

PHARMACODYNAMICS AND DRUG ACTION

Effects of three fluoroquinolones on QT interval in healthy adults after single doses

Objective: A clinical trial was conducted in healthy adult volunteers to assess the effect of levofloxacin, moxifloxacin, and ciprofloxacin on the QT and QTc interval.

Methods: Electrocardiograms were recorded 24 hours before and after subjects took placebo, 1000 mg levofloxacin, 800 mg moxifloxacin, and 1500 mg ciprofloxacin in a double-blind, randomized, 4-period, 4-treatment, 4-sequence crossover trial. Changes in QT and QTc interval from baseline were assessed by several different methods.

Results: Increases in QT and QTc interval compared with placebo were consistently greater after moxifloxacin compared with either levofloxacin or ciprofloxacin. The mean postdose change from baseline QTc (Bazett) intervals for the 24-hour period after treatment with moxifloxacin ranged from 16.34 to 17.83 ms ($P < .001$, compared with placebo). For levofloxacin, this change ranged from 3.53 to 4.88 ms ($P < .05$, compared with placebo), and for ciprofloxacin, this change ranged from 2.27 to 4.93 ms ($P < .05$, compared with placebo, with the use of 3 of 5 baseline methods).

Conclusions: A change in QTc (Bazett) interval from baseline can be demonstrated safely in healthy volunteers after single high doses of fluoroquinolones that achieve approximately 1.5 times the maximum plasma drug concentration that occurs after recommended doses. There is substantial daily variation in both QT and QTc interval, and the magnitude and frequency of changes in QTc interval can depend on the methods used. These factors need to be considered because clinical trials measuring the effects of drugs on QT intervals are used to estimate the risk of using these drugs. Greater changes in QT and QTc intervals after treatment with moxifloxacin compared with levofloxacin or ciprofloxacin are consistent with *in vitro* observations related to the effect of these drugs on rapid potassium (IK_r) channels. The clinical relevance of these differences is not known. (Clin Pharmacol Ther 2003;73:292-303.)

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The potential for antimicrobial agents to influence ventricular repolarization may be important to consider when these drugs are being used.¹ Concern about this potential arises from observations that commonly used agents belonging to several different classes of antimicrobials, including macrolides, azoles, and fluoroquino-

lones, can influence the cardiac action potential in *in vitro* models and in laboratory animal models.¹⁻³ Clinical correlates of these observations include reports of drug-associated cardiac dysrhythmias, particularly torsades de pointes,⁴⁻⁶ and results of clinical trials in which prolongation of the QT interval on electrocar-

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diagrams (ECGs) has been associated with drug exposure.⁷⁻¹⁰

Demonstrating an increase in the QT interval after drug exposure has been considered compelling evidence that a drug has the potential for increasing the risk for clinically important effects on ventricular repolarization. Drawing conclusions about this potential on the basis of these observations at first pass may seem logical. However, considerable controversy exists over how data related to effects of a drug on QT interval should be interpreted with regard to estimating a clinically important risk.¹ Part of this controversy arises from the choice of the methods used to measure changes in QTc interval, as well as methods used to measure the QT interval and to correct QT for heart rate. The use of different methods and study designs has made it difficult, if not impossible, to compare the results reported in small studies of patients or in case reports with those reported in larger clinical trials. Larger clinical trials typically involve a relatively homogeneous population of volunteers and use more rigorous methods of measuring QT and of defining baseline values and changes in measurements associated with treatment. In assessing the potential risk of therapies that they prescribe, clinicians are faced with considering all of these data.

The risk for fluoroquinolones to cause clinically important effects on ventricular repolarization is not entirely clear. The effect of these drugs on QT intervals has been proposed to be a class effect.¹¹ Although some of these agents have been discouraged for use in humans because of this effect, others are generally considered to have little or no effect on the heart.^{3,12} Levofloxacin, ciprofloxacin, and moxifloxacin have been used safely and effectively to treat millions of patients. Recently, it was estimated that in the United States, between January 1996 and May 2001, 66 million, 24 million, and 1.4 million prescriptions were written for ciprofloxacin, levofloxacin, and moxifloxacin, respectively.¹³ Adverse cardiac events associated with these agents have been reported rarely.¹³ There is some evidence that moxifloxacin can influence ventricular repolarization events,^{8,14} and warnings about this effect have been included on its label.¹⁵ There is less information regarding this effect with levofloxacin and ciprofloxacin. Differences among these 3 fluoroquinolones with regard to their potential effect on cardiac function have been suggested on the basis of adverse event reporting,¹³ observations in animal models,³ and in vitro studies.^{14,16,17} However, conclusions about differences among these agents have not been based on results from clinical trials.

A clinical trial was conducted in healthy volunteers to better define the effect of levofloxacin, ciprofloxacin, and moxifloxacin on QT interval. This study was designed to assess changes in QT intervals corrected for heart rate (QTc) from baseline QTc intervals with use of 3 measures of change in QTc, 5 definitions of baseline, and 2 commonly used methods to correct QT for heart rate. The effects of single doses of levofloxacin, ciprofloxacin, and moxifloxacin on QT and QTc interval were measured and compared. Doses equal to twice those commonly prescribed to treat respiratory tract infections were studied. By use of several methods for calculating interval measurements and several analyses for assessing differences among treatment groups, it was possible to explore how these factors might influence conclusions regarding drug-associated effects on QTc. Recognizing how these factors can influence the reported magnitude and frequency of changes in QTc is likely to be increasingly important as clinicians use information generated in these clinical trials to help assess the potential risk of using these drugs.

