Z-score Transformation of T-wave Morphology Values to a Standardized Scale

C Graff[1], J Nielsen[2], JK Kanters[3,4], J Matz[5], SE Schmidt[1], E Toft[1], JJ Struijk[1]

[1]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
[2]Aalborg Psychiatric Hospital, Aarhus University Hospitals, Aalborg, Denmark
[3]Danish National Research Foundation Centre for Cardiac Arrhythmia (DARC), University of Copenhagen, Copenhagen, Denmark
[4]Department of Cardiology P, Gentofte University Hospital, Copenhagen, Denmark
[5]H. Lundbeck A/S, Copenhagen, Denmark

Abstract

Drugs that prolong the QTc interval to clinically relevant magnitudes are likely to be proarrhythmic if they also produce relevant changes in the morphology of repolarization waveforms. Concurrent analyses of QTc and the T-wave Morphology Combination Score (MCS) have already shown how this approach can improve characterization of repolarization effects for a number of drugs.

In this study we develop a transformation of MCS values to standardized T-wave Morphology scores (TWM) which have the important advantage of being directly comparable to QTc. We then examined the relative merits of assessing changes in TWM values in addition to QTcF for 37 schizophrenia subjects exposed to Sertindole, a drug which is not considered acceptably safe as a broad treatment of schizophrenia.

1. Introduction

A heart rate corrected QT interval >500 ms or an increase > 60 ms during drug therapy are commonly used thresholds of concern for Torsade de Pointes (TdP) arrhythmia and sudden cardiac death (SCD), and should lead to discontinuation of the offending drug unless there are compelling reasons to continue [1].

Although the safety profile of a compound is critically dependent on its QTc-prolonging property, this is not the only relevant factor when evaluating arrhythmic risk. Abnormal T-wave morphology can appear without overt QT prolongation [2, 3] and important abnormalities of the repolarization sequence may not be identified by the QT interval, which characterizes only the total duration of depolarization and repolarization.

Regulatory guidance notes for new drugs recommend an integrated risk assessment in which attention is given to both QTc prolongation and T-wave morphology changes during clinical trials [1]. Currently however, there is no consensus on how such T-wave analysis should be performed and this aspect is typically neglected despite the fact that T-wave morphology changes may reflect harmful changes in cardiac repolarization.

Therefore, we propose here, a novel approach to concurrent analysis of QTc intervals and T-wave shape changes following drug exposure. First, we develop a transformation of the Morphology Combination Score (MCS) to standardized T-wave Morphology scores (TWM) which can be directly compared to QTc. We then examined the relative merits of assessing changes in TWM values in addition to QTcF for 37 schizophrenia subjects exposed to Sertindole, a drug for which ECG monitoring for QTc values above 500 ms is mandatory during treatment, particularly around the time of changes in dose.

2. Methods

2.1. Study populations

Data from four typical phase I studies were pooled and used to establish coefficients for standardization of MCS to TWM values. This pooled data comprised 171 healthy volunteers (67 females, 104 males) aged 18-45 who received either placebo or no treatment in their respective trials. Healthy status was confirmed by history, physical examination, normal blood pressure and no use of concomitant medication.

A second data set was obtained from 37 schizophrenia patients (16 females, 21 males) aged 21-59 [4, 5] who were switched from their prior antipsychotic medications (baseline) to Sertindole (Serdolect®, 16 mg tablets) after a minimum of 3-weeks dosing to steady-state concentration, as recommended in the Summary of Product Characteristics of Serdolect®. This data was used to compare the repolarization end-points, QTcF and TWM. Informed consent was obtained.

2.2. ECG recordings

Standard 12-lead ECGs of 10 s duration were derived from all subjects. A total of 10491 ECG recordings were available from the 171 healthy volunteers participating in phase I trials. For patients switching to Sertindole, five consecutive ECGs were recorded at both visits (2x5x37 = 370 ECGs). The median value of the five recordings was used for analysis.

Each 10 s ECG was used to form a median beat in the recorded leads using MUSE/Interval Editor software (GE Healthcare, Milwaukee, WI). Principal Component Analysis (PCA) was used to compute principal component median beats from the median beats in leads (I, II, V1-V6). The first principal component T-wave was used to calculate a composite measure of repolarization morphology (MCS: Morphology Combination Score). Fiducial point detection and QT measurements (Fridericia corrected, QTcF) were made automatically using the 12SL algorithm (12SL, GE Healthcare, Milwaukee, WI).

2.3. Repolarization endpoints

The primary endpoints for Sertindole data were QTcF intervals and the standardized T-wave morphology values (TWM) obtained by transformation of the morphology combination score (MCS), equation 1:

$$(Eq.1) \quad MCS = Asymmetry + Notch + 1.6 \times Flatness$$

These T-wave characteristics have been shown to indicate markedly greater effects of drug-induced disturbed repolarization than QTcF [5-7] or exclude drug effects [8], to identify abnormal repolarization in patients with congenital LQT2 [9], and to be heart rate independent [10].

