Heart Rate Corrected JTp and TpTe as Proarrhythmia Biomarkers in Safety Pharmacology Non-Human Primate Studies: Outcome from a HESI Consortium Prospective Study

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Abstract

QTc is an established biomarker for drug-induced Torsade de Pointes (TdP) but with concerns for a false positive signal. Clinically, JTpc and TpTec 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 TpTe, but without JTpc effects, are likely mixed ion channel blockers with low TdP risk. Drug effects on QTc, JTpc and TpTec 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 JTpc increases but no significant TpTec effect. Quinidine (2 to 50 mg/kg, PO) increased QTc and JTpc but did not change TpTec. Mexiletine (1-15 mg/kg, PO) and verapamil (50 mg/kg, PO) did not induce any significant effect on QTc, JTpc or TpTec. Clinically, predominant hERG blockers (dofetilide and quinidine) prolong QTc, JTpc and TpTec 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 physio-pharmacology species differences or ECG recording and analysis methodology variations. Mixed ion channel blockers verapamil and mexiletine administered to monkeys showed no significant QTc, JTpc or TpTec prolongation as expected based on the similar clinical response for these agents.

Introduction

Drug-induced QT/QTc 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 QT/QTc 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 JT 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, JTp and Tpeak to Tend (TpTe) 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.

Methods

- Prospective studies conducted in accordance with local animal laboratory and welfare guidelines and reviewed and approved by the Institutional Animal Care and Use Committee
- Four (verapamil and quinidine) to eight (mexiletine and dofetilide) male NHPs implanted with ITS/DSI telemetry units or JET with Lead II ECG; PO dosing in an ascending or cross-over dosing design
- Pharmacokinetic (PK) samples during CV collection and/or separate PK phase
- Data acquisition predose + ~24 hours post dose via Ponemah; ECG analysis by single site using Ponemah V6.51; individual animal template/library
- QT subintervals corrected for heart rate using animal specific correction factors from 1-minute data obtained during the vehicle dose or predose period and the Spence formula (Spence, et al., 1998) using a reference heart rate of 120 bpm.
- Data binned into 1hr intervals for statistical analysis using ANOVA (delta from vehicle). Mean values, 95% confidence interval (CI), Root Mean Square Error (RMSE), Least Significant Difference (LSD), and Median value were calculated

Discussion

- 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 un-transformed lead).[1]
  - Differences in ventricular wall thickness between monkey and human (human is >2x thicker). There is a larger repolarization contribution of the mid-myocardium in humans versus monkey and hERG blockers have the largest effect on mid-myocardium in monkeys.[2,3]
  - Potential differences in ion channel contributions and action potential morphologies across species.
- Potential alternatives to JTpeak/TpTe for characterization of the arrhythmic potential of mixed ion channel blockers include CiPA (patch clamp and stem cell) and in vivo evaluation of the electromechanical window.

