

Repolarization Effects of Sertindole Manifest as T-wave Flatness on the ECG

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Abstract

Flattening of the electrocardiographic T-wave has been associated with proarrhythmic risk. It has also been demonstrated that triangulation of the monophasic action potential (MAP) manifests on the ECG as a flattened T-wave.

In this study we investigate the effects of sertindole on the electrocardiographic T-wave using a recently developed ECG marker of T-wave flatness which is directly correlated with sertindole-induced triangulation of the MAP prior to Torsade de Pointes arrhythmia in dogs. The effect of sertindole on T-wave flatness was compared with the effects of moxifloxacin and placebo on the T-wave.

Sertindole caused more flattening of the T-wave compared to moxifloxacin and placebo. Effect sizes also revealed that flattening of the T-wave after sertindole was a more prominent finding compared to QT interval prolongation.

An electrocardiographic measurement linking MAP triangulation and T-wave flatness could potentially be used for cardiac safety assessment in drug trials along with other safety measures.

1. Introduction

The relation between heart rate corrected QT prolongation (QTc) and drug induced Torsades de Pointes (TdP) is still unclear [1, 2]. Although, QTc prolongation has been used as a surrogate marker of proarrhythmic risk, there is no threshold of QTc prolongation beyond which an increased risk of TdP is exists. For regulatory purposes a QTc prolongation of less than 5 ms from baseline is accepted as posing a negligible risk for TdP, whereas a QTc prolongation above 20 ms indicates a substantial increased risk for TdP [3]. In a group of patients with LQTS, it was shown that the TdP risk increased exponentially by 5% for every 10 ms increase of QTc beyond 440 ms [4]. No such relationship has been demonstrated for drugs. In fact Milberg *et al.* [5] reported

that there is no correlation between QT prolongation and torsadogenic potential in a group of quinolones. In addition to the vague relation between QTc prolongation and drug-induced arrhythmic risk, the QT interval is also subject to measurement error [6].

Recent evidence indicates that drug-induced T-wave abnormalities can be used to provide a clearer picture of drug effects on cardiac repolarization than the QT interval. Assessment of T-wave morphology has therefore received much attention and a number of investigators have proposed T-wave morphology measures that characterize drug influence. T-wave morphology has been quantified by T-roundness, T-amplitude, ascending and descending slopes of the T-wave [7] or combination of T-wave asymmetry, flatness and notching [8, 9]. These morphological parameters are less dependent on heart rate compared to the QT interval and thus to lesser error than the QT interval.

The torsadogenicity of drugs has been found to be highly correlated with change in morphology of the Monophasic Action Potential (MAP) [10]. Drugs that block the rapid component of the delayed rectifier potassium current (IKr), manifest on the MAP as prolonged phase-3 duration and 'triangulation' of the MAP morphology. Prolongation of the MAP duration (which is reflected as QT prolongation) itself may be antiarrhythmic provided it is not contaminated by its morphological abnormalities such as triangulation [10]. In other words, MAP morphology is a rather good marker of drug-induced TdP risk but QTc is not.

In a preclinical study in dogs, we developed a T-wave flatness parameter that reflects triangulation of the MAP. The flatness measurements and their associated MAPs attained maximum values just prior to the onset of TdP [11]. In this study, we use the same T-wave flatness measurement to assess the repolarization effects in 35 patients given sertindole.

2. Methods

We have analysed the effect of sertindole, an antipsychotic which is used in treating schizophrenic patients. The effect of sertindole on the T-wave was

compared with the effects of the antibiotic drug moxifloxacin which has a safe cardiac profile [12]. The repolarization effects of both drugs were compared with a placebo group.

2.1. Study population and design

Sertindole data was obtained from 35 patients switching to the drug [13]. The study was approved by the Scientific Ethical Committee of Northern Jutland. None of the patients had a history of cardiac diseases. ECGs were recorded at baseline and at a steady-state dose of 16 mg sertindole. All subjects were normotensive and had normal baseline ECG.

The placebo and moxifloxacin data were extracted from a single-center, randomized, 7-day, parallel-group, phase I study (Parexel Clinical Pharmacology Research Unit, Harrow, UK). Baseline ECGs were recorded in all study subjects before treatment. Subjects were then given either placebo (57 volunteers with 7 days of oral placebo) or moxifloxacin (55 volunteers with 6 days of placebo and 400mg of moxifloxacin on the 7th day). The moxifloxacin (Avelox, 400 mg tablets) was supplied by Bayer Healthcare, Leverkusen Germany.