Asymmetry: Defined as the average of the square of the difference between the slopes of the ascending and descending parts of the T-wave.

Notches: The magnitude of a notch was measured on a unit amplitude T-wave and assigned to one of three categories, as was suggested by Lupoglazoff *et al*. [11]: no deflection = 0, moderate notch (perceptible bulge) = 0.5, and pronounced notch (distinct protuberance above the apex) = 1.0.

Flatness: Calculated as a modified version of the standard kurtosis measure, which is used in statistics to describe the peakedness of a probability distribution.

2.4. Data standardization

To enable direct comparison between QTcF and T-wave morphology, the MCS measurements were converted to z-score equivalents by subtraction of the mean (μ) and division by the SD (σ) of the values for phase I healthy volunteer data. The inverse transformation from z-scores to QTcF was then applied to the z-scores for MCS to get standardized TWM-values with the same mean and standard deviation as QTcF for the phase I healthy volunteer data, see figure 1. Coefficients for the transformation of MCS to TWM were derived this way.

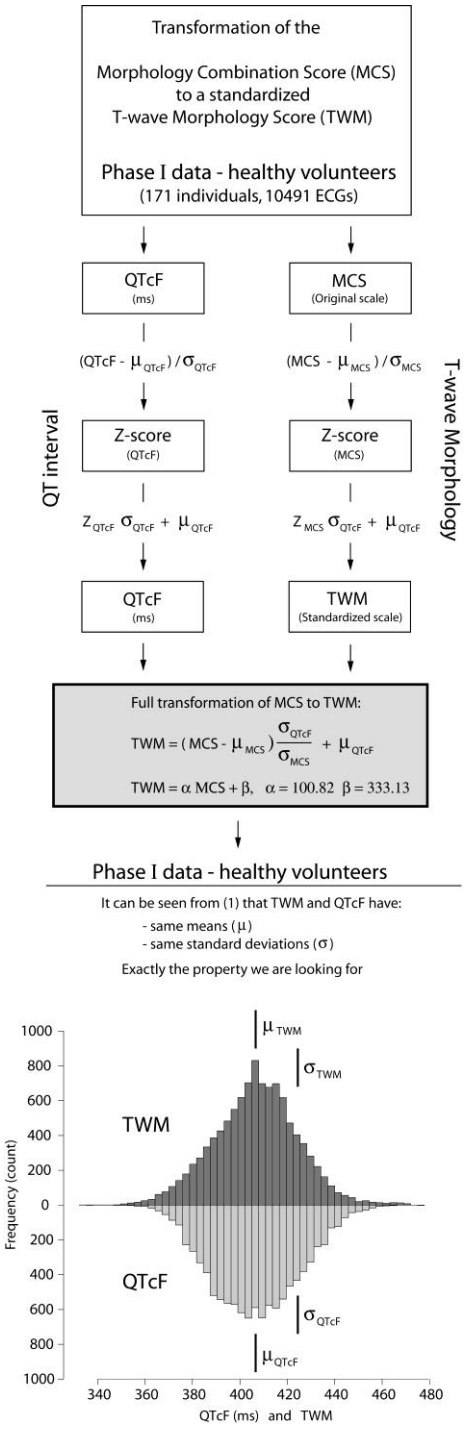

Figure 1. Standardization of T-wave morphology values from the pooled phase I healthy volunteer data.

3. Results

Transformation of MCS to TWM was established from phase I healthy volunteer data as:

$$(Eq.\ 2) \quad TWM = 100.82 \times MCS + 333.13$$

With this standardization, TWM and QTcF have similar means and standard deviations for the pooled phase I healthy volunteer data, figure 1.

This property is an important starting point for comparing the response to Sertindole for the two repolarization endpoints.

The most common ECG finding after Sertindole treatment was a prolongation of the QTcF interval and a coexisting change in morphology to a more abnormal appearing T-wave, figure 2.

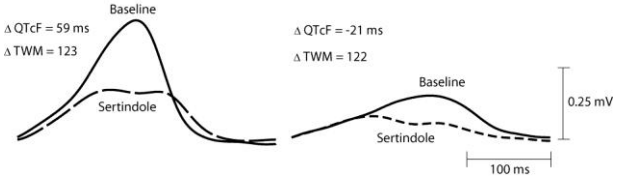

Figure 2. QTcF prolongation and shortening may both be associated with marked T-wave morphology changes (TWM). Recordings are aligned by the R-wave.

