

Levofloxacin can be used effectively as a positive control in Thorough QT/QTc (TQT) studies in healthy volunteers

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Introduction

The effect of medicines on cardiac repolarisation is of great concern in clinical use and the development of new medicines.

Investigational medicinal products (IMP) are expected to undergo rigorous clinical electrocardiographic evaluation and will at some stage usually require a thorough QT/QTc study (TQT) (Camm, 2005).

Relative safeness of fluoroquinolone antibiotics is the basis for use as positive comparators in TQT studies to confirm assay sensitivity.

• Moxifloxacin is commonly used and causes an average QT prolongation (QTcF) of between 6 and 10 msec (400 mg) (Strnadova, 2005) (Morganroth, 2004) and therefore is well characterised.

• Levofloxacin (1500 mg) has shown significant changes on QT/QTc intervals (Strnadova, 2005) (Noel et al, 2004) however, the extent of QT prolongation is poorly defined.

Aims

The aim of this study was to characterise levofloxacin as a potential oral positive control comparator in TQT studies causing a QT prolongation of around 5 msec as required by ICH E14 guidelines.

Methods

Study Design

This was a single-centre, randomised, placebo-controlled, double blind, double dummy, 4x4 crossover study.

ECG profiling was performed over a 24 hour period after each dose of study medication using 10 second 12-lead triplicate recording.

Data Analysis and Statistical Methods

Measurement of the QT interval was performed automatically with subsequent manual on-screen over-reading using electronic callipers (MUSE CV[®] Interval Editor; GE Healthcare).

Under blinded conditions QTcI was determined to be the best correction formula.

Safety Assessments

Adverse events were recorded from the first dose of study medication until follow-up.

Subject Disposition

175 participants were screened - 64 subjects were randomised.

- Subjects were Caucasian (mean age of 29±7 years).
- 53.1% (n=34) were male and 46.9% (n=30) were females.
- Mean BMI value of 24.1±2.3 kg/m².

Results

Effect of Moxifloxacin 400 mg on QTc

Mean QTcI 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 at 3.5 hours post-dose (mean [95%CI]: 13.19 [11.21-15.17] msec) (Table 1) (Figure 1).

QTcI (Statistical analysis of change)		
	Estimate (1)	95% CI (2)
Moxifloxacin 400 mg (N=62)	13.19 (1.00)	[11.21 ; 15.17]
Levofloxacin 1000 mg (N=63)	4.42 (1.00)	[2.44 ; 6.39]
Levofloxacin 1500 mg (N=62)	7.44 (1.00)	[5.47 ; 9.42]
QTcF (Statistical analysis of change)		
	Estimate (1)	95% CI (2)
Moxifloxacin 400 mg (N=62)	12.03 (1.00)	[10.06 ; 14.00]
Levofloxacin 1000 mg (N=63)	4.73 (0.99)	[2.78 ; 6.99]
Levofloxacin 1500 mg (N=62)	7.12 (0.99)	[5.16 ; 9.09]

(1): Estimate (standard error) of the adjusted changes differences.
(2): 95% CI of the adjusted changes differences

Table 1 QTcI and QTcF (msec) change from P-baseline to P-postbaseline for moxifloxacin 400 mg, levofloxacin 1000 mg, levofloxacin 1500 mg and placebo

A similar pattern was seen when heart rate was corrected using QTcF.

- The largest time-matched difference in QTcF occurred at 3.5 hours post-dose (mean [95%]: 12.03 [10.06-14.00] msec) (Figure 1).

Effect of Levofloxacin 1000 mg and 1500 mg on QTc

Mean QTcI was also prolonged in subjects receiving levofloxacin 1000 mg and 1500 mg compared with placebo.

- The largest time-matched difference in QTcI for levofloxacin 1000 mg compared with placebo was observed at 3.5 hours post-dose (mean [95%CI]: 4.42 [2.44-6.39] msec) (Table 1) (Figure 1).
- The largest time-matched difference in QTcI for levofloxacin 1500 mg compared with placebo was observed at 3.5 hours post-dose (mean [95%CI]: 7.44 [5.47-9.42] msec) (Table 1) (Figure 1).

When heart rate was corrected using QTcF, a similar pattern was seen.

- The largest time-matched difference in QTcF was observed at 3.5 hours post-dose (mean [95%]: 4.73 [2.78-6.99] msec for levofloxacin 1000 mg and mean [95%]: 7.12 [5.16-9.09] msec for levofloxacin 1500 mg) (Table 1) (Figure 1).

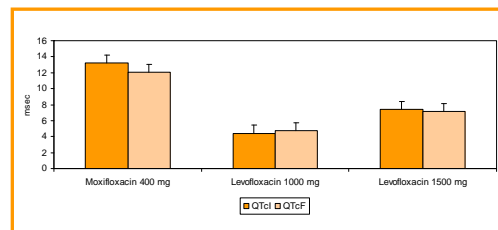


Figure 1 Largest time-matched difference from placebo in QTcI and QTcF

Categorical Analysis

No subject at any time in the study had a QTc greater than 450 msec.

Safety and Tolerability

Overall, both moxifloxacin and levofloxacin were well tolerated by healthy subjects in this study.

The majority of adverse events were considered to be mild (53.1%) with 3.1% being considered moderate. No subject reported a severe adverse event.

No serious or severe adverse events were observed.

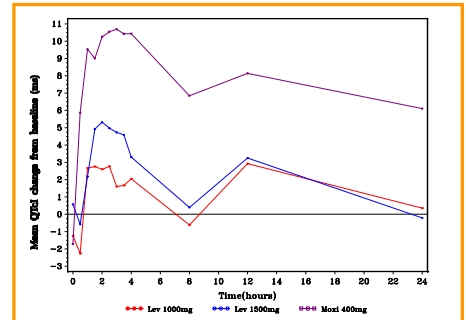


Figure 2 Mean QTcI change from baseline against time for moxifloxacin 400 mg, levofloxacin 1000 mg and levofloxacin 1500 mg

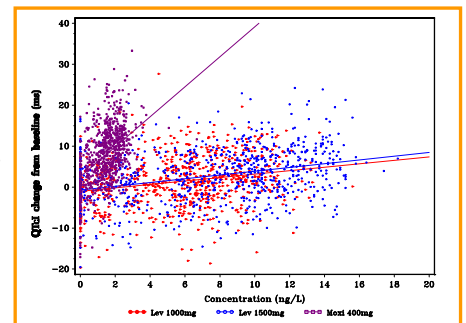


Figure 3 QTcI change from baseline against plasma concentration for moxifloxacin 400 mg, levofloxacin 1000 mg and levofloxacin 1500 mg

Conclusions

- The data demonstrates that both levofloxacin and moxifloxacin can fulfil the criteria for a positive comparator.
- The ICH E14 guidelines recommend a threshold of above 5 msec for a positive QT/QTc study (ICH, 2005).
- 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 a 1500 mg dose of levofloxacin to confirm assay sensitivity resulting in measuring mean QTc changes around 5 msec.

References

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