Original Article

Effect Of Fluor Quinolones On Qt Interval

Iftikhar Adil[1], Amjad Ali[2], Niaz Ali[3]

[1]Department of Pharmacology, Gajju Khan Medical College, Swabi,Pakistan.

[2]Department of Medicine, Bacha Khan Medical College, Peshawar, Pakistan.

[3]Department of Pharmacology, Khyber Medical University, Peshawar, Pakistan.

ABSTRACT

Objective: To assess how recently introduced quinolones affect the electrocardiogram's Qtc interval

Study Design: A Cross-sectional analytical study

Duration And Place Of Study: MMC Mardan from December 2015 to September 2016

Materials and Methods: In MMC Mardan, cross-sectional analytical research was conducted between December 2015 and September 2016. The research comprised 110 participants, regardless of age or gender, who were hospitalized in the medical department for whatever reason and weren't already on fluoroquinolones. Informed consent was obtained before quinolones were administered. Three duplicate baseline ECGs were collected before the injection of quinolones, and three triplicate ECGs were taken 48 hours later. To prevent bias, each participant's ECG was scrambled and read by a single person.

Result: A total of 110 patients underwent evaluation for the research. Thirteen females and nineteen males, making up the 32 patients, had QTc interval prolongation up to 450 ms and 470 ms, respectively. There is a danger to TdP when QTc prolongation of more than 500 ms or a post-dose QTc alteration of more than 60 ms is present in 27 patients, 13 of whom were female and 14 of whom were male.

Conclusion: The ability to extend the Qtc interval is shared by all quinolones. Of the quinolones utilized in the research, moxifloxacin tended to extend the QTc interval.

Key Words: Fluoroquinolones, QT interval calculated (QTc), Torsades de Pointes (TdP).

Introduction ne of the most often utilized classes of antibiotics is the fluoroquinolone family. Lesher discovered in 1962 while making chloroquine [1]. Fluorinating Naladixic acid, the first quinolone, resulted in the formation of distinct structurally evolved fluoroquinolones. Based on their antibacterial action, quinolones have since undergone four rounds of development [2]. The quinolones of the first generation are gram-negative. Fluoroquinolones of the second generation, such as ofloxacin and ciprofloxacin, have enhanced gram-negative activity and resistance to atypical infections. Levofloxacin and sparfloxacin, two third-generation fluoroquinolones, exhibit gram-positive coverage and increased gram-negative and atypical intracellular activity. Moxifloxacin and gatifloxacin, two fourth-generation fluoroquinolones, are effective against gram-positive and gram-negative, atypical, aerobic, and anaerobic microorganisms [3]. Due to its broad spectrum, oral administration, easy absorption, over 50% bioavailability (and up to 97% in some quinolones), good distribution, tissue penetration, lower minimum inhibitory concentration, longer serum elimination half-lives, and simple daily dosage, fluoroquinolones have always been a popular choice for doctors to prescribe [4]. Many urogenital infections, such as gonococcal and chlamydial infections, are treated with fluoroquinolones. Five intestinal illnesses brought on by Salmonella, E. Coli, Shigella, and Campylobacter jejuni.Six respiratory tract infections, including

Correspondence: Iftikhar Adil
Associate Professor Department of Pharmacology, Gajju Khan Medical College, Swabi, Pakistan
Email: iftikharadil22@yahoo.com
Cell: 03005217818
Date Received: **Jan-25-2021**
Date Accepted: **Feb-16-2021**

Citations : Iftikhar Adil, Amjad Ali, & Niaz Ali. (2021). EFFECT OF FLUOR QUINOLONES ON QT INTERVAL: Original Article. Journal of Bacha Khan Medical College, 2(01), Page No. 37–43. https://doi.org/10.69830/jbkmc.v2i01.52

hospital- and community-acquired pneumonia. We refer to the more recent quinolones as respiratory quinolones because of their remarkable efficacy against gram-positive and atypical microorganisms [7]. Fleroxinones are also effective against infections of the bones, soft tissues, joints, meningococcemia, and the prevention and treatment of anthrax and TB [8]. Fluoroquinolones' gram-negative action is attributed to inhibition of DNA gyrase. In contrast, their gram-positive activity is caused by inhibition of topoisomerase IV9.

