Title: Interspecies differences in moxifloxacin-induced QTc-interval prolongation

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Abstract:

Background: Assessment of the propensity of non-antiarrhythmic drugs in prolonging QT/QTc-interval is critical for the progression of compounds into clinical development. Different animal models are used in preclinical assays to assess QTc-interval prolongation liability. However, it’s unclear how the QTc-interval changes in dogs and primates can be translated into accurate risk of QTc-interval prolongation in humans, as proposed by the ICH E-14 guidelines, i.e., >10 msecs.

Objectives: The aim of this investigation is to characterise interspecies differences in QTc-interval prolongation following administration of moxifloxacin to dogs, cynomolgus monkeys and healthy subjects.

Methods: ECG and pharmacokinetic data from experiments in conscious beagle dogs, cynomolgus monkeys and clinical trials in healthy volunteers were evaluated. First, pharmacokinetic models were developed to obtain drug concentrations at the time of each QT-interval measurement. Data analysis was performed using a model-based approach which takes into account the concentration-effect relationship, translating drug effects in terms of the probability of QTc-interval prolongation. NONMEM VII and WinNONLIN 4.1 were used for pharmacokinetic data analysis, whilst PKPD modelling was performed in WinBUGS v1.4.3.

Results: Thanks to model parameterisation, drug-specific and systemic specific parameters could be estimated separately and the overall probability associated with QTc-interval prolongation >10msec compared across species. Measurement noise and feeding procedures are
important sources of variability and as such affect parameter estimates in dogs and monkeys.

**Conclusions**
The magnitude of the QTc-prolonging effect of moxifloxacin at peak concentrations seems to reflect species differences in sensitivity to hERG inhibition. The differences in the slope of the concentration-effect relationship across species suggest that monkeys are slightly more sensitive than dogs to drug effects.

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