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THERAPEUTIC PRODUCTS DIRECTORATE
GUIDANCE DOCUMENT

ASSESSMENT OF THE QT PROLONGATION POTENTIAL
OF NON-ANTIARRHYTHMIC DRUGS

March 15, 2001

FOREWORD

Guidance documents are intended to provide assistance to industry and health care professionals on how to comply with the Therapeutic Products Directorate policies and governing statutes and regulations. They also serve to provide review and compliance guidance to Therapeutic Products Directorate staff, thereby ensuring that the Directorate's mandate is implemented in a fair, consistent, and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternative approaches to the principles and practices described in this document *may be* acceptable provided that they are supported by adequate scientific justification. Alternative approaches should be discussed in advance with the Directorate to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that the Directorate reserves the right to request information or material or define conditions not specifically described in this guidance document, in order to allow the Directorate to adequately assess the safety, efficacy, or quality of a therapeutic product. The Therapeutic Products Directorate is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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OF NON-ANTIARRHYTHMIC DRUGS

INTRODUCTION

The Therapeutic Products Directorate subscribes to the position that an adequate pre-marketing investigation of the safety of a new pharmaceutical agent should include characterization of its effects on the electrocardiogram, particularly the QT interval. This guidance document provides suggestions to industry scientists and Therapeutic Products Directorate evaluators concerning current approaches to the conduct and regulatory review of non-clinical and clinical studies addressing the QT prolongation potential of non-antiarrhythmic drugs. The suggestions are not intended to be requirements, but rather are offered as items of consideration for scientists and physicians involved in the research or regulatory assessment of the effects of a drug on the electrocardiogram. The Therapeutic Products Directorate recognizes that the investigational approach used for a particular drug may have to be individualized depending on the pharmacodynamic, pharmacokinetic, and safety characteristics of the product, as well as its proposed clinical application. As the methodological approaches to the study of electrophysiological phenomena are undergoing rapid evolution, regular consultation of the scientific literature is recommended to determine how the status of research in this field may have changed since the issuance of this guidance document.

BACKGROUND

The ability to prolong the electrophysiological events involved in cardiac repolarization is a property that has been clinically exploited by class III antiarrhythmic agents such as amiodarone, sotalol, and bretylium. However, for many non-antiarrhythmic drugs, prolongation of cardiac repolarization is an undesired side effect, independent of their intended therapeutic effect (e.g. pimozide, thioridazine, amitriptyline, terfenadine, astemizole, cisapride, erythromycin, clarithromycin). Delayed repolarization may result in ventricular arrhythmias, including *torsades de pointes*, a potentially life-threatening polymorphic ventricular tachycardia that has been implicated in the occurrence of sudden cardiac death. *Torsades de pointes* is apparent electrocardiographically as continuous twisting of the QRS complex around the isoelectric baseline.

The Electrocardiogram (1, 2, 3)

Prolongation of cardiac repolarization is detected by means of electrocardiogram (ECG) readings. The QT interval quantifies the duration of ventricular depolarization and subsequent repolarization, beginning at the initiation of the Q wave of the QRS interval and ending where the T wave returns to isoelectric baseline. Because of its dependency on heart rate, the QT interval is routinely transformed by means of certain formulae into a variable independent of heart rate, known as the corrected QT interval (QTc).

Increases in the QT interval of the electrocardiogram are generally a reflection of delayed repolarization of the myocardium. QT prolongation creates an electrophysiological environment that favours the development of early afterdepolarizations. If the early afterdepolarizations become suprathreshold, they can trigger ectopic beats and re-entry phenomena, which may progress to *torsades de pointes*.

Arrhythmias and sudden cardiac death attributed to drug-induced QT interval prolongation have resulted in the withdrawal of several products from the Canadian market, including terfenadine, astemizole, grepafloxacin, and cisapride, as well as the decision to deny or delay marketing authorization for some new drugs.

