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The effects of long acting and different doses of Danofloxacin on oxidative stress, biochemical, and hemogram parameters in rats

Efectos de la acción prolongada y diferentes dosis de danofloxacino sobre el estrés oxidativo, los parámetros bioquímicos y el hemograma en ratas

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ABSTRACT

Danofloxacin is a new generation fluoroquinolone antibiotic. There is limited literature information regarding its toxicity with long-term use. Therefore, likelihood of adverse effects increases. This study was aimed to determine the effects of long-term danofloxacin administration at different doses primarily on serum oxidative stress parameters, as well as biochemical and complete blood count parameters. Forty rats were divided into four groups with equal numbers in each group. While rats in the control group were not subjected to any treatment, other three groups received 5, 10, and 25 mg/kg of danofloxacin (intraperitoneal) daily for three weeks, respectively. At the end of the experiment, the animals were anesthetized, blood samples were collected and they were euthanized. The collected blood samples were centrifuged to separate the serum fractions. Serum levels of oxidative stress parameters (malondialdehyde, superoxide dismutase, glutathione peroxidase) were determined using the Enzyme-Linked Immunosorbent Assay reader. Levels of serum biochemistry parameters (aspartate aminotransferase, gamma glutamyl transferase, blood urea nitrogen, cholesterol, phosphorus, magnesium) were measured using an autoanalyzer. Hemogram parameters (white blood cell, red blood cell, platelet, hematocrit, hemoglobin) were measured using a hemocell counter device. In the study, administration of danofloxacin for 21 days at different doses had no effect on oxidative stress and hemogram parameters ($P > 0.05$). However, high doses (10 and 25 mg/kg) of danofloxacin elevated aspartate aminotransferase, gamma glutamyl transferase, cholesterol, and phosphorus levels ($P < 0.05$). In conclusion, long-term administration of danofloxacin does not cause oxidative stress or affect hemogram parameters; however, patients should be monitored for liver and kidney function and lipid metabolism. Furthermore, more studies using histopathological or molecular methods involving disease models are needed to determine the extent of organ damage in the future.

Key words: Danofloxacin; oxidative stress; biochemistry; hemogram.

RESUMEN

La danofloxacina es un antibiótico fluoroquinolónico de nueva generación. Existe poca información bibliográfica sobre su toxicidad con el uso a largo plazo. Por lo tanto, aumenta la probabilidad de efectos adversos. Este estudio tuvo como objetivo determinar los efectos de la administración prolongada de danofloxacino en diferentes dosis, principalmente sobre los parámetros séricos de estrés oxidativo, así como sobre los parámetros bioquímicos y el hemograma completo. Cuarenta ratas se dividieron en cuatro grupos con el mismo número de ratas en cada grupo. Mientras que las ratas del grupo control no recibieron ningún tratamiento, los otros tres grupos recibieron 5, 10 y 25 mg/kg de danofloxacino (intraperitoneal) diariamente durante tres semanas, respectivamente. Al final del experimento, los animales fueron anestesiados, se tomaron muestras de sangre y posteriormente se les practicó eutanasia. Las muestras de sangre se centrifugaron para separar las fracciones séricas. Se determinaron los niveles séricos de los parámetros de estrés oxidativo (malondialdehído, superóxido dismutasa, glutatión peroxidasa) mediante un lector de ensayo inmunoabsorbente ligado a enzimas. Se midieron los niveles de los parámetros bioquímicos séricos (aspartato aminotransferasa, gamma glutamil transferasa, nitrógeno ureico en sangre, colesterol, fósforo y magnesio) con un autoanalizador. Los parámetros del hemograma (glóbulos blancos, glóbulos rojos, plaquetas, hematocrito y hemoglobina) se midieron con un contador de hemocélulas. En el estudio, la administración de danofloxacino durante 21 días a diferentes dosis no tuvo efecto sobre el estrés oxidativo ni los parámetros del hemograma ($P > 0,05$). Sin embargo, dosis altas (10 y 25 mg/kg) de danofloxacino elevaron los niveles de aspartato aminotransferasa, gamma glutamil transferasa, colesterol y fósforo ($P < 0,05$). En conclusión, la administración prolongada de danofloxacino no causa estrés oxidativo ni afecta los parámetros del hemograma; sin embargo, se debe monitorizar la función hepática y renal, así como el metabolismo lipídico de los pacientes. Además, se necesitan más estudios que utilicen métodos histopatológicos o moleculares que involucren modelos de enfermedad para determinar la extensión del daño orgánico en el futuro.

