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

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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. We used 10.491 baseline and placebo ECG recordings from four phase 1 studies of 171 healthy subjects to convert QTcF and MCS measurements to their respective z-score equivalents by subtraction of the mean (mn) and subsequent division by the standard deviation (sd) of the data. The back-transformation from z-scores to QTcF was then applied to the z-scores for MCS to get TWM values with the same mean and standard deviation as the QTcF data. The full transformation of MCS is thus given as: TWM = [MCS-MCS(mn)]QTcF(sd)/MCS(sd)+QTcF(mn). Sertindole had a more pronounced effect on TWM compared to QTcF: 31 vs. 19 ms respectively, $p<0.05$. No patient had a QTcF $>$ 500 ms at baseline or during sertindole exposure. In contrast, 4 subjects had TWM values above 500 after sotalol administration. Five patients experienced TWM changes above 60, whereas no QTcF changes of this magnitude were observed. Provided that the TWM measure of T-wave morphology has general validity for the identification of harmful drugs, this biomarker might be useful by itself, or in combination with QTc in estimating drug-related proarrhythmic potential.