Abstract

QTc is an established biomarker for drug-induced Torsade de Pointes (TdP) but with concerns for a false positive signal. Clinically, TpTe and TcPc have emerged as ECG sub-intervals to differentiate predominant HERG vs. mixed ion channel blocking drugs that prolong QTc. Drugs that prolong QTc with increased TpTeC, but without TpTeC effects, are likely mixed ion-channel blocking with low TdP risk. Drug effects on QTc, TpTeC and TcPc were characterized with cynomolgus monkeys using telemetry in a lead II configuration. Drugs and vehicle were administered orally to group sizes of 4 to 8 animals, in 4 laboratories. In monkeys, dofetilide (0.03-0.3 mg/kg, PO) was associated with exposure dependent QTc and TpTeC increases but no significant TpTeC effect. Quinidine (200-500 mg/kg, PO) increased QTc and TpTeC but did not change TpTeC. Mexiletine (15-50 mg/kg, PO) and verapamil (50 mg/kg, PO) did not induce any significant effect on QTc, TpTeC or TcPc. Clinically, predominant HERG blockers (dofetilide and quinidine) prolong QTc, TpTeC and TcPc and are associated with an increased risk for TdP. Results from the current study demonstrate that ECG changes after dofetilide and quinidine administration to telemetered monkeys differ from the clinical response, lacking the expected effects on TpTeC. Potential explanations for the lack of translation include physiopharmacology species differences or ECG recording and analysis methodology variations. Mixed ion channel blockers verapamil and mexiletine administered to monkeys showed no significant QTc, TpTeC or TcPc prolongation as expected based on the similar clinical response for these agents.

Methods

- Overall, our results in the cynomolgus monkey confirm the clinical findings for verapamil (no effects on JTpc) and Mexiletine (shortened JTpc interval), however the expected prolongation of the TpTeC interval with dofetilide and quinidine could not be detected.
- The reason for the lack of correlation of TpTeC interval changes between human and monkey is unclear, and may be multifactorial and due to:
  - Different collection (1 lead in monkey vs 12 leads in human) and analysis methods (a vectorgram was created from the human 12 lead data, eliminating biphasic T-wave marking challenges encountered with a single untransformed lead).
  - Differences in ventricular wall thickness between monkey and human (human is >2x thicker). There is a larger regularization contribution of the mid-myocardium in humans versus monkey and HERG blockers have the largest effect on mid-myocardium in monkeys.
  - Potential differences in ion channel contributions and action potential morphologies across species.

Discussion

Drug-induced QTc/TdP prolongation can result in life-threatening arrhythmias and is monitored both in nonclinical and clinical studies to ensure patient safety. While the QTc interval is generally a reliable measure of proarrhythmic risk challenges remain. Nonclinical QTc/TdP prolongation does not always result in a risk in the clinic. Scientists are exploring a new marker, the J to Tpeak interval (JTp), to further differentiate drugs with higher proarrhythmic risk. The HESI Cardiac Safety Committee (IT Peak Subteam) embarked on a retrospective study to explore the usefulness of the JTp marker in nonclinical species (Boulay et al., 2019) This latest work aimed to generate additional data to further evaluate the effects of well-characterized drugs on the QTc, JTpc and TpTeC to TdP (TpTeC) ECG intervals in non-human primates and to compare the results with the ECG evaluation reported with the same drugs in humans. Dofetilide, mexiletine, quinidine and verapamil were selected based on their known ion channel inhibition profiles.

References


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