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Investigation of the Effects of Three Different Generations of Fluoroquinolone Derivatives on Erythrocyte Fragility and Hematological Parameters in Rats

Üç Farklı Kuşak Florokinolon Türevinin Ratlarda Eritrosit Frajilite ve Hematolojik Parametreler Üzerindeki Etkilerinin Araştırılması

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ABSTRACT

Objective: Fluoroquinolones (FQs) are synthetic broad-spectrum antimicrobial agents derived from nalidixic acid. They are used in the treatment of urinary tract infections, respiratory tract infections, skin infections, digestive system infections, genital infections and other bacterial infections. Although the relationship between FQs and oxidative stress has been demonstrated, their effects on erythrocyte fragility have not been adequately studied. In this study, the effects of three different FQ derivatives (ciprofloxacin (CIP), levofloxacin (LVX) and moxifloxacin (MXF)) on erythrocyte fragility and hematological parameters were investigated in rats at the end of the 1st, 7th and 14th day treatments by gavage.

Material and Method: 72 *Wistar albino* male rats were divided into 4 groups with 18 rats in each group and sacrificed at three different time points (1st, 7th and 14th days).

Results: A significant increase in 0.2% sodium chloride (NaCl) concentration erythrocyte fragility value was found in the MXF group on 1st day compared to the control group on 1st day. While the FQ derivatives used in the study did not cause a general change on the erythrocyte and leukocyte parameters, they caused various fluctuations on the platelet parameters such as plateletcrit (PCT), platelet large cell ratio (PLCR), platelet distribution width (PDW), mean platelet volume (MPV) and platelet (PLT).

Conclusion: As a further study, it would be beneficial to reveal the reasons for these effects on platelet parameters with more detailed studies.

Keywords: *Erythrocyte fragility, Hematological parameters, Levofloxacin, Moxifloxacin, Ciprofloxacin*

ÖZET

Giriş: Florokinolonlar (FQ'lar), nalidiksik asitten türetilen sentetik geniş spektrumlu antimikrobiyal ajanlardır. Bu grup idrar yolu enfeksiyonları, solunum yolu enfeksiyonları, deri enfeksiyonları, sindirim sistemi enfeksiyonları, genital enfeksiyonlar ve diğer bakteriyel enfeksiyonların tedavisinde kullanılırlar. FQ'ların oksidatif stres ile ilişkisi gösterilmiş olmasına rağmen, eritrosit frajilite üzerindeki etkileri yeterince araştırılmamıştır. Bu çalışmada oral yolla üç farklı florokinolon türevinin (siprofloksasin (CIP), levofloksasin (LVX) ve moksifloksasin (MXF)) 1, 7 ve 14 günlük tedavilerinin eritrosit frajilite ve hematolojik parametreler üzerindeki etkileri araştırıldı.

Materyal ve Metot: 72 Wistar albino erkek ratlar her grupta 18 rat olacak şekilde 4 gruba ayrılarak üç farklı zaman noktasında (1., 7. ve 14. günler) sakrifiye edildiler

Bulgular: % 0.2 sodyum klorür (NaCl) konsantrasyonu eritrosit frajilite değeri 1. gün MXF grubu 1. gün kontrol grubu ile karşılaştırıldığında anlamlı artış göstermiştir. Çalışmada kullanılan FQ türevleri eritrosit ve lökosit parametrelerinde genel bir değişikliğe neden olmazken trombosit crit (PCT), trombosit büyük hücre oranı (PLCR), trombosit dağılım genişiliğ (PDW), ortalama trombosit hacmi (MPV) ve trombosit (PLT) gibi trombosit parametrelerinde çeşitli dalgalanmalara neden olmuştur.

Sonuç: İleri bir çalışma olarak trombosit parametreleri üzerindeki bu etkilerin nedenlerinin daha detaylı çalışmalarla ortaya konması faydalı olacaktır.