METHODS

Overview. The primary objective of the study was to compare the effect of levofloxacin, ciprofloxacin, and moxifloxacin on the QT and QTc intervals in healthy adults. A double-blind, randomized, placebo-controlled, active-comparator, 4-period, 4-treatment, 4-sequence crossover, single-dose trial was conducted at a single center (PPD Development, Austin, Tex). The protocol was approved by a local institutional review board, and all volunteers gave written informed consent before participating in this study. Healthy subjects who were more than 18 years old, had a normal 12-lead ECG, had a heart rate between 50 and 100 beats/min, had no medical history of cardiac disease, were not taking concomitant medications, and had calculated creatinine clearance greater than 50 mL/min were eligible for the trial. A randomization schedule that was balanced by use of permuted blocks was generated by the sponsor. The randomization code was given to the study pharmacist, and all subjects and investigators were blinded to treatment. Subjects were stratified at entry by gender and age group (<65 years; or ≥65 years). Subjects were assigned randomly to 1 of 4 treatment sequence groups that involved 4 treatments (placebo, 800 mg moxifloxacin [Avelox; Bayer Corporation Pharmaceutical Division, West Haven, Conn], 1000 mg levofloxacin [Levaquin; Ortho-McNeil Pharmaceutical Inc], and 1500 mg ciprofloxacin [Cipro; Bayer Corporation Pharmaceutical Division]). Each treatment was followed by a 7-day washout period.

Subjects stayed in the study unit for 2 days before and 2 days after the treatment dose.

Procedures. ECGs were recorded by a Marquette model MAC 1200 device (GE Medical Systems, Waukesha, Wis) at 24, 23.5, 23, 22.5, 22, 21.5, 21, 20.5, 20, 16, and 12 hours before dosing to correspond to times that were assessed after dosing. The placement of leads was the same for each recording, and the same ECG machine was used for each subject's recordings. Subjects fasted for at least 8 hours before dosing, were not fed until 2 hours after dosing, and were given the dose between 7 and 9 AM with 240 mL of water. Treatment-day ECGs were recorded immediately before dosing (hour 0) and then at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 8, 12, and 24 hours after dosing. ECGs were transmitted electronically to a central reading laboratory (Covance Central Diagnostics, Reno, Nev) and read by an experienced cardiologist who was not aware of the subject's treatment or the time when the ECG was recorded.

Immediately after each treatment-day ECG was recorded, venous blood was sampled for measurement of plasma concentration of each of the drugs. Drug concentrations were measured by HPLC methods. Normalized plasma ratio concentrations for each of the drugs were calculated by dividing the measured plasma concentration by the maximum plasma drug concentration (C_{\max}) associated with recommended doses of levofloxacin (500 mg; $C_{\max} = 6.4 \mu\text{g/mL}^{18}$), moxifloxacin (400 mg; $C_{\max} = 4.5 \mu\text{g/mL}^{15}$), and ciprofloxacin (750 mg; $C_{\max} = 3.6 \mu\text{g/mL}^{19}$). Normalized concentrations were calculated to provide a means of comparing drug exposure after a single high dose with the drug exposure that typically occurs in patients treated with these agents.

Data analyses. A sample size of 48 subjects was considered sufficient to detect differences in mean maximum QTc changes between each treatment to within 8% of the true value with a 95% overall confidence interval. The relationship between exposure to each of these drugs and QTc intervals derived from manually read 12-lead ECGs was assessed. QTc intervals were calculated with the Bazett formula (QT^2/\sqrt{RR}) or the Fridericia formula (QT^3/\sqrt{RR}). QT intervals used in these calculations were measured from the 3 successive heartbeats from the lead with the longest QT interval. The RR interval preceding each measured QT interval was measured. The average of the 3 QTc values calculated with the Bazett or Fridericia formula was used for analysis.

An ANOVA model was fitted to evaluate differences between fluoroquinolone treatment and placebo with

regard to changes from baseline for mean postdose maximum QTc interval, mean 24-hour postdose QTc interval, and mean QTc interval at C_{\max} at a 5% level of significance. Five different baseline QTc values were calculated as follows: (1) the mean of the QTc values at 24, 20, and 16 hours before dosing and the value immediately before dosing for each treatment; (2) the mean of the QTc values from the 4 predose days at the 11 time points from 24 to 12 hours before treatment; (3) the mean of the QTc values on the placebo dosing day at the 12 time points from 0 to 24 hours after treatment; (4) the mean of the QTc values at the 11 time points from 24 to 12 hours before dosing and the value immediately before dosing for each treatment; and (5) the mean of the QTc values on the placebo dosing day at the 0-, 0.5-, 1-, 1.5-, 2-, 4-, 8-, 12-, and 24-hour time points after treatment and the QTc value from the predose day corresponding to the time of maximum QTc value on the dosing day. In addition to assessment of changes in QTc interval, mean QT and QTc values after treatment with each fluoroquinolone were compared with values after treatment with placebo. The mean postdose QT and QTc values (derived from measurements taken 0-24 hours after treatment) for each fluoroquinolone were compared with those obtained after treatment with placebo by ANOVA models appropriate for crossover designs.²⁰ A level of 5% was used for each comparison. In addition, mean QT and QTc values at each time point after treatment with each fluoroquinolone were compared with values obtained after treatment with placebo by ANOVA models. Because of the number of tests involved, an overall 5% level of significance was used. The incidences of subjects with prolonged QTc interval (>450 ms for male subjects and >470 ms for female subjects) and subjects with changes in QTc values that exceeded 30 ms and 60 ms were also determined.