In 1 out of 5 patients, TWM increased after Sertindole exposure despite QTcF shortening, figure 3. The opposite, a QTcF prolongation paralleled by a reduction in TWM was a less common finding (3 patients).

Sertindole had a more pronounced effect on TWM compared to QTcF: Δ31 vs. Δ19 ms. Five patients had TWM changes above 60, whereas no QTcF changes of this magnitude were observed.

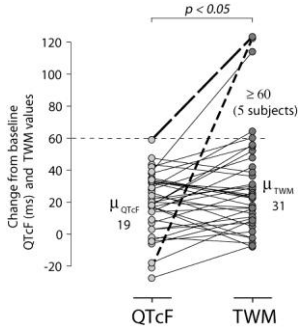

Figure 3. Sertindole induced T-wave morphology changes were greater on average than the corresponding QTcF changes and several patients had pronounced T-wave changes. Dotted lines correspond to ECGs in figure 2.

A Sertindole-induced QTcF prolongation or an increased TWM score was measured from the ECGs of 35 patients (95%).

Although there was no difference between the mean values for QTcF and TWM after Sertindole administration (436 ms vs. 433, p=0.65), no patient had a QTcF > 500 ms after exposure to the drug whereas 4 subjects had TWM values above 500, figure 4.

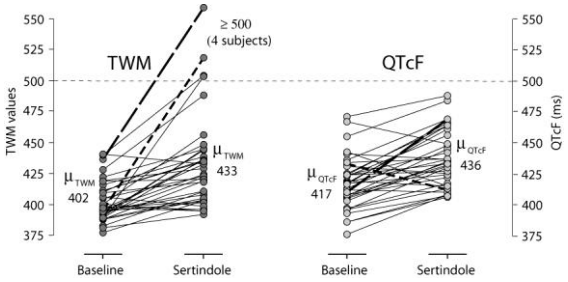

Figure 4. Some patients have markedly abnormal T-waves after Sertindole treatment despite QTcF intervals in the normal range. Dotted lines correspond to ECGs in figure 2.

4. Discussion and conclusions

In this study of Sertindole we added an explorative ECG endpoint enabling us to concurrently assess potential T-wave morphology changes and QTc interval prolongation on a similar scale. This type of assessment can have several advantages.

First, it may play a role in cardiac safety monitoring of patients receiving QT prolonging medications by increasing the likelihood of identifying patients at risk for serious arrhythmias.

Currently there is no consensus on threshold values for absolute QT/QTc intervals or changes from baseline that would indicate concern for TdP arrhythmia. Setting the limit too low would increase false-positives (i.e. drugs that prolong the QTc interval without demonstrable increased TdP risk). Higher limits increase the risk of not identifying patients at risk. In clinical trials, a prolongation to QTc > 500 ms during drug exposure is used as the threshold of particular concern.

However, this threshold for QTcF failed to identify patients in this study with marked repolarization changes (TWM > 500) who may potentially be at increased risk for developing TdP arrhythmia.

Another commonly used threshold of concern in drug trials is a QTc change from baseline exceeding 60 ms. Again, using this ECG criteria no patient was identified as being potentially at risk in the present study despite obvious T-wave morphology changes (ΔTWM > 60).

The current mandatory ECG monitoring with estimation of the QTc interval may therefore fail to identify all subjects with an increased risk of developing TdP if this measurement is used as the only indicator of disturbed repolarization.

Second, the QT interval is not always an optimum marker for estimation of a drug's proarrhythmic risk.

Particularly with QTc durations below 500 ms, the QTc interval lacks a clear correlation with TdP risk. This limitation undoubtedly relates to important abnormalities of the repolarization sequence not being identified by the QT interval, which characterizes only the total duration of depolarization and repolarization. Surely, it is not simply the length of the action potential/QTc interval that is important for eliciting TdP but also factors influencing dispersion of repolarization.

Heterogeneities of repolarization have been hypothesized as arrhythmic substrates in both acquired and congenital long QT syndromes [12] and in the short QT syndrome as well [13]. Drug-induced TRIaD (triangulation, instability, and reverse-use dependency) action potential characteristics, which are thought to reflect heterogeneity and increased proarrhythmia risk, can manifest as asymmetric, flat and notched T-waves on the electrocardiogram (ECG) [14]. The TWM marker of T-wave morphology may therefore contribute in important ways to the evaluation of cardiac safety.

Last, the linear transformation of MCS to TWM values proposed in the present study has the additional important property besides being directly comparable to QTcF, that all previously published effect sizes and comparisons by our group between QTcF and MCS are completely identical for TWM values.

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Address for correspondence.

Claus Graff
Department of Health Science and Technology
Aalborg University
Fredrik Bajers Vej 7 D1-215
9220 Aalborg, Denmark
E-mail address: cgraff@hst.aau.dk