Discrimination of the Effects of Three Cardiac Ion Channel Blockers using ECG Biomarkers and Arrhythmia Incidence in St. Kitts Green Monkeys

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Abstract #0051

Background and Introduction

FDA, HESI and other members of the CiPA working group have demonstrated the potential for using J to T-peak (JTp) interval to differentiate the effect of multichannel vs. pure hERG channel block in clinical and preclinical studies[1,2,3].

Clinical studies typically include 12-lead ECG monitoring with JTp assessed from a vector magnitude[4] (VM) lead while preclinical assessment is often based on a single ECG vector such as Lead II (L2). In this study we evaluated the feasibility of using Stellar multichannel ECG, blood pressure, temperature, and activity telemetry implants (PBBBTA-XL, TSE Systems) in conjunction with the Rhythm Express™ (RE) software (VivaQuant) to assess changes in QT and QT subintervals in NHP for three cardiac ion channel blockers using both VM and L2.

Methods

Study Design

St. Kitts green monkeys (n=4) were instrumented with subcutaneous electrodes to record limb leads I, II, and III. Each subject was orally administered vehicle, Dofetilide (0.5mg/kg, hERG block), Verapamil (30mg/kg, Ca block), and Mexiletine (15mg/kg, Na block) in a balanced crossover design.

Data Analysis

Telemetry data were collected with the Acknowledge software (Biopac) and ECGs were analyzed with RE to remove noise, assess arrhythmias, and derive interval measurements from L2 and VM lead calculated as the square root of the sum of the squares of each measured lead. Results were reviewed/edited for accuracy and aggregated into 15-min bins relative to individual dose times, with single delta calculated relative to pre-dose baseline. QTc used Fridericia's correction and JTpc used the FDA correction JTpc=JTp/RR^0.58. Data aggregation, group stats, and graphics were generated in Matlab (Mathworks).

Results

ECG signals were of good quality for interval and arrhythmia assessment. Dofetilide produced QTcF and JTpc prolongation approaching 110ms and 90ms respectively with a peak at ~9 hours post-dose. Dofetilide produced a high degree of arrhythmias (junctional escape and others) between 1 and 7 hours post-dose in 2 of 4 subjects, resulting in a high degree of interval variability in both VM and L2. Verapamil produced a ~20ms shortening of QTc and JTpc in the first two hours post-dose followed by QTc and JTpc prolongation of ~20-30ms with a peak at 10-15 hours post-dose. Verapamil produced arrhythmias consistent with varying degrees of AV dissociation. Mexiletine shortened QTcF and JTpc by ~8ms from 2-6 hours post-dose followed by peak prolongation of QTc and JTpc of 15-20ms at 17hrs post-dose and produced no notable arrhythmias.

Results

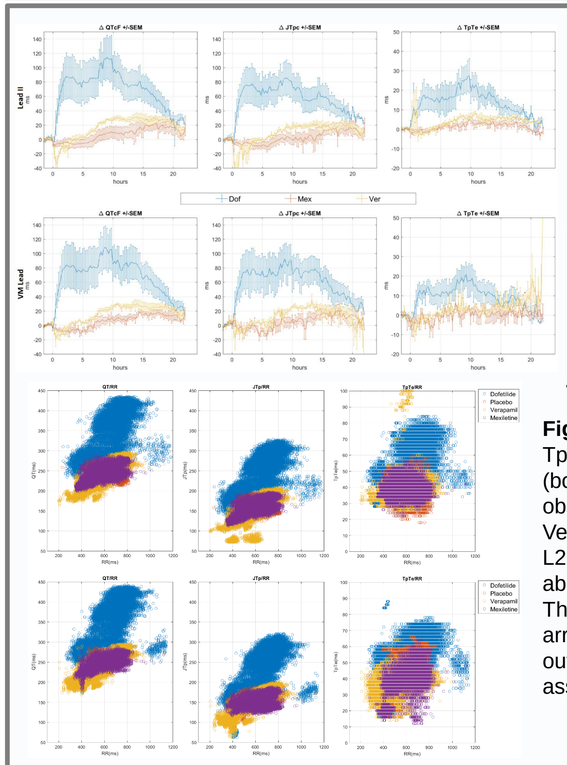


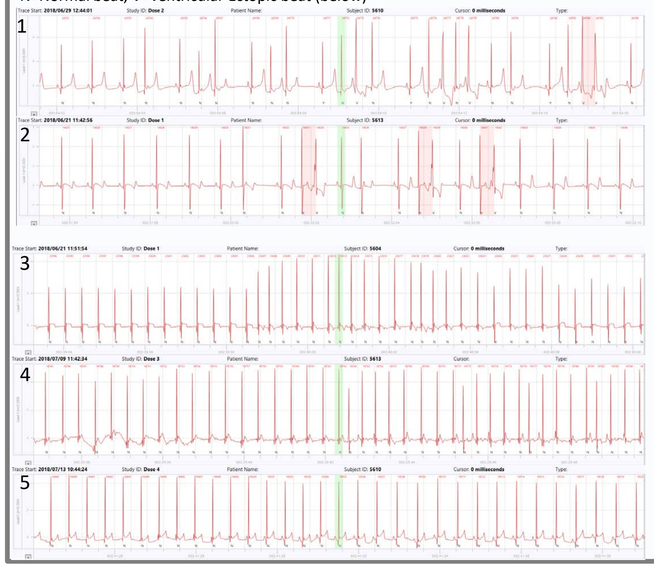
Figure 1 – QTcF, JTpc, and TpTe group delta +/- SEM from pre-dose baseline for Dofetilide, Verapamil, and Mexiletine (L2 top and VM bottom). Similar trends and inter-subject variability are observed for QTcF and JTpc intervals from L2 vs VM.

