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Design and Conduct of the Thorough Phase I ECG Trial for New Bioactive Drugs

Joel Morganroth, MD

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Background

Drug-induced prolongation of the QTc interval, when excessive and in conjunction with the right risk factors, can degenerate into torsades de pointes (TdP), a frequently fatal form of polymorphic ventricular tachycardia. While it is clear that the QT interval on the electrocardiogram (ECG) may not be highly correlated with the risk of TdP, change in the QTc duration is the one relied upon by drug developers and regulatory authorities as the best predictor of a new drug’s cardiac safety. As commented on by Dr. Robert Temple from the Food and Drug Administration (FDA) in an FDA co-sponsored public meeting in Shady Grove, MD, in January 2003, if a drug prolongs the QT interval this effect is the commonest cause of new drug development delays, disapprovals, or removal from the market. Such drugs have come from many different therapeutic groups and from many different, related, and unrelated chemical structures. Some examples include the antihistamine terfenadine; the antibiotic grepafloxacin; the antispasmodic terodiline; the

From: Cardiac Safety of Noncardiac Drugs: Practical Guidelines for Clinical Research and Drug Development
Edited by: J. Morganroth and I. Gussak © Humana Press Inc., Totowa, NJ

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calcium channel blocker lidoflazine; the atypical antipsychotic sertindole; the opioid levomethadyl; and the gastric prokinetic agent cisapride.

In March 2002, the Cardio-Renal Division of the FDA developed the concept of defining a drug’s effect on the standard ECG from a single clinical research trial in a robust, intense, or thorough manner so that the results would be “definitive.” The author believes that the motivation for this new concept was to prevent the public’s exposure to drugs with uncertain or unknown effects on the ECG (with particular focus on cardiac repolarization as determined by the QTc interval duration from the standard scalar ECG). Specific details of this “intensive or definitive ECG Trial” first appeared in the November 2002 FDA–Health Canada ECG concept paper (1) entitled, “The Clinical Evaluation Of QT/QTc Interval Prolongation And Proarrhythmic Potential For Non-Antiarrhythmic Drugs.” The adjectives that have been used to characterize this trial, intensive, definitive, and thorough are comparable, but since no single trial should be viewed as 100% definitive the best descriptor for now is “Thorough ECG Trial” as used by the International Committee on Harmonization (ICH) in their current discussions on this topic. The emphasis of this chapter does not include any changes under consideration since these deliberations are still ongoing and not in the public domain, and final international guidance is likely to still respect local regulatory concepts.

The FDA Concept paper is one in a series of regulatory guidances for cardiac safety determination starting first with the Committee for Proprietary Medicinal Products (CPMP) from Europe in 1997. As these ECG guidances have evolved, they have become more detailed or “recipe-like” on how clinical research should be conducted to determine cardiac safety as defined from drug induced changes in the surface ECG (2,3). Obviously, it is important in defining the cardiac safety of drugs to also understand their agent’s effect on cardiac conduction (PR and QRS interval duration) and morphology (especially the T–U complex) as well as non-ECG derived effects on cardiac function and arrhythmogenic or proarrhythmic potential from adverse cardiac event reports.

Lack of observing TdP or its other manifestations such as syncope in a typically sized 5000 patient marketing application, is not reassuring that a drug has no cardiac liability since the 95% confidence interval for TdP would range from 0 to 1 in 1600, and 1/1600 is a very high event rate for this life threatening adverse event when millions of patients may be exposed in the market following its approval and routine clinical use. Post-marketing surveillance can help in detecting TdP but underreporting and ascribing TdP solely to underlying risks, such as heart disease limits this approach. Thus, the QTc interval duration in clinical development is the best, albeit flawed, surrogate marker available today.

The rational for the selection of which drugs when in development and how to conduct the Thorough ECG Trial is the purpose of this chapter. The principles involved in the analysis of the resultant data from the trial and their interpretation for regulatory decisions will also be addressed. Since this is a new type of trial in drug development, it is likely that many of the recommendations suggested herein will be modified as further experience is gained.

WHICH DRUGS SHOULD HAVE A DEFINITIVE ELECTROCARDIOGRAPH TRIAL? WHEN IN DEVELOPMENT SHOULD THE TRIAL BE CONDUCTED?

The FDA–Health Canada Concept paper (1) states that the need to understand precisely the ECG effects of drugs applies to all new bioactive agents, as well as any marketed drugs that are brought back to the agency for approval of new formulations, dosage