The Use of Alternate QRS Measurement Methods to Improve Detection of Propafenone-Induced QRS Prolongation

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ABSTRACT

The increased use of intracardiac or epicardial electrodes to obtain ECG recordings in various in vivo Safety Pharmacology cardiovascular models has led to QRS complexes that lack a well-defined J point. This has resulted in decreased precision in measurement of the end of the S wave and QRS interval duration. The purpose of this study was to evaluate a variety of alternate methods of QRS interval measurement using propafenone, a compound that increases QRS duration. Beagle dogs were dosed with propafenone (30 mg/kg, oral) followed by simultaneous ECG collection from epicardial telemetry leads and multiple surface leads. ECG data were analyzed with automated analysis software and by hand using digital calipers from a variety of lead vectors and from alternative end-of-S marking points. For each measurement, an average of 10 waves were used. Propafenone produced notable prolongation of the QRS interval. Our ability to measure QRS changes was greatest using V10 and V5 from the surface leads, whereas from the epicardial leads, precision of measurement of QRS interval changes was greatest when the end of the S wave was marked at the greatest negative deflection (trough). This trough measurement was shown to reduce the variability between wave complexes and thus increases sensitivity. In summary, accurate measurement of the QRS interval at a level needed to perform Safety studies can be obtained by using alternative leads or marker placement when a well defined J point is not present in the standard lead II ECG waveform.

INTRODUCTION

The precise measurement of the QRS interval can be difficult even by trained individuals [1,2,3]. This is driven primarily by the ambiguous S end which can occur in some telemetry lead placements. Analysis is further complicated by the fact that some compounds induce a morphological change in the QRS waveform. An alternate measure for the S end is the latest downward deflection point of the S wave, or trough. This point is more distinct and can easily be measured by shape recognition software. The use of this point has not been characterized previously. Although high doses of sodium channel blockers can produce an easily measurable QRS increase, a sensitive method to measure the QRS interval is needed to detect small changes that are more likely at lower doses used in Safety Pharmacology studies.

METHODS

Four beagle dogs that were previously implanted with DSI telemetry transmitters (model D70 PCPT) were used in this study. The ECG leads from the transmitters were placed epicardially in a lead II configuration.

Dogs were weighed and dosed orally with 30 mg/kg Propafenone in 0.5% methylcellulose/0.1% polysorbate 80 (1 mL/kg). Approximately 5 mins of ECG data were collected from each dog predose, 90, and 180 minutes postdose. External ECG was collected using a Ponemah acquisition system (ver 3.4) from leads I, II, aVL, aVR, aVF, V5, V10, and CV6LL simultaneously with the telemetry acquired data. External ECG was also collected using the Ponemah Jacketed External Telemetry system (JET). The internal telemetry and external lead ECG were collected at the times described while the JET telemetry data was collected continuously predose up to 180 minutes postdose.

Ten time matched ECG waves from each lead and the epicardial signal were then analyzed to determine the QRS interval using a variety of measurement methods. Ponemah derived data was used in addition to hand analysis (digital calipers) as well as a shape recognition software (EMKA). Lastly, waveform overlays were used to evaluate the presence of QRS conformational changes that were difficult to quantify from the interval measures. Historical Flecainide data (3 mg/kg), acquired in this lab, were used for overlay comparison purposes. Statistical analysis was performed to determine sensitivity of detecting a propafenone induced QRS increase based on the lead selected, automated analysis compared to hand measurement, and using a traditional end of S marking compared to an alternative placement (s trough). The sensitivity of each lead or marking method was then ranked based on p values. A power analysis was performed on the trough method to determine a lower limit of detection compared to traditional marking methods.

RESULTS

Figure 1: QRS confirmation from a wave with a well defined S end or J point (wave 1) and a wave with an undistinguishable S end (wave 2). Small QRS interval increases can be detected by using the trough as the end of S measure.

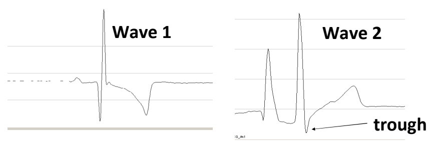


Figure 2: Multilead QRS variations. ECG waveforms from eight surface leads showing the variation in S end confirmation.

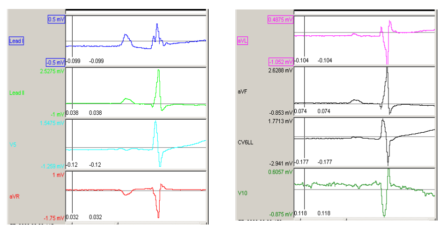


Figure 3: Overlay of waves from two animals dosed with Propafenone compared to two animals dosed with Flecainide, taken predose (blue) and postdose (red). These overlays demonstrate that morphological changes in the QRS complex do not always produce a clear increase in QRS interval.