	Baseline (ms)			Peak (ms)			Peak % Change			Time of Peak		
Lead II	**QTcF**	**JTpc**	**TpTe**	**QTcF**	**JTpc**	**TpTe**	**QTcF**	**JTpc**	**TpTe**	**QTcF**	**JTpc**	**TpTe**
Placebo	290.6	223.4	38.3	313.5	250.2	45.4	7.9%	12.0%	18.5%	17.8	19.8	10.3
Dofetilide	294.0	225.7	38.0	408.3	310.9	65.3	38.9%	37.7%	71.8%	9.0	9.0	9.5
Verapamil	289.9	219.6	38.7	320.9	241.9	47.2	10.7%	10.2%	22.0%	10.8	13.5	10.8
Mexiletine	296.4	222.5	39.8	317.8	239.1	44.0	7.2%	7.5%	10.6%	16.8	16.8	17.5
VM Lead												
Placebo	294.9	213.8	37.9	316.7	252.1	49.3	7.4%	17.9%	30.1%	19.8	19.8	11.8
Dofetilide	300.4	213.2	38.5	408.9	305.7	59.6	36.1%	43.4%	54.8%	8.8	8.8	8.5
Verapamil	293.2	201.3	40.4	323.2	236.2	58.2	10.2%	17.3%	44.1%	10.8	13.3	20.3
Mexiletine	296.9	205.3	39.7	315.1	224.2	46.7	6.1%	9.2%	17.6%	17.5	17.3	9.8

Table 1 – Baseline and Peak Changes

Figure 2 – QT/RR, JTp/RR, and TpTe/RR plots for L2 (top) and VM (bottom). Similar characteristics are observed in VM and L2, with some Verapamil outliers for JTp and TpTe in L2, also observed on the trend plots above, immediately following dose. These outliers are synchronous with arrhythmias noted below. Dofetilide outliers (at longer RR intervals) are also associated with areas of arrhythmias.

N=Normal beat, V=Ventricular Ectopic beat (below)



Dofetilide Observations (panels 1 and 2):

- 100ms QTcF and 80ms JTpc prolongation
- Junctional escape w/ retrograde activation
- Aberrant SVE conduction
- Parasystole

Verapamil Observations (panels 3-5):

- Delayed QTcF and JTpc prolongation
- AV Block, Junc Rhythm
- Sinus arrest w/ nodal escape
- Accelerated AV node conduction, automatic junctional tachy
- No PR prolongation

Mexiletine Observations:

- No QTcF and JTpc prolongation
- No arrhythmias observed

Discussion

The total time for beat-to-beat analysis and review required less than 15 minutes per 24hr recording with RE. We observed expected drug-related changes in QTcF and JTpc intervals in L2 and VM. We did not observe shortening of JTpc relative to QTcF for Verapamil and Mexiletine, but we did see over 2x the percentage increase in TpTe vs JTpc for Verapamil and nearly 2x percentage increase with Mexiletine.

High doses of Dofetilide are associated with arrhythmias typical of hERG channel blockade, consistent with our arrhythmia observations. High doses of Verapamil are known to be associated with PR prolongation and AV block. Our high doses of Verapamil produced varying degrees of AV block and related arrhythmias with no obvious PR prolongation (PR interval not shown).

Brockway et. al. previously found that the VM lead provided more consistent results in canine model[5]. In this study of an NHP model, VM and L2 provide similar results. The superiority of VM vs. L2 in the prior study on a canine model may have been due to changes in electrical axis during respiration and changes in posture. Superiority was especially prominent in the canine model when T-waves were biphasic. VM has the effect of mitigating changes in QRS and T-wave morphology observed due to the change in electrical axis, effectively computing a global lead that provides a composite of all dipolar electrical activity of the heart. We hypothesize that if the test article induced biphasic T-waves in NHP, VM may prove superior in that model as well.

The RE software facilitated effective ECG baseline correction, which is critical to derivation of a VM lead and accurate measurements of JTp and TpTe intervals. Use of multiple ECG leads facilitates improved detection accuracy for Ventricular Ectopic (VE) beats where differences between Normal and VE beats are subtle as seen with Dofetilide. Ongoing studies with Dofetilide+Verapamil and Dofetilide+Mexiletine will provide further insights into the ability to differentiate multi-channel block.

Conclusions

We efficiently generated a high-quality VM lead and reliable interval measurements from both L2 and VM in St. Kitts green monkeys, including observation of expected changes in QTcF and JTpc and arrhythmias typical of each test article. This novel research model used in conjunction with the Rhythm Express software capabilities opens new possibilities for detailed evaluation of cardiovascular safety and efficacy.

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Conflict of Interest Statement

Brockway is an employee and shareholder of VivaQuant. Hamlin is a consultant to VivaQuant and employee of QTest Labs. Liddie, Moddrelle, and Morton are employees of RxGen. Delahanty is Technical Director of Stellate Telemetry.

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