Triangulation of the Monophasic Action Potential Causes Flattening of the Electrocardiographic T-wave

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Abstract

It has been proposed that triangulation on the cardiac action potential manifests as a broadened, more flat and notched T-wave on the ECG but to what extent such morphology characteristics are indicative of triangulation is more unclear.

In this paper, we have analyzed the morphological changes of the action potential under the effect of the IKr blocker sertindole and associated these changes to concurrent changes in the morphology of electrocardiographic T-waves in dogs.

We show that, under the effect of sertindole, the peak changes in the morphology of action potentials occur at time points similar to those observed for the peak changes in T-wave morphology on the ECG. We further show that the association between action potential shape and ECG shape is dose-dependent and most prominent at the time corresponding to phase 3 of the action potential.

1. Introduction

Prolongation of the QT interval is a problem in drug development because of its relation with the polymorphic ventricular arrhythmia Torsades de Pointes (TdP) [1–3]. A large number of drugs have not been approved due to the potential of increasing the QT interval. QT prolongation is the traditionally used surrogate marker for assessment of the potential risk of pro-arrhythmia, yet it is not precise, partly because QT interval changes are subject to measurement error [4]. In particular, drug-induced T-wave changes (e.g. flattening of the T-wave) may complicate the measurement of the QT interval. Despite these limitations, a QTc interval of >500 ms for an individual patient or an increase of >60 ms from baseline are commonly regarded as thresholds for increased risk of TdP [5].

In addition to the QT interval, which has been used as a regulatory indicator for proarrhythmic effects, other biomarkers, based on T-wave shape, have been used in clinical tests. We have shown that the effect of QT prolonging drugs manifests prominently as T-wave morphology changes when quantified by the combination of T-wave asymmetry, flattening, and a notch score [6,7].

In the pre-clinical phase of drug development, monophasic action potentials (MAP) are evaluated and various changes in their shape have also been used as signs of proarrhythmia. Prolongation of AP duration (APD) is directly related to prolongation of the QT interval but prolongation of the APD is not by itself proarrhythmic provided that it is not contaminated by other morphological changes such as triangulation [8,9].

Associations between AP shape and T-wave morphology are to be expected, but have not been reported yet. In [10], it was attempted to relate the transmembrane APs from the epicardial, endocardial, and the M-cell regions to the T-wave, but the relation between specific morphology characteristics of the AP and the T-wave was not demonstrated. Only the correlation between the QT interval and APD was shown. Also, a transmural ECG may not be representative of a surface ECG of the intact in situ heart.

In the present study we have investigated the electrophysiological effect of an Ikr blocker – sertindole - on both the MAP and the T-wave at clinically relevant doses in anesthetized dogs. Sertindole (5-Chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)-ethyl)-4-piperidyl)-1*H*-indole) is an anti-psychotic compound which was used as a medication for schizophrenia [11], The drug was withdrawn from the market due to concerns about possible risks of cardiac arrhythmias [12]. The present experimental setup has been reported upon earlier [13]; however the analysis was limited to the durations of MAPs and QT intervals.

Here we show a significant correlation between characteristic changes in the shape of MAPs and the development of flat T-waves on the ECG when sertindole is administered. We also show that the timing of the peak changes due to drug effect is almost similar for both MAPs and T-waves.

2. Methods

2.1. Study design

Five healthy dogs (29±4 kg) were used for the experiment. Anaesthesia was introduced by sodium pentobarbital (20 mg/kg intravenously) and maintained by halothane (in O_2 and N_2O, 1:2). Sertindole was administered intravenously as a 5 minute infusion to the dogs at cumulative doses of 0.05 mg, 0.10 mg and 0.2 mg/kg, which can be considered as clinically relevant doses. No dog had TdP at these low doses. Each dose was followed by a thirty minute interval before next dose was administered.

2.2. ECG and MAP recording

A 10-lead ECG I, II, III, aVR, aVL, aVF, V1, V2, V3, V4 was continuously recorded at a sampling frequency of 1000 samples/second. The endocardial MAP was recorded from both the left and the right ventricle. Left ventricular MAPs were chosen for the analysis. For each of the dogs, 15 minutes of baseline recording was taken just before the first dose was given. The peak electrophysiological effect of the drug was prominent at each new dose after about 8-10 minutes of drug infusion.

