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Investigating the effect of sotalol on the repolarization intervals in healthy young individuals

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Abstract

Background: The dissociation between a drug-induced increase of the QT interval prolongation and an increased risk for ventricular arrhythmias has been suggested by academic investigators and regulatory agencies. Yet, there are no alternative or complimentary electrocardiographic (ECG) techniques available for assessing the cardiotoxicity of novel compounds. In this study, we investigated a set of novel ECG parameters quantifying the morphology of the T-loop. In a group of healthy individuals exposed to sotalol, we compared their drug-induced changes to the drug-induced prolongations of the QTc, QTc apex and T-peak to T-end intervals.

Methods: We implemented a set of parameters describing the morphology of the T loop in its preferential plane. These parameters measure the time interval needed for the heart vector amplitude to change from its maximum value to a time when its amplitude has been reduced by 30%, 50%, and 70%. These measurements are called *early repolarization duration* (ERD) when they are located before the T-wave apex and *late repolarization duration* (LRD) when measured after the apex. They depend on both the speed of the repolarization process and the morphology of the T loop. Thirty-nine healthy individuals were exposed to sotalol in a crossover-design study. Sixteen ECGs were recorded per day during 3 days. The first day (day 0) was baseline; a single dose of sotalol (160 mg) was given during day 1, and a double dose was given during day 2 (320 mg). The plasma concentration of the drug was measured just before the ECG recordings.

Results: The values of all investigated parameters revealed a dose-dependent effect of sotalol (in average between parameters, ρ = 0.9, $P < .001$). Our investigations described profound and statistically significant changes in the morphology of the vectorial T loop for day 1 (peak effect of sotalol: $\Delta ERD_{50\%} = 23 \pm 6$ msec, $P < .05$; $\Delta LRD_{50\%} = 8 \pm 3$ msec, $P = .05$) and day 2 (peak effect of sotalol: $\Delta ERD_{50\%} = 51 \pm 14$ msec, $P < .05$; $\Delta LRD_{50\%} = 20 \pm 12$ msec, $P = .05$). When investigating the timing of peak drug concentration and peak effect of the drug on the various repolarization parameters, we found asynchrony between ERDs/LRDs (≥3.5 hours after dosing) and QTc/QTc apex profiles (<3.5 hours after dosing), suggesting that the time of maximum prolongation on the repolarization process was not synchronized with the time of maximum drug-induced heterogeneity of repolarization.

Conclusion: This study describes the sotalol-induced changes of the T-loop morphology in healthy individuals based on novel vectocardiographic parameters. These observations might help in improving the next generation of ECG markers for the evaluation of drug cardiotoxicity.

Keywords: QT interval; Torsades de pointes; Long QT syndrome; Sotalol; Vectocardiography; ECG

Introduction

While the association of increased arrhythmia risk with QTc prolongation is well established,[1] the association between a rate-corrected QT prolongation and the presence

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of an arrhythmogenic substrate has been strongly questioned. Indeed, the releases of several postmarketing reports have described noncardiac drugs with small QTc prolonging effect associated with significant torsadogenic properties,[2,3] whereas other drugs that have no history of cardiac events were significantly prolonging the QTc interval.[4,5] Consequently, one faces a challenging exercise related to the design and validation of a more reliable ECG surrogate marker of drug cardiotoxicity than QTc prolongation.

The mechanisms involved in the triggering of drug-induced arrhythmias remain to be fully elucidated, yet one recognizes the role of the repolarization heterogeneity as a required arrhythmogenic substrate.[6,7] For instance, the TriAd concept suggests the importance of the combined roles of action potential triangulation, reverse use dependency of the drug, and repolarization instability. An unbalanced contribution of these factors could lead to an increased ventricular heterogeneity and an increased propensity to torsades de pointes (TdPs).[7] Another concept, mainly based on in vitro experiments, emphasizes the association between ventricular transmural heterogeneity and the promoting role of early after-depolarization as primary factors triggering ventricular tachyarrhythmias.[8,9]