Palabras clave: Danofloxacino; estrés oxidativo; bioquímica; hemograma

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INTRODUCTION

Danofloxacin is a second-generation fluoroquinolone antibiotic. Fluoroquinolones show bactericidal effect by inhibiting the activity of DNA gyrase and topoisomerase IV enzymes in susceptible microorganisms, thereby preventing cell division [1, 2]. Danofloxacin, enrofloxacin, ciprofloxacin, marbofloxacin, sarafloxacin, pradofloxacin, difloxacin, and ibafloxacin are fluoroquinolone antibiotics. They have a broad spectrum of activity. Their spectrum of activity includes especially, gram-negative aerobic bacteria (*E. coli, Salmonella* spp., *Shigella* spp., *Enterobacter* spp., *Brucella* spp., *Pasteurella* spp., *Klebsiella* spp., among others.), *Mycoplasma* spp., and gram-positive bacteria such as *Staphylococcus* spp. Fluoroquinolones distribute very well throughout the body and transit the blood-brain barrier. They are used in the treatment of gastrointestinal infections, urinary tract infections, skin infections, eye infections, *Mycoplasma* spp. infections, sepsis, and septic shock [2]. Fluoroquinolones are generally used for one week for therapeutic purposes [2], but in some cases, they may be used for longer periods [3, 4].

Fluoroquinolones can affect the oxidative status in *living* organisms [5, 6, 7]. In living organisms, the highest number of oxygen-derived free radicals form in biological systems. These structures are unstable and cause damage by affecting the structures or molecules around them (DNA, membrane lipids, proteins, carbohydrates). Free oxygen radicals are tried to be neutralized by enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase or by non-enzymatic structures (bilirubin, vitamin E, vitamin A, etc.) [8, 9].

An oxygen molecule that accepts an electron is converted into a superoxide radical. The superoxide radical is continuously produced in all aerobic cells during cellular respiration. The SOD enzyme converts superoxide radicals into hydrogen peroxide and molecular oxygen. The resulting hydrogen peroxide is then inactivated by GPX or catalase enzymes, which convert it into water and molecular oxygen [8].

When free oxygen radicals are produced in excess or when antioxidant capacity is insufficient, oxidative stress develops in the organism. Membrane lipids are the structures most affected by this condition, and the resulting damage is defined as lipid peroxidation. Malondialdehyde (MDA) is the most abundant product of lipid peroxidation, and measured MDA levels are associated with structural damage [8].

Despite fluoroquinolones have a wide range of applications, they can cause serious side effects. These drugs should not be used in immature organisms due to their chondrotoxic effects, nor in epileptic patients as they can trigger epileptic seizures [1, 2].

Other side effects are reported as hepatotoxicity, nephrotoxicity, tendinitis, phototoxicity, dizziness, and convulsions [10]. In addition, it has been determined that danofloxacin can cause sedentariness [11], ciprofloxacin can cause acute renal failure [12], enrofloxacin can cause blindness in cats [13], and fluoroquinolones can cause rupture or dissection of aortic aneurysms [14].

It is known that the drugs used can cause side effects even at the recommended doses, in addition to their positive effects. These side effects can be clinically detected as well as determined by measuring certain parameters in the blood. Some of the biochemical or physiological parameters evaluated in these tests are defined as indicators of damage developing in organs or systems [15, 16].

Aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) levels measured from serum provide information about liver function [17], blood urea nitrogen (BUN) level provides information about kidney function [18], and cholesterol level provides information about lipid metabolism [19]. Serum phosphorus and magnesium levels change in certain endocrine and metabolic disorders [20].

The measured hemogram parameters [white blood cell counts (WBC), red blood cell counts (RBC), platelet counts (Plt), hemoglobin (Hgb), hematocrit (Htc)] are used in the diagnosis and prognosis of many diseases, as well as in determining the side effects of some drugs [21].

Considering that fluoroquinolones may affect the oxidative status [6, 13], cause hepatotoxicity and nephrotoxicity [10] and affect hemogram parameters [22], it has been hypothesized that administration of danofloxacin at different doses for 21 days (d) could affect serum oxidative status, organ damage markers, cholesterol, elements, and hemogram parameters.

The aim of this study is to determine how administration of danofloxacin (5, 10, 25 mg/kg, SID) to rats (*Rattus norvegicus*) different doses for 21 d affects serum oxidative stress (MDA, SOD, GPX), biochemical (AST, GGT, BUN, cholesterol, phosphorus, and magnesium), and hematological (WBC, RBC, Plt, Hgb, Htc) parameters.

