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Safety of Levofloxacin in Older Adults
Yaşlılarda Levofloksasin Kullanımının Güvenliliği

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ÖZET

Amaç: Levofloksasin en sık reçete edilen antibakteriyel ajanlardan biridir. Geriatri pratiğinde önemli olan birçok enfeksiyonun tedavisinde kullanılmaktadır. Bu çalışmada yaşlı hastalarda birçok avantaj sağlayan levofloksasinin güvenilirliğini araştırmayı amaçladık.

Gereç ve Yöntemler: Geriatri polikliniğine başvuran ve herhangi bir nedenle levofloksasin tedavisi alan 92 yaşlı hastanın tıbbi kayıtları retrospektif olarak incelendi. Demografik özellikler, ilaçlar ile tedavinin başlangıcında ve üçüncü gününde elektrokardiyografi parametreleri, Apati Değerlendirme Ölçeği puanı ve Konfüzyon Değerlendirme Ölçeği ile değerlendirilen deliryum varlığı kaydedildi. Ayrıca yedinci günde verilerine ulaşılabilen verileri kaydedildi. Tüm hastalar veya bakım verenler tedaviden sonraki 90 gün içinde tendinit veya tendon rüptürü açısından sorgulandı.

Bulgular: Hastaların yaş ortalaması 80,75±7,01 yıl ve %57,6'sı kadındı. Başlangıç ve üçüncü gün QT (p:0,008) ve QTc (p<0,001) değerleri arasında anlamlı fark varken, 7. günde fark yoktu (p>0,05). Deliryum ve Apati Değerlendirme Ölçeği puanları tedavi süresince iyileşme gösterdi (p>0,05). Hiçbir hasta nöbet geçirmedi. Tedavi sırasında veya tedaviden sonraki 3 ay içinde tendinit ve tendon yırtılması tespit edilmedi.

Sonuç: Bu sonuçlar ışığında, yaşlı erişkinlerde ek risk faktörlerine dikkat edilerek levofloksasin kullanımı güvenli görünmektedir.

Anahtar kelimeler: Apati, deliryum, levofloksasin, yaşlı, QTc

ABSTRACT

Aim: Levofloxacin is one of the most prescribed antibacterial agents. They are used for the treatment of many infections, which are of paramount importance for geriatric practice. In this study, we aimed to investigate the safety of levofloxacin, which provides many advantages in older patients.

Material and Methods: The medical records of 92 older patients admitted to the geriatric clinic and treated with levofloxacin for any reason were retrospectively reviewed. Demographic characteristics, drugs, electrocardiography parameters, Apathy Evaluation Scale score, and delirium evaluated by Confusion Assessment Method were recorded on the baseline and the third day. We also recorded 21 patients' seventh-day data, which can be available. All the patients or caregivers were questioned about tendinitis or tendon rupture within 90 days after treatment at the outpatient controls.

Results: The mean age of the patients was 80.75±7.01 years, and 57.6% were female. There was a significant difference between baseline and third day QT (p:0.008) and QTc (p<0.001) values, but on the 7th day, not (p>0.05). Delirium and Apathy Evaluation Scale scores improved during the treatment (p>0.05). No patient had a seizure. Tendinitis and tendon rupture were not detected during or within the three months after the treatment.

Conclusion: In the light of these results, the use of levofloxacin seems to be safe in older adults, with caution on additional risk factors.

Keywords: Apathy, delirium, levofloxacin, older adult, QTc

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INTRODUCTION

Fluoroquinolones (FQ), including Levofloxacin (LFX), sparfloxacin, grepafloxacin, moxifloxacin, gatifloxacin, are a class of antibiotics commonly used in the treatment of bacterial infections (1). They are used for the treatment of many infections such as acute bacterial sinusitis, acute bacterial pneumonia, exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, uncomplicated urinary tract infections, and infected pressure ulcers (2,3), which are of paramount importance for geriatric practice (4). LFX, a fluoroquinolone, is one of the most commonly prescribed antibacterial agents worldwide with a broad-spectrum (2,5). In addition to a broad spectrum of efficacy, LFX has other advantages in older patients. Oral formulations are bioequivalent to intravenous since LFX is completely and rapidly absorbed after oral administration (6).

FQs may be associated with many serious adverse events, including Clostridium difficile infections, prolonged QT interval, tendinitis and tendon rupture, dysglycemia, hepatic toxicity, phototoxicity, acute renal failure, and seizures (7). Most LFX-related adverse events are mild, which generally do not require discontinuation of treatment. The most common side effects are gastrointestinal (e.g., nausea, diarrhea) or central nervous system (CNS) events (e.g., headache, insomnia, dizziness, seizures). Furthermore, side effects that can be seen with fluoroquinolones include QT interval prolongation, tendinitis and tendon rupture, dysglycemia, LFX, and liver damage (8).

