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Correction of the QRS duration for heart rate

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ABSTRACT

Objective: To determine the clinical value of correcting the QRS duration for heart rate.
Background: We recently observed [1] that the QRS duration shortens during spontaneous increases in heart rate. In the current study, we analyzed ECG and pharmacokinetic data of 21 subjects who received quinidine in a recent study [2]. They experienced the expected post-quinidine increase in heart rate, allowing us to determine if quinidine's well-known QRS prolongation might be attenuated due to the concomitant rate increase.
Methods: In a crossover-designed study, after baseline ECG recording, the subjects received quinidine 400 mg orally or placebo, and ECGs and quinidine plasma concentrations were then obtained at 15 prespecified timepoints over 24 h. The previously determined QRS-RR regression slope (0.0125) [1] was used to rate-correct QRS. Change in QRS from baseline (dQRS) and rate-corrected change in QRS from baseline (dQRSc) over time were plotted with the mean quinidine concentration and the correlation of plasma concentration with dQRS and dQRSc was assessed by pairwise correlation and linear regression.
Results: There was a statistically significantly greater increase in heart rate at all timepoints combined in the quinidine arm compared with the placebo arm (9.9 ± 6.80 vs. 5.2 ± 7.42, respectively, $p < 0.0001$). dQRSc was significantly greater at all timepoints combined compared with dQRS (1.99 ± 4.824 vs -0.68 ± 4.640 msec, respectively, $p < 0.0001$). dQRS correlated poorly with quinidine plasma concentration ($p = 0.127$), with no clear change in QRS observed. On the other hand, dQRSc correlated well with quinidine concentration ($p = 0.010$), with a clear rise and fall in dQRSc that mirrored the rise and fall of quinidine concentration.
Conclusion: Rate correction of the QRS duration improves detection of QRS prolongation in the presence of heart rate change.
Condensed abstract: Using the mean QRS – RR slope determined previously in normal volunteers [1], we corrected the QRS duration for its known dependency on heart rate in 21 subjects who received quinidine and experienced the expected post-quinidine increase in heart rate in a recent clinical trial [2]. We found that uncorrected QRS did not correlate with quinidine concentration ($p = 0.127$), while rate-corrected QRS correlated well ($p = 0.010$) and mirrored the rise and fall of quinidine concentration. Rate correction of the QRS duration improves detection of QRS prolongation in the presence of heart rate change.

Introduction

The purpose of this study was to determine if correction of the QRS duration for heart rate (HR) is clinically useful. We recently documented a consistent relationship between spontaneously varying HR, and the electrocardiographic QRS interval duration within individual subjects [1]: Decreasing HR was associated with increasing QRS duration on 24-hour Holter monitor recordings. A similar relationship between the QT and RR intervals has been noted within individuals [3] and within populations [4], and correction of the QT interval for HR is generally considered necessary to determine change in repolarization time if HR is different at the compared timepoints. In this report, we examine change in QRS duration in

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subjects receiving quinidine, which both prolongs QRS duration and increases HR [5–8]. The correlations of uncorrected change in QRS (dQRS) and rate-corrected change in QRS (dQRSc) to quinidine plasma concentration were compared to determine if the correlation was improved by HR correction.

Materials and methods

The definitions of acronyms used in this report are listed in Table 1.

Subjects

Standard 10-second, 12-lead electrocardiograms were recorded in 22 normal volunteers participating in a previously reported FDA-sponsored trial [2] designed to evaluate ECG markers of cardiac ion channel effects of QT-prolonging drugs. The analyses in this population were designed to explore the potential importance of correcting QRS duration for heart rate. All 22 subjects received placebo and 21 received quinidine in a crossover design.

Electrocardiography

Triplicate 10-second ECGs with stable heart rates and maximum signal quality were extracted from continuous ECG recordings using Antares software (AMPS, LLC, New York, NY) [9] immediately prior to drug administration and at 15 time-points after dosing while subjects were resting in a supine position for 10 min. The ECGs were interpreted by cardiologists, who were blinded to subject identity and treatment status, using a Mortara EScribe workstation (Mortara Instrument, Milwaukee, WI). The readers were presented with algorithmically annotated median beats from lead II (provided by the Mortara Veritas algorithm) and they adjusted the interval annotations as needed. The same ECG reader evaluated all ECGs from the same subject and determined QRS onset and offset using lead II. Thus, any potential bias in measurements between readers was nullified, and consistent use of lead II removed any systematic bias that might have been associated with use of different leads.

