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EFFECTS OF MOXIFLOXACIN ON QT IN CONCIOUS TELEMETERED GUINEA PIGS AND ITS TRANSLATION TO HUMANs.

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Introduction: The pre-clinical evaluation of the effects of drugs to induce slowing of ventricular repolarisation and QT interval prolongation is important for the development of new drugs (ICH S7A, S7B Guidelines). However, the translational value of these pre-clinical models to predict human QT prolongation is not widely reported. The principle aim of this study was to develop and validate a suitable conscious guinea pig model for assessing the effects of drugs on QT interval and to determine appropriate rate correction for QT in the conscious state. Guinea pigs (GP) have been found to be a suitable species to evaluate QT interval prolongation, because of their small size, easy handling and similar cardiac ion channel profile to humans. Furthermore the application of telemetry enables the evaluation of drug induced QT effects in conscious unstressed animals avoiding the potential confounding effects of anaesthesia. The effects of the fluoroquinolone antibiotic, moxifloxacin which is widely used as a positive control in human through QT studies was used to validate the model, and enable comparisons between clinically relevant doses and exposures between guinea pigs and man.

Methods: Dunkin Hartley guinea pigs were surgically implanted using different surgical approaches in order to optimize the quality of the lead II ECG signal for chronic measurement. Validation of this guinea pig model was assessed using doses of moxifloxacin, that induced induced QT and QTc prolongation and by comparing the results and achieved plasma levels to those reported for clinical studies of moxafloxacin in the literature. Each animal (n=12) received vehicle, 3; 10; 30 and 90mg/kg moxafloxacin by subcutaneous injection, with a washout period of one week between administrations.

Results: The subcutaneous implantation of the telemetry transmitter in a lateral flank was found to be the most appropriate surgical approach to ensure longevity of the implantation. Placement of the ECG leads with the negative pole in the right forelimb and the positive pole on the left of the xiphoid process of the sternum was the best combination to obtain well-defined T-waves. Several standard QT formulas were used to correct the QT interval for heart rate including: Bazett's, Fridericia and Van de Water formulas. In addition an individualised rate correction QTi, which provided the most adequate rate correction of QT, was also calculated for each animal based on a linear fit of pre-dose values for heart rate and QT values. Moxifloxacin induced dose related increases in QTi which achieved significance (11%), with only a small change in heart rate, following the highest dose (90 mg/kg sc). This level of QTc change is similar to that expected when moxifloxacin is used as positive control in humans. The determination of free plasma levels associated with this level of QT change provides a further understanding of the sensitivity of this model and its human translation.

Conclusion: This study demonstrates that the in vivo assessment of the individual rate corrected QT interval assessment in conscious, unrestrained guinea pigs is a suitable model for assessing QT liability potential in humans.