Effects of the fluoroquinolones moxifloxacin and levofloxacin on the QT subintervals: sex differences in ventricular repolarization

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Background: The effects of medicines affecting cardiac repolarization can be further evaluated by assessing the balance of inward and outward currents. These can be detected in the ECG by analysing the QT subintervals. Pure hERG potassium channel block was shown to prolong both early repolarization (J-Tpeak) and late repolarization (Tpeak-Tend), whereas multichannel blockers may shorten or have no effect on J-Tpeak.

The gender dependency of ventricular repolarization is also well known. Recently, Matsukura indicated that moxifloxacin significantly increased J-Tpeak and Tpeak-Tend and females in their study were more sensitive than males to the drug-induced J-Tpeak prolongation and QTcF.

Purpose: The purpose of the present study is to use data from two Thorough QT (TQT) studies to characterize the differences in depolarization (QRS), early repolarization (J-Tpeak), and late repolarization (Tpeak-Tend) between moxifloxacin and levofloxacin and further define the sex differences in QTc and subintervals.

Methods: Data from two TQT studies were used to further investigate the impact of moxifloxacin (400 mg) and levofloxacin (1000 and 1500 mg) on QT subintervals using validated algorithms for measurement of QRS, J-Tpeak and Tpeak-Tend intervals. Concentration-effect analyses were performed to establish a potential relationship between the ECG effects and the concentrations of the two fluoroquinolones as typically males and females also show differences in plasma concentrations due to differences in body weight.

Results: The relationships between moxifloxacin and levofloxacin plasma concentrations and their respective predicted ??QTcF, ??QRS, ??J-Tpeakc and ??Tpeak–Tend values are shown in Fig 1. The plasma concentrations were higher for females than males in both drugs. Moxifloxacin was shown to be a more potent prolonger of QTcF and had a pronounced effect on J-Tpeakc, consistent with its effects on both IKr and IKs channels while levofloxacin had little effect on J-Tpeakc. For moxifloxacin, the concentration-effect modelling showed a greater effect for females on QTcF and J-Tpeakc while for levofloxacin the inverse was true. Based on the assumption that repolarization reserve of females relies to a greater extent on IKs channels it would be reasonable to assume that they are more affected by a medicine that blocks IKs in addition to IKr.

Conclusions: This study showed that levofloxacin elicited a smaller ??QTcF and ??J-Tpeakc prolongation when compared to moxifloxacin. The results of this study also showed a different pattern of sex difference in repolarization after administration of both drugs, which may suggest a difference in expression of IKs and possibly IKr channels.
Abstract: The effects of medicines affecting cardiac repolarization can be further evaluated by assessing the balance of inward and outward currents. These can be detected in the ECG by analysing the QT subintervals. Pure hERG potassium channel block was shown to prolong both early repolarization (J-Tpeak) and late repolarization (Tpeak-Tend), whereas multichannel blockers may shorten or have no effect on J-Tpeak. The gender dependency of ventricular repolarization is also well known. Recently, Matsukura indicated that moxifloxacin significantly increased J-Tpeak and Tpeak-Tend and females in their study were more sensitive than males to the drug-induced J-Tpeak prolongation and QTcF.

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