Effects of the Fluoroquinolones Moxifloxacin and Levofloxacin on the QT Subintervals: Sex Differences in Ventricular Repolarization

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Abstract

Women are associated with longer electrocardiographic QT intervals and increased proarrhythmic risks of QT-prolonging drugs. The purpose of this study was to characterize the differences in cardiac electrophysiology between moxifloxacin and levofloxacin in men and women and to assess the balance of inward and outward currents through the analysis of QT subintervals. Data from 2 TQT studies were used to investigate the impact of moxifloxacin (400 mg) and levofloxacin (1000 and 1500 mg) on QT subintervals using algorithms for measurement of J-Tpeak and Tpeak-Tend intervals. Concentration-effect analyses were performed to establish potential relationships between the ECG effects and the concentrations of the 2 fluoroquinolones. Moxifloxacin was shown to be a more potent prolonger of QT interval corrected by Fredericia (QTcF) and had a pronounced effect on J-Tpeakc. Levofloxacin had little effect on J-Tpeakc. For moxifloxacin, the concentration-effect modeling showed a greater effect for women on QTcF and J-Tpeakc, whereas for levofloxacin the inverse was true: women had smaller QTcF and J-Tpeakc effects. The different patterns in repolarization after administration of both drugs suggested a sex difference, which may be related to the combined lKs and lKr inhibitory properties of moxifloxacin versus lKr suppression only of levofloxacin. The equipotent inhibition of lKs and lKr appears to affect women more than men. Sex hormones are known to influence cardiac ion channel expression and differences in QT duration. Differences in lKs and lKr balances, influenced by sex hormones, may explain the results. These results support the impact of sex differences on the cardiac safety assessment of drugs.

Keywords

J-Tpeak, Tpeak-Tend, moxifloxacin, levofloxacin, ion channel effects, lKs, lKr

Distinct ion channels contribute to defining the morphology and duration of the cardiac action potential. To characterize drug proarrhythmic properties, it is of interest to explore which ionic currents play a significant role. It has been demonstrated that the balance of inward and outward currents can be detected in the ECG by analyzing the QT subintervals. lKs or hERG-encoded potassium channel blockade prolongs both early repolarization (J-Tpeak) and late repolarization (Tpeak-Tend), whereas multichannel blockers may shorten or have no effect on J-Tpeak depending on which channels are blocked and how potently as well as whether these channels facilitate depolarization or repolarization currents.

It is widely accepted that women are more prone to developing drug-induced arrhythmia.2-4 Vicente et al reported sex- and age-specific measurements for all the QT subintervals in healthy subjects in 2014, demonstrating men to have a shorter rate-corrected QT interval (QTc) than women. Despite longer depolarization (QRS) and late repolarization (Tpeak-Tend) phases, men have reduced early repolarization (J-Tpeak) when compared with women, which summates to an overall shorter QTc.5 This difference develops during puberty and diminishes with age. It is thought that sex hormones may play a role; simulated testosterone studies have shown that the male sex hormone affects both lICaL and lIKr, contributing to sex differences in
early repolarization. Additionally, it has been suggested that endogenous testosterone (I_{Kr}, and I_{Kr} up-regulator) and progesterone (I_{Ks}, up-regulator) shorten the cardiac action potential. Endogenous estrogen (I_{Kr} and I_{Kr} downregulator) is thought to lengthen the cardiac action potential. Studies of menopausal hormone therapy in the form of estrogen-alone therapy and estrogen plus progesterone therapy have suggested a countering effect of exogenous estrogen and progesterone on the QT. Specifically, estrogen-alone therapy lengthens the QT, whereas estrogen plus progesterone therapy has no effect.