Quinidine administration and plasma sampling

Quinidine was administered as a single 400 mg oral dose of quinidine sulfate. Plasma samples were drawn at hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 14 and 24 post-dose for determination of quinidine concentration. The latter was performed by Frontage Laboratories (Exton, PA, USA) using a validated liquid chromatography method with tandem mass spectroscopy.

Table 1
Acronyms used in this article.

Acronym	Definition
R	Pearson correlation coefficient
ECG	electrocardiogram
HR	heart rate
dHR	change from baseline in HR
RR	the RR interval or inter-beat cycle length
QRS	the duration of the QRS complex
dQRS	change from baseline in QRS
QRSc	QRS corrected for HR
dQRSc	change from baseline in QRSc
QT	the QT interval

Statistical methods

Descriptive statistics and linear regression analyses were carried out using JMP 13.0.0 (SAS Institute, Cary, NC, USA). Each subject had 48 ECG recordings in total (triplicate recordings before dosing and at 15 timepoints after dosing) in the placebo (N = 22) and quinidine (N = 21) arms. Change from baseline of RR, QRS and QT was determined by subtracting the mean values of baseline triplicates from the on-treatment values at each timepoint. At each timepoint, blood for plasma concentration determination was drawn immediately after the ECG triplicate was recorded.

Change in heart rate over time was compared for the placebo and quinidine treatments by calculation of the group mean and standard deviation and standard error at each timepoint.

This previously determined QRS-RR regression slope (0.0125) [1] was used to correct QRS for HR using the formula QRSc = QRS + 0.0125 x (1000 – RR).

The strength of correlation of dQRS and dQRSc with plasma concentrations at the 15 post-dose timepoints in this study was assessed with Pearson's correlation coefficient.

Group mean values were tested for significant differences using one-way analysis of variance.

Results

Heart rate

Change in heart rate (dHR) at each timepoint in the placebo and quinidine treatment arms is shown in Fig. 1 and Table 2. As expected, there was a clear separation between the two groups. The mean dHR during quinidine treatment was greater than that of placebo at all time points. The maximum separation was 9.5 bpm at 1.5 h, and the separation was at least 7 bpm at post-dose hours 1, 1.5 and 2, the latter of which was the population Tmax for quinidine. dHR then diminished steadily in both groups. The rise and fall of HR in the placebo group was the result of expected diurnal variation; the quinidine effect was added to the diurnal change in the quinidine arm.

Comparison of QRS and rate-corrected QRS

Quinidine resulted in a small, early, increase in baseline-subtracted, uncorrected QRS duration (dQRS), followed by a decrease after hour 2 to predominantly negative values, despite substantial plasma concentration of quinidine (upper panel, Fig. 2 and Table 3). Baseline-subtracted,

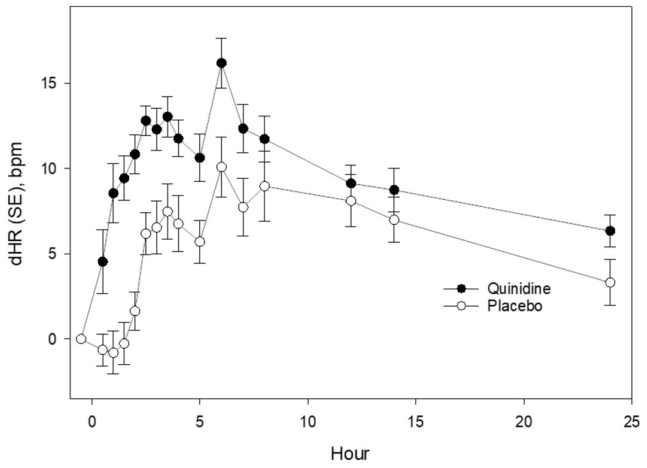

Fig. 1. Comparison of HR changes during placebo and quinidine treatment. dHR in the quinidine group was higher than in the placebo group at all timepoints.

