Effects of Three Fluoroquinolones on QT Analysis After Standard Treatment Courses

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Background: Fluoroquinolone (FQ) agents have been speculated to influence the risk of Torsades de pointes (Tdp). Methods of evaluating this risk are varied and not systematic. QTc interval (QTc) prolongation is the most commonly used marker of Tdp, but has questionable utility. QT dispersion (QTd) may be a more selective marker of Tdp. No assessment of QTd for FQs has been reported. The current study evaluates the effects of three commonly prescribed FQs by comprehensive QT analysis.

Methods: In an open-label crossover study, 13 healthy participants received 3 treatments in random order: ciprofloxacin 500 mg twice daily, levofloxacin 500 mg once daily, and moxifloxacin 400 mg once daily. Each treatment was given for 7 days with a 1-week washout period. Twelve-lead electrocardiographic measurements were performed prior to the first dose, 2 hours after the first dose, and following the 7-day medication course. QTc prolongation was determined by measurement of lead II, and QTd from the difference between the maximum and minimum QTc intervals among the 12 leads. The data were analyzed using Friedman ANOVA, with the Wilcoxon signed rank test post hoc analysis, with $P < 0.05$ significance.

Results and Conclusions: No difference was seen in baseline QTc ($P = 0.48$) or QTd ($P = 0.92$). Following 7 days of moxifloxacin, the QTc was prolonged by 6 ms relative to baseline (408 ms, $P = 0.022$), and 11 ms from the 2-hour measurement (403 ms, $P = 0.003$). Ciprofloxacin and levofloxacin had no effect on QTc, and no FQ changed the QTd. Within our study population, ciprofloxacin and levofloxacin did not display an increased risk for Tdp. Moxifloxacin, while showing QTc prolongation, did not affect QTd, and an increased Tdp risk is questionable. **A.N.E. 2006;11(1):52–56**

fluoroquinolones; torsades de pointes; arrhythmia; electrocardiography

Noncardiovascular medications receive scrutiny by the Food and Drug Administration when displaying the potential to increase the QTc interval (QTc) and presumably the risk for the life-threatening ventricular arrhythmia, Torsades de pointes (Tdp). Due to this risk, a number of medications have been either withdrawn from drug development (e.g., sparfloxacin, grepafloxacin), or withdrawn from the existing pharmaceutical market (e.g., cisapride, terfenadine) or have undergone significant study for risk of QTc prolongation (e.g., ziprasidone, voriconazole). Various published lists of agents that potentially increase the risk for Tdp are available.[1–6] Fluoroquinolone (FQ) antimicrobial agents, either individually or as a group, can be found in different list categories including probable, not recommended in long QT syndrome, improbable, or in no listing whatsoever. As well, the Food and Drug Administration and others have perceived the FQs as having a class effect on QTc prolongation and Tdp risk,[3,7] whereas others have suggested an individual effect with each agent.[1,2,4–6] There seems to be a discrepancy in the perceived effect of this group of medications on inducing Tdp.[2]

To describe the arrhythmogenic potential of medications, preliminary use of in vitro tissue electrophysiologic studies show, by means of blocking the cardiac delayed-rectifier potassium channel (I_{kr}), a

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propensity to increase the length of cardiac tissue repolarization. This in vitro evidence has led to Tdp risk warnings for some FQs, as well as other noncardiovascular medications. The FQ agents have differing affinities for I_{kr} blockade.[8] This evidence lends itself to a FQ agent-specific effect on Tdp risk.

The effect of treatment duration on QTc prolonging medications has also been questioned.[9,10] Sotalol has increased the QTc after single-dose observations, but repeated administration has displayed no increase in the QTc.[10] Therefore, single-dose studies of QTc-prolonging medications may not describe the effects seen with repeated-dose administration. Small participant size, single-dose, single-agent studies have shown conflicting results with respect to QTc prolongation.[9,11,12] Ciprofloxacin has displayed little, if any, QTc change while moxifloxacin repeatedly prolongs the QTc between 6 and 16 ms. Levofloxacin has shown variable prolongation.[3,13] No study has compared all three FQs and their ability to prolong the QTc after a multiple-dose treatment course.

Although QTc prolongation is the most widely used electrophysiological marker for the risk of Tdp, a stronger correlation has been suggested with QT-dispersion (QTd).[14,15] QTd is a gross estimate of repolarization abnormalities. No studies have yet looked at the effect of FQs on QTd.

The purpose of this study was to evaluate the relative influence of various FQs on QTc prolongation and QTd in healthy participants taking standard doses and treatment courses of FQs.