Fluoroquinolones are one of the most commonly prescribed classes of antibiotics. Prolongation of the QT interval is an adverse effect associated with the use of fluoroquinolones and has been the basis for their use as positive controls for thorough QT studies. Fluoroquinolones prolong the QT interval by blocking voltage-gated potassium channels, especially the “rapid” component of the delayed rectifier current I_{Kr}, expressed by hERG (the human ether-á-go-go-related gene). However, the degree of QT interval prolongation appears to differ among fluoroquinolones. The overall risk of torsades de pointes (TdP) is small with the use of fluoroquinolones but has been documented in clinical studies and case reports. Moxifloxacin has been used in the majority of TQT studies, and it is known to influence ventricular repolarization by inhibiting the I_{Kr} channel. Oral moxifloxacin leads to an average QTc prolongation of 10-14 ms at a dose of 400 mg. Levofoxacin, another fluoroquinolone, has also been shown to block hERG channels and cause changes in the QTc interval. The effect of supratherapeutic oral doses of levofloxacin on the QTc intervals of healthy volunteers was compared with a placebo group. Each of the 4 periods consisted of 2 days: 1 placebo baseline day and 1 treatment day. These were separated by a 2-day washout period. The study design, ECG, and pharmacokinetic assessments were fully detailed by Taubel et al.

Recently, Matsukura et al indicated that moxifloxacin significantly prolonged both J-T peak and T_peak-T_end. Additionally, women were found to be more sensitive to overall QTc by Fredericia (QTcF) prolongation and (more specifically) to J-T peak prolongation in a concentration-effect model analysis.

The purpose of the present study was to use combined data from 2 TQT studies comparing QTcF changes after supratherapeutic doses of levofloxacin (which is thought to primarily block hERG channels) and therapeutic doses of moxifloxacin (which has been shown to block both hERG and KsLQTL/mink). The 2 studies were performed in the same year at the same clinical research unit using identical procedures for clinical conduct and ECG analysis. Both studies were balanced for sex, and the analyses performed in the moxifloxacin arm of each study were identical. This investigation characterizes the differences in early repolarization (J-T peak) and late repolarization (T_peak-T_end) between moxifloxacin and levofloxacin and further defines observed sex differences in QTcF and its subintervals.

Materials and Methods

Study Design

Study 1 (EudraCT: 2006-006376-38) was approved by the local ethics committee (Covance Clinical Research Unit, Independent Ethics Committee, Leeds, UK) and the Medicines and Healthcare Products Regulatory Authority and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. This was a randomized, placebo-controlled, double-blinded, double-dummy, single-center, 4 × 4 crossover study. It consisted of 64 healthy, white volunteers (34 male and 30 female) who all provided written, informed consent before any study-specific procedures.

The study evaluated the effects of 2 single supratherapeutic oral doses of levofloxacin (1000 mg and 1500 mg Tavanic; Laboratoire Aventis, Groupe Sanofi-Aventis, Paris, France) and 1 single standard oral dose of moxifloxacin (400 mg Izilox; Bayer Pharma SAS, Puteaux, France) on the QTc intervals of healthy volunteers compared with a placebo group. Each of the 4 periods consisted of 2 days: 1 placebo baseline day and 1 treatment day. These were separated by a 2-day washout period. The study design, ECG, and pharmacokinetic assessments were fully detailed by Taubel et al.

Study 2 (EudraCT: 2006-002504-34) was approved by the local ethics committee (North London REC 3, Harrow, UK), and the Medicines and Healthcare Products Regulatory Authority and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. This was a randomized, placebo-controlled, positive-controlled, double-blinded, double-dummy, single-center, 3 × 3 crossover study. It consisted of 96 healthy, white volunteers (47 male and 49 female) who all provided written, informed consent before any study-specific procedures.

The study evaluated the effects of supratherapeutic repeated dosing of 4 g of once-daily strontium ranelate (Protelos; Les Laboratoires Servier, Neuilly-sur-Seine, France) for 15 days on the QTc interval of healthy volunteers. Eligible subjects were randomized to strontium ranelate, placebo, or moxifloxacin for the 3 treatment periods. Each treatment period consisted of 16 days: day 1 was the placebo baseline day at the unit; days 2-15 were out of the unit, and participants were on placebo or strontium ranelate. The final day (day 16) was spent at the unit, and the volunteers had either placebo, strontium ranelate, or moxifloxacin (Izilox; Bayer Pharma SAS, Puteaux, France). The treatment...
periods were separated by 28-day washout periods. The methods used for ECG and pharmacokinetic assessments are described elsewhere.22