Anahtar kelimeler: *Eritrosit frajilite, Hematolojik parametreler, Levofloksasin, Moksifloksasin, Siprofloksasin*

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INTRODUCTION

Fluoroquinolones (FQs) used in the treatment of various bacterial infections are synthetically derived from nalidixic acid (Stahlmann and Lode, 2010; Dönmez et al., 2018). At the beginning of these bacterial infections are lower and upper respiratory tract, urinary tract, skin, bone, soft tissue infections and community-acquired pneumonia (Hu et al., 2017). Bactericidal FQs prevent bacterial division by inhibiting DNA gyrase and DNA topoisomerase IV enzymes (Donmez and Dogan, 2022). The classification of FQs was made by considering their antimicrobial spectra and clinical indications. Drugs in the same group have similar antimicrobial activities. The next generation affects the pathogens of the previous generation and a new group of pathogens (Ezelarab et al., 2018). So far, ciprofloxacin (CIP), ofloxacin, levofloxacin (LVX), moxifloxacin (MXF), gemifloxacin, and delafloxacin, respectively, have been approved by the US Food and Drug Administration (FDA) (Maris et al., 2021).

The blood is responsible for the transport of oxygen, nutrients, drugs, and waste products (Xie et al., 2020; Gladysz et al., 2022). In humans and rodents, approximately 6 to 7% of the total body weight is composed of the blood compartment (Bertrand and Leroux, 2012). Approximately 55% of this blood is plasma (90% water, 10% protein), while 45% (99% red blood cells, 1% leukocytes, and platelets) consists of blood cells (Meinke et al., 2007). Considering all these, it is important to investigate the effects of drugs on the blood. Studies conducted in this direction have revealed the relationship between FQs and oxidative stress on erythrocytes (Akyol et al., 2003; Donmez and Dogan, 2022). However, its effects on blood parameters have not been sufficiently investigated. In this study, the effects of three different FQ derivatives (CIP, LVX and MXF) on erythrocyte fragility and hematological parameters were investigated in rats at the end of the 1st, 7th and 14th day treatments.

MATERIAL AND METHOD

Chemicals

Sodium chloride (NaCl), sodium dihydrogen phosphate (NaH_2PO_4), and disodium hydrogen phosphate (Na_2HPO_4) were supplied by Sigma Chemical Co. (St. Louis, MO, USA). In addition, all pharmaceutical drugs used in the study were purchased from commercial pharmacies in tablet form. CIP, LVX, and MXF suspended in 1 ml of distilled water were administered as gavage to the rats at 80 mg/kg/day (Rawi et al., 2011), 40 mg/kg/day (Afolabi and Oyewo, 2014), and 40 mg/kg/day (Huang et al., 2016), respectively.

Animals

This experimental study was carried out with 72 male Wistar albino rats, 2-3 months old, weighing 150–300 g, obtained from the Van Yüzüncü Yıl University Experimental Animals Unit. Ethics committee number was given by Van Yüzüncü Yıl University Experimental Animals Research Center (2023/09–11). Rats in a 25 ± 2 °C temperature and 12:12 hour light-dark light environment were fed ad libitum (as desired) with standard plastic containers. All experimental procedures were performed according to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

Experimental Design

In the study, rats were randomly divided into four groups, with 18 animals in each group. Six rats from each group were sacrificed at the end of 1, 7, and 14 days of treatment.

(I) Control group (n = 18): The animals were given distilled water by gavage for the specified periods and fed with standard feed and water *ad libitum*. Six rats each time were sacrificed at the end of the 1st, 7th, and 14th days, respectively.

II) CIP treated group (n = 18): CIP (80 mg/kg) was given to the animals CIP by gavage for the specified periods and fed with standard feed and water *ad libitum*. Six rats each time were sacrificed at the end of the 1st, 7th, and 14th days, respectively.

(III) LVX treated group (n = 18): LVX (40 mg/kg) was given to the animals by gavage for the specified periods and fed with standard feed and water *ad libitum*. Six rats each time were sacrificed at the end of the 1st, 7th, and 14th days, respectively.

(IV) MXF treated group (n = 18): MXF (40 mg/kg) was given to the animals by gavage for the specified periods and fed with standard feed and water *ad libitum*. Six rats each time were sacrificed at the end of the 1st, 7th, and 14th days, respectively.