RESULTS

Demographics of subjects. The demographic characteristics of the 48 subjects enrolled in the study are summarized in Table I according to the treatment sequence to which each subject was assigned. Forty-seven healthy volunteers who were randomized and started the trial completed the study. One subject, a 22-year-old woman, was withdrawn from the study after having an apparent allergic reaction to levofloxacin.

Comparison of effects of levofloxacin, ciprofloxacin, and moxifloxacin on QT intervals. The mean plasma concentrations and mean normalized plasma concentrations for each of the treatments are shown in

Table I. Demographic characteristics of all subjects enrolled by their assignment to one of 4 treatment sequences

Characteristic	Treatment sequence group				Total (N = 48)
	Placebo-Cipro- Levo-Moxi (n = 12)	Levo-placebo- Moxi-Cipro (n = 13)	Moxi-Levo- Cipro-placebo (n = 11)	Cipro-Moxi- placebo-Levo (n = 12)	
Sex					
Male	6 (50%)	6 (46%)	6 (55%)	6 (50%)	24 (50%)
Female	6 (50%)	7 (54%)	5 (45%)	6 (50%)	24 (50%)
Race					
White	11 (92%)	12 (92%)	8 (73%)	9 (75%)	40 (83%)
Black	0 (0%)	0 (0%)	1 (9%)	1 (8%)	2 (4%)
Asian	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (2%)
Hispanic	1 (8%)	0 (0%)	2 (18%)	2 (17%)	5 (10%)
Age group					
18-64 y	8 (67%)	9 (69%)	8 (73%)	8 (67%)	33 (69%)
≥65 y	4 (33%)	4 (31%)	3 (27%)	4 (33%)	15 (31%)
Age (y)					
Mean and SD	48.1 (21.71)	49.5 (19.47)	44.6 (20.47)	47.7 (21.51)	47.6 (20.19)
Median	46.5	53.0	38.0	50.5	47.0
Range	19-84	22-76	21-73	19-76	19-84

Cipro, Ciprofloxacin; Levo, levofloxacin; Moxi, moxifloxacin.

Fig 1. As expected, the plasma drug concentrations at C_{max} after a single dose of each of the fluoroquinolones exceeded the reported mean C_{max} of normal subjects receiving the recommended dose of each of these agents for the treatment of lower respiratory tract infection. Normalized plasma concentrations at C_{max} were approximately 1.5 times the mean maximum concentration of each of the fluoroquinolones after a dose commonly used to treat patients with lower respiratory tract infections.

The mean QT interval of subjects over the 24-hour period before and after dosing demonstrated a pattern of an initial increase followed by a decrease over several hours after waking (Fig 2). Resting heart rate (as determined on ECG) rose soon after waking (Fig 2). Correcting the QT interval for heart rate blunted some of this variation. Nevertheless, over this period, mean QTc interval, as calculated with the Bazett or Fridericia formula, demonstrated a pattern of an initial decrease after waking with a gradual rise in the waking hours. This pattern was more evident in the QTc calculated with the Bazett formula than in the QTc calculated with the Fridericia formula. The mean QTc (Bazett) 4 hours after treatment with placebo was 12.68 ms greater than the mean QTc (Bazett) at 1 hour after treatment with placebo (410.23 ms versus 397.55 ms) (Fig 3).

Differences between moxifloxacin, levofloxacin, and ciprofloxacin were evident in comparing mean QT intervals and mean QTc intervals after treatment (Figs 2 and 3). The mean postdose QT and mean postdose QTc

(Bazett and Fridericia) corrections after treatment with moxifloxacin were significantly greater ($P < .001$) than those values after treatment with placebo. In contrast, the mean postdose QT and mean postdose QTc (Fridericia) values after treatment with levofloxacin were not significantly different from those values after treatment with placebo. The mean postdose QTc (Bazett) value after treatment with levofloxacin was significantly greater ($P < .05$) than the mean postdose QTc value after placebo. As with levofloxacin, the mean postdose QT and mean postdose QTc (Fridericia) values after treatment with ciprofloxacin were also not significantly greater than those values after placebo. For ciprofloxacin, the mean postdose QTc (Bazett) value was also not significantly different from that after treatment with placebo.

In addition to assessment of differences between the mean QT and QTc values 24 hours after dosing, differences between values at each time point after dosing were also assessed. Analyses of differences of mean QT values at each time point showed that the values after treatment with moxifloxacin were significantly higher ($P < .05$) than those values after treatment with placebo after 1 hour (Fig 2, bottom panel). In contrast, there were no differences between means for QT values after treatment with either levofloxacin or ciprofloxacin and placebo. In agreement with differences observed in QT values, the mean QTc (Bazett) values were significantly greater ($P < .001$) for each time point after treatment with moxifloxacin compared with the mean