Results

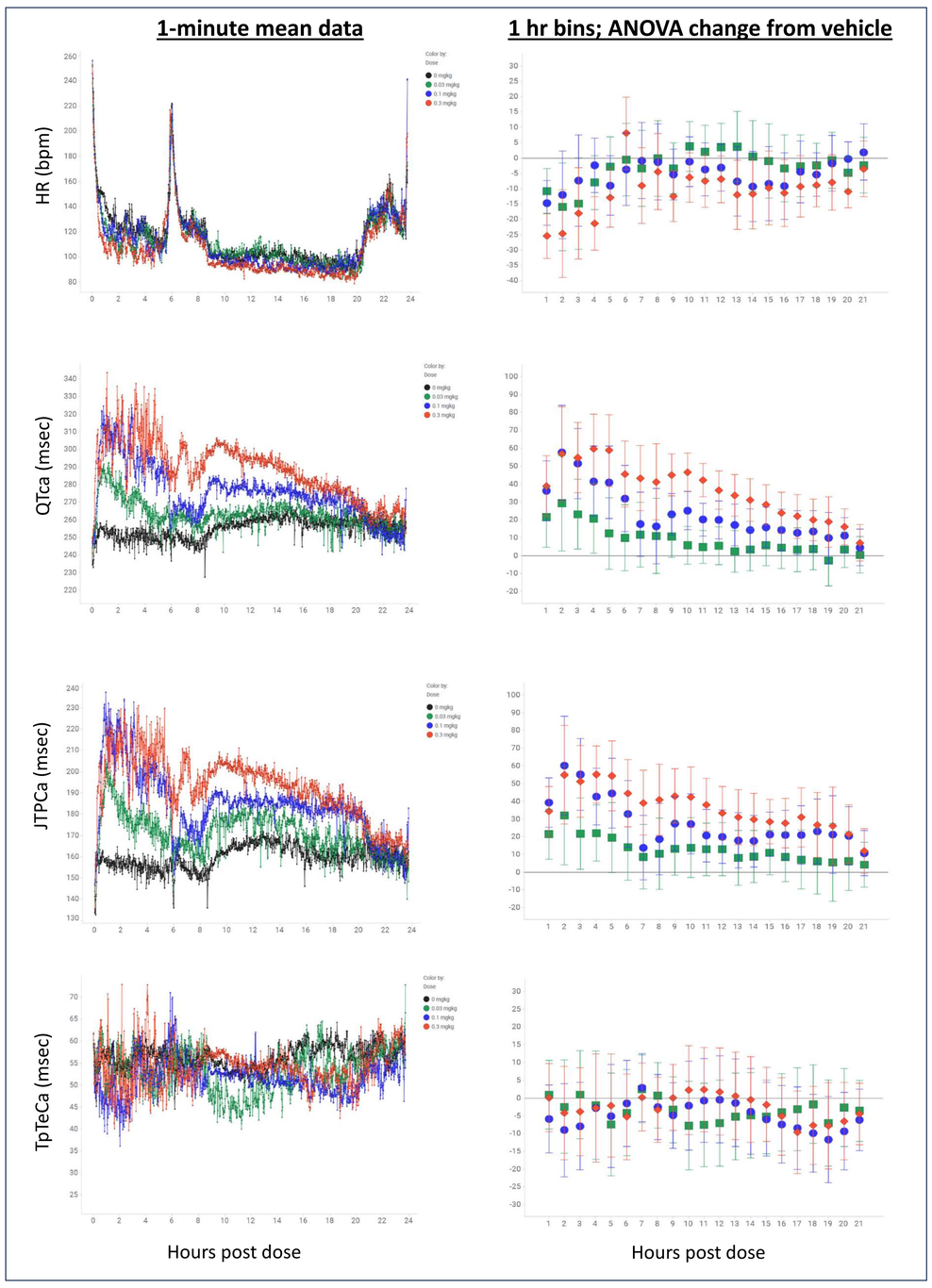

Figure 1 - Time course of dofetilide effects on ECG endpoints is shown as a function of time (left; 1-minute means). Statistical output (right; 1-hour intervals) performed by ANOVA, mean values and 95% confidence intervals are shown.

Test Article MW (NHP fu)	Ion Channel Block (IC_{50} µM) hERG	Cav1.2	Nav1.5	Doses mg/kg	PK Phase C_{max} total ng/ml	PK Phase C_{max} free µM	Clinical C_{max} free µM	ECG Effects ↑QTc NHP	↑QTc Human	↑JTpc NHP	↑JTpc Human	↑TpTec NHP	↑TpTec Human	Torsades Risk Category
Mexiletine	$Nav1.5_{late}$			1	340	0.7*	3.0	No	No (↓QTc)	No	No (↓JTpc)	No	No	Low risk
215.7 (0.45)			9[1]	5	2300	4.8*		No		No		No		
				15	7000	14.6		No (↓QTc)		No (↓JTpc)		No		
Verapamil	Cav1.2~hERG			50	117	0.029	0.045	No	No	No	No	No	No	Low risk
491.1 (0.12)	0.7	0.1												
Quinidine	$hERG>Cav1.2>Nav1.5_{peak}$			2	117	0.029	0.843	No	Yes	No	Yes	No	Yes	High risk
324.4 (0.08)	0.03	6.4	14.6	10	248	0.061		No		No		No		
				50	1864	0.46		Yes		Yes		No		
Dofetilide	hERG			0.03	2.6	0.002	0.002	Yes	Yes	Yes	Yes	No	Yes	High risk
441.6 (0.29)	0.002			0.1	8.4	0.006		Yes		Yes		No		
				0.3	26.2	0.017		Yes		Yes		No		

