



Levofloxacin can be used effectively as a positive control in thorough QT/QTc studies in healthy volunteers

Jorg Taubel, Asif Naseem, Tomohiko Harada, Duolao Wang,¹ Radivoj Arezina, Ulrike Lorch & A John Camm²

Richmond Pharmacology Ltd, St George's University of London, ¹Department of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine and ²Department of Cardiological Sciences, St George's University of London, UK

Correspondence

Dr Asif Naseem, Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK.
Tel: +44 (0)20 8664 5200
Fax: +44 (0)20 8664 5201
E-mail: a.naseem@richmondpharmacology.com

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- New drugs are expected to undergo rigorous clinical electrocardiographic evaluation ('thorough QT/QTc study') during their early clinical development in order to determine any effect on cardiac repolarization.
- The fluoroquinolone antibiotic moxifloxacin (400 mg) has been used as a positive comparator for thorough QT/QTc studies due to its QT prolongation (QTcF) of between 6 and 10 ms.
- Positive comparators that are able to produce mean changes close to the regulatory guidelines of 5 ms, and which can be detected by the assay in use, would enable a more rigorous evaluation of the assay conditions used in evaluating new chemical entities.

WHAT THIS STUDY ADDS

- This thorough QT/QTc study directly compares the effects of two doses of levofloxacin and moxifloxacin on QTc in the same healthy subjects.
- Mean QTc was prolonged in subjects receiving levofloxacin compared with placebo as determined by both individual and Fridericia's heart rate correction methods.
- The largest time-matched differences in QTc for two doses of levofloxacin compared with placebo suggest the potential for using levofloxacin in more rigorous QT/QTc studies, providing a robust evaluation of the assay conditions used in determining potential effects on cardiac repolarization.
- There is evidence to suggest that levofloxacin moderately increases heart rate in a dose-dependent fashion.

AIMS

To characterize the effects of levofloxacin on QT interval in healthy subjects and the most appropriate oral positive control treatments for International Conference on Harmonization (ICH) E14 QT/QTc studies.

METHODS

Healthy subjects received a single dose of levofloxacin (1000 or 1500 mg), moxifloxacin (400 mg) or placebo in a four-period crossover design. Digital 12-lead ECGs were recorded in triplicate. Measurement of QT interval was performed automatically with subsequent manual onscreen over-reading using electronic callipers. Blood samples were taken for determination of levofloxacin and moxifloxacin concentrations.

RESULTS

Mean QTcI (QT interval corrected for heart rate using a correction factor that is applicable to each individual) was prolonged in subjects receiving moxifloxacin 400 mg compared with placebo. The largest time-matched difference in QTcI for moxifloxacin compared with placebo was observed to be 13.19 ms (95% confidence interval 11.21, 15.17) at 3.5 h post dose. Prolonged mean QTcI was also observed in subjects receiving levofloxacin 1000 mg and 1500 mg compared with placebo. The largest time-matched difference in QTcI compared with placebo was observed at 3.5 h post dose for both 1000 mg and 1500 mg of levofloxacin [mean (95%) 4.42 ms (2.44, 6.39) in 1000 mg and 7.44 ms (5.47, 9.42) in 1500 mg]. A small increase in heart rate was observed with levofloxacin during the course of the study. However, moxifloxacin showed a greater increase compared with levofloxacin.

CONCLUSIONS

Both levofloxacin and moxifloxacin can fulfil the criteria for a positive comparator. The ICH E14 guidelines recommend a threshold of around 5 ms for a positive QT/QTc study. The largest time-matched difference in QTc for levofloxacin suggests the potential for use in more rigorous QT/QTc studies. This study has demonstrated the utility of levofloxacin on the assay in measuring mean QTc changes around 5 ms.