ECG Recording and Data Processing

Twelve-lead ECGs were recorded as described by Taubel et al.19,22 Data were processed by the Department of Health Science and Technology of the Faculty of Medicine, University of Aalborg (Denmark). They used the commercially available GE Healthcare Marquette 12SL ECG analysis program and the US Food and Drug Administration 510(k)-cleared GE research package QT GuardPlus.18,19 This software uses the simultaneous vector magnitude of all 12 leads to determine the onset and offset of the QRS complex as well as the offset of the T wave. The vector magnitude is a global single-lead representation of all 12 leads that did not display a biphasic (+/– or –/+ ) T wave. In cases with clear biphasic T waves in some of the leads, the vector magnitude representation may have displayed 2 obvious positive peaks in the T wave. In these cases the algorithm used the second peak of the T wave, the peak closer to the end. The end of the T wave is determined by the method of small windows.23,24

\( J-T_{\text{peak}} \) was heart-rate corrected using \( J-T_{\text{peak}}cJ \).25 At resting heart rates \( T_{\text{peak}}-T_{\text{end}} \) exhibits minimal heart-rate dependency, and, therefore, correction was not made.26

Statistical Analyses

The moxifloxacin ECG and pharmacokinetic data from studies 1 and 2 were combined. In total, 9315 ECGs were used in the moxifloxacin analysis: 1364 and 1741 triplicate ECGs from 61 subjects in the moxifloxacin treatment in study 1 and 72 subjects in the moxifloxacin treatment in study 2, respectively. To ensure consistency across the 2 studies, the values from the first day of each period (placebo baseline day) at the time points 0, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours (common time points to the 2 studies) were averaged by subject and period to calculate baseline. The levofloxacin data were taken from study 1 only: 1385 triplicate ECGs from 62 subjects in the 1000-mg levofloxacin treatment and 1361 triplicate ECGs from 62 subjects in the 1500-mg levofloxacin treatment, resulting in a total of 8238 ECGs that were analyzed. The baseline-corrected variables (\( \Delta QTcF \), \( \Delta J-T_{\text{peak}}cJ \), and \( \Delta T_{\text{peak}}-T_{\text{end}} \)) were obtained by subtracting the baseline from the postdose value, by subject and time point within each period. The baseline and placebo-corrected variables were obtained by subtracting the baseline-corrected variable of the placebo period from the baseline-corrected variable of the drug administration period. All time points were used for these variables: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 8, 12, and 24 hours for study 1 and 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours for study 2.

Mixed Models. The analysis follows the general statistical principles described by Garnett et al.27 To ascertain whether the ECG markers differed between sex groups through the concentration profile, the analysis involved a mixed model for each outcome variable (\( \Delta QTcF \), \( \Delta J-T_{\text{peak}}cJ \), and \( \Delta T_{\text{peak}}-T_{\text{end}} \)), with sex and the interaction between concentration and sex as fixed effects. The random term included intercepts and concentration by subject.

The mixed models were fitted in SAS Enterprise Guide version: 7.1 (7.15 HF3 [7.100.5.6132]) with SAS version 9.4 (9.04.01M5P09132017) using the Restricted Maximum Likelihood method. For the degrees of freedom, the Kenward-Roger approach was used. All 2-sided confidence intervals are calculated using \( \alpha = 0.1 \). An unstructured covariance matrix was assumed for the random effects.

Results

Subject Demographics and Disposition

Subject demographics are presented by descriptive statistics in Table 1.

Three subjects from study 1 were withdrawn, 2 because of adverse events following treatment with moxifloxacin 400 mg (1 subject suffered from sustained supraventricular tachycardia, and the second suffered from anxiety). No serious or severe adverse events were observed.14

Twenty-six subjects were withdrawn in study 2. This was because of the very long duration of the trial due to a multiple-dose crossover design. One withdrew due to an adverse event after receiving moxifloxacin 400 mg (the subject experienced flu-like symptoms and was found pyrexial). Twenty-two participants were withdrawn for nonmedical reasons, and 3 were withdrawn due to noncompliance with protocol requirements (testing positive for drugs of abuse in subsequent treatment periods). There were no serious or severe adverse events in this study.