Some changes occur in body metabolism with advancing age. Gastric pH is increased; gastric emptying is delayed; total body water, lean body mass, and serum albumin are reduced. Liver mass and hepatic blood flow can be reduced, as well as glomerular filtration rate and kidney blood flow. All these can affect the absorption, distribution, and excretion of drugs, leading to changes in the drug pharmacokinetics (9). Studies on the use of LFX in older patients are limited. However, there are reports that older people are at greater risk of adverse events such as tendon disorders and QT prolongation. Therefore, it has been reported that care must be taken when prescribing corticosteroids and QT-prolonging drugs with LFX in older adults (8).

This study aimed to investigate the safety of LFX, which provides many advantages in older patients.

MATERIAL AND METHODS

The medical records of 92 patients who were admitted to Dokuz Eylul University, Department of Geriatrics between January 2015 and December 2017, and who were treated with LFX for any reason, with follow-up parameters for at least three days and without exclusion criteria were retrospectively reviewed.

Patients' characteristics

Patients were evaluated for their age, gender, self-reported comorbidities (hypertension, diabetes mellitus (DM), coronary artery disease (CAD), chronic heart failure (CHF), hyperlipidemia, chronic renal failure (CRF), dementia, history of thyroid disease, chronic obstructive pulmonary disease (COPD), osteoporosis), smoking history. Medications used by the patients were recorded. In addition, the duration and dose of LFX were recorded. LFX drug dosages were adjusted according to the estimated glomerular filtration rate (eGFR) (10).

Exclusion Criteria

Patients under 60 years of age, who have a history of severe illness that may impair general health status, such as an acute cerebrovascular event, gastrointestinal bleeding, sepsis, acute renal failure, acute liver failure, and acute respiratory failure were

excluded. Patients with pacemakers were also excluded due to the fact that cardiac rhythm could not be evaluated clearly.

Electrocardiography (ECG)

The 12-lead surface ECG measurement was recorded with an ECG 1350-K (Nihon Kohden Corporation, Tokyo, Japan) using 25 mm/s paper speed and standardized at 0.1 mV/mm after the patients had rested for at least 10 minutes in a supine position. ECG parameters were recorded at baseline and on the third day of the treatment. ECG parameters of 21 patients who had ECG measurements on the 7th day of the treatment were also recorded. ECG parameters, including heart rate, PR interval (PR), QT interval (QT), and corrected QT interval (QTc), were calculated automatically by the apparatus. The QT interval was corrected for the heart rate by using Bazett's formula (QTc 1⁄4 QT/square root of RR) (11). Prolonged QTc interval is defined as an OTc interval > 450 ms in men and > 470 ms in women (12,13). Furthermore, ECG measurements were also evaluated by a geriatrician.

Evaluation of Apathy and Delirium

The presence of apathy was evaluated by The Apathy Evaluation Scale (AES). AES was developed to quantify and characterize apathy in adult patients (14). It focuses on the hobbies and occupations of the patient in daily life and on the pleasure he/she takes from them and measures their loss in those areas. AES has 18 items with a scoring value ranging from 18 to 72, to assess discrepancy in behavioral, cognitive, and emotional domains during the last four weeks. In 2001, AES was validated in Turkish (15). In the analysis, scores of 24 or higher in AES were accepted as 'apathy', and scores of less than 24 were considered as 'no apathy' (15). Patients were evaluated with Confusion Assessment Method (CAM) for delirium (16). All patients' AES and CAM values were recorded on the baseline and on the 3rd day of treatment. Whether there was a history of seizures during treatment was examined. Data of 21 patients who were evaluated by CAM and AES on the 7th day of treatment were also recorded.

Evaluation for Tendinopathy

Patients or caregivers were questioned about pain, swelling, tenderness, stiffness, tendon thickening, warmth or erythema, and limitation of movement on the Achilles tendon within 90 days after treatment in outpatient controls (17). In addition, muscular and skeletal system examination notes in outpatient clinics were examined.

Ethics approval

The study protocol was approved by the ethics committee of Dokuz Eylul University, Turkey, with a decision number 2017/28-20. Each participant or a legal guardian provided written, informed consent to participate in the study. We carried out this study in accordance with the provisions of the Declaration of Helsinki.

Statistical Analyzes

Demographics and baseline characteristics were reported as the number (n) and percentage (%) for nominal variables and as the mean ± standard deviation for continuous variables. Continuous variables were evaluated with the Shapiro Wilk test and Kolmogorov-Smirnov test for normal distribution. The variables with normal distribution were evaluated by paired-samples T-Test. In non-normal distribution, the variables were evaluated by the Wilcoxon test. Differences in proportions were evaluated with the Mc-Nemar test. The differences were considered to be significant at $P < 0.05$. Statistical analyses were performed using the SPSS 22.0 (SPSS Inc.)

