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Comparison of Six Commonly Used QT Correction Models and Their Parameter Estimation Methods

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COMPARISON OF SIX COMMONLY USED QT CORRECTION MODELS AND THEIR PARAMETER ESTIMATION METHODS

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This paper compares six commonly used QT correction models and three available parameter estimation methods using five indices for QTc evaluation based on real and simulated electrocardiograph (ECG) datasets. The results show that the golden section approach always finds the correction factor making QTc interval uncorrelated to heart rate for all six formulas. However, the correction formulas derived from mixed model sometimes fail to make QTc interval invariant of heart rate. The performance of an individual least-square regression method lies between the golden section iteration approach and the mixed model in terms of QTc-RR relationship.

Key Words: Clinical trial; Golden section; QT correction model; QTc; Thorough QT study.

1. INTRODUCTION

Assessment of drug-induced QT interval prolongation has recently attracted a great deal of attention from both regulatory agencies and the pharmaceutical industry (ICH, 2005). Since the 1990s, new and existing drugs have been subjected to close scrutiny for their potential prolongation of QT interval, and the evaluation of QT interval prolongation as a surrogate maker of potential proarrhythmia has become an important part of Phase I and Phase II of drug development.

Over the past several decades, many correction formulas have been proposed and a comprehensive review of this topic has been given by Malik (2001). However, there is lack of systematic assessment of the sensitivity of formula parameters and the performance of QTc intervals to parameter estimation methods. The purpose of this paper is to compare six commonly used QT correction methods (linear, hyperbolic, parabolic, logarithmic, shifted logarithmic, and exponential models) and three parameter-estimating methods (golden section, least-square regression model, and mixed model). The comparisons assess each method's performance using various measurements of QTc-RR relationships and QTc variability by analyzing

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