Usefulness of common marmosets to detect drug-induced QT interval prolongation: moxifloxacin case study

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[Introduction] Moxifloxacin is the most widely used positive reference agent in clinical cardiac repolarization studies, but it has not been characterized in common marmosets which are uniquely suited to studies in early-stage development due to their small size and minimal test article requirements. The purpose of this study was to evaluate the sensitivity of the common marmoset to detect moxifloxacin-associated QT interval prolongation.
[Methods] Eight telemetered common marmosets were monitored for 24 h following oral administration of moxifloxacin by gavage at 0, 10, 30, and 100 mg/kg using a Latin square design. Concurrently, a pharmacokinetic evaluation in 8 non-telemetered animals was conducted. A rate-corrected QT (QTc) interval was derived using an individual probabilistic QT rate-correction. QTc (placebo-adjusted QTc change from the individual baseline) was calculated and the relationship between pharmacokinetics (PK) and pharmacodynamics (PD) was analyzed.
[Results] A slight, but not significant, increase in QTc was detected with 10 mg/kg of moxifloxacin. Moxifloxacin at 30 and 100 mg/kg elicited dose-dependent increases in QTc correlated with the plasma concentration of moxifloxacin. From the PK/PD relationship, the plasma concentration which would attain QTc of 5 to 10 ms was estimated to be 1.67-3.73 microg/mL. The results were consistent with typical clinical trial results (QTc of 6.6-14.8 ms at 2.5-3.5 microg/mL).
[Conclusion] The present study demonstrates that the common marmoset is highly sensitive to moxifloxacin-associated changes in cardiac repolarization, assessed as QTc. As such, this species is suitable for precise and reliable detection of small, but significant, drug-associated increases in QTc interval. Thus, the common marmoset should be regarded as a validated animal model for the detection of QT risk in early-stage drug development.

日本語表題

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