MATERIAL AND METHODS

Experimental design and animal applications

Forty healthy female Wistar-Albino rats (8-12 weeks, 235-275 g, SF-400D scale, Gromy Industry, Zhejiang, Chine) were used in the study. The animals obtained from Selcuk University Experimental Medicine Application and Research Center (Konya, Türkiye) were kept at 54-56 % relative humidity and 21 ± 2 °C temperature with a 12/12-hour (h) light-dark cycle. Water and feed were provided ad libitum.

In the study, 40 rats were divided into 4 groups with an equal number in each group. No treatment was carried out on the control group (n: 10). The other 3 groups received daily intraperitoneal injections of 5 mg/kg, 10 mg/kg, and 25 mg/kg of danofloxacin (Advocin 180 inj., Zoetis, Istanbul, Türkiye for three weeks, respectively. At the end of the experiment, the animals were anesthetized with a combination of Xylazine (8 mg/kg, intraperitoneally, Xylazin Bio 2 % inj., Bioveta, Ankara, Türkiye) + Ketamine (75 mg/kg, intraperitoneally, Ketasol 10 % inj., Interhas, Ankara, Türkiye).

Blood samples were taken from the hearts of the animals, and they were euthanized by cervical dislocation. The blood samples were centrifuged (Sigma 3K-18, Osterode am Harz, Germany) at 2000 g for 10 min to separate the serum fractions. In addition, whole blood samples were collected in Potassium3-Ethylenediaminetetraacetic acid (K3-EDTA) tubes for measuring hemogram parameters.

ELISA and serum biochemical and hemogram analyses

In the study, rat-specific ELISA kits obtained from a commercial company (Bioassay Technology Laboratory, Shangai, China) were used to measure serum oxidative stress parameters MDA, SOD, and GPX using an Enzyme-Linked Immunosorbent Assay (ELISA) reader (MWGtLambda Scan 200, Bio–Tec Instruments, Winooski, VT, USA).

While AST, GGT, BUN, cholesterol, phosphorus, and magnesium levels were measured in serum using an autoanalyzer (aV-280 - A Validity Biochemitry Auto Analyzer, Istanbul, Türkiye), hemogram parameters (WBC, RBC, PLT, Hgb, Htc) were measured using a hemocell counter device (Abbott Cell-Dyn 3700 Hematology Analyzer, Minnesota, USA).

Statistical analysis

Results of the study are presented as mean ± standard error. Data were analyzed using Analysis of variance (ANOVA) and Scheffe's post hoc test (SPSS 29.0). The value of $P < 0.05$ was accepted as statistically significant limit.

RESULTS AND DISCUSSION

TABLES I, II, and III show the effects of danofloxacin on serum oxidative stress, biochemistry, and hemogram parameters. While the effect of danofloxacin on oxidative stress and hemogram parameters was not determined ($P > 0.05$), serum AST, GGT, cholesterol, and phosphorus levels were higher in the groups where danofloxacin was administered at 10 and 25 mg/kg than in the control and 5 mg/kg danofloxacin groups ($P < 0.05$).

TABLE I

The effect of different doses of danofloxacin (5, 10, 25 mg/kg, intraperitenoally, single in a day, 21 days) on serum oxidative stress parameters in rats (mean ± standart error)*

Parameters	Control (n: 10)	5 mg/kg (n: 10)	10 mg/kg (n: 10)	25 mg/kg (n: 10)
MDA nmol/mL	1.94 ± 0.17	1.50 ± 0.16	1.34 ± 0.18	1.31 ± 0.11
SOD ng/mL	2.54 ± 0.25	2.96 ± 0.20	2.43 ± 0.19	2.46 ± 0.15
GPX pg/mL	469.44 ± 29.65	447.14 ± 17.58	396.85 ± 19.64	449.30 ± 23.43

MDA: Malondialdehyde, SOD: Superoxide dismutase, GPX: Glutathione peroxidase.
*No statistical difference was detected in the same line.

Fluoroquinolone antibiotics are widely prescribed in veterinary medicine for poultry, pets, and ruminants due to their broad spectrum of activity (gram-negative bacteria, some gram-positive bacteria, *Mycoplasma* spp., etc.). These drugs are frequently preferred antibiotics for the treatment of gastrointestinal infections, respiratory infections (especially *Mycoplasma* spp.), bone/joint infections (especially *Staphylococcus* spp.), skin infections, intra-abdominal infections, anthrax, and urinary tract infections [2, 4, 23]. Fluoroquinolones are often used for one week in the treatment of normal infections [2].