| Table 1. Subject Demographics | Study 1 | Study 2 |
|--------------------------------|---------|---------|
| Number of subjects enrolled   | 64      | 96      |
| Age (y)                       | 29 ± 7  | 27.7 ± 7.5 |
| Sex (n)                       |         |         |
| Male                          | 34 (53%)| 47 (49%)|
| Female                        | 30 (47%)| 49 (51%)|
| BMI (kg m$^{-2}$)             | 24.1 ± 2.3 | 24.1 ± 2.8 |
| Race (n)                      |         |         |
| White                         | 64 (100%) | 96 (100%) |

BMI indicates body mass index.
In the descriptive and statistical analysis described here, data from 61 subjects (28 women and 33 men) who received 400 mg moxifloxacin and data from 62 subjects who received levofloxacin (29 female and 33 male) have been included from study 1. From study 2, data from 72 subjects (35 female and 37 male) who received 400 mg moxifloxacin were included. The time course analysis data for moxifloxacin by study are presented in Supplemental Tables S1-S3. Overall, the point estimates were very similar between studies.

Time Course Analyses

The effects of moxifloxacin and levofloxacin on the ΔΔQTcF, ΔΔJ-TpeakcJ, and ΔΔTpeak-Tend are summarized in Figure 1. Generally, the effects on women were greater than those on men. This is unsurprising given the higher plasma concentrations due to demographic differences between sexes.

ΔΔQTcF. The largest ΔΔQTcF with moxifloxacin was registered at 3.5 hours for both men (12.43 ms, 90%CI 10.56-14.31) and women (16.80 ms, 90%CI 13.88-19.72). Similarly, 1000 mg of levofloxacin produced the largest ΔΔQTcF at 2 hours for men (6.86 ms, 90%CI 5.11-8.62) and at 2.5 hours for women (7.51 ms, 90%CI 5.70-9.33). Following a 1500-mg dose, men showed the greatest ΔΔQTcF at 3 hours (9.91 ms, 90%CI 7.83-12.00), whereas women still showed the biggest difference at 3.5 hours (10.28 ms, 90%CI 8.16-12.40).

ΔΔJ-TpeakcJ. When moxifloxacin is administered, the highest ΔΔJ-TpeakcJ value observed in women was at 2 hours (10.86 ms, 90%CI 8.71-13.01). Men showed a smaller effect, and their highest value was displayed at 1 hour (7.21 ms, 90%CI 5.69-8.73).

When compared with moxifloxacin, the levofloxacin effect on ΔΔJ-TpeakcJ was short-lived, particularly in men, where values returned to baseline within 3-4 hours. In women, effects persisted for longer, returning to baseline by 8 hours. Notably, at the 8 hours’ time point, women still showed a greater prolongation of ΔΔJ-TpeakcJ after a dose of moxifloxacin. The effects of 1000 mg levofloxacin on ΔΔJ-TpeakcJ were highest at 1.5 hours in women (3.86 ms, 90%CI 1.82-5.91) and at 2 hours in men (4.52 ms, 90%CI 3.17-5.88). The 1500-mg dose of levofloxacin led to an increase of 5.08 ms (90%CI 3.29-6.87) at 1.5 hours in men and 4.43 ms (90%CI 2.77-6.08) at 2 hours in women.

ΔΔTpeak-Tend. The highest ΔΔTpeak-Tend values following administration of moxifloxacin were observed at 3.5 hours in both men (5.31 ms, 90%CI 4.12-6.49) and women (5.69 ms, 90%CI 3.89-7.50). The largest values with 1000 mg levofloxacin were at 3.5 hours for men (2.05 ms, 90%CI 1.12-2.98) and at 3 hours for women (4.42 ms, 90%CI 3.29-5.55). The 1500-mg levofloxacin cohort showed the same pattern with a maximum increase of 4.32 ms (90%CI 3.09-5.55) for men at 3.5 hours and 7.02 ms (90%CI 5.37-8.68) at 3 hours for women. The curves for ΔΔTpeak-Tend clearly separate after both doses of levofloxacin and remain elevated up to 4 hours.