Measurement of Erythrocyte Fragility

30 µl of blood samples incubated for 24 hours at room temperature were pipetted into a series of test tubes containing 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9 g/L NaCl (pH 7.4). Mixtures incubated for 30 minutes at room temperature were centrifuged at 3000 rpm for 5 minutes. The absorbance of the supernatant fractions was measured at 546 nm by a spectrophotometer (Doğan et al., 2020).

Calculation: Haemolysis (%) = (OD of Test Solution) / (OD of Standard Solution) x 100

Haematological Parameters

At the end of the experiment, blood samples were taken from the cardiac puncture using a syringe for the determination of hematological parameters. haemoglobin (HGB), mean cell haemoglobin (MCH), mean cell corpuscular haemoglobin concentration (MCHC), red blood cells (RBC), mean corpuscular volume (MCV), haematocrit (HCT), red cells distribution width (RDW), white blood cell (WBC), lymphocyte (LYM), monocytes (MID), granulocyte (GRA), platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), platelet large cell ratio (PLCR), and plateletcrit (PCT) were measured by

an automatic hematological assay analyzer (Swelab Alfa Hematology Analyzer).

Statistical Analysis

The GraphPad Prism 8 package program was used in the statistical analysis of the data obtained in the study. One-way analysis of variance (ANOVA) was used to determine the differences between groups, and Tukey's multiple comparison test was used to determine the differences between groups with more than two. Significance was accepted as $p<0.05$ for all tests.

RESULTS

Effects of FQ Derivatives on the Erythrocyte Osmotic Fragility

The erythrocyte fragility value of 0.2% NaCl concentration 1st day MXF group significantly increased compared to 1st day control group (Figure 1). Besides, 7 and 14 day treatments of FQs did not affect erythrocyte fragility (Figure 2 and Figure 3).

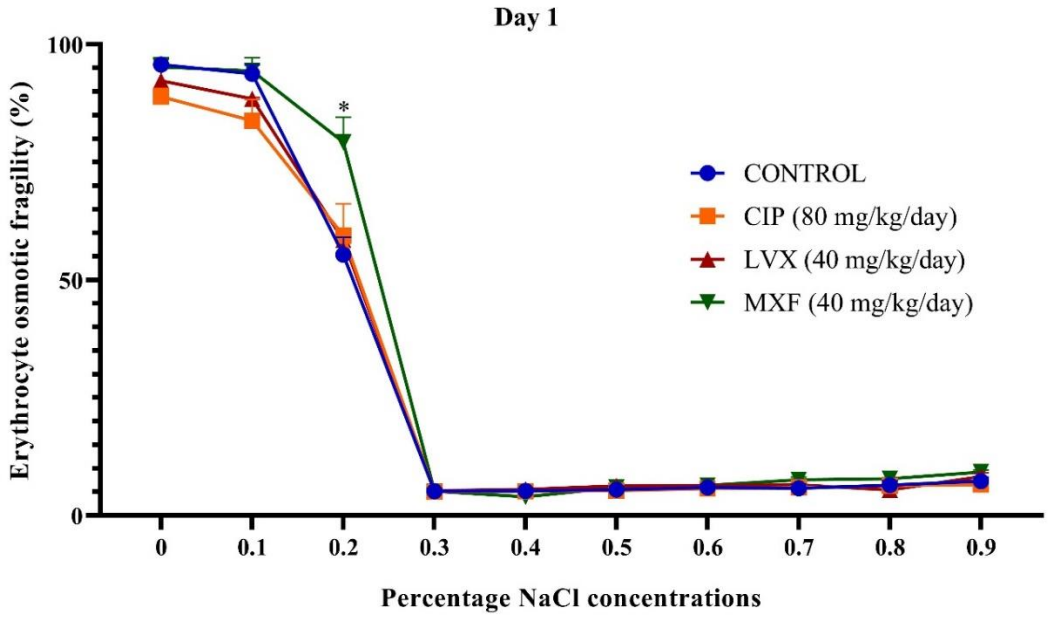

Figure 1. Effect of three different fluoroquinolone derivatives on 1st day rat erythrocyte fragility.
*: Difference between the Control group and the other groups was significant ($p<0.05$)

