ORIGINAL ARTICLE

MOXIFLOXACIN INDUCED QT INTERVAL PROLONGATION: A RISK TO TORSADE DE POINTES IN ELDERLY PATIENTS

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Background: Quinolones are notorious for QT interval prolongation and sometimes carry risks for development of Torsade de Pointes. Objective of this study was to determine the effect of moxifloxacin on QT interval prolongation on electrocardiogram. **Methods:** It was a cross-sectional study, conducted in Medical Department of Mardan, Medical Complex, Mardan, from January to December 2021. Moxifloxacin was given for treatment of different ailments to 57 patients after approval of study protocols from Ethical Committee of Gajju Khan Medical College/Bacha Khan Medical Complex Swabi. Their baseline ECGs, second ECG on its T_{max} and third set of ECGs were recorded, in triplicates, on 48 hours of treatment. QTc was calculated using Bazett's formula either using lead II or alternatively AVR, AVF, V_5, V_6, or V_4, leads. Moxifloxacin was administered in recommended doses. **Results:** Of the 57 patients, 24 patients (42%) showed QTC prolongation (prolonged QTc: For male >450 ms, and for female >470 ms); and 19 patients (33%) reached to the limits for a risk (Patients with QT_c >500 ms or QTc change over baseline >60 ms) for development of Torsade de pointes. Remaining 14 patients (25%) faced no complications. Statistically significant changes were observed for both male and female patients (p<0.05). However, QT prolongation was sustained for 48 hours in female only. **Conclusion:** Moxifloxacin produced significant changes in QTc particularly in elderly patients. Mean changes in QTc on 48 hours were prolonged in females than males.

Keywords: Moxifloxacin, QT interval, Torsade de Pointes, Bazett's Formula, ECG

Pak J Physiol 2023;19(4):11–4

INTRODUCTION

Safe and effective uses of drugs are basics for pharmacotherapeutics. Fluoroquinolones are used for treatment of different infections like skin and soft tissues infections, respiratory tract infections, gastroenteritis and genitourinary tract infections. Most frequent adverse effects of quinolones are connective tissues damage, headache, oral thrush, skin rash and photosensitivity and prolongation of QT interval.[1,2]

QT interval consists of time for QRS complex and JT interval. QRS complex represents time for ventricular depolarization. JT interval reflects ventricular repolarization time.[3] More than 120 ms value for QRS Complex indicates widening of QRS complex which is sometimes attributed to blockade of sodium channels, Class IA and IC anti arrhythmic drugs, local anaesthetics, tricyclic antidepressants and $5HT_3$, antagonists have been reported for QT interval prolongation along with widening of QRS complex.[4,5] Prolongation of the QT interval may lead to reflex ventricular tachycardia and Torsade de Pointes (TdP), If not dealt promptly, it may lead to syncope,[6] ventricular fibrillation and sudden cardiac death.[7] It has been reported that most of QT interval prolonging drugs block rapid component of the delayed rectifier Potassium K_{ir} or IRK.[8,9] The term 'Torsade de Pointes' which is continuous twisting of QRS complex around isoelectric line was coined by French physician Francois Dessertenne in 1966 that occurred in an old lady with heart block.[10] In previous decades, QT interval prolongation associated with TdP was the only parameter which became the cause of withdrawal of many drugs in post-marketing surveillance.[11] Drugs are withdrawn during post-marketing surveillance period as information about prolongation of QT interval are usually missed in preclinical studies.[12]

Predisposing factors for QT interval prolongation and TdP include old age, female sex, decreased left ventricular ejection fraction, bradycardia, left ventricular hypertrophy, ischemia and electrolytes imbalance, especially hypokalemia, hypomagnesaemia, hypocalcaemia, genetic polymorphism and heart block.[13,14]

The measured QT interval is transformed by heart rate as reported by Bazett's, Fridericia, and Framingham. Bazett's correcting formula has got popularity and is commonly used because of its simplicity. Thus, QT interval is an important tool for clinicians to predict serious adverse effects like TdP and ventricular fibrillation and even in preclinical phase of new drug development. Though, the risk of TdP is not a linear function of QT interval, yet QT interval of 500 ms or more is considered an increased risk.[15] According to Pratt *et al*, minimal changes in QT interval (5–10 ms) in population study should be taken seriously.[16]

Withdrawal of grepafloxacin and sparfloxacin

from market has raised questions on quinolones. New generation fluoroquinolones are commonly used in variety of community acquired infections and nosocomial infections. Moxifloxacin is frequently used these days. It is studied for QT interval prolongation in different populations.[17–19] Current work is an attempt to study the effects of moxifloxacin on QT interval in our set-up.

MATERIAL AND METHODS

Fully informed consents were obtained from patients who participated in the study. The Ethical Committee of Gajju Khan Medical College/Bacha Khan Medical Complex, Swabi approved the protocols. All protocols were carried out in light of Helsinki declaration for ethical procedures.

Twelve-lead ECGs were recorded using conventional 12-lead ECG machine. Stable patients, 57 of either sex or age, to whom moxifloxacin was prescribed, were followed for changes in QT interval. Baseline ECGs were recorded in triplicate. Second set of ECGs were recorded after the administration of first dose on respective T_{max} 1–2 hours of administration of drugs. The third set of ECGs were obtained in 48 hours as most of patients were discharged on day 3rd. An additional ECG was also recorded when patients complained of possible adverse effects, syncope, TdP or arrhythmic episodes during the therapy.