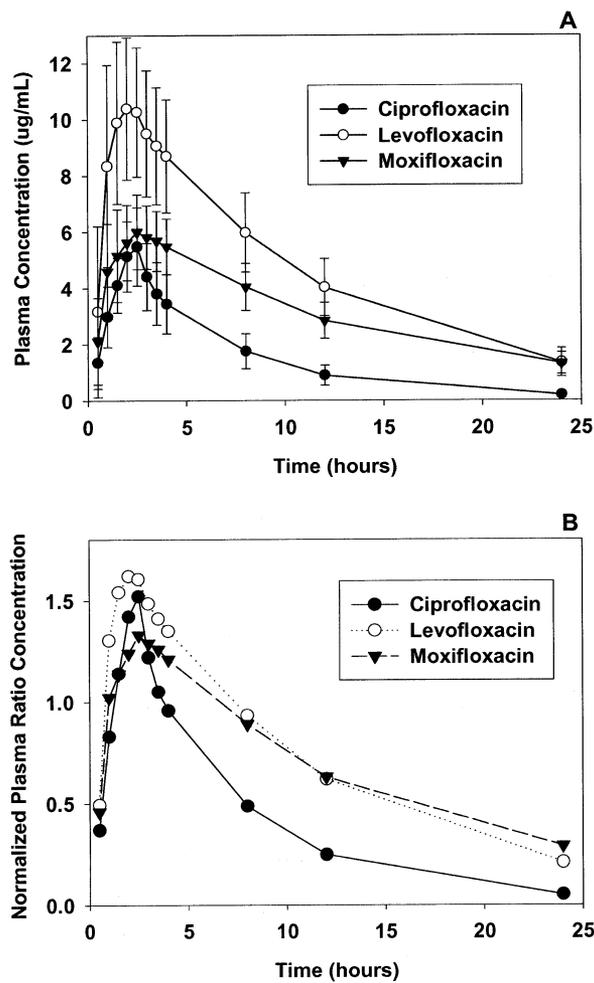


Fig 1. Mean plasma concentration (\pm SD) (A) and normalized plasma ratio concentration (B) after single dose of levofloxacin (1000 mg), moxifloxacin (800 mg), or ciprofloxacin (1500 mg).

QTc values after placebo for every time point measured after 0.5 hours (Fig 3, upper panel). Similarly, the mean QTc (Fridericia) values were significantly greater ($P < .001$) for each time point after treatment with moxifloxacin compared with the mean QTc values after placebo for every time point measured after 1 hour (Fig 3, lower panel). In contrast, the mean QTc (Bazett) values were significantly greater ($P < .05$) after levofloxacin treatment compared with the mean QTc (Bazett) values after placebo only at 1.5, 2, and 2.5 hours. The differences between mean QTc (Fridericia) values after treatment with levofloxacin and the values after treatment with placebo were not significant at any time point. The differences between mean QTc (Bazett or

Fridericia) values after treatment with ciprofloxacin and values after treatment with placebo were not statistically significant at any time point.

Because the assessment of changes in QTc rather than comparison of QTc values has been used extensively to estimate the influence of drugs on ventricular repolarization, the major focus of this study was on analysis of changes after treatment with fluoroquinolones. Measuring a change in QTc after drug exposure requires both definition of a baseline value and definition of the QTc value being assessed after drug exposure. Changes in QTc calculated with either the Bazett or Fridericia formula and based on 5 different definitions of baseline values and 3 different assessments of QTc after drug exposure are shown in Fig 4. The change in QTc varied depending on whether assessment of QTc after drug exposure was the change in mean QTc for the measurements 24 hours after dosing, the change in maximum QTc after dose, or the change from baseline at C_{max} . Mean change in QTc for measurements 24 hours after dosing, maximum change, and change in QTc at C_{max} were greatest with moxifloxacin for all analyses and were significantly greater than those of levofloxacin or ciprofloxacin. The differences in these changes between levofloxacin and ciprofloxacin were not significant. By some analyses, the differences between changes after levofloxacin and placebo and between ciprofloxacin and placebo were statistically significant (as indicated by asterisks in Fig 4).

The occurrence of changes in QTc greater than 30 ms and greater than 60 ms after drug exposure has also been suggested to indicate that a drug may increase risk for slowing ventricular repolarization.²¹ The incidences of changes in QTc (Bazett) greater than 30 ms and greater than 60 ms also varied depending on the definition of baseline QTc (Fig 5). The incidences of subjects with a change in QTc greater than 30 ms from baseline were greatest after moxifloxacin (72%-81%) and were similar for levofloxacin (33%-38%) and ciprofloxacin (34%-40%). The frequency of this degree of change was lowest with placebo but still occurred in 17% to 26% of these subjects. Five subjects had QTc change from baseline greater than 60 ms in 12 instances. Nine of these instances occurred in 4 subjects after doses of moxifloxacin.

The definition of prolongation of QTc interval has been suggested to be a QTc (Bazett) of greater than 470 ms for female subjects and greater than 450 ms for male subjects.²¹ QTc (Bazett) above these values appeared to occur in these subjects unrelated to exposure to fluo-