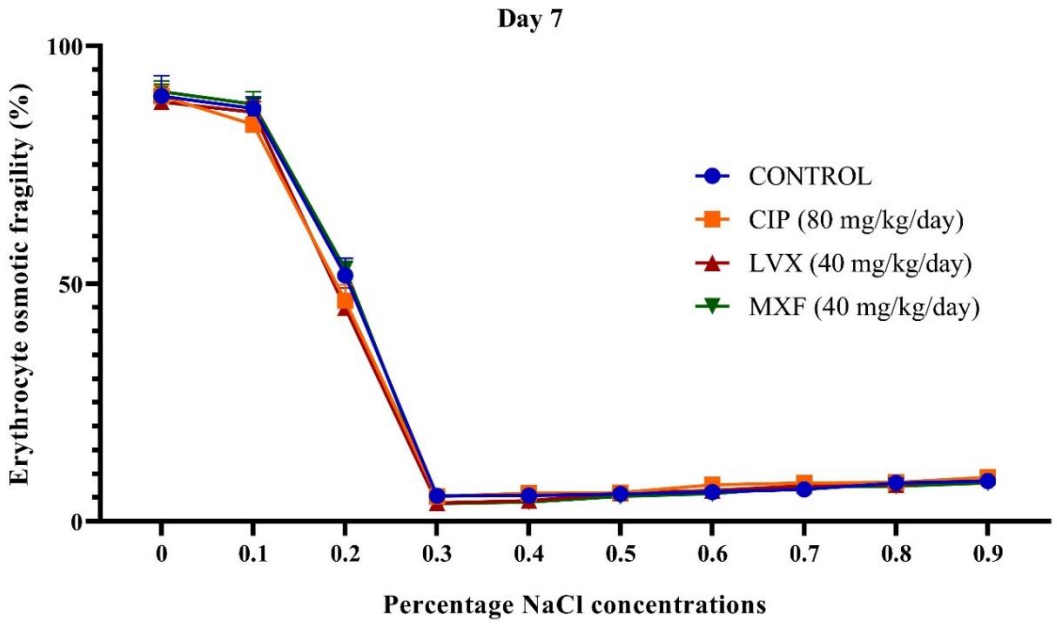

Figure 2. Effect of three different fluoroquinolone derivatives on 7th day rat erythrocyte fragility.
*: Difference between the Control group and the other groups was significant ($p<0.05$).

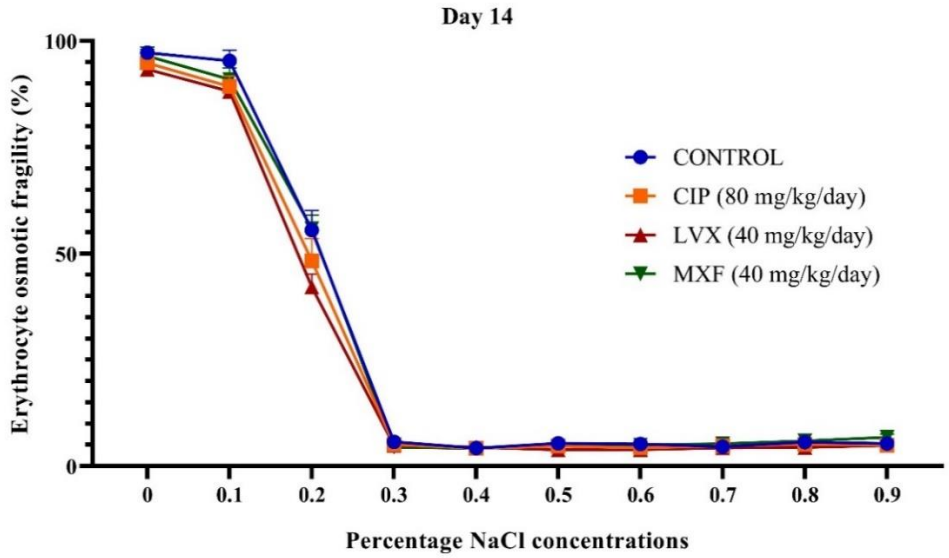

Figure 3. Effect of three different fluoroquinolone derivatives on 14th day rat erythrocyte fragility.
*: Difference between the Control group and the other groups was significant ($p<0.05$).