Stable patients of either sex who required quinolones for treatment of their illnesses were enrolled in the study using purposive sampling technique. Patients with normal serum electrolytes levels for sodium, potassium and calcium were included in the study. Patients already taking quinolones or other pro arrhythmogenic drugs, hypertensive drugs, comatose patients and patients with ongoing baseline ECG changes of ischemia, infarction or arrhythmia were excluded from the study.

Lead II of 12-lead ECG was selected for measuring possible changes in QT interval and QRS complex in pre-dose and post-dose states. When Lead II was not readable, then Leads AVR, AVF, V_5, V_6, or V_4 were selected for analysis.[20] QRS complex was measured from the beginning of Q wave to the end of S-wave. QRS complex values equal to less than 120 ms were considered normal. QT interval was measured from the beginning of Q wave to the end of T wave.

Bazett's formula was used for determination of QTc.[21] Bazett's formula for: $QTc=QT/\sqrt{RR}$, where R-R is preceding risk for TdP the QT interval.

Patients were declared to be at risk for development of TdP whence their QTc values were more than 500 ms, or difference in their QTc values were more than 60 ms versus baseline QTc values.[3,22] QTc was considered prolonged if its value in males and females were respectively >450 ms and >470 ms.[7]

Data was expressed in tables using SPSS-21. One way ANOVA was used for testing the significance of differences at 95% CI and $p<0.05$.

RESULTS

Mean age of the patients (n=57) was 64.71±15.65. Frequencies of patients who reached the limits for (i) prolongation of QTC interval, and (ii) for reaching limits for possible risks of TdP were expressed. There were 24 cases of prolonged QTc, and 19 cases reaching limits for risks for development of possible TdP (Table-1).

Remaining 14 patients in the study faced no known and related complications that are inferred in this study protocol.

Table-1: Effects of Moxifloxacin on QTc and reaching limit for TdP

	Number of patients
Patients with QTc prolongation	24
Patients at risk to TdP	19
Patients with no related ECG changes	14

Prolonged QTc= for male >450 ms and for female >470 ms + patient with QTc >500 ms or QTc change over base line >60 ms.

Cases that reached the limits for QTc (500 ms or above) were subdivided on the basis of gender. Mean changes in QTc on 1–2 hours and 48 hours were recorded against baseline QTc values. Only those cases are presented here where changes were more than 500 ms (Table-2).

Table-2: Effects of Moxifloxacin on QTc. Mean changes in QTc at baseline, after 1–2 hours and after 48 hours are shown ($p<0.05$)

Parameter	Males	Females
Mean Basline QTc	439.2	470.2
QTc After 1–2 hours	518.4	534.4
QTc after 48 hours	487.8	508.4

DISCUSSION

Moxifloxacin is one of the current antibiotics that are frequently prescribed for treatment of respiratory tract infections, urinary tract infections, skin and soft tissues infections and gastrointestinal tract infections. Their spectrum against atypical pathogens gives them an edge over some Cephalosporins in addition to cover typical microorganisms. Therefore, nowadays fluoroquinolones are used as broad-spectrum antibiotics similarly and emergence of resistance to cephalosporins and penicillins makes quinolones the priority drugs. Since very long, it is evident that quinolones and some anti-malarials prolong the QT interval. All the quinolones, as a class, have been implicated to prolong QTc.[23] But the potential to prolong QT interval is not the same for all fluoroquinolones. The preclinical and clinical studies suggest that there are significant differences in potencies to prolong QT interval and develop risk for arrhythmia

among the fluoroquinolones. All quinolones block voltage gated potassium channels especially the K_{ir} or IRK a rapid component of delayed rectifier potassium current. However, the degree of K_{ir} or IRK blockage is not the same for all quinolones. Our findings are consistent with the reports of Owen[23] and Tsikouris[24] as moxifloxacin has shown highest mean QTc changes both in males and females.

Nevertheless, it is imperative to keep in mind the associated risk factors in addition to drugs that may have direct effect on heart. Like studies have shown that even non cardiac drugs in the presence of associated risk factors like female gender, heart disease, electrolyte disturbances, excessive dosing, drug interactions, and history of familial long QT syndrome have led to the precipitation of *Torsade de Pointes*. Therefore, a deliberate approach is necessary while opting for a drug which is notorious for QT interval prolongation especially when two of associated risk factors co-exist.[25–27]

More reports say that any changes more than 35 ms in QTc while taking a drug is considered as drug effect.[28] Hence, these changes in the QTc cannot be ignored and requires further work to answer the concerns been raised in our findings. Our findings show that moxifloxacin significantly changes QTc in elderly patients. Hence the prescribers shall be conscious about the use of moxifloxacin particularly in elderly patients especially with mean age more than 64 years.

CONCLUSION

Moxifloxacin produced significant changes in QTc particularly in elderly patients. Mean changes in QTc on 48 hours were prolonged in females than males.

LIMITATIONS AND RECOMMENDATIONS

It was a single centre study in limited number of patients, detailed randomized controlled studies are recommended to establish safety of fluoroquinolones particularly of moxifloxacin in elderly patients.

ACKNOWLEDGMENT

The authors wish to thank Professor Dr. Niaz Ali, Head of Pharmacology Department, Khyber Medical University, Peshawar for designing the conceptual framework of this study.

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Received: 28 Apr 2023 **Reviewed:** 17 Nov 2023 **Accepted:** 5 Dec 2023

Contribution of Authors:
MIA: Main Author, Concept
MS: Write-up
SAK: Concept, write-up, fallow-up of data and interpretation
AA: Helped in methodology
QN: Data analysis
IK: Data analysis
MNS: Sampling and data collection
S: Sampling and data collection

Conflict of Interest: None
Funding: None