Fluoroquinolones are extremely effective antibiotics, but they also have side effects, some of which are significant from a therapeutic standpoint. For instance, torsades de pointes, a potentially fatal arrhythmia if left untreated, is a side effect of prolonged QT interval linked to fluoroquinolones. Due to QT interval prolongation and TdP, several quinolones, including Grepafloxacin, Sparfloxacin, and Trovofloxacin, have been taken off the market since 1985. From the Q wave's beginning to the T wave's conclusion, it is known as the 10 QT interval on the ECG. It shows how long it takes for ventricles to repolarize after depolarization [11]. QT intervals may be divided into JT intervals exhibiting repolarization and QRS complexes demonstrating depolarization. An extension of the depolarization or repolarization duration may cause QT interval prolongation [12]. Various schools of thinking consider various leads when measuring the QT interval. Lead II is often the initial option, with others closer to Lead II, including Lead AVR, AVF, V5, V6, and V4. Old age, female gender, cardiac diseases such as ischemia, infarction, congestive heart failure, cardiomyopathy, atrial fibrillation, bradycardia, obesity, acute intracranial hypertension, electrolyte imbalance, particularly hypocalcemia, hypokalemia, and hypomagnesaemia, abnormal drug elimination compared to oral administration, and genetic polymorphism are among the 13 risk factors for QT interval prolongation [14]. QT prolongation or torsade de pointes are also more likely to occur with rapid intravenous injection of arrhythmogenic or teratogenic medications [15].

In addition to QT interval prolongation and TdP, additional class effects linked to all fluoroquinolones include convulsion, tendon rupture, dysglycemia, nausea, vomiting, dizziness, insomnia, drowsiness, headache, strange dreams, disorientation, tremors, phototoxicity, and tendinopathy [16].

Some research from outside examine how fluoroquinolones affect the QT interval on an ECG, but none focus on the people of Khyber Pakhtunkhwa. Thus, the present research aims to investigate how the recently approved quinolones, such as ciprofloxacin, levofloxacin, gemifloxacin, and moxifloxacin, affect the electrocardiogram's QT/QTc interval.

MATERIALS AND METHODS

This cross-sectional analytical investigation was conducted at MMC Mardan's medical department. The research involved 110 participants prospectively afflicted with various viral illnesses between December 2015 and September 2016. Convenient nonprobability sampling procedures were used to register the patients. Individuals of any age or gender who were admitted to the medical unit for whatever reason and intended to take certain Quinolones, such as Levofloxacin, Ciprofloxacin, Gemifloxacin, and Oxygen, were chosen for the research. Acute infarction, ischemia, arrhythmia, congenital long QT syndrome, patients in shock, patients with continuing baseline ECG alterations of QTc prolongation, patients who were taking quinidines at the time of admission, and patients with a history of sensitivity to quinidines were all excluded.

Before administering quinolones, baseline ECGs in triplicate were collected at the time of admission after a short clinical assessment and inquiry on the required history form. A second set of ECGs was taken 48 hours later, or when the patient was released from the hospital. An extra ECG was recommended when the patient reported experiencing any side effects from the recommended treatment, such as syncope, dizziness, palpitations, or a potential TdP or arrhythmic event. Every patient gave their full informed permission. They received a thorough and understandable verbal description of the study's procedures and objectives.

Before starting the investigation, the ethics committee's approval was obtained.

If the results were more than 450 millis econds for men and more than 470 milliseconds for women, the QTc was deemed extended. If a patient's QTc was more than 500 ms or their QTc change from baseline was more than 60 ms, they were deemed to be at risk of developing TdP [18].
To compute QTc, Bazett's formula 19 was used.

Using Bazett's method, QTc = QT/, categorical factors such as gender and age were shown as percentages and frequencies. Mean ± SD was used to represent continuous variables like QTc at the predose and postdose phases. The mean significant difference between the mean QTc predose and postdose at various time points was determined using the Paired "t" test. All parameters were compared using a one-way or twoway ANOVA to find the mean significant difference. A P-value of less than 0.05 was deemed statistically noteworthy.

RESULTS

One hundred ten patients were followed up during the research, with a mean age of 58±26 and 64 males (58%) and 46 women (42%). Thirty-nine patients fell into the 40–60 age group, 37 patients in the 61–80 age group, and 10 patients in the 81–100 age group—table 2.