Table 1. Time dependent changes in the effect of three different fluoroquinolone derivatives on rat erythrocytic parameter.

Parameters	Groups	Day 1	Day 7	Day 14
HGB (g/dL)	Control	16.47±0.48	16.40±0.78	16.30±0.70
	CIP	15.97±0.87	16.54±0.90	16.93±0.62
	LVX	15.24±0.86	15.24±0.78	16.82±0.86
	MXF	16.22±0.48	16.57±0.62	16.36±1.06
MCH (pg)	Control	19.77±0.29	19.65±0.23	19.38±0.38
	CIP	19.07±0.32	19.83±0.31	19.53±0.38
	LVX	19.22±0.23	19.52±0.67	19.47±0.42
	MXF	19.16±0.40	19.67±0.33	19.72±1.11
MCHC (g/dL)	Control	32.38±0.42	33.27±0.33	33.52±0.52
	CIP	32.05±0.33	31.70±2.16	32.98±0.94
	LVX	32.52±0.69	32.87±1.60	32.77±0.52
	MXF	31.96±0.46	32.47±0.53	32.54±0.71
RBC (10^6/µL)	Control	8.34±0.25	8.36±0.46	8.42±0.48
	CIP	8.36±0.39	8.12±0.87	8.67±0.27
	LVX	8.00±0.55	7.88±0.43	8.65±0.50
	MXF	8.47±0.41	8.44±0.33	8.32±0.62
MCV (fL)	Control	61.08±1.35	59.02±0.67	57.84±1.75
	CIP	59.53±1.30	61.12±2.41	59.27±2.65
	LVX	59.12±1.23	59.35±2.60	59.43±1.69
	MXF	59.92±1.44	60.55±1.13	60.64±3.44
HCT (%)	Control	50.9±1.14	49.32±2.47	49.48±3.16
	CIP	49.82±3.20	50.96±3.75	51.43±3.22
	LVX	47.18±2.29	47.26±1.93	51.35±2.40
	MXF	50.76±1.71	51.05±2.33	50.38±3.05
RDWa (fL)	Control	34.63±1.38	33.50±0.42	33.32±1.03
	CIP	34.53±0.90	35.12±1.85	34.15±2.26
	LVX	32.68±1.37	34.20±2.33	34.35±1.25
	MXF	34.26±1.43	38.52±8.49	36.76±4.26
RDW% (%)	Control	13.58±0.18^{ab}	13.78±0.34	14.24±0.42
	CIP	14.35±0.33^{a}	13.86±0.44	14.03±0.23
	LVX	13.33±0.52^{b}	14.15±0.70	14.22±0.37
	MXF	13.94±0.27^{ab}	14.08±0.51	14.84±0.77

Different lowercase letters (a, b), the difference is significant when comparing different groups in the same time period ($p < 0.05$).

Effects of FQ Derivatives on the Haematological Parameters: The RDW% level of the 1st day CIP group increased significantly compared to the 1st day LVX group (Table 1).

The LVX GRAN level on the 7th day showed a significant increase compared to the CIP group on the 7th day, similarly, the LVX GRAN level on the 14th day showed a significant increase compared to the MXF group on the 14th day. On the contrary, the GRAN% level of the MXF group on the 14th day showed a significant decrease compared to the MXF group on the 1st day (Table 2).

On the 14th day, LVX PLT and PCT levels increased significantly when compared with the 1st day LVX groups. LVX MPV level on the 7th day showed a significant increase compared to the LVX group on the 1st day and control groups on the 7th day. Similarly, when the 7th day LVX PDW and PLCR levels were compared with the 1st and 14th day LVX and 7th day control groups, an increase was found to be significant. In addition, the PLCR level of CIP on the 7th day increased significantly compared to the CIP and control groups on the 1st and 14th days (Table 3).

Table 2. Time dependent changes in the effect of three different fluoroquinolone derivatives on rat leukocyte parameter.