The Action Potential (4)

The cardiac action potential is a pattern of electrical activity generated within the myocytes by a series of currents resulting from the passage of ions across the cell membrane through voltage-gated ion channels and ionic pumps. Depolarizing ionic currents convey positive charges into the myocyte, whereas repolarizing currents convey positive charges from the intracellular to the extracellular compartment.

The human cardiac action potential, whether atrial or ventricular, consists of five successively activating phases:

- phase 0: a rapid, transient influx of Na^+ (I_{Na}) through Na^+ channels, appearing in electrophysiological recordings as the upstroke of the action potential

- phase 1: early repolarization phase resulting from the transient efflux of K^+ through K^+ channels (I_{to}), appearing in electrophysiological recordings as the termination of the upstroke of the action potential

- phase 2: influx of Ca^{2+} though L-type Ca^{2+} channels (I_{Ca}), appearing in electrophysiological

-2-

recordings as the plateau of the action potential

- phase 3: late repolarization phase resulting from the efflux of K^+ through various K^+ channels (I_{Kr} or HERG, I_{sus}, and I_{Ks}), appearing in electrophysiological recordings as the sustained downward stroke of the action potential

- phase 4: inward rectifier (I_{K1}) current, which serves to maintain the resting potential

In theory, prolonged repolarization can result from decreased inactivation of the inward Na^+ current or inhibition of one or more of the outward K^+ currents. The HERG (human ether-à-go-go-related gene) and KVLQT1 potassium channels seem to have the most influential role in determining the QT interval (5). The HERG channel conveys the I_{Kr} current, whereas KVLQT1 carries the I_{Ks} current. The HERG and KVLQT1 potassium channel proteins are capable of forming hetero-oligomeric complexes with the auxiliary KCNE gene-encoded protein subunits, MiRP and MinK, respectively. The MiRP and MinK subunits may function to modulate the gating properties of the channel proteins.

Channel Subtype	Gene	Current
HERG-MiRP	KCNH2-KCNE2	I_{Kr}
KVLQT1-MinK	KCNQ1-KCNE1	I_{Ks}

The most common mechanism of QT prolongation by drugs appears to be inhibition of the rapidly-activating delayed rectifier potassium current, I_{Kr}, by blockade of HERG and/or HERG-MiRP. Astemizole, terfenadine, sotalol, thioridazine, cisapride, and quinidine are examples of drugs that impair repolarization by means of this process.

NON-CLINICAL STUDIES (1A, 4, 5, 6, 7)

The major non-clinical methodologies used in screening for QT prolongation potential include:

- *in vitro* studies of ionic currents in animal or human cardiac myocytes or heterologous expression systems
- *in vitro* studies of action potential duration in isolated hearts or cardiac tissues from laboratory animals or disaggregated cardiac myocytes from human or animal sources
- *in vivo* electrocardiogram studies in animals

- *in vivo* proarrhythmia models in animals

In Vitro Electrophysiology Studies

In vitro electrophysiology studies are capable of providing useful information on the effect of a test drug on cardiac ionic currents and action potential duration. Myocytes can be studied as single cells or as multicellular preparations. Multicellular preparations are stable model systems in which to study action potential duration. While more fragile, isolated cells minimize the diffusional barriers to the site of drug action and have the advantage of being suitable for the study of both action potential duration and ionic currents (7).

Multicellular preparations include isolated intact heart, ventricular muscle, Purkinje fibres, and papillary muscles obtained from laboratory animal species such as the rabbit, guinea pig, dog, or swine. Single cell preparations include disaggregated ventricular or atrial myocytes from humans or laboratory animals, as well as cloned human ion channels in various expression systems (4, 6, 7).

The use of human experimental material for *in vitro* cardiac electrophysiology studies has particular advantages (4). Owing to inter-species differences in the expression and pharmacology of cardiac ion channels, the morphology and duration of the cardiac action potential is species specific. Consequently, observations based on tissues obtained from laboratory animals may not be predictive of drug effects on human myocytes.

The drug concentrations tested in *in vitro* studies should span a range of at least 3 log units, covering and well exceeding the anticipated maximal therapeutic plasma concentrations of the test drug (or the EC_{50}/IC_{50} of the drug at its target site).