Before the data were analysed, a moving average filter was used to reduce the effects of noise.

Each MAP was normalized to its plateau amplitude in order to remove any time dependent loss of MAP amplitude due to declining contact pressure of the catheter.

2.3. Formation of representative beats

From the baseline recordings, a representative baseline median beat was constructed from both the ECG and MAP recordings for each of the dogs. After sertindole infusion was initiated, median beats (MAPs and ECGs) were constructed at shorter intervals (10 second periods) and used compared with the baseline median so the effect of sertindole could be followed. Hence, there was one baseline median beat for each dog and one series of median beats for each of the three doses.

2.4. Alignment of MAPs and ECGs

For each treatment group the series of 10 second MAP medians were aligned with the baseline median at the 90% repolarization point as shown in figure 1. The maximum morphological difference between the baseline and the treatment segments were found in a window between the 90% repolarization point and 130 ms earlier.

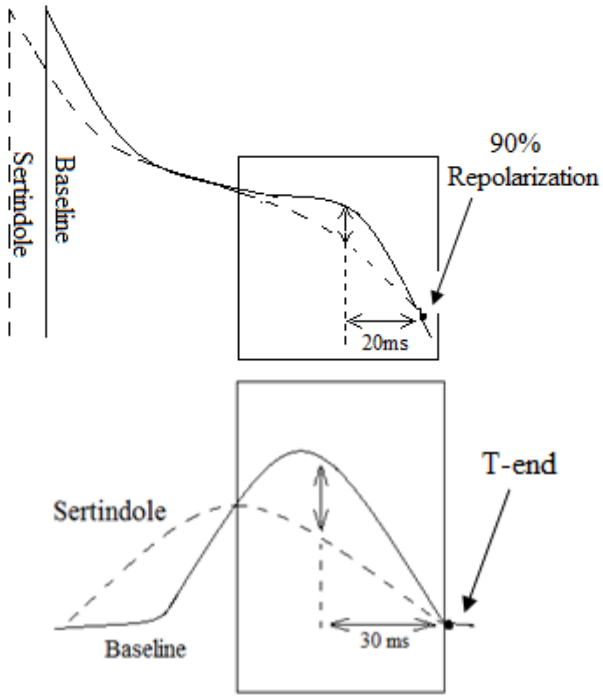

Figure 1. Morphology changes and alignment of MAPs and T-waves with baseline. Dotted vertical lines on the MAP recordings indicate the 90% repolarization point and the point of peak morphological change. The peak morphological change is also indicated with a vertical dotted line on the ECGs which are aligned to T-end.

The series 10 second ECG medians for each treatment group were aligned with the corresponding baseline median ECG at T-end. The root mean squared difference in T-wave shape between baseline and treatments was calculated within the selected 130 ms window. The QT interval and AP durations were corrected by Van de Water's formula [14].

3. Results

Sertindole increased MAP duration and the QT interval. Morphological changes of the MAPs and ECGs were also observed following sertindole infusion.

Figures 2 and 3 show, for each dose, the peak sertindole-induced changes in percentages for MAPs and T-waves with respect to the baseline

Each of the curves in figures 3 and 4 represent the average change from baseline for all five dogs at the time of peak change in MAP and T-wave morphology.

Peak changes in MAP morphology with respect to the baseline MAP were 3.4%, 4.8% and 5.5% for the three

cumulative doses and they occurred at 14 ms, 21 ms and 23 ms before the 90% repolarization point, respectively. The peak changes in T-wave morphology with respect to the baseline were 47%, 63% and 73% and they occurred at 29 ms, 30 ms and 40 ms before the end of the T-wave.