The mean age of the fifty-seven patients (52%) was 64. Moxifloxacin was provided for 7 years to 20 patients (18%), whose mean age was 59. Levofloxacin was administered for 7 years to 23 patients (21%) whose mean age was 40. Gemifloxacin was administered for nine years to ten patients (9%) whose mean age was 53. Ciprofloxacin was used for four years. Table One

Thirteen female and nineteen male patients—32 in total—had QTc prolongation based on the criteria published by Yap and Camm. Four patients were using Ciprofloxacin, three patients were on Levofloxacin, one patient was taking Gemifloxacin, and twenty-four instances were taking Moxifloxacin. Of the 110 patients, 27 individuals—13 men and 14 women—showed an absolute QTc interval > 500 ms or a QTc change more than 60 ms over baseline, which was deemed to have a high risk of developing torsades at any point throughout therapy. Table III shows that 19 instances of moxifloxacin, 5 cases of levofloxacin, 1 case of gemifloxacin, and 2 ciprofloxacin cases displayed this risk (Table III).

Of these 27 instances, 13 patients had postdose absolute QTc prolongation of more than 500 ms, and 22 had postdose QTc change of more than 60 ms. Table IV shows that 8 individuals had postdose QTc changes greater than 60 ms and QTc > 500 ms.

Table 1: Average age of patients (N = number of patients) taking various Quinolones

Table 1: Average age of patients (N = number of patients) taking various Quinolones

Type of Quinolones used	Mean age (years)	Std. Deviation	N
Moxifloxacin	64.7193	15.65790	57
Levofloxacin	59.7500	22.56190	20
Gemifloxacin	40.9130	18.04266	23
Ciprofloxacin	53.4000	19.21342	10
Total	57.8091	19.96396	110

Table 2: Age groups of the patients included in the study

Age group	Frequency	Percent	Valid Percent	Cumulative Percent
<40	23	20.9	20.9	20.9
40-60	39	35.5	35.5	56.4
61-80	37	33.6	33.6	90.0
81-100	10	9.1	9.1	99.1
>100	1	.9	.9	100.0

Table 3: Quinolone types: connection to QTc prolongation and potential risk for TdP

Quinolones	Frequency	Percent	Patients with QTc prolongation >450 M or 470 ms F	No of patients at risk to TdP, QTc > 500ms or postdose change >60ms
Moxifloxacin	57	51.8	24	19
Levofloxacin	20	18.2	3	5
Gemi-floxacin	23	20.9	1	1

Ciprofloxacin	10	9.1	4	2
Total	110	100.0	32	27

Table 4: To show the postdose absolute QTc > 500 ms.

Drugs	Genders	Mean baseline QTc	QTc after 48 hr
Moxifloxacin (N=57)	Males (n=5)	439.2±37.53**	518.4±6.98**
	Females (n=5)	470.2±23.4*	534.4±36.5*
Levofloxacin (N=20)	Males	0	0
	Females (n=2)	485.5±6.3***	500± 0
Gemifloxacin (N=23)	Males	0	0
	Females	0	0
Ciprofloxacin (N=10)	Males	0	0
	Females (n=1)	393±0	516±0

