# Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drugs that inhibit the human cardiac delayed rectifier potassium current may lead to prolongation of the cardiac QT interval and are associated with a fatal, polymorphic, ventricular tachycardia known as torsades de pointes.
- Lamotrigine is indicated in the treatment of epilepsy and the prevention of mood episodes in patients with bipolar disorder.
- Lamotrigine inhibits the human cardiac delayed rectifier potassium current *in vitro*, and it has been hypothesized that QT prolongation may contribute to the risk of sudden unexpected death in epilepsy patients.

## WHAT THIS STUDY ADDS

- This is the first reported thorough QT/QTc study with lamotrigine conducted to International Conference on Harmonization guidelines.
- The mean QTc interval was not prolonged by lamotrigine in healthy subjects, as assessed by the standard heart rate correction methods (Fridericia's and Bazett's).
- The *in vitro* inhibition of the delayed rectifier potassium current does not translate into an effect on QT in man.

## AIM

To characterize the effects of lamotrigine on QT interval in healthy subjects.

## METHODS

Healthy subjects received a single oral dose of moxifloxacin (400 mg) or placebo in crossover design, followed by a dose-escalating regimen of lamotrigine ($n = 76$) over a 77-day period, or matched placebo ($n = 76$). Blood samples were taken for determination of moxifloxacin and lamotrigine concentrations and digital 12-lead ECGs were recorded. The relationships between individual QT values and respective individual moxifloxacin or lamotrigine concentrations were explored using population pharmacokinetic–pharmacodynamic (PK–PD) modelling.

## RESULTS

Moxifloxacin was associated with a maximum mean increase from baseline in QTcF of 14.81 ms [90% confidence interval (CI) 13.50, 16.11] 2.5 h after dosing. Steady-state exposure to lamotrigine (50, 150 or 200 mg b.d.) was not associated with an increase in QTc interval. Small reductions in QTcF (maximum mean difference from placebo −7.48 ms, 90% CI −10.49, −4.46) and small increases in heart rate (maximum mean difference from placebo 5.94 bpm, 90% CI 3.81, 8.06) were observed with lamotrigine 200 mg b.d. *vs.* placebo. No effect of lamotrigine on QRS duration or blood pressure was observed. No outliers with QTcF > 450 ms, or with an increase from baseline of >60 ms were observed in the lamotrigine group. PK–PD modelling indicated statistically significant decreases in individually corrected QT intervals for lamotrigine and statistically significant increases in individually corrected QT intervals for moxifloxacin over the concentration ranges studied.

## CONCLUSIONS

Therapeutic doses of lamotrigine (50–200 mg b.d.) were not associated with QT prolongation in healthy subjects.