RESULTS

Ninety-two patients over 60 years of age were included in the study. The mean age of the patients was 80.75 ± 7.01 years, and 57.6% were female. 58 (63%) patients were treated

Table I. Characteristics of the patients

Feature	
Age, years (SD)	80.75 ± 7.01
Gender (women/men), *n* (%)	53 (57.6) / 39 (42.4)
Comorbidities, *n* (%)	
Hypertension	53 (57.6)
Diabetes	20 (21.7)
Chronic renal failure	35 (38.0)
Congestive heart failure	18 (19.6)
Coronary artery disease	18 (19.6)
Dementia	62 (67.4)
Chronic obstructive pulmonary disease	15 (16.3)
Hyperlipidemia	7 (7.6)
Hypothyroidism	10 (10.9)
Osteoporosis	19 (20.7)
Arrhythmia	7 (7.6)
Drugs, *n* (%)	
Amiodarone	4 (4.3)
Beta-blockers	28 (30.4)
Rivastigmine	18 (19.5)
Neuroleptics	6 (6.5)
Antiepileptics	16 (17.4)
Antihistamines	1 (1.1)
Proton pump inhibitors	13 (14.1)
Statins	8 (8.7)
Steroids	7 (7.6)
Diuretics	21 (22.8)
Antidiabetics	14 (15.2)
Smoking, *n* (%)	16 (17.4)
Indications for treatment with levofloxacin, *n* (%)	
Lower respiratory tract infection	81 (88)
Urinary tract infection	7 (7.6)
Soft tissue infection	4 (4.3)

with IV, and 34 (37%) with oral LFX. Demographic characteristics and drugs of the patients are summarized in Table I. Patients treated with a daily dose of 500 mg LFX, or equivalent to 500 mg LFX daily according to the estimated glomerular filtration rate (eGFR), for less than 14 days (median: 6 days). None of the drugs used were ordered simultaneously with LFX. Indications for treatment of LFX and dosages are shown in Table I. The ECG parameters, number of the patients with apathy, delirium, seizure, and tendinitis on the baseline, the 3rd day, and the 7th day of the treatment are shown in Table II.

There was a significant difference between baseline and third day QT (p=0.008) and QTc (p<0.001) values. However, on the 7th day, the increase was not observed in 21 patients who had ECG measurements (p>0.05). There were 2 (97.8%) patients with basal QTc values greater than 500 ms. On the third day of treatment, the QTc values of the same patients were higher than 500 ms. During follow-up, the QTc value of any patient did not exceed 500 ms for the first time. There were four patients receiving amiodarone. Only one of these patients had a prolonged baseline QTc, while three patients had prolonged QTc on the

Table II. ECG parameters and other assessments of patients before, 3rd day of the treatment and seventh day of the treatment

Parameters	Baseline	3rd day	7th day	p_1	p_2
Heart rate (beats/min) ± SD	79.5±14.3	81.2±15.2	87.1±12.4	0.467	0.135
QT (ms)	372.1±34.2	380.2±34.5	368.9±31.6	**0.008**	0.455
QTc (ms)	424.6±34.1	438.1±30.9	441.6±29.3	**<0.001**	0.664
Prolonged QTc, *n* (%)	15 (16.3)	16 (17.4)	3 (14.2)	0.841	0.375
Apathy, *n* (%)	89 (96.7)	87 (94.5)	18 (85.7)	**<0.001**	**0.05**
Delirium, *n* (%)	16 (17.4)	3 (3.3)	0	**<0.001**	-
Seizure	0	0	0	**-**	-
Tendinopathy	0	0	0	**-**	-

p_1: Comparison of values baseline and on the third day of treatment
p_2: Comparison of 21 patient's value baseline and on the seventh day of treatment

3rd day. During the treatment, none of the patients developed new delirium, apathy, or a seizure. There were no patients with tendinopathy or tendon group within three months after the procedure.

DISCUSSION

This retrospective observational study demonstrated that the LFX treatment was not related to new developing delirium, apathy, seizure, tendinopathy or tendon rupture, and changes in heart rate or arrhythmia. Compared to baseline, we only found clinically non-significant prolongation in QT and QTc on the 3rd and seventh days.