Table 2
HR and dHR (bpm) by timepoint and treatment.

Hour	Placebo HR mean	Placebo HR Std Dev	Quinidine HR mean	Quinidine HR Std Dev	Placebo dHR mean	Placebo dHR Std Dev	Quinidine dHR mean	Quinidine dHR Std Dev
−0.5	58.6	7.43	57.1	7.47	0.0	0.00	0.0	0.00
0.5	58.2	6.84	61.7	8.03	−0.4	4.33	4.5	8.61
1	57.9	8.25	65.7	9.17	−0.7	5.65	8.5	7.91
1.5	58.5	7.68	66.6	8.35	−0.1	5.46	9.4	6.01
2	60.4	6.14	68.0	8.18	1.9	5.04	10.8	5.23
2.5	65.0	7.80	69.9	8.44	6.4	5.65	12.8	3.93
3	65.7	8.24	69.4	8.27	7.2	7.53	12.3	5.59
3.5	66.7	8.29	70.2	9.29	8.1	7.82	13.0	5.47
4	66.0	8.95	68.9	8.61	7.4	7.95	11.8	4.94
5	64.9	8.52	67.8	10.92	6.3	6.25	10.6	6.32
6	69.1	9.35	73.3	10.55	10.6	8.18	16.2	6.64
7	66.6	8.52	69.5	9.76	8.1	7.68	12.3	6.48
8	67.8	10.05	68.9	9.25	9.2	9.27	11.7	6.18
12	66.7	7.69	66.3	8.01	8.2	6.85	9.1	4.98
14	65.6	8.63	65.9	8.64	7.1	5.97	8.7	5.89
24	62.0	10.17	63.5	8.62	3.4	6.05	6.3	4.26

heart rate-corrected QRS (dQRSc), however, increased more substantially and the increase was maintained at all but one timepoint through 24 h (lower panel, Fig. 2). Mean dQRSc peaked at 4.5 msec, at quinidine's Tmax (2 h). Visually, the rise and fall of dQRSc appeared to correlate well with the rise and fall of the quinidine plasma concentration, while the time course of uncorrected dQRS did not. Correlation analysis found dQRSc to correlate significantly with plasma concentration ($p = 0.0100$, $R = 0.1457$), while uncorrected dQRS did not ($p = 0.1272$, $R = 0.0861$).

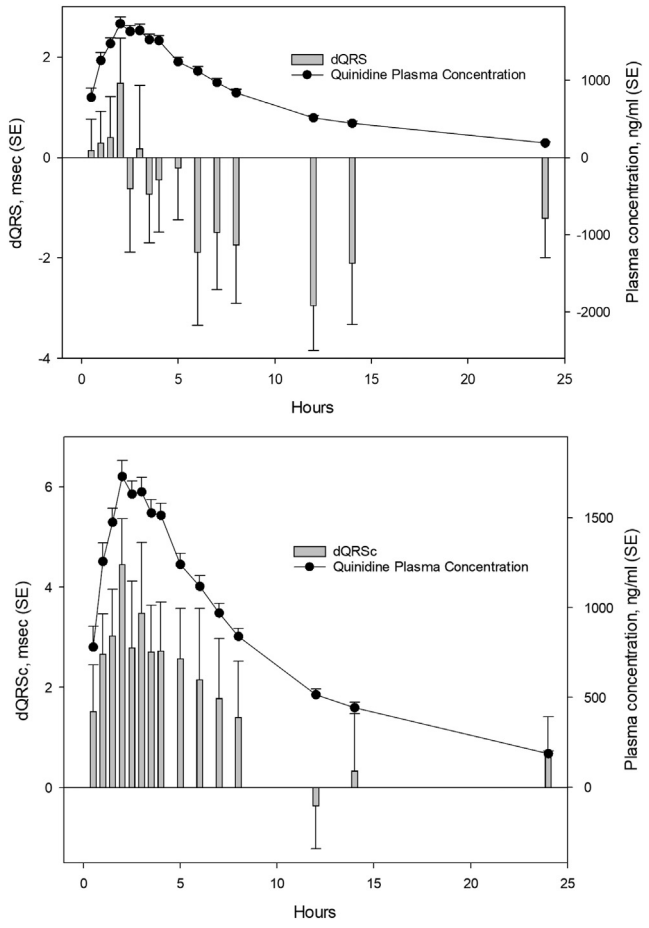

Fig. 2. Comparison of the relationships to quinidine plasma concentration of dQRS (upper panel) and dQRSc (lower panel). dQRS showed only a small, brief rise in QRS duration after quinidine, followed by a decrease despite substantial levels of quinidine. dQRSc showed a larger, sustained rise that correlated well with plasma concentration.