TABLE II

The effect of different doses of danofloxacin (5, 10, 25 mg/kg, intraperitenoally, single in a day, 21 days) on serum biochemical parameters in rats (mean ± standart error)

Parameters	Control (n: 10)	5 mg/kg (n: 10)	10 mg/kg (n: 10)	25 mg/kg (n: 10)
AST U/L	80.80 ± 17.49^b	78.30 ± 13.98^b	144.76 ± 19.28^a	151.10 ± 13.10^a
GGT U/L	6.60 ± 0.16^b	6.60 ± 0.16^b	7.80 ± 0.13^a	8.10 ± 0.45^a
BUN mg/dL	21.70 ± 3.27	19.30 ± 2.42	31.70 ± 1.69	32.30 ± 4.59
Chol mg/dL	52.77 ± 8.12^b	56.75 ± 9.78^b	165.54 ± 5.86^a	168.73 ± 3.77^a
P mg/dL	4.21 ± 0.61^b	4.63 ± 0.58^b	7.49 ± 0.27^a	7.38 ± 0.23^a
Mg mg/dL	2.35 ± 0.42	2.70 ± 0.43	2.55 ± 0.21	2.29 ± 0.17

AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, BUN: Blood urea nitrogen, Chol: Cholesterol, P: Phosphorus, Mg: Magnesium.
^{a,b}: Different letters in the same line are statistically significant ($P < 0.05$)

However, antibiotics can be used for long periods and at high doses in some infections such as urinary tract [3, 4], pyothorax [24], and gallbladder [25]. In this study, danofloxacin was administered at 3 different doses for 21 d.

In this study, the administration of danofloxacin at different doses (5, 10, 25 mg/kg, SID) for 3 weeks had no effect ($P > 0.05$) on serum oxidative stress parameters (MDA, SOD, GPX) (TABLE I). It has been reported that danofloxacin causes a temporary increase in liver SOD levels and a decrease in GPX levels, but enrofloxacin has no effect on liver SOD and GPX levels in mice [26]. Administration of highest dose of gatifloxacin for 21 days to rabbits caused a decrease in SOD levels and increases in GPX and MDA levels [27], and ciprofloxacin (10 days) caused an increase in MDA levels and a decrease in SOD levels in kidney tissue of rats [28]. It has been stated that enrofloxacin (10 mg/kg/day, SC, 14 d) did not affect the MDA, SOD, and GPX levels in serum and joint fluid of sheep [6]. The differences between the results of the studies may be caused by the antioxidant capacity of the animals and the differences in the body fluids and tissues measured. According to the results of this study, it can be stated that danofloxacin may not cause oxidative stress at the normal and high doses.

TABLE III

The effect of different doses of danofloxacin (5, 10, 25 mg/kg, intraperitenoally, single in a day, 21 days) on hemogram parameters in rats (mean ± standart error)*

Parameters	Control (n: 10)	5 mg/kg (n: 10)	10 mg/kg (n: 10)	25 mg/kg (n: 10)
WBC x10^9/L	5.13 ± 0.82	4.99 ± 0.71	5.11 ± 0.40	4.57 ± 0.62
Neutrophil x10^9/L	1.27 ± 0.43	1.17 ± 0.36	1.53 ± 0.34	0.93 ± 0.25
Lymphocyte x10^9/L	3.32 ± 0.63	3.53 ± 0.54	3.07 ± 0.39	3.30 ± 0.45
Monocyte x10^9/L	0.31 ± 0.12	0.07 ± 0.02	0.10 ± 0.03	0.10 ± 0.04
Eosinophil x10^9/L	0.08 ± 0.02	0.12 ± 0.05	0.05 ± 0.01	0.08 ± 0.02
Basophil x10^9/L	0.13 ± 0.04	0.09 ± 0.03	0.05 ± 0.01	0.14 ± 0.04
RBC x10^{12}/L	6.63 ± 0.32	6.64 ± 0.11	6.58 ± 0.15	6.46 ± 0.11
PLT x10^9/L	709.20 ± 23.24	691.20 ± 39.87	691.90 ± 24.50	790.60 ± 38.16
Hgb g/dL	13.12 ± 0.80	14.51 ± 0.25	14.48 ± 0.27	14.11 ± 0.24
Htc %	33.54 ± 1.56	34.33 ± 0.62	34.15 ± 0.64	32.94 ± 0.54

WBC: White blood cell counts, RBC: Red blood cell counts, PLT: Platelet counts, Hgb: Hemoglobine, Htc: Hematocrit. *No statistical difference was detected in the same line.