Although fluoroquinolones (FQ) are well tolerated and have high oral bioavailability in older patients (18), they have also been reported to have various side effects (7), one of which is the prolongation of QT interval, a measure of the cellular ventricular action potential generated by the passage of current through ion channels (1,19). All FQs may cause prolongation of QT interval by inhibiting various levels of ion channels (1,8); however, many studies have reported that LFX is related to a higher rate of severe cardiac arrhythmia, although it has a lower ion channel inhibitor potential than other FQs (8). In contrast to these studies, no change in heart rate, no arrhythmia, and no QT interval prolongation exceeding 500 ms was detected in any of our patients using LFX. However, although there was an increase in QT interval according to baseline value on the 3rd day of LFX treatment, this was not clinically significant; additionally, there was no increase in QT interval at baseline on the 7th day of treatment. Therefore, we can say that LFX treatment is not associated with cardiac arrhythmia in older adults. It was also reported that FQs might exacerbate the risk of serious arrhythmias in patients with QT interval prolongation-related concomitant risk factors, such as electrolyte disturbance, hypothyroidism, and concurrent use of antiarrhythmic agents (20). On the other hand, we did not exclude any comorbidities in our study, and despite the inclusion of amiodarone and/or other arrhythmic drugs that caused prolongation of the QT interval, it was striking that LFX treatment did not have any clinically significant effect on the QT interval, which gives our study the nature of a real work that reflects real life.

Competitive binding of fluoroquinolones (FQ) to the gama-aminobutyric acid-A (GABA-A) receptors in CNS and N-methyl-D-aspartate (NMDA) agonist activity play a role in the development of CNS side effects. Such characteristics of FQs have been reported to cause reduced seizure threshold and development of FQ-induced delirium in cases (8,21). In the FQ group, the development of

seizures and delirium associated with LFX treatment is only available in case reports; therefore, there are no case-controlled follow-up studies on this issue, particularly in older adults. On the other hand, because LFX has a bulky alkylated side chain at the position of R7, its lower GABA receptor activity than other FQ suggests that it may be a reliable agent in this regard (8). In this context, neither a new seizure nor a new development of delirium under LFX treatment was not only detected in our study population, but the number of patients with delirium decreased significantly with the treatment as well. Certainly, treatment of infection with LFX plays an important role in treating delirium-precipitating factors.

The effects of LFX on CNS are not limited to these only. In some case reports, it is reported that LFX may be effective in the treatment of apathy as well (22). This may be related to the effects of LFX on the GABA and NMDA receptors and may be associated with nalidixic acid in its structure that induces CNS as a result of its similarity to a CNS stimulant amfonelic acid (22). In this study, a significant decrease in the number of patients with apathy on the 3rd and seventh days of LFX treatment suggests that LFX may be effective in treating apathy. However, the effect of treatment of the underlying infection in the recovery of apathy cannot be ignored.

Achilles tendon pathologies, such as Achilles tendinitis and tendon rupture, are other undesirable effects associated with FQ treatment, and FQ treatment is shown to have a 3.8-fold higher risk than other antibiotics (23). Although various theories have been suggested to explain the development of tendinopathy with FQ treatment, the pathogenesis of this drug-induced toxic effect has not yet been elucidated (2). However, studies indicate that the risk of Achilles tendon disorders increases, especially in long-term and high-dose use of FQs with male gender, age over 60 years, normal body mass index, chronic renal failure and hemodialysis, and concurrent use of corticosteroids (2,24,25). Although all FQs are blamed, they are more common in Achilles tendon pathologies, particularly in pefloxacin treatment (24). In addition, it is reported in the case reports that LFX treatment may also be associated with Achilles tendon pathologies (26). Despite this data, in our study, we did not detect any tendinopathy during the treatment or in the 90-day impression of any of our 7-14-day LFX-administered cases. Furthermore, considering that all of our study group consisted of older adults, 35% were CRF, and 7.6% also received corticosteroid treatment, it is essential that tendinopathy was not detected during and after LFX treatment, even in cases with the risks indicated for the development of tendinopathy in previous studies (2,24,25). The results exhibit that LFX treatment at a daily dose of 500 mg is not related to the development of tendinopathy.

In this study, the fact that all cases consisted of older adults, the number of cases was sufficient, and the results of up to 3 months with treatment were evaluated are the strengths of the study. In addition, the fact that any chronic disease (except acute worsened forms) or drug use is not considered as an exclusion criterion for the study is crucial in terms of reflecting the real life of this study. On the other hand, the limitations were that the study was retrospective and that no data were evaluated for more than seven days except tendinopathy.

CONCLUSION

LFX is an essential agent for the treatment of common infections in geriatric practice. Low-dose short-term LFX treatment is not associated with seizure, delirium, and tendinopathy in older adults but also reduces the incidence of apathy in treating patients. In other words, short-term LFX is well tolerated by older adults.

Conflict of Interest and Funding

The authors declare no conflict of interest.
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Ethics Committee Approval

The study protocol was approved by the ethics committee of Dokuz Eylul University, Turkey, with a decision number 2017/28-20.

Authors' Contributions

Author KS performed manuscript writing and data collection; Author AEA contributed to data acquisition and interpretation; Author OD contributed to data interpretation, performed analysis and manuscript writing; Author SEK performed analysis and drafting the manuscript. All authors have approved the final article.

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