** P=0.0058, * P=0.0195, †P= 0.0269 (One way AN

p=0.0058,*p=0.0195,*p=0.0269(one way ANOVA,95%CI P≤ 0.05

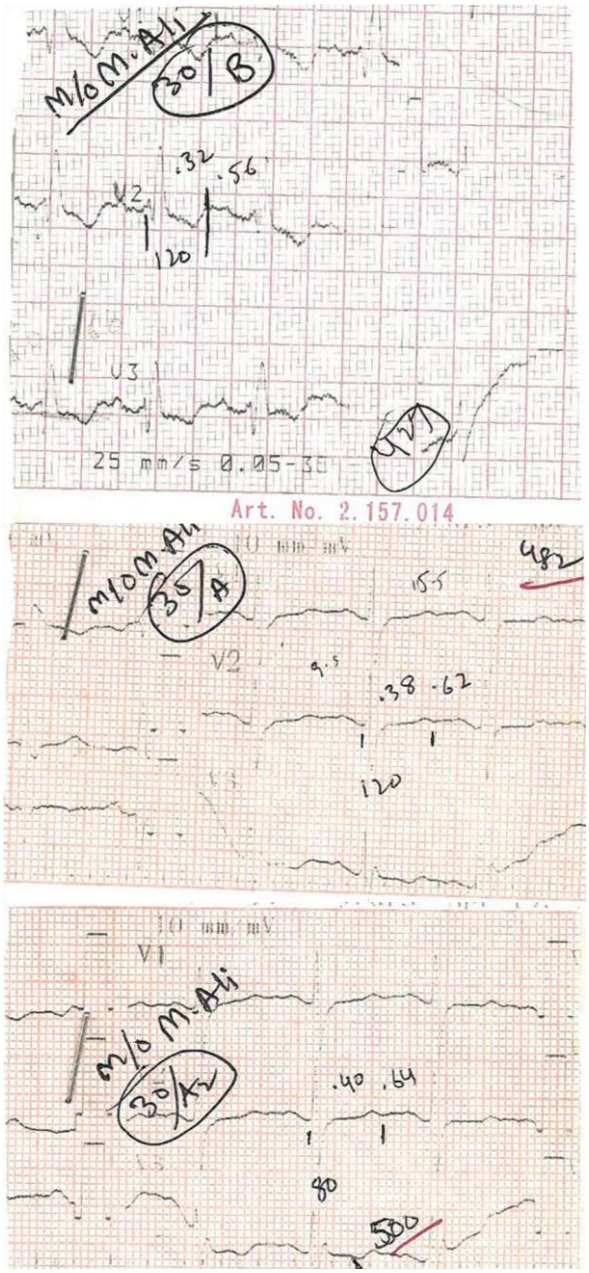

Figure 2: Representative graph tracing of ECG of case no 30 showing QTc changes at different interval predose and postdose.

DISCUSSION

Quinolones are nowadays the most widely prescribed drug, but until now, it has not received remarkable attention from clinicians regarding their cardiac toxicity. From 1975 to 2000, the US Food and Drug Administration banned 16 drugs due to safety

concerns; 4 of these drugs were removed because of their association with QT interval prolongation and torsades de pointes.[20]
Clinically, QT prolongation is often asymptomatic, but if the causing substance is not treated appropriately, it may lead to TdP. Although this arrhythmia usually ends on its own, ventricular fibrillation and sudden cardiac death may result if it persists and intensifies
quickly [21, 22].

Although torsades are not invariably the result of drug-induced QT prolongation, there is no cutoff point below which TdP cannot happen. Even in the absence of QT prolongation, TdP is documented. In two of our levofloxacin patients, the post-dose change was greater than 60 ms, posing a risk of torsades even if the Yap and Camm criteria did not extend the QTc.

Twenty-seven participants in this research were at risk for torsades and had a QTc change of more than 60 ms or an absolute QTc prolongation of more than 500 ms. It has been suggested that the quinolones as a class may affect QTc interval prolongation[23]. As shown by our research, table III shows every quinolone used in the investigation had therapeutic importance. The QTc interval for moxifloxacin is statistically significant, as shown by Table IV's P value < 0.005. Consequently, not all fluoroquinolones have the same ability to lengthen the QT interval. Moxifloxacin > levofloxacin > ciprofloxacin and gemifloxacin is the order in which it is found. Hence, moxifloxacin has the greatest capacity to lengthen the QT interval, while gemifloxacin and ciprofloxacin have the lowest potential. Hagiwara et al.'s investigation demonstrated that 100μM of moxifloxacin and 10% of levofloxacin prolong APD, respectively. At 100μM, ciprofloxacin and gemifloxacin exhibit little to no APD prolongation, consistent with our findings. When moxifloxacin, levofloxacin, gemifloxacin, and ciprofloxacin are compared, it has been shown that moxifloxacin interacts with potassium channels to produce the most noticeable QT prolongation [27].

Ciprofloxacin and levofloxacin showed the lowest and highest mean QTc changes, respectively, at 9.8±64.1 ms and 10.13±23.3 ms, while moxifloxacin showed the greatest mean QTc change, 23.7±44.6 ms, our research is thus consistent with the previous investigations.

Dale and Altin (2007) found TdP linked to moxifloxacin in two individuals with various risk factors for QTc interval prolongation, with age being the primary culprit. Our results agreed with theirs, which showed that moxifloxacin-induced QTc interval prolongation was mostly seen in older adults. The patients who had taken moxifloxacin were 64.7 years old on average.