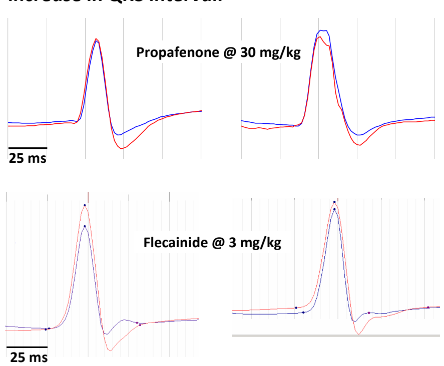


Table 1: P value rank from various external leads (hand analysis of 10 waves). Although lead aVF shows detection sensitivity, this lead is not commonly used in telemetry.

lead	Difference (ms)	Time	Adjp
aVF	3.5750	180	0.0427
V10	3.5250	90	0.0632
II	4.0250	180	0.1337
V5	4.0750	90	0.1849
aVF	2.3250	90	0.1890
aVL	3.3023	180	0.2219
aVR	3.9250	180	0.2282
II	3.2750	90	0.2334
I	2.8750	90	0.2912
aVR	3.2750	90	0.3275
aVL	2.6023	90	0.3479
V10	1.7250	180	0.3764
CV6LL	1.9500	180	0.4005
V5	2.3750	180	0.4882
CV6LL	1.2000	90	0.6736
I	0.9250	180	0.8461

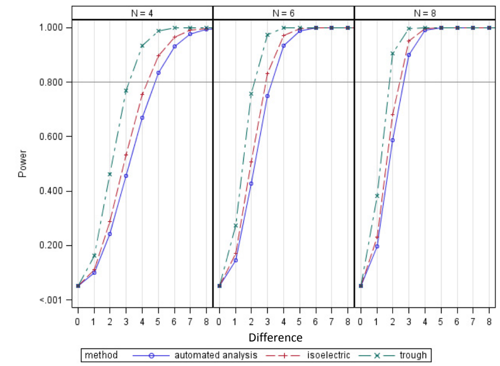
Table 2: P value rank from various external leads (automated analysis of 10 waves). Lead V10 and V5 show QRS interval sensitivity.

lead	Difference (ms)	Time	Adjp
V10	5.7750	90	0.0068
V5	3.2000	90	0.0283
aVL	7.8000	90	0.0610
aVL	7.3000	180	0.0786
aVR	4.5000	90	0.1318
V5	1.9000	180	0.1620
CV6LL	4.7878	90	0.1701
aVF	2.4000	90	0.2037
CV6LL	3.8500	180	0.2197
aVR	2.4000	180	0.4647
II	1.6000	90	0.6045
II	1.5000	180	0.6384
aVF	1.1500	180	0.6385
V10	0.5750	180	0.7815

Table 3: P value rank from various S mark locations. Use of the trough mark provides enhanced sensitivity.

measure_method	Difference (ms)	P value
trough	3.35	0.0199
isoelectric	3.25	0.0476
Automated analysis	2.40	0.1208

Figure 4: Power analysis between various marking positions. Marking the S end at the trough has the highest power of detection at ~ 3 msec with n=4.



DISCUSSION

The use of intracardiac or epicardial leads to acquire ECG signals may increase the prevalence of QRS complexes with less distinct J points, however these waves can have a sharp negative deflection in the S wave (trough). Using this landmark as an alternative measurement point has increased our ability to detect compounds that increase the QRS interval. For traditional end of S placement, leads V10 and V5 have more distinct J points that are more amenable to current automated analysis software. With the increasing usage of pattern recognition software, the trough placement or leads with definitive S ends offer precision advantages that should be considered. A power to detect < 3 msec QRS increase is possible with the trough marking. Using waveform overlay methods, it can be seen that Propafenone induces small conformational changes that are difficult to measure using standard QRS interval measurement techniques.

CONCLUSIONS

- Propafenone @ 30 mg/kg induces statistically significant QRS interval increases.
- Using external leads, lead V10 and V5 have the greatest power to detect a QRS interval increase.
- An alternative measurement, the trough of the S wave, is more sensitive in detecting QRS interval increases than traditional S end measures.
- Compound related changes in QRS morphology may be present in the absence of definitive QRS interval measurement increases. Further work to produce a better method for QRS characterization is warranted.

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