Concentration-Effect Analysis

For each subject, the maximum concentration of the analytes moxifloxacin and levofloxacin was measured and used for calculating the overall and by-sex geometric means. The moxifloxacin geometric mean peak concentration (Cmax) was 2.49 μg/mL (men 2.27; women 2.75). The levofloxacin geometric mean Cmax was 11.37 μg/mL for men and 13.97 μg/mL for women (overall Cmax 12.54 μg/mL).

The relationships between moxifloxacin and levofloxacin plasma concentrations and their respective predicted ΔΔQTcF, ΔΔJ-TpeakcJ, and ΔΔTpeak-Tend values are shown in Figure 2. The slopes and intercepts for all parameters are summarized in Table 2.

### Table 2. Summary of Intercepts and Slopes Obtained by Concentration-Effect Modeling

|                  | Moxifloxacin | Levofloxacin |
|------------------|--------------|--------------|
| **Moxifloxacin** | **Slope**    | **Intercept** |
|                  | (ms/μg/mL)   | (ms)         |
| ΔΔQTcF Male       | 4.7030       | 1.9757       |
| Female            | 4.9893       | 1.3651       |
| ΔΔJ-TpeakcJ Male  | 3.3362       | 0.1106       |
| Female            | 3.5921       | 1.8607       |
| ΔΔTpeak-Tend Male | 1.2338       | 1.8283       |
| Female            | 1.3462       | 0.8986       |
| **Levofloxacin**  | **Slope**    | **Intercept** |
|                  | (ms/μg/mL)   | (ms)         |
| ΔΔQTcF Male       | 0.8636       | -0.6135      |
| Female            | 0.7115       | -0.4185      |
| ΔΔJ-TpeakcJ Male  | 0.3376       | 0.3337       |
| Female            | 0.2047       | -0.6236      |
| ΔΔTpeak-Tend Male | 0.3201       | -0.7692      |
| Female            | 0.4446       | -0.6903      |
Figure 1. Time course of (A) \(\Delta\Delta QTcF\), \(\Delta\Delta J-T_{peakc}\), and \(\Delta\Delta T_{peak-T_{end}}\) and (B) plasma concentration following administration of 400 mg moxifloxacin and 1000 mg and 1500 mg levofloxacin. Vertical bars represent 2-sided 90% CIs of the mean. Te indicates \(T_{end}\); \(T_p\), \(T_{peak}\).

(90%CI 11.02-14.21) for men and 16.9 ms (90%CI 15.17-18.63) for women.

There was a positive relationship between moxifloxacin plasma concentrations and the predicted \(\Delta\Delta J-T_{peakc}\) (Figure 2 and Table 2). The estimated \(\Delta\Delta J-T_{peakc}\) at \(C_{max}\) for men was 7.66 ms (90%CI 6.21-9.11) and 11.75 ms (90%CI 10.17-13.33) for women. The overall estimate at \(C_{max}\) was 9.56 ms (90%CI 8.49-10.63).

No difference was found for \(\Delta\Delta T_{peak-T_{end}}\) with the 90%CI of both populations almost completely overlapping (Figure 2): at \(C_{max}\) men presented values of 4.62 ms (90%CI: 3.79; 5.46) whereas women presented slightly higher values: 4.85 ms (90%CI: 3.95; 5.74). The predicted \(\Delta\Delta T_{peak-T_{end}}\) values at the overall \(C_{max}\) were 4.70 ms (90%CI: 4.08; 5.31).

The intercept and slope differences between men and women are shown in the Supplemental Table S4.