Appropriate positive control agents (i.e. ion channel blockers clinically associated with arrhythmias, e.g. d-sotalol) should be used to establish assay sensitivity. Temperature and electrolyte concentrations in the incubation medium should represent physiological conditions.

Problems that may confound the interpretation of *in vitro* electrophysiology studies include the following (4, 6):

- The testing of high concentrations of the drug may be precluded by limited solubility in aqueous incubation solutions.

- Adsorption of the drug to the glass or plastic of the perfusion device may necessitate concentration checks pre- and post-perfusion.

- If cardiotoxic effects are dependent on chronic exposure or long-term accumulation in myocardial tissue, the single exposure conditions of *in vitro* studies may not have predictive value.

- Because isolated cardiac cells and tissues lack metabolic capacity, *in vitro* studies using the parent compound cannot provide information on the potential effect of metabolites. The major human metabolites of the drug should be synthesized and tested independently in these systems.

- Plasma concentration may not be a reliable reference for determining the cardiac safety margin, if the myocardial concentration of the drug differs significantly from its plasma concentration. In some cases, drug concentrations in the myocardium may actually exceed plasma levels. Predictions based on free fraction plasma concentrations may result in an underestimation of the clinical outcome, as the tissue accumulation of some lipophilic compounds is not necessarily limited by protein binding. At the end of repeat dose toxicity studies, efforts should be made to quantify the concentration of the test drug and any active metabolites in myocardial tissue.

- Test articles that are susceptible to drug interactions at the level of metabolizing enzymes or the P-glycoprotein transporter may be subject to abrupt, dramatic increases in plasma levels. For such drugs, action potential prolongation or ion channel inhibition may have clinical significance even if the effect occurs only at *in vitro* concentrations anticipated to be in excess of normal therapeutic plasma concentrations. Drugs having low oral bioavailability due to extensive first-pass metabolism or active extrusion represent a particular risk in this regard.

Ionic Currents (4, 5, 6, 7)

Conventional two-electrode voltage clamp technology can be used to selectively measure ionic currents in isolated myocytes from humans or laboratory animals. Alternatively, single channel currents can be measured from whole cells or membrane fragments using patch clamp technology. While the I_{Kr} current tends to be the most usual site of action of QT prolonging drugs, prolongation of repolarization through actions on other currents (e.g. I_{Na}, I_{Ca}, I_{to}, I_{K1}, and I_{Ks}) is theoretically possible. The potency of ionic current inhibition as measured by voltage or patch clamp recordings is expressed as a 50% inhibitory concentration (IC_{50}) value. If the test drug is demonstrated to influence ion channel activity, the possible stimulation rate-dependency of this effect should be explored.

Ionic currents can also be studied using the cloned human I_{Kr} channel, produced by introduction of HERG or HERG-MiRP complementary DNA or RNA into a suitable heterologous expression system (e.g. injection of mRNA into *Xenopus* oocytes or transfection of mammalian cell lines or non-cardiac human cell lines with vectors containing the gene for the channel of interest). However, expression systems

can have marked effects on the configuration and pharmacology of ion channels (e.g. cell type-specific post-translational modifications or intracellular regulation) such that the IC_{50} values obtained are model-dependent. *Xenopus* oocytes present particular difficulties as their extensive surface area, large volume of lipophilic contents, and membrane capacitance can result in over-estimation of the IC_{50}. Mammalian expression systems such as human embryonic kidney cells (HEK293), mouse fibroblasts, and Chinese hamster ovary cells are preferred owing to their smaller size, low endogenous voltage-gated channel activity, and suitability for evaluation at physiological temperatures (5, 7).

Heterologous expression systems for HERG or HERG-MiRP have the advantage of offering single channel models in which to investigate the ability of a drug to inhibit a specific ionic current. However, the absence of a full complement of ion channels prevents these systems from identifying drugs that influence repolarization through effects on ionic currents other than I_{Kr} unless heterologous expression of additional channels (e.g. KVLQT1-MinK) is performed as well. The use of expression systems and cloned channels as the sole approach to determining the ion channel-blocking profile of a drug is, therefore, undesirable.