In the present study, high doses (10 and 25 mg/kg) of danofloxacin caused increases ($P < 0.05$) in liver function parameters (AST, GGT) (TABLE II). Fluoroquinolones may cause cholestasis, hepatitis, and liver failure [10]. Cases of fluoroquinolone-induced hepatotoxicity can range from mild transient aminotransferase elevations to hepatitis and jaundice, and even severe and acute liver damage and liver failure [29]. Elevated aminotransferase levels and acute liver failure may occur the following fluoroquinolone administration [30, 31]. While administration of danofloxacin for 14 d to sheep elevated AST levels [32], marbofloxacin [22] did not effect GGT levels.

In addition to these, enrofloxacin (14 d) did not affect AST and GGT levels in sheep [6], whereas enrofloxacin (10 d) caused a temporary increase AST levels in dogs [33]. Although fluoroquinolone-induced liver damage is rare, it has been noted that it can result in prolonged jaundice, liver transplantation, or acute liver failure leading to death. Patients with fluoroquinolone-induced liver injury should avoid repeated exposure to other members of this antibiotic group [34]. Based on this research result, it can be stated that liver injury may be observed with long-term high-dose use of danofloxacin.

In this study, high-doses (10 and 25 mg/kg) of danofloxacin caused statistically insignificant (≈50 %, $P > 0.05$) increases in the BUN levels which is kidney function parameter (TABLE II). Fluoroquinolones are known to cause crystalluria, renal tubular damage, interstitial nephritis, and oliguric nephrotoxicity [10, 13].

Ciprofloxacin has been reported to cause acute renal failure [12] and interstitial nephritis [35]. Administration of ciprofloxacin (10 d) to rats caused infiltration, tubular atrophy, narrowing of the Bowman's space, congestion, hemorrhage, and necrosis in the kidneys [28]. Administration of danofloxacin (14 d) to sheep caused statistically significant fluctuations in BUN levels [32], while marbofloxacin caused elevations in BUN levels ($P < 0.05$) [22], but enrofloxacin (14 d) did not affect BUN levels in sheep [6]. Based on the results of this study, it can be stated that renal function parameters should be monitored during long-term high-dose use of danofloxacin.

In the peresent, it was determined that administration of danofloxacin at high doses (10 and 25 mg/kg) elevated ($P < 0.05$) serum cholesterol and phosphorus levels (TABLE II). A literature review revealed no studies on the direct effect of fluoroquinolones on serum cholesterol and phosphorus levels. It has been reported that certain kidney diseases and cholestatic disorders cause hypercholesterolemia [19]. It can be stated that the liver and kidney damage observed in this study may elevate cholesterol levels.

Considering that a decrease in glomerular filtration rate in the kidneys of cats and dogs may elevate serum phosphorus levels [20], it can be stated that long-term high-dose administration of danofloxacin may cause high phosphorus levels due to its effect on the kidneys.

In the current research, administration of danofloxacin at different doses (5, 10, 25 mg/kg, SID) for 21 d to rats had no effect ($P > 0.05$) on hematological parameters (TABLE III). It has been reported that fluoroquinolones may cause temporary bone marrow suppression, thrombocytopenia, and neutropenia [23].

In related studies, administration of danofloxacin to sheep lowered WBC, RBC, Hgb, and Htc levels and elevated platelet levels [32], while administration of marbofloxacin caused temporary decreases in WBC, RBC, Hgb, and Htc values within reference ranges [22], and enrofloxacin administration had no effect on WBC, RBC, platelet, Hgb, and Htc levels [6].

Administration of enrofloxacin in dogs was reported not to cause changes in WBC, RBC, Hgb, and Htc levels [33]. It can be stated that the differences in the study results may be due to the difference in the administered fluoroquinolone dose and duration of administration and/or the animal species to which the drug was administered, and that danofloxacin may not have adverse effects on hemogram data.

CONCLUSIONS AND IMPLICATIONS

Danofloxacin, a second-generation fluoroquinolone antibiotic, is used to treat a variety of infections, including Mycoplasma spp. infections, sepsis, and septic shock, at doses of 1.25 or 8 mg/kg. In some cases, it can be used at different doses and for extended periods. This study provides information on the safety of long-term use of danofloxacin at different doses. It can be stated that danofloxacin, one of the fluoroquinolones frequently prescribed in Veterinary field, may not cause oxidative stress or affect hemogram parameters when used at high doses for long periods, but it may cause liver and kidney damage. Furthermore, it may alter serum cholesterol and phosphorus levels due to its undesirable effects on the liver and kidneys.

Ethical approval

Ethical approval of this research (Approval no: 2025/104) was obtained from Selcuk University Experimental Medicine and Application Center Ethics Committee (SUDAM).

Conflict of interest

The authors declare that they have any conflict of interest.

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