**Levofloxacin**

Levofloxacin elicited a smaller \(\Delta\Delta QTcF\) and \(\Delta\Delta J-T_{peakc}\) than moxifloxacin. The \(\Delta\Delta QTcF\) slope was
Figure 2. Relationship between moxifloxacin and levofloxacin plasma concentrations and $\Delta \Delta QTcF$, $\Delta \Delta \Delta T_{peak}cJ$, and $\Delta \Delta T_{peak}-T_{end}$. Regression lines with 2-sided 90% confidence regions are denoted by shaded areas. The means and whiskers show the predicted values for $\Delta \Delta QTcF$, $\Delta \Delta \Delta T_{peak}cJ$, and $\Delta \Delta T_{peak}-T_{end}$ at $C_{\text{max}}$ concentrations (the overall geometric mean of the individual $C_{\text{max}}$ values and the geometric means of the individual $C_{\text{max}}$ values by sex). $C_{\text{max}}$ indicates peak concentration; $T_e$, $T_{end}$, $T_{peak}$.
greater for men than for women (Table 2), which is the opposite of what is seen after moxifloxacin administration. Figure 2 shows that the $\Delta \Delta QTcF$ overlap zone of the 90% confidence regions is wider at smaller concentrations, indicating that sex-related differences in $\Delta \Delta QTcF$ seem to be more evident at higher concentrations. The concentration-effect analysis shows that the $\Delta \Delta QTcF$ value at the overall C_max was 9.40 ms (90%CI 8.21-10.59); 9.20 ms (90%CI 7.64-10.76) for men and 9.52 ms (90%CI 7.68-11.35) for women.

Almost consistently, men had slightly higher values of $\Delta J-\Delta T_{peak-cJ}$ than women across the concentration profile (Figure 2). Estimates for $\Delta \Delta J-\Delta T_{peak-cJ}$ at C_max were 4.17 ms for men (90%CI 2.78-5.56) and 2.70 ms for women (90%CI 1.07-4.34). The overall estimate was of 3.54 ms (90%CI 2.48-4.60). Again, this was the opposite of the effect seen with moxifloxacin.

In contrast to the previous parameters, women had greater $\Delta J-\Delta T_{peak-cJ}$ than men at C_max, and women presented values of 5.52 ms (90%CI 4.51-6.53). The $\Delta J-\Delta T_{peak-cJ}$ value at the overall C_max was 4.03 ms (90%CI 3.36-4.69). Slope and intercept differences between men and women are shown in Supplemental Table S4.

**Discussion**

The literature indicates that of all the available fluoroquinolones, moxifloxacin carries the greatest risk of QT prolongation. As a result, it is advised that it should be used in caution in patients with predisposing factors for TdP.28,29

Women generally have a longer QTc than men and an increased risk of drug-induced TdP.30 These sex differences seem to be multifactorial and are still not very well understood.32–35 Testosterone was reported to shorten the action potential duration in guinea pigs by decreasing the inward-depolarizing L-type calcium current ($I_{Ca-L}$) and increasing the outward-repolarizing “slow” delayed rectifier potassium current ($I_{Ks}$).35 In healthy adult subjects the shorter QTc in men than in women was related to a shorter J-Tpeak interval, a difference that diminished with age. The influence of sex hormones is also supported by findings showing similar QTc intervals at birth in male and female subjects.36 The early repolarization changes in men were shown to be influenced more by the effect of testosterone on calcium currents than its effects on $I_{Kr}$.3 Testosterone also diminished the proarrhythmic effects of the pure hERG blocker dofetilide in female rabbits.30 Jonsson et al.12 have found that both $I_{Ks}$ and $I_{Kr}$ are influenced by sex hormones whereby estrogen reduces $I_{Ks}$ and $I_{Kr}$ expression, whereas progesterone enhances $I_{Ks}$. Testosterone, by contrast, enhances both $I_{Kr}$ and $I_{Ks}$.

This suggests that sex differences must be considered in thorough QT studies and that hormonal cycles may impact their results. The actions of sex hormones on cardiac ion channels are likely to contribute to the sex differences in cardiac repolarization processes and susceptibility of TdP.

In this study the assessment of ECG subintervals showed clear sex differences with moxifloxacin and levofloxacin. The QTcF prolongation of moxifloxacin in women was due to a prolongation of $T_{peak-cJ}$ of approximately 12 ms and a prolongation of $T_{peak-cJ}$ by approximately 5 ms. Men registered smaller values of $J-\Delta T_{peak-cJ}$ (8 ms) and similar time-course values of $T_{peak-cJ}$ (5 ms) when compared with women. This suggests that the greater effect in women on QTcF is due to their greater increase of $J-\Delta T_{peak-cJ}$. Our results are well aligned with the previous work from Matsukura et al. In their study, women were also shown to be more sensitive than men to the moxifloxacin-induced $J-\Delta T_{peak-cJ}$ prolongation and QTcF, whereas $T_{peak-cJ}$ values were similar between the sex groups.21 In women levofloxacin prolonged $T_{peak-cJ}$ by 6 ms and $J-\Delta T_{peak-cJ}$ by 3 ms. Men presented higher $J-\Delta T_{peak-cJ}$ values and smaller $T_{peak-cJ}$ values. With moxifloxacin, women demonstrated greater increase in QTcF and $J-\Delta T_{peak-cJ}$, whereas with levofloxacin, they demonstrated a greater increase in $T_{peak-cJ}$.