Table 1 - Summary of ion channel inhibition, results in NHP and comparison of ECG effects versus human for each compound. * = estimated Cmax

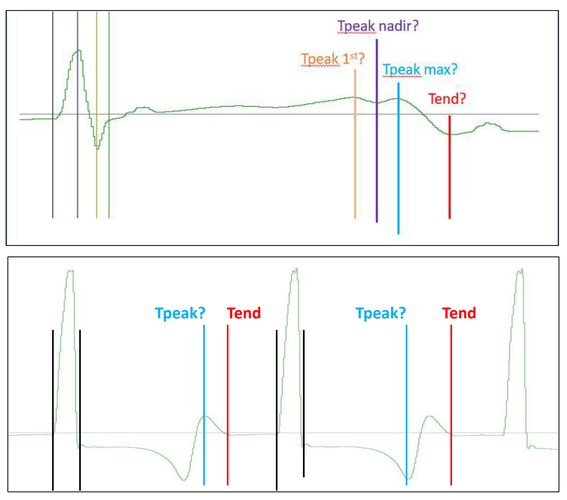

Figure 2 - Representative ECG waveforms from NHP illustrating notched (upper) and biphasic (lower) T-wave morphology and challenges in consistent markings fiducial marks. For ECGs with notched T-waves the 'largest' peak was marked as Tpeak; for biphasic T-waves the 'positive' peak was marked as Tpeak.

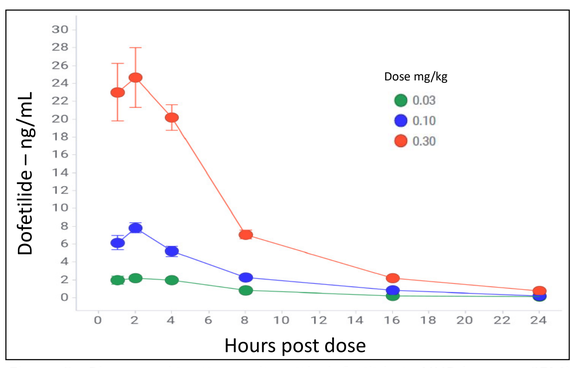

Figure 3 - Pharmacokinetic results with dofetilide in NHP (mean ± SEM)

Median Value	QTc (msec) LSD	QTc (msec) RMSE	JTpc (msec) LSD	JTpc (msec) RMSE	TpTec (msec) LSD	TpTec (msec) RMSE
Dofetilide	12	11	17	16	12	11
Quinidine	22	13	19	11	6	3
Verapamil	12	4	9	4	9	4
Mexiletine	14	11	12	9	15	12

Table 2 - LSD and RMSE values for QTc, JTpc and TpTec across studies.

	Quinidine JET; n=4		Verapamil Internal; n=4		Mexiletine Internal; n=6		Dofetilide Internal; n=8		NHP Average		Clinical[4]	
	msec	% of QTc	msec	% of QTc	msec	% of QTc	msec	% of QTc	msec	% of QTc	msec	% of QTc
QTc	247		281		280		255		266		396	
JTpc	174	70%	173	62%	161	58%	159	62%	167	63%	226	57%
TpTec	30	12%	67	24%	80	29%	56	22%	58	22%	73	18%

Table 3 - Comparison of baseline/vehicle ECG intervals, and % duration of JTpc and TpTec relative to QTc, for NHP and human.

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References

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