In the arena of development of novel ECG markers, different techniques are currently investigated; they include T-wave and T-loop morphologies[10,11] as well as time intervals such as the T-peak to T-end (TpTe) interval. TpTe interval has been suggested to be a predictor of ventricular arrhythmias in an increasing number of studies involving animal and human data.[12-15] However, its association with transmural dispersion and/or apicobasal ventricular heterogeneity is actively debated. In this work, we will consider the duration of this interval as an index of global ventricular repolarization heterogeneity.[12,13]

We investigated the effects of dl-sotalol, a class III antiarrhythmic agent with strong I_{Kr} inhibitory properties and associated with numerous cases of TdPs, on the morphology of the T-loop.[16,17] Our objective was to describe the sotalol-induced changes of QTc and TpTe intervals and compare them with the changes of novel computerized indices quantifying the morphology of the T loop. As noted above, the dissociation between the level of QT/QTc prolongation and the propensity to arrhythmic events may suggest the existence of "malignant" and "benign" QT/QTc prolongations; the level of ventricular heterogeneity may help distinguish them.

Method

Study populations and ECG recordings

A group of 38 healthy individuals were enrolled (28 men; 28 ± 8 years; body mass index, 24.4 ± 3.4 kg/m^2) and underwent repeated digital 12-lead ECG recordings during a 3-day protocol. The first day of the experiment was the baseline. During the second day, patients were exposed to a single dose of sotalol (160 mg); and during the third day, a double dose of 320 mg of sotalol was used. All recordings were preceded by a 5-minute resting period in supine position. Standard 12-lead ECGs were recorded for 10 seconds using a commercial equipment (Mortara Instruments, Milwaukee, WI). Sixteen recordings were done at identical times each day, first during baseline (day 0) and then immediately after the dosing (at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 13, 16, and 22.5 hours after dosing during day 1 and day 2). The recordings were sampled at 500 Hz with a 16-bit amplitude resolution.

Sotalol blood plasma concentration was measured before each ECG. The protocol is described in details elsewhere.[18]

The interval measurements: QT, QT apex, and TpTe intervals

In this analysis, the *repolarization interval* (RI) is defined between the J point and the point located 220 milliseconds before the next R peak. Such approach requires that the patients remain at rest during the ECG recording to avoid high heart rates, that is, short RR intervals in which 220 milliseconds before the next R peak would encompass the beginning of the P wave. All measurements of RIs are based on the singular value decomposition (SVD) from the 12-lead signals. The SVD is used to reduce the dimension of the ECG lead systems from 12 leads to 2 leads.[19] We refer to the resulting 2 leads as the *eigenvectors 1* (ev_1) and *2* (ev_2).

We measured the QT, QT apex, and TpTe intervals (TpTe = QT − QT apex) from ev_1. The software[20] was used to automatically measure the QT interval in all available cardiac beats in sinus rhythm. The median values from all measured beats are reported. The apex and the end of the T wave were identified in a fully computerized manner.

ERD and LRD parameters

$ERD_{\%}$ and $LRD_{\%}$ are measurements of interval durations based on the T loop. The starting point of these intervals is the time at which the length (magnitude) of the repolarization vector is maximized (Vmax in the lower panel of Fig. 1). The ending point of these intervals is identified by a circle of diameter equal to 30% of Vmax (Fig. 1 illustrates $ERD_{30\%}$ and $LRD_{30\%}$). Consequently, these parameters measure the time needed for the repolarization vector to vary from its maximum length to a time point corresponding to a 30% reduction of its maximum length. The $LRD_{\%}$ is a measure toward the end of the RI, and the $ERD_{\%}$ is directed toward the J point (Fig. 1, lower panel). The durations of these intervals increase when the electrical vector slows down or/and the roundness of the T loop increases. Consequently, these parameters measure time interval duration reflecting both the velocity of the repolarization vector and the repolarization heterogeneity.

The SVD and the repolarization measurements were computed in each cardiac beat, and we reported the average values from all beats for a given ECG tracing.

Heart rate correction

All repolarization measurements were heart-rate corrected using a pooled technique. A linear regression analysis was used to model the relationship between repolarization measurements and RR intervals during baseline periods. For a given parameter, we pooled all data from the overall