Action Potential Duration (1A, 4, 5, 6, 7)

QT prolonging drugs are usually associated with lengthening of action potential duration regardless of the ionic current affected. Measurement of transmembrane action potentials is possible using the microelectrode method. Parameters that may provide useful information on proarrhythmic potential include action potential duration at 90% of repolarization, early post-depolarization events, and subsequent triggered activities. Secondary electrophysiological parameters include action potential duration at 30% and 60% (or 50% and 70%) of repolarization, membrane resting potential, action potential amplitude, and maximal rate of depolarization.

As action potential prolongation generally exhibits an inverse relationship to stimulation rates, action potential studies should be conducted using a broad spectrum of stimulation frequencies to characterize this reverse rate dependency phenomenon (e.g. 12-60 pulses/min for dog tissues). Exploration of a wide range of drug concentrations is also important, as a bell-shaped concentration-response curve may be obtained if the selectivity of the test drug for a particular ion channel becomes generalized to other channels at higher concentrations. Experiments should be of sufficient duration to obtain steady-state action potential prolongation (1A, 4, 5, 6).

Isolated myocytes represent the only model in which action potential duration can be studied using human material, thus avoiding the problems involved in extrapolation of electrophysiological findings between species (4). However, disaggregated cells exhibit a high variability of action potential duration even when paced at a constant cycle length (7). Moreover, dedifferentiation of isolated myocytes following disaggregation results in a progressive alteration in action potential characteristics over time.

Purkinje fibres, papillary muscles, and ventricular muscle from animals (e.g. dog, rabbit, guinea pig) are more stable than single cells and, therefore, useful for the screening of multiple compounds. Stimulation rates and electrolyte concentrations can be readily altered in these experimental systems (7).

Isolated, intact, Langendorff-perfused hearts from cats, guinea pigs, or rabbits are suitable preparations for the screening of multiple drug candidates using either electrocardiogram or action potential recordings (7).

Any drug that produces even a modest concentration-dependent prolongation of the action potential *in vitro* should be considered a candidate for QT prolongation in clinical settings. However, as not all QT prolonging drugs cause increases in action potential duration in all tissues and species evaluated, false negative results may be an issue with any of the above models. If action potential duration is studied in non-human experimental systems, multiple species, tissues, or preparations should be tested before dismissing the possibility of a positive effect.

Other *In Vitro* Studies for the Screening of Cardiotoxic Potential (5)

Fluorescence assays can be performed in which cultured cells transfected with HERG, HERG-MiRP, or KVLQT1-MinK are incubated with potentiometric fluorescent dyes. These dyes respond to alterations in membrane potential by redistributing between the intracellular compartment and the incubation medium or by translocating between the inner and outer faces of the plasma membrane bilayer, actions that are associated with changes in the intensity of the fluorescent signal. Until the predictive value of these assays is better established, their use should be limited to the preliminary screening of test compounds to identify candidates for subsequent electrophysiological testing.

Another screening option is to perform competition binding experiments in which test drugs are studied for their ability to displace tritium-labelled dofetilide, a potent HERG antagonist, from cardiac muscle cells, cultured cells bearing heterologously expressed HERG, or membrane preparations from such cells. However, competition for dofetilide-binding sites provides no information on agonistic or antagonistic effects of the test drug on the I_{Kr} current. Moreover, this test will not identify drugs that bind to HERG at sites other than the dofetilide-binding site. The use of this assay should, therefore, be confined to the early stages of screening. Test compounds that are considered to be candidates for further drug development must be subjected to full electrophysiological studies of cardiotoxic potential.

