INTRODUCTION

Prolongation of the QTc interval on the surface electrocardiogram (ECG) reflects a delay in ventricular repolarization, and, when drug-induced, it is almost always a result of inhibition of the rapid component of the delayed rectifier potassium current (I_{Kr}). The other current that is infrequently inhibited is its slow component (I_{Ks}). Drug-induced prolongation of the QTc interval, when excessive in the right setting, can be pro-arrhythmic and degenerate into torsade de pointes (TdP), a potentially fatal and unique form of polymorphic ventricular tachycardia. One review in 1993 concluded, “At present, our knowledge base about the relation of the QT interval and torsades de pointes is grossly incomplete” (1). Unfortunately, despite extensive research for more than a decade since, this still remains the case today. It is therefore not surprising that more than any other drug-induced adverse reaction, it has been responsible in recent times for the withdrawal of many drugs from the market.
Significance of Drug-Induced QTc Interval Prolongation for Drug Development

Prolongation of the QTc interval is inevitable with class III antiarrhythmic drugs which, by design, are intended to produce their desired therapeutic benefit by delaying ventricular repolarization, and thereby increasing myocardial refractory period. As might be expected, these class III antiarrhythmic drugs are frequently associated TdP. Unfortunately, the potential to prolong the QTc interval and induce TdP is not confined to class III antiarrhythmic drugs. A number of class I antiarrhythmic drugs and antianginal agents as well as many noncardiovascular drugs carry what has been termed the “QT-liability.” There are now well over 10 antianginal and 90 noncardiovascular drugs recognized to have this liability (2), and the number of such drugs continues to increase almost daily. Over the last decade, regulatory authorities have rejected many new drugs or placed restrictions on the use of many old and new drugs because of concerns arising from their potential to prolong the QTc interval. Regulatory focus on drug-induced QTc interval prolongation has changed from one of a potentially desirable antiarrhythmic mechanism to that of a potentially fatal torsadogenic/pro-arrhythmic proclivity. QT interval prolongation has been regarded as a liability since it is the one measure that has been used most frequently as a marker of delayed ventricular repolarization. As will become apparent later in this chapter, assessment of clinical risk following drug-induced delay in ventricular repolarization by an NCE should be an integrated evaluation of all parameters indicative of changes in repolarization and not just the QT interval.

The frequency of TdP with noncardiac drugs is largely unknown but it is typically well below 0.1% of the patients receiving such a drug. Trials conducted during the clinical development of a new chemical entity (NCE) usually include 1500 to 3000 plus highly selected patients showing little pharmacokinetic or pharmacodynamic variability. Whereas vigorous monitoring of these patients may provide information on the potential of the NCE to prolong the QTc interval, these trials are unlikely to identify its potential to induce TdP. A database of 1500 patients will barely detect an event that occurs at the rate of 1 in 1000 and almost certainly miss the one that occurs with a frequency of 1 in 5000 or less (α error of 0.05 and β error of 0.05). Long-term safety studies also do not usually include adequate ECG monitoring at peak plasma concentrations of the drug or its metabolites. Therefore, it is highly desirable that NCEs that have systemic bioavailability should be tested during their development for their effect on ventricular repolarization with a more robust, efficient, and rational approach.

Regulatory Guidance on Investigating Drug-Induced Prolongation of the QTc Interval

In December 1997, the European Union's Committee for Proprietary Medicinal Products (CPMP) was the first regulatory authority to issue a formal guidance note on a strategy by which all NCEs should be investigated for their effect on QTc interval (3). This guidance includes recommendations on a set of nonclinical as well as clinical investigations. All strategies devised subsequently are an elaboration of, or minor variations on, the broad pattern set by the CPMP.

On November 15, 2002, the U.S. Food and Drug Administration (FDA) and Health Canada (HC) issued a joint document on clinical strategies for evaluating the effects of NCEs on QT/QTc interval prolongation (a preliminary concept paper for discussion) (4). The detailed strategy described in this document was discussed in great depth at an