Original Article

Postural Change-associated Alterations in QT/QTc Intervals on Electrocardiograms

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In a new drug development, regulatory authorities recommend the "thorough QT/QTc study", in which the use of a positive control group was recommended for evaluating assay sensitivity that allows the detection of a QT/QTc interval prolongation about 5 msec. The effects of postural change on the QT/QTc intervals were examined to determine its potential usefulness as a nonpharmacological positive control. Standard 12-lead electrocardiograms of 72 healthy male subjects (mean age: 22.6 ± 2.0 years) were recorded in the morning and evening in 6 positions (supine, 30-degree semisitting, standing, supine, 90-degree sitting, and standing). The QT-RR relationships during postural changes seemed to be similar in the morning and the evening. The QTc interval calculated by the Fridericia's or Framingham's formula shortened in the sitting (7 to 10 msec) and the standing position (11 to 14 msec) compared to that in the supine position. On the other hand, the QTc interval calculated by the Bazett's formula prolonged by nearly 4 msec in the sitting position and by nearly 9 msec in the standing position. The results suggest that the difference in QTc interval during postural change, especially from supine to sitting position, could be useful as a nonpharmacological positive control.
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Key words: QT interval, Postural change, Heart rate correction formula, Nonpharmacological positive control

Introduction

QT interval prolongation and associated ventricular arrhythmias, including torsade de pointes (TdP), are critically important examples of drug-induced fatal cardiotoxicity.[1,2] QT prolongation represents part of the pharmacological actions of antiarrhythmic drugs which exert them by directly affecting the process of myocardial repolarization. Other classes of drugs are expected to exhibit this activity to a lesser extent. However, drug-induced QT prolongation and associated proarrhythmias have been major causes for the withdrawal of non-antiarrhythmic drugs, which include antiallergic drugs.[1,3] There-

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fore, it is essential to evaluate in detail the potential of a drug to prolong the QT interval at each stage of a clinical trial.

The ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) developed a guideline for "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs".[4] This guideline is featured by its recommendation for a healthy subject to undergo "thorough QT/QTc study" at a relatively early stage of clinical trial. This study requires the evaluation of assay sensitivity which allows the detection of a QT/QTc interval prolongation by less than 5 msec on average.[4] To evaluate assay sensitivity itself, furthermore, the study recommends the use of a drug—whose average QT interval prolongation is known to last approximately 5 msec—as positive control. In Japan, however, the following aspects concern the use of positive control: 1) the occurrence of many drawbacks is foreseen in acquiring positive control in the case that the drug is not prepared internally at an institution; and 2) concern about the safety of positive control which provokes QT interval prolongation; and 3) ethical issue of administering such a drug.

Postural changes, e.g., from the supine to sitting or standing position, are known to affect the QT/QTc intervals[5,6] or QT dispersion.[7] We postulated a hypothesis that the alterations in QT/QTc intervals which are associated with postural changes can possibly be used as "nonpharmacological positive control" to evaluate assay sensitivity as does pharmacological positive control. In this study, we examined the relevant alterations to verify our hypothesis.

Methods

1) Subjects

Seventy-two Japanese healthy male subjects 20 to 30 years of age (mean age: 22.6 ± 2.0 years) were enrolled in this study. All subjects took no drugs of any kind for at least one week before this study. Alcohol was prohibited for at least two days before this study. All the subjects provided their written informed consent for enrollment.

2) Postural change procedure and data acquisition

This study was conducted in the evening (between 5 p.m. and 7 p.m.) and in the morning (between 9 a.m. and 11 a.m.). Posture was changed according to the following sequence: (1) supine position (10 minutes); (2) 30-degree passive semisitting position (4 minutes); (3) spontaneous standing position (4 minutes); (4) supine position at rest (10 minutes); (5) 90-degree passive sitting position (4 minutes); and (6) spontaneous standing position (4 minutes). The subject took the supine/semisitting and sitting positions on an electrically reclinable bed. The semisitting position was defined as a position in

Table 1 RR and QT intervals during postural changes in healthy subjects.

	RR interval	QT	
		II	V5
evening			
supine	968.8 ± 140.3	408.2 ± 27.8	409.7 ± 27.9
semisitting	947.3 ± 133.4 *	404.3 ± 26.5 *	404.6 ± 26.6 *
standing	734.4 ± 111.9 *	360.1 ± 23.7 *	361.7 ± 25.5 *
supine	996.0 ± 140.4	413.8 ± 26.7	414.7 ± 27.1
sitting	829.5 ± 119.0 *	381.2 ± 24.2 *	380.9 ± 25.0 *
standing	732.5 ± 116.3 *	361.5 ± 24.3 *	363.2 ± 25.9 *
morning			
supine	1101.8 ± 132.0	431.5 ± 23.4	433.6 ± 24.9
semisitting	1063.8 ± 128.7 *	424.9 ± 23.2 *	426.1 ± 24.6 *
standing	810.0 ± 124.3 *	377.1 ± 25.7 *	381.4 ± 26.4 *
supine	1092.5 ± 133.7	430.6 ± 22.0	433.8 ± 23.4
sitting	915.8 ± 124.5 *	396.7 ± 23.6 *	398.3 ± 25.2 *
standing	787.4 ± 121.2 *	373.4 ± 22.8 *	377.1 ± 24.3 *

All values represent mean ± SD
*$p < 0.0001$