Discussion

We have demonstrated that correction of the QRS interval duration to offset its dependence on heart rate yields a drug-induced change from baseline in QRSc duration that parallels the changes in HR and plasma concentration of quinidine. The uncorrected dQRS did not correlate well with plasma concentration. This observation suggests that at least in the presence of a change in HR, the QRS duration, like the QT interval, should be heart-rate corrected.

We previously observed the negative relationship of QRS duration to HR (QRS increasing with a decrease in HR) in continuous 24-hour ambulatory recordings in normal individuals [1]. The relationship was observed during spontaneous change in HR during restful daily activity, rather than in association with a physiological intervention. The slope of the QRS - RR regression observed in that study (0.0125) was used to rate-correct the QRS in this study.

The purpose of this analysis was to evaluate the hypothesis that correction of the QRS duration for its dependence on heart rate yields a more accurate estimate of change in the QRS duration than uncorrected QRS, and, therefore, rate correction of the QRS is clinically useful in some settings. Quinidine is an ideal drug for testing the hypothesis because quinidine has been shown in animal models and humans to increase both heart rate and QRS duration in a dose-dependent manner [5–8]. Without correction, as heart rate is increased by quinidine, its concomitant increase in QRS duration would be expected to be underestimated by the raw QRS duration because of the QRS shortening effect of cardiac acceleration. Our observations are consistent with that expectation and validate the hypothesis. Raw dQRS correlated poorly with quinidine plasma concentration, while dQRSc showed an orderly dose-related response (Fig. 2).

In summary, our observations show that HR changes mask QRS duration changes unless the QRS is corrected for its HR dependency. Correction of the QRS duration for HR may provide a more accurate assessment of QRS duration in general. For example, correction of the QRS might be useful in more accurate selection of candidates for resynchronization pacing, especially in patients with varying heart rate, or in assessing the true change in QT in patients with both QRS and QT alterations related to a change in heart rate.

Disclaimer

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

Table 3
QRS, dQRS, QRSc and dQRSc by timepoint.

Hour	Quinidine QRS mean	Quinidine QRS Std Dev	Quinidine QRSc mean	Quinidine QRSc Std Dev	Quinidine dQRS mean	Quinidine dQRS Std Dev	Quinidine dQRSc mean	Quinidine dQRSc Std Dev
−0.5	97.3	8.25	96.5	7.94	0.0	0.00	0.0	0.00
0.5	97.4	8.52	97.6	8.38	0.1	2.83	1.5	4.28
1	97.6	7.72	98.5	7.95	0.3	2.92	2.7	3.68
1.5	97.7	8.10	98.7	8.02	0.4	3.77	3.0	4.27
2	98.8	8.14	100.1	8.15	1.5	4.12	4.5	4.19
2.5	96.7	8.53	98.3	8.27	−0.6	5.82	2.8	6.09
3	97.5	8.95	99.0	8.69	0.2	5.78	3.5	6.46
3.5	96.6	7.95	98.2	7.88	−0.7	4.45	2.7	4.29
4	96.8	7.60	98.3	7.59	−0.4	4.78	2.7	4.50
5	97.1	8.09	98.2	7.78	−0.2	4.72	2.6	4.62
6	95.4	8.66	97.5	8.37	−1.9	6.64	2.2	6.53
7	95.8	8.15	97.3	8.05	−1.5	5.20	1.8	5.50
8	95.5	7.41	97.0	7.40	−1.7	5.31	1.4	5.15
12	94.3	7.22	95.4	7.32	−3.0	4.08	−0.4	3.94
14	95.2	9.02	96.1	8.88	−2.1	5.56	0.3	5.24
24	96.1	7.67	96.6	7.19	−1.2	3.64	0.6	3.65

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