Parameters	Groups	Day 1	Day 7	Day 14
WBC (10^3/µL)	Control	4.33±1.30	4.02±0.83	4.58±1.13
	CIP	3.60±1.05	3.82±0.80	3.73±0.49
	LVX	3.64±1.06	5.48±1.51	4.07±0.72
	MXF	2.94±0.36	3.63±1.01	4.28±0.89
LYM (10^3/µL)	Control	3.70±1.17	3.35±0.61	4.02±0.79
	CIP	2.88±0.96	3.38±0.75	3.27±0.39
	LVX	2.63±0.78	4.44±1.48	3.32±0.59
	MXF	2.34±0.39	3.14±0.74	3.80±0.71
LYM% (%)	Control	84.67±1.89	83.77±2.86	87.70±2.58
	CIP	79.17±4.30	79.80±9.82	87.57±5.84
	LVX	82.12±10.28	78.60±6.01	81.68±4.04
	MXF	78.70±7.86	82.48±4.39	89.04±1.25
MID (10^3/µL)	Control	0.30±0.06	0.35±0.06	0.28±0.05
	CIP	0.37±0.12	0.30±0.07	0.25±0.08
	LVX	0.34±0.06	0.35±0.06	0.35±0.11
	MXF	0.28±0.08	0.27±0.08	0.28±0.08
MID% (%)	Control	6.43±1.06	7.97±1.75	5.28±1.10
	CIP	9.38±1.69	7.52±2.79	5.80±1.91
	LVX	9.38±2.72	9.00±2.96	8.13±1.90
	MXF	9.04±2.82	7.82±2.29	5.12±0.58
GRAN (10^3/µL)	Control	0.33±0.05	0.32±0.07^{ab}	0.28±0.05^{ab}
	CIP	0.35±0.08	0.28±0.08^{a}	0.28±0.08^{ab}
	LVX	0.42±0.08	0.48±0.10^{b}	0.42±0.08^{a}
	MXF	0.34±0.06	0.30±0.08^{ab}	0.20±0.10^{b}
GRAN% (%)	Control	8.90±0.98	8.27±1.44	7.02±1.51
	CIP	11.45±2.64	9.62±4.54	6.63±1.38
	LVX	12.98±3.01	10.67±2.58	10.18±2.76
	MXF	12.86±4.37^{A}	9.70±2.50^{AB}	5.80±1.29^{B}

Different lowercase letters (a, b), the difference is significant when comparing different groups in the same time period ($p < 0.05$). Different capital letters (A, B), the difference is significant when the same drug is compared in different timeframes ($p < 0.05$).

Table 3. Time dependent changes in the effect of three different fluoroquinolone derivatives on rat platelets parameter.

Parameters	Groups	Day 1	Day 7	Day 14
PLT (10^3/µL)	Control	614.33±39.76	698.33±84.81	749.20±31.26
	CIP	605.00±55.91	630.80±106.27	721.12±42.92
	LVX	593.50±37.35^{A}	668.20±111.61^{AB}	779.83±48.80^{B}
	MXF	593.00±97.14	679.33±68.31	702.8±44.29
MPV (fL)	Control	6.23±0.21	6.38±0.26^{a}	6.42±0.16
	CIP	6.37±0.50	6.92±0.08^{ab}	6.45±0.19
	LVX	6.16±0.13^{A}	7.00±0.46^{Bb}	6.48±0.15^{AB}
	MXF	6.22±0.38	6.65±0.16^{ab}	6.64±0.26
PDW (fL)	Control	8.23±0.21	8.52±0.25^{a}	8.48±0.18
	CIP	8.42±0.54	8.93±0.14^{ab}	8.52±0.16
	LVX	8.24±0.21^{A}	9.18±0.56^{Bb}	8.57±0.10^{A}
	MXF	8.26±0.37	8.77±0.16^{ab}	8.70±0.26
PLCR (%)	Control	4.33±0.88	5.02±1.00^{a}	4.86±0.56
	CIP	3.92±0.67^{A}	6.98±0.80^{Bb}	4.98±0.85^{A}
	LVX	3.66±0.77^{A}	7.60±1.76^{Bb}	4.83±0.49^{A}
	MXF	3.68±0.36	5.75±0.86^{ab}	5.72±1.32
PCT (%)	Control	0.40±0.04	0.45±0.05	0.49±0.02
	CIP	0.38±0.03	0.42±0.08	0.47±0.03
	LVX	0.36±0.02^{A}	0.46±0.05^{AB}	0.50±0.03^{B}
	MXF	0.37±0.09	0.45±0.04	0.46±0.03

Different lowercase letters (a, b), the difference is significant when comparing different groups in the same time period ($p < 0.05$). Different capital letters (A, B), the difference is significant when the same drug is compared in different timeframes ($p < 0.05$).