In Vivo Electrophysiology in Animal Models (4, 6, 7)

While drug-induced QT prolongation has been demonstrated in both conscious and anaesthetized laboratory animals, the use of anaesthesia has the disadvantage of precluding repeat-dose studies and

introducing potential confounding effects on the QT interval and/or heart rate. Studies in conscious animals are generally preferred unless pronounced tachycardia interferes with correct determination of the QT interval, in which case the use of animals anaesthetized with propofol or volatile anaesthetics (e.g. halothane) may be a better option. In studies of conscious animals, the use of unrestrained, free-moving animals with chronically implanted telemetry systems represents an advantage over the use of restrained animals by circumventing the acceleration of heart rate secondary to restraint-induced increases in sympathetic tone. Avoidance of stress-related increases in heart rate is important as lower heart rates enhance the likelihood of detecting QT prolongation and *torsades de pointes*. Existing technology for radiotelemetry enables the collection of both single (lead II) and multi-lead ECGs.

Laboratory species that have been used in *in vivo* electrophysiology studies include dogs, monkeys, swine, rabbits, and guinea pigs. Dogs (4, 6) and monkeys are often considered to be the most suitable species for such studies, while the use of rats is discouraged (8). Animals of both sexes should be included in these investigations to enable the exploration of gender-dependent differences in the sensitivity to electrophysiological effects.

Safety parameters of interest include blood pressure, heart rate, QRS duration, PR and QT intervals, T wave morphology, U wave appearance, and the occurrence of arrhythmias or arrhythmic deaths. The QT interval should be computed as an average from at least three consecutive beats. Heart rate correction formulae used for human data are often not suitable for animal ECGs. Alternative approaches to addressing the heart rate-dependency of QT data in animal models may be pacing of the heart rate to a constant value or the generation of QT-RR plots (6, 7).

To characterize the dose-effect curve, *in vivo* electrophysiology studies should employ escalating doses of the test drug over a period of successive days or parallel treatment groups receiving different doses. The dose range should include and surpass the anticipated human dose, unless precluded by toxic effects that confound ECG interpretation (e.g. tremors, hyperactivity, seizures). The highest dose should be selected to yield plasma or, if known, myocardial levels of the active species (parent drug and/or metabolite) that are at least an order of magnitude in excess of therapeutic levels in humans. Blood samples should be collected for pharmacokinetic measurements to verify sufficient exposure. The selected administration route should be the same as that intended for clinical use. Studies conducted in conscious animals can employ the oral route of administration, while experiments in anaesthetized animals are limited to parenteral or intraduodenal dosing. Electrocardiogram parameters should be monitored prior to dosing and throughout the full duration of the pharmacodynamic effect of the drug with particular efforts to ensure that some measurements are obtained at the approximate T_{max}. A vehicle control group should always be included. Investigational drugs associated with QT interval prolongation should be compared with positive control agents, preferably of the same therapeutic class or having structural similarities (1A, 4, 6).

In vivo non-clinical electrophysiology studies have the advantage of exploring the potential QT-prolonging effects of both the parent drug and its metabolites. QT prolongation in *in vivo* studies that is not corroborated by *in vitro* studies using the parent compound may be indicative of a cardiotoxic metabolite.

A dose-related QT prolongation of any magnitude should be considered an adequate basis for concern. However, owing to inter-species differences in cardiac electrophysiology, *in vivo* models are not considered to have high predictive sensitivity for arrhythmogenic drugs.

Electrophysiology of Metabolites and Enantiomers

If subsequent human drug metabolism studies reveal the presence of major metabolites that are different from those generated in laboratory animals, these should be synthesized and tested independently of the parent compound in the *in vitro* and *in vivo* electrophysiology studies.

In the case of a drug that is chirally active, the potential electrophysiological effects of each of the resolved enantiomers should be explored independently in both *in vitro* and *in vivo* tests.

Special Electrophysiology Studies

If electrophysiological changes suggestive of repolarization impairment are observed in *in vitro* or *in vivo* studies at concentrations within the expected therapeutic range, discontinuation of the drug development programme for the test agent may be warranted. If there is an intention to proceed with clinical trials despite positive non-clinical evidence of delayed repolarization, or if QT prolongation is observed in clinical trials despite negative findings in the laboratory, additional non-clinical studies are recommended to examine the electrophysiological effects of the drug under simulated pathological conditions *in vitro* and in proarrhythmia models. Such experiments should be completed prior to initiating or continuing phase I trials.