2.2. ECG acquisition

12 lead ECGs from patients treated with sertindole were recorded digitally with GE MAC5000 and GE CardioSoft (GE Medical system, Milwaukee, WI). Five consecutive ECGs of 10 s duration at baseline and after sertindole treatment were recorded at a sampling frequency of 500 Hz and transferred to the MUSE database. The participating hospitals were: Bronderslev Hospital, Aalborg Psychiatric Hospital and Odense University hospital.

Standard 12 lead ECGs were recorded at baseline and after the administration of moxifloxacin and placebo at the time points corresponding to 30 min and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 23.5 hr after dosing. Moxifloxacin and placebo ECG data were recorded in 7.5-s segments at a sampling frequency of 1000 Hz.

2.3. ECG processing

The left precordial ECG lead V5 was used for analysis. A moving average filter of 15 taps (30 ms) was used for smoothing the data. All ECG data was resampled to 500 Hz and median beats were formed using MUSE/Interval Editor Software (GE Healthcare, Milwaukee, WI).

2.4. Parameter extraction

The details of the flatness parameter reflecting MAP triangulation have been presented previously (13). In

brief, T-end was identified by the tangent method and a horizontal line of 180 ms was drawn connecting the ascending and descending part of the T-wave without intercepting the QRS complex. A rectangle was formed enclosing the T-wave segment with a height between the horizontal line and the T-peak. The ratio of the area enclosed by the T-wave and the area of the surrounding rectangle was defined as the Relative T-wave Area (RTA). The RTA is used to measure T-wave flatness. The QT interval was corrected according to the Fridericia's formula.

2.5. Statistical analysis

Within-subject differences were evaluated by a paired Student's t-test and between group differences were determined by an independent sample t-test. Effect size was calculated as the change in mean values (baseline and after dose) with respect to the baseline standard deviation. Results are presented as mean±standard error.

3. Results

Prominent T-wave morphology changes were seen after sertindole treatment. The changes were reflected in an increase in both RTA and QTc.

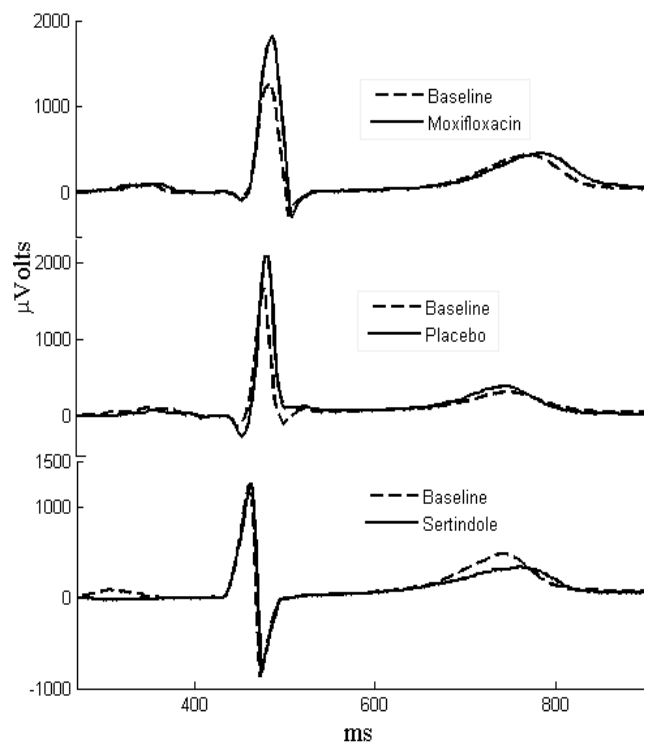


Figure 1. Representative ECGs of three groups in this study. Sertindole causes flattened T-wave whereas moxifloxacin and placebo have very little effect on the T-wave morphology.

The mean effect size (ES) was higher for RTA (ES=1.42; 95% CI: 1.05-1.78) compared to the mean effect size for QTcF (ES=0.83; 95% CI: 0.50-1.165), see figure 2. This difference in effect sizes was significant ($p=0.02$).

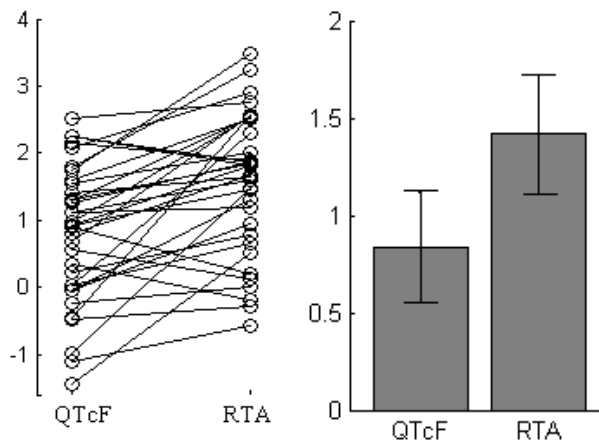


Figure 2. Effect sizes for QTcF and RTA. Left: individual responses. Right: average effect sizes with confidence intervals.