Compared to men, women are more likely to have longer QTc intervals [28]. Our data supports this, showing that 42% of females and 40% of men experienced QTc prolongation. 31% of females and 21% of men were at risk of developing TdP.

Amankwa reported that a patient with moderate hypokalemia and hypomagnesaemia had TdP and a QTc interval prolongation of 605 ms after using levofloxacin. Within hours after stopping levofloxacin, QTc dropped to 399 ms. In animal experiments, levofloxacin has been found to induce QT prolongation [29, 30, 31]. Levofloxacin has been shown in certain trials to have no impact on QTc prolongation.32and. As a result, there was ongoing debate regarding how levofloxacin affected QTc prolongation. Our research aligns with Amankwa, whereby twenty patients were prescribed levofloxacin, and five of the twenty individuals (or 25%) had QTc prolongation to the extent that it posed a risk for TdP development.

Prabhaker reported two cases of supra-ventricular tachycardia stable with sotalol and amiodarone when given ciprofloxacin for 24 hours, developed marked QTc prolongation and documented TdP requiring defibrillation. Regarding torsades de pointes, this study showed that Ciprofloxacin had a higher risk than Gemifloxacin to develop torsades.

CONCLUSION

All the above studies showed that all the Quinolones can prolong the QTc interval. Moxifloxacin has the highest propensity to prolong QTc interval among the quinolones used in this study. Only when used in conjunction with other proarrhythmic medications or conjunction with other risk factors may

fluoroquinolones result in TdP. According to the findings of one research, almost all patients who acquired TdP as a result of noncardiac medications had at least one concurrent risk factor. In 71% of cases, there were two or more concurrent risk factors [32]. It has been noted that metronidazoles, beta-agonists, H1 and H2 antagonists, proton pump inhibitors, and steroids—all of which increase the risk of QTc prolongation—are often administered with fluoroquinolones. To reduce the incidence of torsades de pointes, clinicians prescribing fluoroquinolones should consider predisposing risk factors and drug-drug interactions for QTc prolongation.