Simulated Pathological Conditions (4)

Specialized *in vitro* studies should explore the effect of simulated pathological conditions on the ability of the test drug to prolong the action potential or inhibit ionic currents (e.g. low potassium concentrations to reproduce conditions of hypokalemia, slow stimulation frequencies to mimic bradycardia, oxygen deprivation to reproduce ischemia). The co-administration of established QT prolonging drugs can be investigated for the possibility of additive or synergistic effects on ionic current blockade or action potential prolongation.

Proarrhythmia Models (7, 9)

Drugs that show evidence of impaired repolarization in *in vitro* or *in vivo* non-clinical studies or in clinical trials should be tested for their effects in experimental proarrhythmia models. One such model uses anaesthetized rabbits concomitantly treated with the alpha-1 agonist, methoxamine, to increase the level of adrenergic stimulation. Other models use anaesthetised dogs with bradycardia induced by atrioventricular block or vagal stimulation, often under conditions of hypokalemia. A canine model of myocardial infarction has also been developed. These experimental systems have been used to demonstrate QT prolongation and polymorphic ventricular tachycardias with certain I_{Kr} blockers. Their predictive value for drugs prolonging the QT interval by other mechanisms is not known.

Drug-induced *torsades de pointes* has likewise been demonstrated in arterially perfused left ventricular wedge preparations from dogs. Isolated, Langendorff-perfused rabbit hearts have proved to be a useful experimental model for *torsades de pointes* under conditions of simulated hypokalemia (low potassium concentration in the perfusion medium) and bradycardia (complete AV block).

Embryotoxic Signals

Some I_{Kr} blockers have been associated with embryotoxicity in reproductive toxicology studies. Embryotoxicity may be evident as decreases in the number of litters or the number of live fetuses per dam or increases in group mean (or percentage) post-implantational losses.

Summary Comments for Non-Clinical Drug Development Phase

In vitro and *in vivo* electrophysiology studies are complementary approaches to exploring the potential of a drug to impair cardiac repolarization. No single, standardized non-clinical test is considered to have sufficient predictive value to obviate the need for other screening methods. *In vitro* studies of ionic currents and action potential duration in combination with *in vivo* electrocardiogram studies in animals represent a reasonable approach to the non-clinical detection of repolarization impairment. Drugs eliciting a signal in these tests should be subjected to further non-clinical investigations under simulated pathological conditions and in proarrhythmia models.

Any non-antiarrhythmic drug that blocks repolarizing ionic currents, enhances depolarizing currents, prolongs the cardiac action potential, increases the QT interval, or elicits arrhythmic events in non-clinical studies at concentrations comparable to the anticipated therapeutic plasma concentration should be considered to pose a theoretical safety risk to humans. The clinical development of such a drug should be pursued only if it is expected to provide a major benefit for a serious disease or disorder for which safer alternatives are not available or if the cardiotoxicity is attributed to a metabolite that is generated in animals,

but not in humans.

CLINICAL TRIALS (1A, 10, 11)

General

All drugs should receive a systematic electrocardiographic evaluation in phase I and II clinical trials whether or not positive findings were noted in non-clinical electrophysiology studies. A suspicion of delayed repolarization on the basis of non-clinical studies necessitates an intensive ECG screening programme having increased power in terms of subject/patient enrollment and the frequency of ECG measurements. Because phase I trials are generally limited to healthy volunteers, negative findings in these studies should not be automatically extrapolated to the intended patient population, in which risk factors may be present. Evidence of QT prolongation in phase I and II clinical trials may be adequate justification for terminating the clinical development programme for a drug. If clinical development is to be pursued despite QT prolongation, regular ECG monitoring should be performed on all patients receiving the drug in phase III and IV clinical trials.