Individual responses for sertindole, moxifloxacin and placebo are shown in figure 3. RTA increased from 0.51 ± 0.004 at baseline to 0.56 ± 0.007 after treatment. Such marked difference between baseline and treatment was not observed for moxifloxacin or the placebo, see table 1.

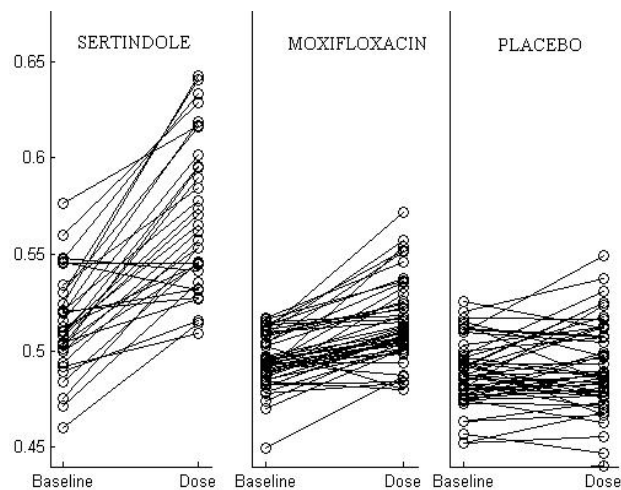


Figure 3. Individual RTA measurements for sertindole, moxifloxacin and placebo. Sertindole has the highest effect on T-wave flatness as quantified by RTA.

Table 1. ECG measurements of T-wave flatness (RTA) and the Fridericia's corrected QT interval (QTcF) for three treatment arms.

Drug		Before Dose mean \pm SE	After Dose mean \pm SE	p value
Sertindole	QTcF(ms)	422 \pm 2.26	436 \pm 3	<0.01
	RTA	.51\pm0.004	.56\pm0.007	<0.01
Moxifloxacin	QTcF(ms)	409 \pm 2.31	418 \pm 2.47	<0.01
	RTA	.498\pm0.003	.518\pm0.003	<0.01
Placebo	QTcF(ms)	408 \pm 2.45	407 \pm 2.47	NS
	RTA	.488\pm0.003	.493\pm0.004	NS

The change in RTA from baseline (Δ RTA) with sertindole was significantly higher than the change from baseline seen with moxifloxacin (Δ RTA_{sertindole} 0.05 vs Δ RTA_{moxifloxacin} 0.02, $p<0.001$). In contrast, the change in QTcF from baseline (Δ QTcF) was not greater for sertindole compared to moxifloxacin (Δ QTcF_{sertindole} 13 ms vs Δ QTcF_{moxifloxacin} 10 ms, $p=0.23$).

4. Discussion

In this paper we have analysed the effect of sertindole on T-wave flatness (RTA) in 35 patients switching to the drug. Sertindole caused marked flattening of the T-wave. We know from preclinical data with sertindole administered to dogs that RTA responds to changes in ventricular MAP morphology and that both measurements change concurrently prior to the onset of TdP arrhythmia [11]. There is also evidence showing that triangulation of MAP morphology is a surrogate marker of drug-induced risk of TdP [10]. Therefore, RTA could be a surface representation of MAP triangulation. If further studies can corroborate this RTA may be useful as a marker of repolarization changes in drug safety studies.

In comparison to the QTcF prolongation the increase in RTA was somewhat more sensitive since 89% of the subjects had an increased RTA after sertindole treatment whereas only 78% had an increased QTcF.

Concurrent analyses were done for both moxifloxacin and placebo. Moxifloxacin is generally thought to have low proarrhythmic risk and only a small number of TdP cases have been reported, always with confounding factors [12]. The RTA for moxifloxacin was increased by only 0.02 from the baseline. This was less than sertindole where RTA increased by 0.05 and the difference in effects on RTA was significant. In contrast, no difference was found between the two drugs in their effect on QTcF change from baseline.

5. Conclusion

A new measurement of T-wave flatness which is directly correlated with triangulation of the monophasic action potential prior to onset of Torsade de Pointes arrhythmia may be useful in drug safety studies.

Acknowledgment

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