
Shortening of the QT Interval After Food Can Be Used to Demonstrate Assay Sensitivity in Thorough QT Studies

Jorg Taubel, MD, FFPM, Alex H. Wong, MBChB, MRCS, MBA, Asif Naseem, BSc, PhD, Georg Ferber, PhD, and A. John Camm, MD, FRCP

The effect of food was investigated under conditions of a thorough QT (TQT) study and with confirmation of assay sensitivity by the use of a positive control (400 mg of moxifloxacin). Fifty-five healthy subjects were randomized to treatment and a sequence of fasted and fed baseline electrocardiography days. Subjects received standard breakfast 30 to 10 minutes prior to dosing. Measurement of QT interval was performed automatically with subsequent manual onscreen overreading using electronic calipers. A profound increase in heart rate of 9.4 bpm was observed in the fed condition compared with the fasted condition at 1.5 hours after dose with a corresponding shortening of QT (27 milliseconds); (baseline data). When corrected, QTcF interval was shortened significantly with the maximal effect observed at 2 hours after dose of 8.2 (95% confidence interval, 6-10) milliseconds. A concurrent shortening of the PR interval

with a maximum value of 5.6 milliseconds was also observed. The findings of this study demonstrate that food alters the QT-RR relationship and shortens QTc and PR for at least 4 hours after a carbohydrate-rich meal. The findings are of regulatory interest as this study shows that normal physiological causes can shorten QTc significantly and that it could be used as a method to demonstrate assay sensitivity.

Keywords: Safety; 12-lead electrocardiograph; food effect; QTc; pharmacology; clinical trial methods; QT studies; assay sensitivity; oncology; pediatrics; QTc shortening; QTc prolongation; autonomic affects

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The challenge of conducting and analyzing a thorough QT study (TQT) is that one cannot readily distinguish between the effects of heart rate (HR) changes, autonomic effects, and the effects caused by ion channel blockade. The International Conference on Harmonization (ICH) E14 guideline has set narrow limits for QTc changes that will not raise any regulatory safety concern, and it follows that it is desirable to remove all factors that may lead to a false signal in these studies. Bazett's¹ initial investigations in the 1920s concluded that the QT varies with the HR, and various correction

methods have been proposed to normalize this effect to define the underlying intrinsic QT-RR relationship. Nonetheless, the autonomic nervous system effects on cardiac repolarization are still poorly understood, which complicates the interpretation of QT measurements in the context of TQT studies.

The QT-RR relationship is influenced by the autonomic nervous system, with various publications in the past 3 decades showing that the intrinsic QT-RR relationship changes in response to changes in sympathetic and vagal tones. The present study shows a significant effect of food of a magnitude that might be viewed as being of regulatory concern had it been elicited by a drug.²

The effects of food on the QT interval have been described in a number of publications, which appear at first to contradict the findings of our study. There are several reports of prolonged QT resulting from low-calorie meals and starvation.³⁻⁵ Long QT interval was also reported in anorexia nervosa,⁶ in healthy subjects undergoing experimental starvation,⁷ in

From Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, United Kingdom (Dr Taubel, Dr Wong, Dr Naseem, Dr Ferber); and Department of Cardiological Sciences, St George's University of London, Cranmer Terrace, London, United Kingdom (Professor Camm). Submitted for publication September 14, 2010; revised version accepted July 4, 2011. Address for correspondence: Dr Asif Naseem, Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK; e-mail: a.naseem@richmondpharmacology.com. DOI: 10.1177/0091270011419851