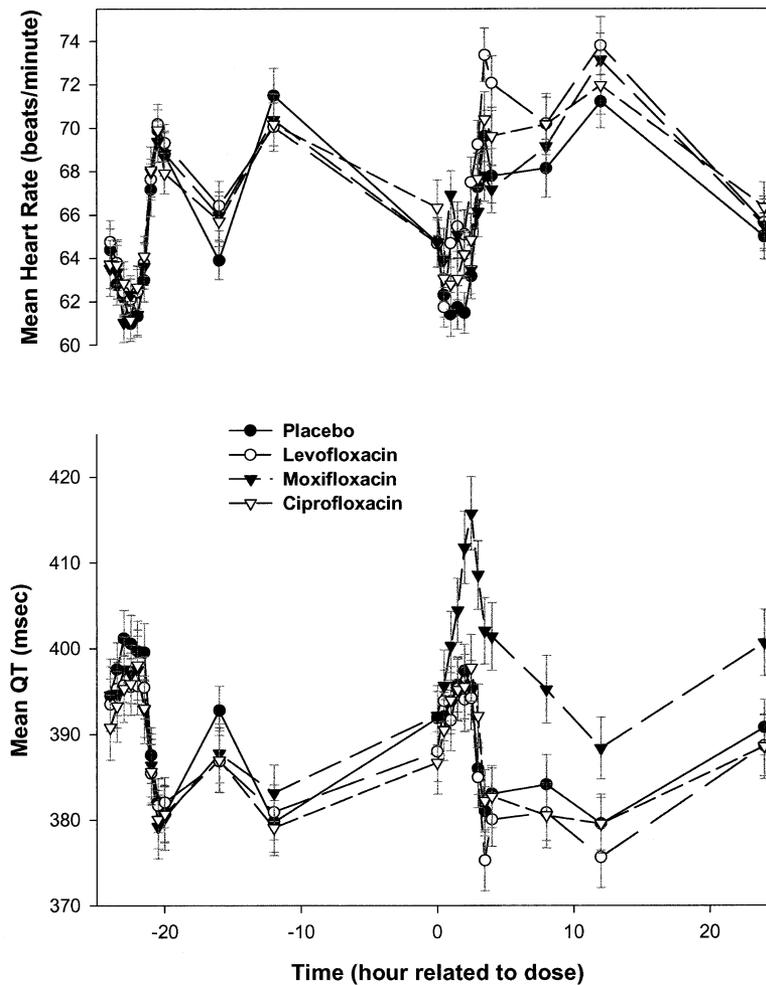


Fig 2. Mean heart rates (\pm SEM) (*top*) and mean QT intervals (\pm SEM) (*bottom*) in subjects for 24-hour period before and after treatment with placebo, levofloxacin, moxifloxacin, and ciprofloxacin. Mean values of QT 1 hour after moxifloxacin dosing were significantly different ($P < .05$) from mean values of QT after placebo dosing. Differences between mean QT values after levofloxacin or ciprofloxacin dosing were not different from those after placebo dosing.

roquinolones. QTc (Bazett) above these values occurred in 4 of 47 subjects (8.5%) before dosing and in 3 (6.4%) of these of subjects after treatment with placebo. In the moxifloxacin group, 2 of 47 subjects (4.3%) before dosing and 6 of 47 subjects (12.8%) after dosing had abnormally long QTc intervals. In the levofloxacin group, 2 of 48 subjects (4.2%) before dosing and 2 of 48 subjects (4.2%) after dosing had abnormally long QTc intervals. In the ciprofloxacin group, 1 of 47 subjects (2.1%) before dosing and 1 of 47 subjects (2.1%) after dosing had abnormally long QTc intervals. QTc (Bazett) values above normal occurred after dosing in 19 instances in 9 subjects. Nine of these

instances occurred in the 76-year-old woman who also had a QTc (Bazett) interval of 500 ms 1 hour after receiving moxifloxacin. She had an abnormally high QTc (Bazett) interval once after placebo, levofloxacin, and ciprofloxacin and in 6 instances (at 1, 2, 3, 3.5, 4, and 12 hours) after moxifloxacin.

Adverse events. Adverse events of special interest (events possibly associated with delayed ventricular repolarization and arrhythmia) occurred in 11 subjects. Twelve events were described as episodes of dizziness that occurred in 1, 2, 6, and 3 subjects after treatment with placebo, levofloxacin, moxifloxacin, and ciprofloxacin, respectively. One subject had dizziness after

