ciprofloxacin.[24,26,30] Finally, human follow up studies are required to keep caution regarding negative effect of ciprofloxacin and levofloxacin on human fertility specially couples seeking for children.

CONCLUSION

Treatment with either ciprofloxacin or levofloxacin exhibited variable degree of testicular degeneration via induction of histopathological alterations in the seminiferous tubules and interstitial tissues, impaired sperm parameters and affect hormone level. The severity of these changes was dose dependent. Levofloxacin relative to ciprofloxacin is slightly less gonadotoxic but relative to control, levofloxacin retained gonadotoxicity. So, monitoring the patient under therapy is required.

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