METHODS

Approved by the Texas Tech University Health Sciences Center Institutional Review Board, this was a randomized, open-label crossover study design involving healthy volunteers. All participants included were at least 18 years old, and did not have a history of cardiovascular disease, renal dysfunction (CrCl<50 ml/min), and were not on medications that prolong the QTc. Before study enrollment, female subjects were tested for pregnancy with serum beta-human chorionic gonadotrophin, and pregnant volunteers were excluded. Women enrolled in the study were required to take oral contraceptives for the study duration.

The medications studied were ciprofloxacin, levofloxacin, and moxifloxacin. The medications were given during weeks 1, 3, and 5, with weeks 2 and 4 serving as medication washout periods. The doses of medications were determined by the Food and Drug Administration-approved regimens of ciprofloxacin 500 mg twice daily, levofloxacin 500 mg once daily, and moxifloxacin 400 mg once daily. The duration of each treatment course was 7 days. Medication adherence was monitored by post-regimen pill counts of returned vials.

A 12-lead electrocardiogram was obtained, using the GE Marquette MAC 5000® (GE Marquette Inc., Milwaukee, WI), immediately prior to each medication course (baseline, BSL), 2 hours after the first dose of each treatment (i.e., the expected pharmacokinetic peak concentration[9]), and within 5 hours of the last dose of medication following the 7-day course of each medication. The QTc and QTd were analyzed using the QT Guard software (GE Marquette Inc.). Before QTc analysis, our software program calculates the heart rate corrected QT interval using the Bazett's formula[16] and this was done on each separate ECG measurement. QTd is determined by the difference measured between the longest and shortest of the heart rate uncorrected QT intervals on a 12-lead electrocardiogram. Our reported QTd data were not corrected for heart rate. Because of the potential for diurnal variation with QT measurement, the patient electrocardiograms were measured at the same time on days 1 and 7.

The QT Guard software program (GE Marquette Inc.) has the ability to analyze diskette ECG files, recorded from individual 12-ECG measurements, to measure and calculate the QTc and QTd. The use of a computer to analyze 12-lead ECGs provides a consistent, reproducible, objective measurement of QTc prolongation and QTd.[17,18]

Our data (i.e., QTc and QTd) were analyzed using the Friedman test and Wilcoxon signed rank post-hoc analysis. A 2-tailed analysis with a significance level of 0.05 was used. We determined our sample size by using QTd data from a past pilot study. Assuming a 40% difference in QTd required, letting sigma = 30, alpha = 0.05, 3 levels, difference to detect of 40, and power = 0.8, we found a sample size of 12 receiving each therapy needed for this crossover study. All data herein are reported using mean ± standard deviation, and median with 25th and 75th percentiles of the median.

RESULTS

The participants enrolled (n = 13) completed all of the study medication courses without serious adverse effects. Seven participants complained of nausea after taking moxifloxacin, but resolved

when taken with food. As well, two participants experienced lightheadedness and one patient had dry mouth. One participant experienced indigestion with ciprofloxacin that resolved by taking it with food. No adverse effects were noted with levofloxacin. The average age of the participants was 34 years (range: 18–51 years), and there were 5 males and 8 females. Three volunteers were Hispanic and the rest were Caucasian. Two participants were taking lansoprazole, one participant was taking conjugated estrogens and valdecoxib, and two participants were taking multivitamins. As mentioned in the inclusion criteria, women were also taking oral contraceptives, except for one participant with a prior hysterectomy.

Baseline QTc and QTd measurements, as well as heart rates, were not different between treatment courses ($P = 0.48$, 0.92, and 0.92, respectively). Analysis of the QTc measurement displayed no differences within treatment of either ciprofloxacin or levofloxacin (Table 1). QTc prolongations of 6 and 11 ms were seen with moxifloxacin between the baseline and 7-day ($P = 0.022$, Table 1), and 2-hour and 7-day measurements ($P = 0.003$, Table 1), respectively. Heart rates did not differ significantly over the treatment periods. No differences were found between the QTd measurements of any treatment courses (Table 2).

DISCUSSION

Critical to the design of a crossover study is an effective washout period between medications. The washout period allows subsequent treatment courses to not be affected by prior courses. Analysis of the baseline QTc and QTd data showed the duration of our washout periods to be sufficient.