REFERENCES

1. Lesher GY. In: Hooper DC, Wolfson JS (eds): Quinolones antimicrobial agent, ed 2, Washington D.C, American Society for microbiology.1993; 12-14
2. Andersson MI, MacGowan AP.Development of the quinolones. J Antimicrob Chemother.2003; 51(1):1-11.
3. Oliphant CM, Green GM. Quinolones a Comprehensive Review Am Fam physician.2002; 65(3):455-64.
4. William A, Petri Jr. Sulfomamide, Trimethoprim, Quinolones and agents for urinary tract In Bruton LL, Chabnar BA, Knollmann BC (Eds) Goodman & Gilman's.The Pharmacologic Basis of Therapeutics 12th ed.NewYork Mc GrawHill Medical 2008; 1470-75.
5. Newman L.M, Wang S.A, Ohye R.G. The epidemiology of fluoroquinolones resistant Neisseria gonorrhoea in Hawai, Clin Infect Dis.2004; 38:649-54.
6. Miedouge M, Hacini J, Grimont F, and Watine J (2004). Shiga toxin-producing Escherichia Coli urinary tract infection associated with hemolytic uremic syndrome in an adult and Possible adverse effect of ofloxacin therapy, Clin Infect Dis.2004; 30:395-96.
7. Chamber HF, Deck DH. Sulfonamide, Trimethoprim & Quinolones. In: Katzung BG, Master SB and Trevor AJ (eds).Basic Clinical Pharmacology. Ed11, New York; Tata McGraw Hill2009; 819-21.
8. Hooper D. Quinolones. In: Mandell GL, Bennett JE, Dolin R, Douglas, and Bennet' Principles and practice of infectious diseases. 5th Ed. Philadelphia: Churchill Livingstone.2000; 404-23.
9. Hooper DC. In: Mandell GL, Bennet JE and Dolin R (eds): Urinary tract agents Nitrofuranation and methenamine. Mandell, Douglas, and Bennett's Principles and Practice of infectious Diseases, 5th ed. Churchill Livingstone, New York.2000b; 423 - 28.
10. Rubinstein E. History of Quinolones and their side effects, chemotherapy.2001; 47: 3-8.
11. Li EC, Esterly JS, Pohl S.Drug induced QT interval Prolongation: considerations for Clinicians. Pharmacotherapy.2010; (30): 684-70
12. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN.The QT interv prog cardiovasc Dis 2001;(43):1-45.
13. Salvi V, Karnad DR, Kerkar V, Panicker GK, Manohar D, Natekar M. Choice of an alternative lead for QT interval measurement in serial ECGs when lead II is unsuitable for analysis. Indian heart journal xxx. 2012;1-6.
14. Locati EH, Zareba W, Moss AJ. Age- and sex-related differences in clinical manifestations in patients with Congenital long QT syndrome: findings from the International
LQTS Registry. Circulation 1998; 97: 2237-44
15. Klotz U. Antiarrhythmics: elimination and dosage considerations in hepatic impairment. Clin Pharmacokinet. 2007;46:985-96.
16. Rouveix B. Clinically significant toxicity and tolerance of the banned antibiotics used in lower respiratory tract infection, Med Mal infect .2006;36: (11-12): 697-05.
17. Yap YG, Camm AJ. Drug-induced QT prolongation and torsades de points.Heart.2003; 89:1363-72.
18. Crouch MA, Limn L, Cassino AT.Clinical prevalence and management of drug-related QT interval prolongation pharmacotherapy.2003; 23(7): 881-908.
19. Bazett HC. An analysis of the time relations of electrocardiogram. Heart (7)1920; 353-70.
20. Lasser KE, Allen PD, Woolhandler SJ. Timing of new black box warnings and Withdrawal for prescription medication.JAMA. 2002; 287: 2215-20.
21. Schoepp. Medication forum. Pharm Pract.2001;17(10): 30–31.
22. Jayasinghe R, Kovoor P. Drugs and the QTc interval. Australian Prescriber.2002; 25(3): 63–65.
23. Ball P.Quinolones induced QT interval prolongation: a not-so-unexpected class effect. J Antimicrob Chemther2000;45:557-59.
24. Owens RC Jr (2001). Risk assessment for antimicrobial agent-induced QTc interval prolongation and torsades de pointes. Pharmacother.2001; 21:301-19.
25. Hagiwara T, Satah S, Kasai Y. Comparative study of the various fluoroquinolones antibacterial agents on the

cardiac action potential in guinea pig right ventricular myocardium. Jpn J Pharmacol.2001 87: 231-34.

26. Lannini PB, Tilloson GS (2001).Evaluating the risk of cardiac toxicity Pharmacotherapy, 21:261-262.

27. Tsikouris JP, Peeters MJ, Cox CD. Effects of three fluoroquinolones on QT analysis after Standard treatment courses. Ann Noninvasive Electrocardial.2006; 11: 5256.28- Drici MD (2001). Influence of gender on drug acquired long QT syndrome. Eur Heart J; 45-47

28. Akita M, Shibazaki Y, Izumi M, Hiratsuka K, Sakai T, Kurosawa T, Shandon Y. Comparative assessment of prurifloxacin, sparfloxacin, gatifloxacin and levofloxacin in the rabbit model of proarrhythmic. J Toxicol Sci.2004; 29:63-71.

29. Nykamp DL, Blackmon CL, Schmidt PE, Roberson AG. QTc prolongation is associated With combination therapy of levofloxacin, imipramine, and fluoxetine.

30. Ann Pharmacother. 2005; 39: 543–46.

31. Taubel J, Naseem A, Harada T, Wang D, Arezina R, Lorch U, Camm AJ (2010).

32. Levofloxacin can be used effectively as a positive control in thorough QT/QTc studies in healthy Volunteers. Br J Clin Pharmacol; 69:391–400.

33. Zelster D, Justo D, Hakim A, Prokhorov V, Heller K, Viskin S. Torsade de pointesdue to noncardiac drugs: most patients have easily identifiable risk factors. Medicine. 2003; 82(4): 282-90.

Disclaimer: Nil

Conflict of Interest: There is no conflict of nterest.

Funding Disclosure: Nil

Authors Contribution

Concept & Design of Study: Iftikhar Adil1

Data Analysis: Amjad Ali2

Critical Review: Niaz Ali3

Final Approval of version: Iftikhar Adil1