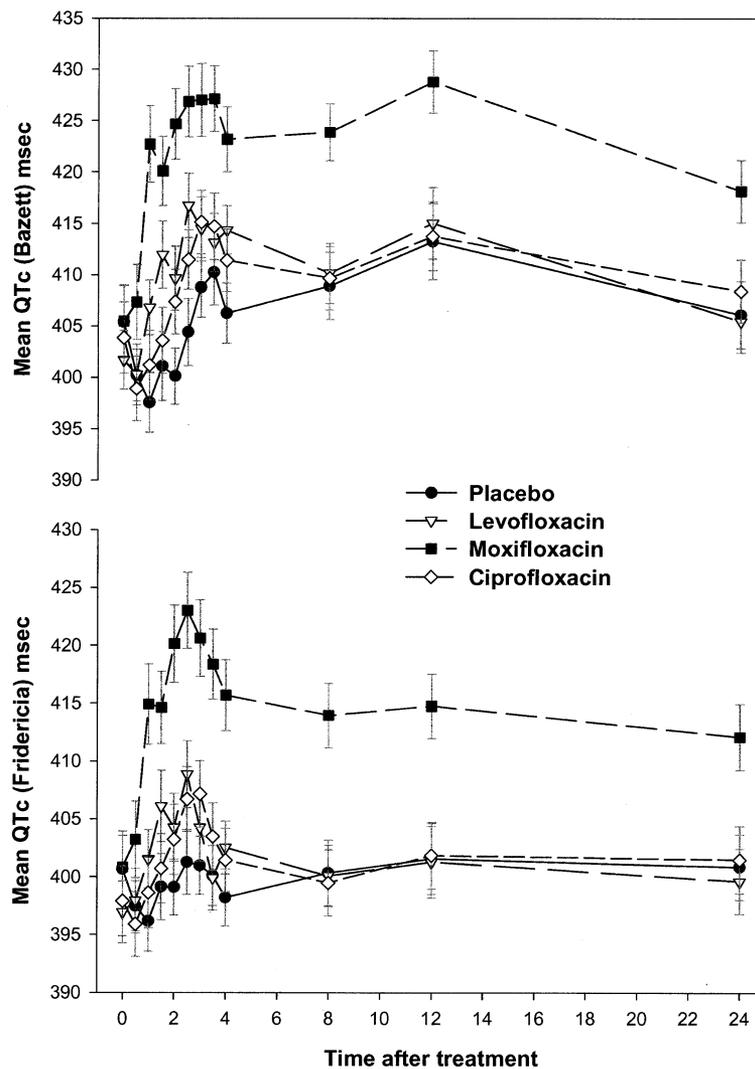


Fig 3. Mean QTc intervals (\pm SEM) for 24-hour period after treatment with placebo, levofloxacin, moxifloxacin, or ciprofloxacin. QTc intervals were calculated with the Bazett formula (*top*) or Fridericia formula (*bottom*). Mean values of QTc (Bazett) from 1 to 24 hours after moxifloxacin dosing and mean values of QTc (Fridericia) from 1.5 to 24 hours after moxifloxacin dosing were significantly greater ($P < .001$) than corresponding mean QTc values after placebo dosing. Mean values of QTc (Bazett) at 1.5, 2, and 2.5 hours after levofloxacin dosing were significantly greater ($P < .05$) than mean values of QTc (Bazett) after placebo dosing.

treatment with moxifloxacin and ciprofloxacin. One subject who had an episode of dizziness after moxifloxacin had an episode of postural hypotension after treatment with ciprofloxacin. All but one episode (dizziness that occurred 2 days after placebo) occurred on the day of dosing. All episodes were brief, resolved spontaneously, and were considered to be mild.

DISCUSSION

The results presented here demonstrate that an effect on QTc interval in healthy volunteers can be measured after single doses of moxifloxacin, levofloxacin, or ciprofloxacin. These effects were evident and were shown to be statistically significant by comparing changes in QTc intervals with baseline measurements. In these healthy vol-

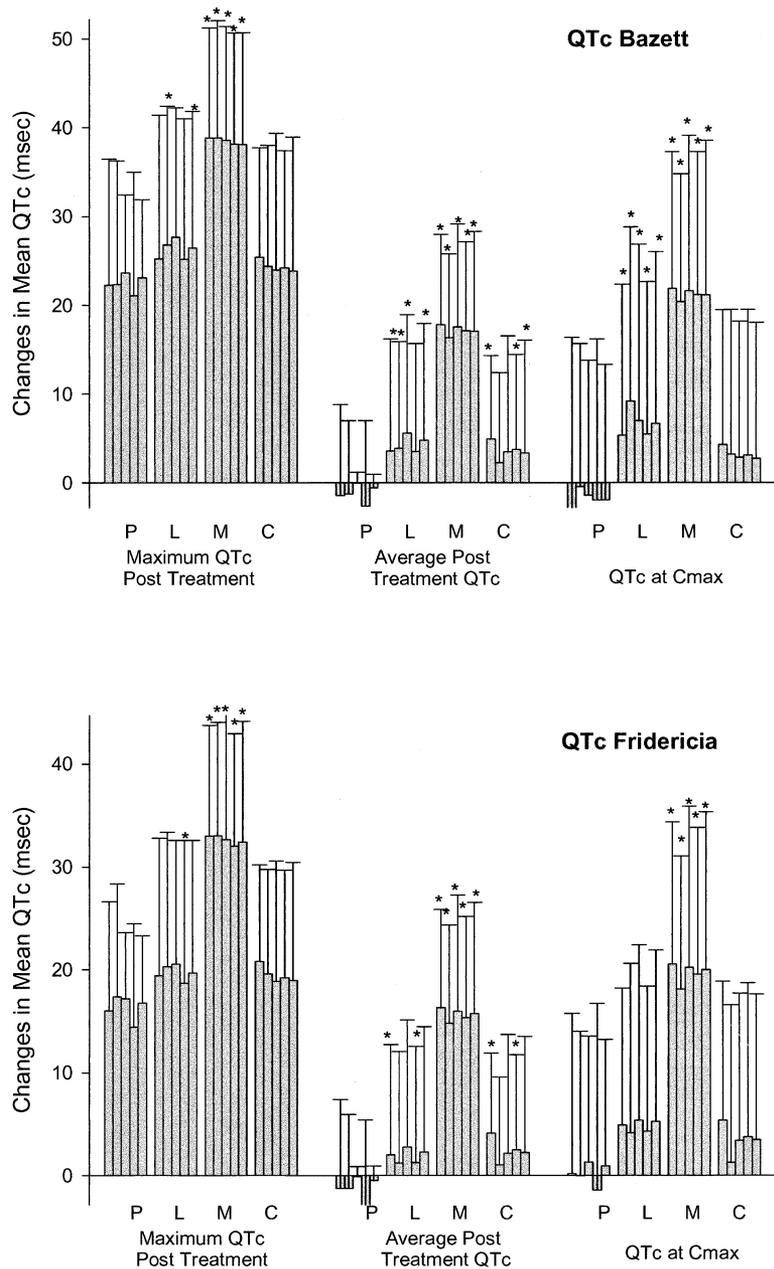


Fig 4. Change from baseline values in means of (1) maximum QTc intervals after treatment, (2) average QTc intervals measured for 24-hour period after treatment, and (3) QTc intervals at maximum plasma drug concentration (Cmax). Bars represent mean change (+SD) from baseline for subjects after treatment with placebo (P), levofloxacin (L), moxifloxacin (M), or ciprofloxacin (C). Each grouping of 5 bars represents changes measured by each of the 5 baseline methods (methods 1-5 from right to left in each grouping). Asterisks indicate statistically significant differences ($P < .05$) between the mean change from baseline after treatment with placebo and the mean change from the corresponding baseline after treatment with a drug. Top, QTc Bazett measurements; bottom, QTc Fridericia measurements.