DISCUSSION

FQs with bactericidal effect are used in the treatment of diseases such as lower and upper respiratory tract, urinary tract, skin, bone, soft tissue infections, and community-acquired pneumonia (Hu et al., 2017; Donmez and Dogan, 2022). Due to the high permeability of the erythrocyte membrane to this group of antibiotics, it shows a very rapid distribution (Colino et al., 1998). Erythrocyte fragility depends on various factors such as age, sex, species, membrane composition, ion transport, and lipid peroxidation (Igbokwe, 2018). In our study, no significant increase was observed in time-dependent erythrocyte fragility of FQ derivatives in general (excluding 1st day MXF 0.2% NaCl concentration). It has been previously demonstrated *in vitro* that various antibiotics cause increases in erythrocyte fragility (Luqman et al., 2006). This increase in erythrocyte fragility caused by various antibiotics (including FQs) can be interpreted as a result of oxidative stress.

Changes in hematological parameters give important information about various diseases such as anemia, immune system disorder and bleeding. Antibiotics are used to treat infections caused by a number of microbes, such as bacteria and some parasites. However, when antibiotics are not used rationally, they can cause side effects such as the development of unwanted antibiotic resistance. Moreover, this situation can lead to the formation of undesirable pictures in the immune system. FQs have very important immunomodulatory effects in the pathogenesis of many infectious and inflammatory diseases by their effects on arginase and nitric oxide synthase (Kovalenko et al., 2019). As seen in Table 1 and Table 2, while FQs did not have a significant effect on erythrocytic and leukocytic parameters, it was observed that they caused visible changes on thrombocytic parameters (Table 3). The exact reason for this effect of FQs on thrombocytic parameters is not known. However, it was emphasized that moxifloxacin, one of the FQ derivatives, has an effect on thrombotic thrombocytopenic purpura (Surana et al., 2012). In another study, it was determined that local PLT application, which is a rich source of growth factor, has a potential curative effect to increase tendon healing in patients receiving glucocorticoid or FQ therapy (Baboldashti et al., 2011). When the data are evaluated as a whole, it is seen that fluoroquinolones have an effect on thrombocytic parameters and previous studies support our findings, but still more studies are needed on this subject.

Conclusion

It was shown that the FQ derivatives examined in this study did not have a significant effect on erythrocyte fragility. While the FQ derivatives used in the study did not cause a general change on the erythrocyte and leukocyte parameters, they caused various fluctuations on the platelet parameters such as PCT, PLCR, PDW, MPW and PLT. As a further study, it would be beneficial to reveal the reasons for these effects on platelet parameters with more detailed studies.

Acknowledgements

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Disclosure statement

The authors declare that they have no conflicts of interest.

Ethics Approval

The present study was approved by Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee with the decision dated 27.07.2023 and numbered 2023/09-11.

REFERENCES

Afolabi OK, Oyewo EB. (2014). Effects of ciprofloxacin and levofloxacin administration on some oxidative stress markers in the rat. *International Journal of Biotechnology and Bioengineering,* 8(1), 72-76.

Akyol S, Mas MR, Comert B, Ateskan Ü, Yasar M, Aydogan H, et al. (2003). The effect of antibiotic and probiotic combination therapy on secondary pancreatic infections and oxidative stress parameters in experimental acute necrotizing pancreatitis. *Pancreas,* 26(4), 363-367.

Baboldashti NZ, Poulsen RC, Franklin, SL, Thompson MS, Hulley PA. (2011). Platelet-rich plasma protects tenocytes from adverse side effects of dexamethasone and ciprofloxacin. *The American Journal of Sports Medicine,* 39(9), 1929-1935.

Bertrand N, Leroux JC. (2012). The journey of a drug-carrier in the body: an anatomo-physiological perspective. *Journal of Controlled Release,* 161(2), 152-163.

