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Drugs that Prolong the QT Interval: Regulatory and QT- Measurement Issues from the USA and European Perspectives

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I recently attended a meeting in Philadelphia entitled "How to Obtain, Interpret and Analyze ECGs In Clinical Research Trials: USA and European Regulatory Perspectives,"[1] with focus on drugs that have a modest QT-prolonging effect. The background of this conference that involved faculty from universities, industry, and regulatory agencies is that many cardiac and non-cardiac drugs during development are noted to have some effect on ventricular repolarization. The central theme of the conference was how to measure, interpret, and integrate a QT-prolongation signal into drug development. Three questions dominated the conference: 1) Which QT measurements should be used to evaluate the clinical effects of drugs on ventricular repolarization? 2) How should modest QT prolongation be interpreted during Phase I-III clinical trials? 3) Which QT signals during drug-development are warning signs for serious life-threatening ventricular arrhythmias?

QT prolongation by drugs is well known, and common examples include antiarrhythmic agents like quinidine, sotalol, and dofetilide as well as non-cardiac drugs like terfenadine, erythromycin, and cisapride. The general regulatory attitude is that the risk of malignant ventricular arrhythmias is directly related to the magnitude of the QT-prolonging effect of the drug. But what is the QT-prolongation threshold of concern? This is a difficult question since the incidence of drug-induced malignant ventricular arrhythmias is very low for most drugs and usually not seen during drug-development trials. There is evidence that the risk of malignant ventricular arrhythmias bears a direct exponential relationship to the QTc duration.[2]

Before clinical trials are initiated in patients, *in vitro* and *in vivo* screening studies are carried out. Most QT-prolonging drugs block the rapidly-activating delayed rectifier potassium current, I_{kr}. If there is any evidence from these screening studies that the drug effects ventricular repolarization or the ion currents involved in repolarization, then focused preclinical studies are indicated in patients, with ECG screening for QT prolongation and proarrhythmia. Even drugs without pre-clinical evidence of a QT effect should undergo some screening for QT prolongation in patients.

How should QT-prolonging effects of drugs be measured during pre-release Phase I-III clinical studies? Presently, the USA regulatory agency (FDA) accepts measurement of the QT interval on the 12-lead ECG with correction for heart rate by both the Bazzett[3] ($QTc=QT/\sqrt[2]{RR}$) and Fredericia[4] ($QTc=QT/\sqrt[3]{RR}$) formulae in view of the complex relationship between QT and RR. The Framingham linear-regression method can also be utilized to adjust for heart rate.[5] There are essentially no regulatory guidelines about which lead or leads should be used when measuring the QT interval, how many leads or complexes should be measured, or what ECG paper speed should be used. Measurement techniques are not specified, but manual as opposed to automatic

(digital) measurement is preferred. Accurate identification of the end of the T wave is a problem, and there is no agreement on whether to include the U wave in the repolarization measurement. That is, should one measure simply the QT interval and comment on the U wave, or should one also measure the QT-U interval? How should one describe changes in the morphology of the T wave following administration of a drug? The FDA believes that virtually any statistically significant QTc prolongation identified during drug development raises safety concerns. This concern is based on the following two issues: 1) some people, such as those with Long QT Syndrome, are at increased risk for induced ventricular arrhythmias when exposed to drugs that are known to produce only a modest effect on the QTc interval; and 2) patients are frequently receiving multiple drugs that can influence the metabolism of the parent drug or its metabolite through effects at the liver's cytochrome P450 3A4 site, with marked increase in the concentration of the QT-prolonging drug and the associated risk of ventricular arrhythmias.

The Europeans have approached this drug-related repolarization problem with the formulation of specific guidelines entitled, "Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products."[6] In brief, manual measurements and interpretation of the ECG are recommended, and it is suggested that experienced cardiologists should evaluate or over-read the ECGs. The usual measurements (P-R, QRS, and QT intervals) should be assessed as the mean of 3-5 beats. QT dispersion should also be assessed. The QT interval should be reported uncorrected and corrected for heart rate using formulae appropriate for the heart rate. The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products defined three categorical levels of concern for QTc changes relative to baseline measurements during developmental clinical trials: 1) clinically insignificant drug effects = QTc<30msec above baseline; 2) drug effects with potential concern about development of torsades de pointes = QTc 30-60msec above baseline; and 3) drug effects with significant concern about development of torsades de pointes = QTc>60msec above baseline. In addition, an absolute QTc >500msec during drug administration raises concern about the potential for drug-induced torsades de pointes. It is unclear whether these QTc concerns apply only to group data or also to individual outliers. The CPMP also suggests that drug-related QT dispersion >100msec on 12-lead ECGs is also a cause for concern. However, most of the faculty at the meeting did not feel that increased QT dispersion should be considered a risk signal.

The Philadelphia meeting was also interesting for what was not discussed. The American and European regulatory agencies have minimal experience with Holter-recorded QT measurement, the dynamics of ventricular repolarization, or heart rate variability as related to QT-prolonging drugs. The effects of drugs on ventricular repolarization are surely influenced by circadian variations in the autonomic nervous system. An important area of investigation is the circadian variation in drug-related QT effects.

It seems to me that our International Society for Noninvasive Electrocardiology has an opportunity and responsibility to develop guidelines and recommendations in these murky waters of drug-related repolarization effects. These guidelines should be evidence-based and should take into account the evolving improvement in noninvasive electrocardiology with digital signal processing for accurate and reproducible quantification of QT and RR intervals, repolarization variability, microvolt T-wave alternans, and repolarization morphology. These guidelines should

be useful to regulatory agencies, to pharmaceutical companies involved in new drug development, and to ECG and Holter manufacturers.

REFERENCES

1. Morganroth J. University of Pennsylvania's Symposium on ECGs in Clinical Drug Development. March 30, 1999, Philadelphia, PA, USA.
2. Moss A. Measurement of the QT interval and the risk associated with QTc interval prolongation: A review. Am J Cardiol 1993;72:23B-25B.
3. Bazett HC. An analysis of the time-relationship of electrocardiograms. Heart 1920;7:353-370.
4. Frederica LS. Die systolendauer im elektrokacardiogramm bei normalen menschen und bei herzkranken. Act Med Scan 1920;53:469-486.
5. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992;70:797-801.
6. Committee for Proprietary Medicinal Products. Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products. The European Agency for the Evaluation of Medicinal Products. December, 1997.