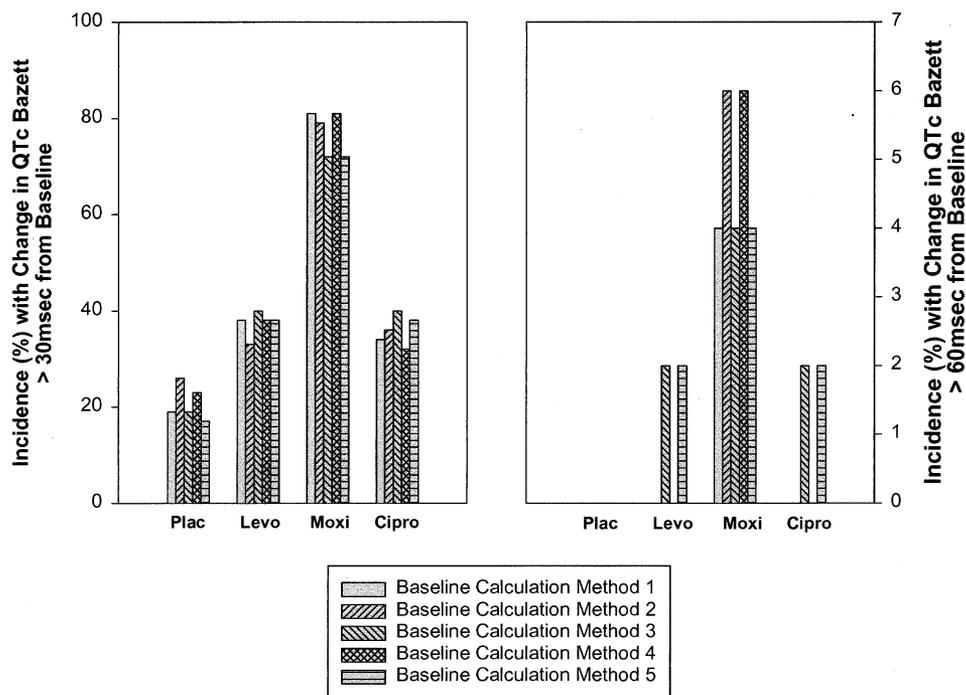


Fig 5. Influence of baseline method on incidences of subjects with QTc (Bazett) intervals greater than 30 ms from baseline (*left*) or greater than 60 ms (*right*) over 24-hour period after treatment with placebo (Plac), levofloxacin (Levo), moxifloxacin (Moxi), or ciprofloxacin (Cipro). Each bar represents the incidence based on 1 of the 5 baseline methods. Subjects with more than 1 QTc measurement greater than 30 or 60 ms from baseline were counted once.

unteers, the effects of these fluoroquinolones on QTc intervals were not associated with cardiac dysrhythmia. The magnitude of these effects on QTc varied depending on baseline methods used, correction methods used, and the fluoroquinolone studied.

Two methods for calculating QTc and several methods for determining differences between QTc intervals before and after treatment were used in this trial. Analyses of these results indicate that the effect on QTc after treatment with moxifloxacin is different from the effect seen after treatment with either levofloxacin or ciprofloxacin. This difference is consistent with observations that demonstrated that moxifloxacin has a greater effect on rapid potassium (IK_r) channel function than either ciprofloxacin or levofloxacin. In this *in vitro* work the 50% inhibitory concentration (IC_{50}) for human ether-a-go-go-related gene (*HERG*) channel-transfected Chinese hamster ovary (CHO) cells was 129 $\mu\text{mol/L}$ for moxifloxacin, 915 $\mu\text{mol/L}$ for levofloxacin, and 966 $\mu\text{mol/L}$ for ciprofloxacin, and the IC_{50} /peak therapeutic plasma ratio was estimated to be 20, 70, and 88 for moxifloxacin, levofloxacin, and ciprofloxacin, respec-

tively.¹⁴ Furthermore, the similarity of the effect of levofloxacin and ciprofloxacin on QTc is consistent with the observation that these 2 agents have comparable effects on these channels. Although these *in vivo* and *in vitro* observations are consistent, they should not be considered sufficient to conclude that the risk for slowing ventricular repolarization associated with moxifloxacin is greater than that associated with either levofloxacin or ciprofloxacin. This conclusion clearly requires a better understanding of how these differences are associated with differences in clinically important events in patients.

In addition to comparing the effect of 3 fluoroquinolones on QT interval, this clinical trial underscores the importance of defining the methods used in measuring this effect. This study design permitted analyses of differences in mean QT and QTc values in addition to the more widely accepted analyses of differences in changes in QTc. Analyses of differences in mean QT and QTc (Bazett and Fridericia) values demonstrated that these values were significantly and consistently greater after treatment with moxifloxacin compared

with placebo. This finding contrasted with the results for levofloxacin and ciprofloxacin, which either were not significant or were significant only when mean QTc Bazett values were analyzed. The observation that significant differences were evident when mean values of QTc (Bazett) at 1.5 to 2.5 hours after treatment with levofloxacin and mean postdose QTc (Bazett) values after levofloxacin were compared with placebo but were not evident when mean QTc (Fridericia) values were compared demonstrates that QT correction formulas can influence these analyses. Such findings, particularly when they coincide with no effect on uncorrected QT, may reflect an effect of drug on heart rate rather than an effect on ventricular repolarization.