For drugs having some evidence of prolonged repolarization in non-clinical studies, initial phase I and II clinical trials should employ restrictive eligibility criteria to exclude patients and volunteers considered to be at an enhanced risk for arrhythmic events. If QT prolongation is not observed in these subject groups, subsequent phase II and III clinical trials may use expanded eligibility criteria that permit the cautious study of patients with risk factors, under conditions of electrocardiogram and electrolyte monitoring. However, drugs associated with QT prolongation in phase I and II clinical trials with restrictive exclusion criteria should not normally be studied in higher risk patient groups unless the seriousness of the disease or disorder under treatment and the lack of therapeutic alternatives is considered to justify the risk of an arrhythmic event.

If a potentially QT prolonging drug is advanced to clinical trials, the Investigators' Brochure should contain a detailed account of the nature and implications of the non-clinical and, if available, clinical findings. The Patient Informed Consent Form should provide an explanation of the theoretical arrhythmogenic risk in lay language.

Design

Where not precluded by ethical or safety considerations, clinical studies addressing the issue of QT prolongation should be placebo-controlled, of randomised design, and have sufficient statistical power to detect clinically significant differences between the treatment groups. The recording of ECGs at the anticipated time of peak plasma levels for the drug or metabolite of interest should always be an objective.

In all treatment groups and treatment periods, ECGs should be scheduled for approximately the same time of the day to minimize the confounding effects of diurnal fluctuation and postprandial effects.

Dose-Effect Relationships

An adequate drug development programme should ensure that the dose-response or concentration-response relationship for QT prolongation has been adequately characterized, with a sufficient number of ECGs being collected in patients receiving the highest recommended dose. For all clinical trial phases, collection of plasma samples near the time of the ECG measurement is encouraged so as to permit an exploration of possible relationships between ECG effects and drug or active metabolite levels.

In phase I and II clinical trials, a range of dose groups should be studied. Investigation of one or more doses in excess of the proposed therapeutic dose is recommended, if not precluded by considerations of safety or tolerability. In initial studies, electrocardiograms should be collected at screening, prior to dosing on the morning of the first dose administration, at time points throughout the blood sampling period, and prior to release from the clinic. The time course of the possible effect should be adequately addressed (e.g. first dose effect, effect of increasing doses at steady-state, long-term effects, discontinuation effects). In phase III clinical trials, multiple electrocardiograms should be scheduled for baseline and screening as well as time points anticipated to coincide with steady-state peak plasma levels of the parent drug or the metabolite implicated in QT prolongation.

Important considerations in characterizing the dose- or concentration-response relationship include the maximal degree of the QTc prolongation, the steepness of the slope between QTc prolongation and dose/concentration, the relationship between the threshold dose for QTc prolongation and the therapeutic dose range, linearity or nonlinearity of the dose/concentration-effect dependency, and the time course of QTc prolongation in relation to plasma levels.

Demographic Considerations

The importance of studying QT intervals in both male and female subjects should be emphasized. Gender-dependent differences have been reported, with females having higher baseline QT intervals. Females are considered to be at a greater risk for *torsades de pointes* than are males (2). The effects of age (e.g. pediatric, geriatric), metabolic capacity (e.g. hepatic impairment, phenotypic poor metabolizers), and drug-drug interactions (e.g. co-administration with metabolic inhibitors if the parent drug is cardiotoxic or inducers if a metabolite is cardiotoxic) on QT prolongation potential may also warrant exploration.

METHODOLOGICAL ISSUES IN THE COLLECTION OF ECG DATA (1, 1A, 10, 11, 12)

The electrocardiogram database for the clinical phase of the drug development programme should be based on the collection of standard 12 lead ECGs. If the resolution for QT verification is within the desired range of <5.0 msec, a paper speed of 25 mm/sec is preferred as higher speeds (e.g. 50 mm/sec) may lead to distortion of low amplitude waves such as U waves. If the accuracy of measurements is more variable, however, a paper speed of 50 mm/sec provides improved reliability (11).