In summary, moxifloxacin showed a greater effect in women on the $J-\Delta T_{peak-cJ}$ interval, which accounted for most of their prolongation of QTcF. Levofloxacin showed a different pattern of effect as women had less effect on $J-\Delta T_{peak-cJ}$, a more pronounced effect on $T_{peak-cJ}$, and the net effect on QTcF was a smaller effect in women.

The prolongation of $J-\Delta T_{peak}$ seen for moxifloxacin and levofloxacin is in agreement with electrophysiology studies and indicates that drug-induced changes in T-wave morphology are directly related to the amount of hERG potassium channel block. Moxifloxacin was shown to be a more potent prolonger of QTcF and had a pronounced effect on $J-\Delta T_{peak-cJ}$, consistent with its effects on both $I_{Kr}$ and $I_{Ks}$ channels, whereas levofloxacin had small and short-lived effect on $J-\Delta T_{peak-cJ}$. Patch-clamp analyses suggested a roughly equipotent binding of moxifloxacin to $I_{Ks}$ and $I_{Ks}$ potassium channels.1,14 In contrast, levofloxacin has been shown to have effects on $I_{Kr}$ channels only at relatively high concentrations, and $I_{Ks}$ was not a target for block by levofloxacin because high concentrations produced only modest reductions in $I_{Ks}$.18

In this study moxifloxacin and levofloxacin presented inverse sex-specific effects. The increase of early repolarization duration in women, measured as the heart rate corrected $J-\Delta T_{peak}$ interval (where $I_{Ca-L}$, $I_{Kr}$, and late sodium current play a major role) was less...
pronounced with levofloxacin than with moxifloxacin. Therefore, women seem to be more sensitive to a dual block, in this case to moxifloxacin, a recognized $I_{Ks}$ and $I_{Kr}$ inhibitor. In principle, considering that a larger prolonging effect of the $J - T_{peak}$ interval may result in a greater risk of TdP, our data would suggest that therapeutic doses of moxifloxacin have a considerably higher risk of TdP in women than supratherapeutic doses of levofloxacin. These findings suggest that sex hormone–dependent differences in $I_{Ks}$ may be involved in these apparent differences in QT subintervals between moxifloxacin and levofloxacin. Our results provide valuable insights into possible sex differences, the importance of female enrollment in cardiac assessments, and contribute to the estimated proarrhythmic potential of new chemical entities.

Limitations

This was a retrospective analysis, and the studies were not designed to explore the effects of moxifloxacin and levofloxacin on the QTc subintervals and the respective sex differences. However, the sample size utilized and the statistical analyses are sufficiently robust, and the results align well with previous published work by our research group and others.

In addition to the above outlined hormone effects, progesterone was shown to shorten action potential duration in guinea pigs mostly through inhibition of inward $I_{Ca}$ and enhancement of $I_{Kr}$.

In women progesterone fluctuates through the menstrual cycle, and estrogen seems to have an opposing effect on cardiac repolarization. This study does not explore the individual contributions of sex hormones and their effects in combination with moxifloxacin or levofloxacin on T-wave morphology.

The study did not record menstrual cycles and did not measure sex hormones. More studies considering hormonal fluctuations would be desirable.

Conflicts of Interest

Jörg Täubel, Helen Wibberley, Samuel Thomas Cole, Leen Van Langenhoven, Sara Fernandes, and Dilshat Djumanov are employees of Richmond Pharmacology Ltd. Georg Fäber is an employee of Statistik Georg Fäber GmbH.

Data Sharing

Requests for access to data should be addressed to the corresponding author.

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**Supplemental Information**

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.