Colino CI, García Turiño A, Sanchez Navarro A, Lanao JM. (1998). A comparative study of ofloxacin and ciprofloxacin erythrocyte distribution. *Biopharmaceutics and Drug Disposition,* 19(2), 71-77.

Doğan A, Dönmez F, Anuk ÖO. (2020). Evaluation of the erythrocyte fragility, haematological parameters and antioxidant properties of *Platanus orientalis* leaf infusion against ethanol toxicity in rats. *Alinteri Journal of Agriculture Science,* 35(1), 22-28.

Donmez F, Dogan A. (2022). Investigation of the effects of three different generations of fluoroquinolone derivatives on antioxidant and immunotoxic enzyme levels in different

rat tissues. *Drug and Chemical Toxicology,* 45(6), 2686-2698.

Dönmez F, Yardım Y, Şentürk Z. (2018). Electroanalytical determination of enrofloxacin based on the enhancement effect of the anionic surfactant at anodically pretreated boron-doped diamond electrode. *Diamond and Related Materials,* 84, 95-102.

Ezelarab HA, Abbas SH, Hassan HA, Abuo-Rahma GEDA. (2018). Recent updates of fluoroquinolones as antibacterial agents. *Archiv der Pharmazie,* 351(9), 1-13.

Gladysz MZ, Stevanoska M, Włodarczyk-Biegun MK, Nagelkerke A. (2022). Breaking through the barrier: Modelling and exploiting the physical microenvironment to enhance drug transport and efficacy. *Advanced Drug Delivery Reviews,* 184, 1-20.

Hu YQ, Zhang S, Xu Z, Lv ZS, Liu ML, Feng LS. (2017). 4-Quinolone hybrids and their antibacterial activities. *European Journal of Medicinal Chemistry,* 141, 335-345.

Huang L, Liu J, Yu X, Shi L, Liu J, Xiao H, et al. (2016). Drug-drug interactions between moxifloxacin and rifampicin based on pharmacokinetics *in vivo* in rats. *Biomedical Chromatography,* 30(10), 1591-1598.

Igbokwe NA. (2018). A review of the factors that influence erythrocyte osmotic fragility. *Sokoto Journal of Veterinary Sciences,* 16(4), 1-23.

Kovalenko IV, Onufrovych OK, Vorobets NM, Melnyk OV, Vorobets ZD. (2019). Arginase/NO-synthase system characteristics in blood lymphocytes under effect of fluoroquinolones. *Regulatory Mechanisms in Biosystems,* 10(2), 203-208.

Luqman S, Prabu KO, Pal A, Saikia D, Darokar MP, Khanuja SP. (2006). Antibiotic-induced alterations in the osmotic resistance of erythrocytes is modulated by β-carotene and L-ascorbic acid. *Natural Product Communications,* 1(6), 481-486.

Maris AS, Mody P, Brewer DJ, Humphries RM. (2021). The Fluoroquinolones: An update for the clinical microbiologist. *Clinical Microbiology Newsletter,* 43(12), 97-107.

Meinke M, Müller G, Helfmann J, Friebel M. (2007). Optical properties of platelets and blood plasma and their influence on the optical behavior of whole blood in the visible to near infrared wavelength range. *Journal of Biomedical Optics,* 12(1), 1-9.

Rawi SM, Mourad IM, Arafa NM, Alazabi NI. (2011). Effect of ciprofloxacin and levofloxacin on some oxidative stress parameters in brain regions of male albino rats. *African Journal of Pharmacy and Pharmacology,* 5(16), 1888-1897.

Stahlmann R, Lode H. (2010). Safety considerations of fluoroquinolones in the elderly: an update. *Drugs and Aging,* 27, 193-209.

Surana SP, Sardinas Z, Multz AS. (2012). Moxifloxacin (avelox) induced thrombotic thrombocytopenic purpura. *Case Reports in Medicine,* 2012, 1-3.

Xie R, Zheng W, Guan L, Ai Y, Liang Q. (2020). Engineering of hydrogel materials with perfusable microchannels for building vascularized tissues. *Small,* 16(15), 1-17.