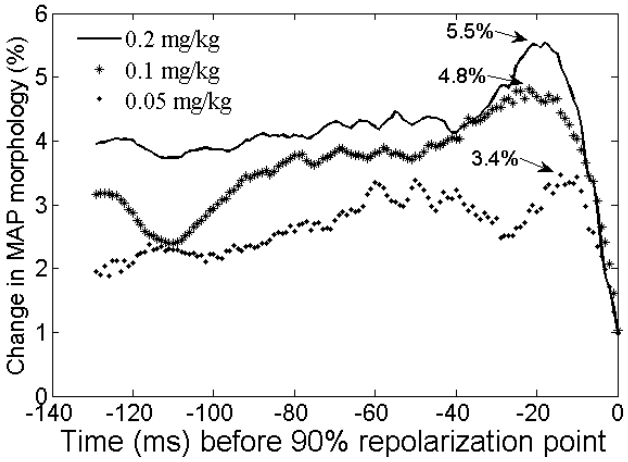

Figure 2. Peak sertindole-induced changes in MAP morphology for each of the three doses. Each curve is the average of all 5 dogs. MAP shape changes are dose-dependent and most prominent in phase 3 of the action potential.

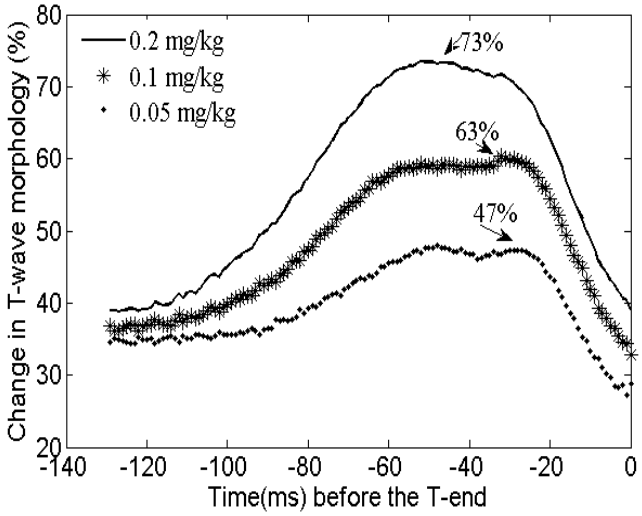

Figure 3. Peak sertindole-induced changes in T-wave morphology. Each curve is the average of all 5 dogs. ECG shape changes are dose-dependent and most prominent at the time corresponding to phase 3 of the action potential.

4. Discussion

We have shown that sertindole slowed down phase 3 of the monophasic action potential (MAP) which is a regular effect of an Ikr blocker. This effect can be referred as triangulation because the action potential assumes a more triangular appearance when this phase of repolarization slows down. Sertindole also affected the morphology of electrocardiographic T-waves. The morphological changes in this case can be described as flattening of the T-wave. Both MAP changes and ECG changes were dependent on the dose administered and importantly, the peak changes for both the MAP and ECG occurred at almost the same point in time. These time-aligned changes indicate that the pronounced changes in T-wave morphology were mostly caused by shape changes in phase 3 of the cardiac action potential. Whether this correlation exist for all IKr inhibiting drugs or only those drugs which cause triangulation of the cardiac action potential and potentially cause proarrhythmia is presently uncertain. Invasive studies measuring Triangulation, Reverse use dependency, electrical Instability and Dispersion (TRIaD) have suggested that TRIaD may have a better predictive value for the occurrence of TdP, than the action potential prolongation (QT prolongation) [8, 9]. The potential value of TRIaD was largely substantiated in more than 700 trial drugs [15].

We have shown that a torsadogenic drug which causes triangulation of the action potential also has a large effect on the electrocardiographic T-wave. We believe that computerized measures of T-wave morphology have the potential to be an important addition to QT interval measurements because such measures may contribute to an expanded ECG safety evaluation in future drug studies through more careful characterization of repolarization abnormalities. We therefore propose to further investigate how TRIaD representations on the cardiac action potential are reflected in the ECG

5. Conclusion

Triangulation of the monophasic action potential following administration of a torsadogenic drug was associated with a flattening of the electrocardiographic T-wave. Further studies are needed to investigate the relationship between triangulation on the action potential and changes in the morphology of the electrocardiographic T-wave.

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