The QTc prolongation data confirmed prior study results.[3,11,13] Ciprofloxacin and levofloxacin did not affect the duration of the QTc, but moxifloxacin did show a propensity to prolong the QTc. Within our results, moxifloxacin showed a median 6 ms increase in QTc (BSL vs 7-day). Prior clinical data have described QTc lengthening of between 6 and 16 ms with moxifloxacin.[11] From tissue studies of I_{kr}, moxifloxacin has displayed a much greater inhibition of potassium-current movement than either levofloxacin or ciprofloxacin.[8] Nevertheless, changes less than 30 ms are generally thought unlikely to raise significant concerns about the potential risk of an agent inducing arrhythmias including Tdp in the clinical setting.[19] Interestingly, we did not see a change between the QTc at BSL and at 2 hours, the pharmacokinetic peak concentration of moxifloxacin, as expected based on prior reports. Our 7-day effect of moxifloxacin on QTc lengthening was predictably enhanced, and we estimate that the difference seen between the single dose and 7-day course was due to total body drug accumulation over the treatment period. Prior single-dose QTc studies of moxifloxacin at both 800 mg and 400 mg produced a significant prolongation.[9,12] While the 800 mg single-dose effect can be explained by the resulting higher serum drug concentrations, our results did not agree with the QTc prolongation found with 400 mg. Demolis et al. characterized their study population as young, nonsmoking, healthy volunteers, but did not mention if other medical

Table 1. QTc Interval and Heart Rate

	QTc (ms)		Heart Rate
	Mean (± SD)	Median (25–75%)	Median (25–75%)
Ciprofloxacin			
BSL	409 (10)	407 (403–417)	68 (65–79)
2-hour	408 (11)	406 (404–415)	71 (69–79)
7-day	414 (16)	409 (405–420)	70 (68–73)
Levofloxacin			
BSL	411 (17)	408 (401–425)	71 (65–74)
2-hour	404 (8)	404 (402–405)	78 (64–83)
7-day	409 (10)	406 (402–416)	74 (69–78)
Moxifloxacin			
BSL[a]	409 (12)	408 (402–414)	70 (66–74)
2-hour[b]	408 (11)	403 (401–414)	69 (65–73)
7-day[a,b]	421 (19)	414 (410–435)	76 (70–78)

[a]Baseline vs 7-day ($P = 0.022$); [b]2-hour vs 7-day ($P = 0.003$).

Table 2. QT Dispersion (ms)

	Mean (± SD)	Median (25–75%)
Ciprofloxacin		
BSL	27 (12)	28 (16–36)
2-hour	22 (11)	20 (12–28)
7-day	28 (21)	24 (16–32)
Levofloxacin		
BSL	28 (14)	24 (20–36)
2-hour	34 (29)	24 (16–44)
7-day	29 (15)	24 (16–36)
Moxifloxacin		
BSL	28 (20)	20 (16–32)
2-hour	30 (20)	20 (16–40)
7-day	23 (6)	24 (20–24)

diseases or medications were present. These patient characteristics could assist in identifying whether their study group and ours were indeed similar. Most levofloxacin studies have had similar results to ours, except for a case series report displaying an increased QTc among hospitalized patients after a single-dose,[20] and a very high-dose (i.e., 1500 mg) study, in which the participants were of a significantly older age.[12] Overall, our data compares favorably with the prior literature.

A central hypothesis to the generation of Tdp is regional repolarization differences within the cardiac tissues.[21] With variations in cardiac tissue regional repolarization and after depolarization, arrhythmias are more likely to propagate. Single lead QTc measurement cannot convey this multifocal information. On the other hand, QTd is a measurement of the heterogeneity of repolarization, and seems to better predict adverse cardiac arrhythmias.[14,15]

Because this study involved a small group of healthy volunteers and used conventional doses, the results cannot be extrapolated to patients at high risk for Tdp. Patient risk factors for Tdp include female gender, hypokalemia, hypomagnesemia, bradycardia, recent conversion from atrial fibrillation, chronic heart failure, digitalis therapy, long-QT syndrome, and ion-channel polymorphisms.[1] Of particular concern is the influence of high drug concentrations from high medication doses, rapid intravenous administration, or renal dysfunction. Our study findings do present an interesting hypothesis for future study in high-risk groups.

The results of our investigation on QTc prolongation and QTd, after a full treatment course of each antibiotic, call into question the suggested effects of FQ agents on the incidence of Tdp. While the QTc was prolonged after a 7-day course of moxifloxacin, there remained no significant difference in the QTd. Within our study population, Tdp would not be predicted with any FQ use. Based on our QT-analysis, we conclude that in a healthy population, weeklong treatment periods with FQs does not appear to increase the risk for Tdp.

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