Differences among the 3 fluoroquinolones studied that were suggested by analyses of mean QTc values were also evident when changes in QTc were analyzed. Analyses of changes in QTc further demonstrated that small differences in the degree of changes in QTc depend on the definition of baseline QTc and the methods used for calculating QTc. Although these differences were small, in some instances they meant that the change was statistically significant with one method but not another. Differences in the degree of change were also evident depending on whether this change represented a change from maximum QTc measured 24 hours after dosing, from the average QTc measured over the 24-hour period after dosing, or from the QTc measured at the time when the serum concentration of the drug was maximal. These results underscore the importance of considering the definition of the methods used to measure QTc and the basis for calculating changes in QTc before reaching conclusions based on comparing results from different clinical trials or collections of case reports.

Agreement on a single set of methods by which to assess QTc change and define the correction factor and baseline QTc would make it much easier for results of clinical trials to be compared. It is unlikely, however, that it will be possible to decide on a single set of such methods until it is demonstrated that one set of methods is better for identifying clinically relevant effects than another. Nevertheless, there have been attempts to ascribe clinical significance to observations of certain degrees of changes in QTc or to prolongation of QTc above normal values.^{21,22} Our experience suggests there can be problems with this approach, particularly if the assessment of these values does not include a precise definition of how these values were calculated. The occurrence of a change from baseline QTc of 30 to 60 ms has been recognized as indicating a "concern" about a potential risk for torsades de pointes.²¹ In our expe-

rience it was possible to measure this degree of change in as many as 26% of subjects after treatment with placebo. This change in QTc (Bazett) was likely the result of normal physiologic changes and reflected a normal elongation of QTc (Bazett) that occurred in the subjects participating in the study from the period that extended from a time soon after waking to the late morning and early afternoon hours. A change of more than 60 ms has been recognized as indicating a "clear concern" for potential risk for this serious dysrhythmia.²¹ Our experience demonstrates that this degree of change may be detected inconsistently and can depend on methods used to measure this change. For levofloxacin and ciprofloxacin, changes in QTc interval of greater than 60 ms occurred only when 2 of the 5 definitions of baseline were used. These observations strongly suggest that using such a criterion as a way of identifying an agent associated with risk, without a clear definition for measuring these changes, can be inaccurate.

In addition to the concern that this study raises about the use of the frequency of certain degrees of change in QTc to assess risk, the results also serve to demonstrate how the methods used or the analysis performed could influence conclusions about clinical relevance of changes in QTc. The data collected indicate that if changes in QTc after levofloxacin and ciprofloxacin had been measured 8 hours after dosing an increase in mean QTc above that observed in placebo-treated subjects would not have been identified. In contrast, measurement of QTc 8 hours after moxifloxacin would have clearly shown an effect. Data collected before 8 hours after dosing indicate that the maximal effect on QTc for ciprofloxacin and levofloxacin is associated with peak plasma concentrations. However, the sustained increase in QT and QTc after treatment with moxifloxacin demonstrates that there can be differences between the timing of an effect on QTc and peak plasma levels, even among drugs belonging to the same class. This observation indicates that making frequent observations over many hours may be necessary to detect both the frequency and the degree of effect of a drug on QTc. Furthermore, this experience demonstrates that the maximal effect on QTc may not be observed at the time when the peak plasma concentration of the drug is attained. It is important to recognize that this rigorous assessment of QTc-interval changes, which is dependent on frequent observations, is typically not made in case reports or in small collections of experiences with patients in whom drug-associated dysrhythmias have been recognized.

Another important observation that has been made in this experience is the variation of QT and QTc intervals over the day. The mean QTc (Bazett) interval from early to late morning increased by more than 12 ms in subjects after treatment with placebo. This observation should be considered in ascribing clinical significance to this degree of change. This normal variation in QTc (Bazett) interval must be taken into account when changes in this value are assessed. This is particularly important to recognize because many clinical trials will be designed to dose subjects in the morning and then make observations over the course of the day and most trials will continue to use the Bazett formula to correct QT intervals on the basis of the wide acceptance and familiarity with this correction formula.^{23,24}

New information related to the potential effects of fluoroquinolones and other drugs on cardiac function is likely to become available, because clinical investigation of these effects is being encouraged by the Food and Drug Administration and other health regulatory authorities. Assessing these effects should involve methods that can be reproduced reliably and provide a basis for assessing the clinical relevance of the results. It is becoming more evident with clinical experience that the clinical relevance of these effects is likely to be influenced by drug-drug interactions, the patient's underlying illness, the patient's ability to clear drug normally, and possibly the effect of multiple doses of a drug.²⁵ The results presented here do not address all of these issues. However, these results and those recently reported²⁶ clearly demonstrate that small effects on QTc can be measured reproducibly in single-dose trials in healthy volunteers treated with fluoroquinolones. Furthermore, the relative degree of these effects in volunteers is consistent with that described in molecular models of the effect of these agents on IK_r channel function. Establishing methods that can be safely and reliably used to detect the effect is an important first step toward a better way of assessing the potential risks of fluoroquinolone use. With this study having taken the first step by demonstrating that 3 widely used fluoroquinolones can produce this effect, it is apparent that the next great challenge comes in translating how these effects might contribute to the risk of using these drugs to treat patients.

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