The QT interval should be determined as a mean value derived from 3-5 cardiac cycles (heart beats). Although lead II is often preferred for QT interval measurements, as the end of the T wave is usually most clearly discerned in this lead, limiting measurements to a single lead may create a selection bias, owing to variability in the distribution of maximal QT intervals among the leads (7). Use of a multi-channel recorder is, therefore, desirable to enable simultaneous recording of limb and precordial leads and selection of the longest QT interval in any lead (1).

A discrete U wave should be excluded from the QT interval measurement. However, if the T and U waves have merged to form a morphologically bizarre T wave, the QT interval should be estimated by means of linear extrapolation from the downstroke of the T wave (1) or by computerized curve fitting models. If the size of the U wave and the extent of T-U overlap is such that the end of the T wave cannot be determined, inclusion of the U wave in the QT interval measurement may be appropriate (2, 7).

ECG readings can be performed by manual or automated approaches. ECG recorders can be programmed to calculate many ECG intervals, such as the RR, QRS, QT, QTc, and PR, from digital data signals. However, while these automated recordings have a useful role in the rapid assessment of patient safety, manual recalculation of the intervals ("overread") is required for the purpose of the clinical trial database, owing to concerns about the accuracy of machine-read data. Automated measurements of low amplitude wave forms, such as the P, T, and U waves, often result in inaccurate PR and QT interval measurements (10, 11, 12). Inconsistency between manufacturers in terms of the algorithms used for calculation of the intervals is another problem to contend with in the interpretation of computerized readings. Nevertheless, computerized algorithms are the only practical option for the large volumes of data collected during Holter monitoring.

Manual ECG readings are performed using visual determinations ("eyeball")/caliper techniques or digitizing methods. Visual determinations/caliper techniques are considered to be less accurate than digitizing methods (accuracy within 20-40 msec versus • 5 msec). Digitizing methods employ a digitizing pad, magnifying lamp, and pointing device to identify the beginning and end of the QT interval for automatic recording in the ECG database (11).

ECG readings should be performed by qualified cardiologists blinded to both treatment and patient identity. Expert ECG interpretive skills should not be presumed for non-cardiologists (11). All ECGs in the clinical trial database should be interpreted by a few designated cardiologists operating from a centralized (core) ECG laboratory. The generation of multiple databases should be discouraged. Inter-reader variability can be minimized by having two cardiologists serve as readers for the entire database. The degree of intrareader reliability should be established by having the cardiologists reread a subset of the data. The participation of cardiology specialists is also valuable for diagnostic evaluation of the ECG recordings. Criteria to assess ECG diagnoses and identify adverse events should have been pre-defined by the sponsor and cardiologists (10, 12).

The quality of the ECG database will, of course, be dependent on the use of modern equipment with the capacity for digital signal processing. Such equipment should be recently serviced and calibrated. Machine calibration records and performance data should be maintained on file. All sites should use identical or similar machines, preferably obtained from a single manufacturer. For a given subject, repeat ECG measurements should be performed using the same machine. In the case of multicentre trials, training sessions are encouraged to ensure consistency of operator technique (e.g. skin preparation, lead placement, patient position) and data acquisition practices (10, 12).

Holter Monitoring

Holter monitoring is an ambulatory ECG recording obtained from one or multiple (up to 12) leads. Holter ECGs can be a valuable alternative to classical ECGs in clinical trials. In particular, if a new drug is suspected of being associated with QT prolongation and/or the occurrence of arrhythmias, Holter monitoring should be used in some studies to detect asymptomatic or transient disturbances in cardiac rhythm. A specialist consultation including Holter monitoring should be obligatory for all patients experiencing clinical symptoms or ECG findings suggestive of arrhythmias during treatment with an investigational drug.

Holter monitoring has the advantage of being amenable to measurement of the QT interval over an extended period (up to 72 h) so that the effects of diurnal fluctuation and variations of heart rate during exercise and rest can be explored. ECG measurements obtained during sleep are of particular interest as QT intervals are known to be maximal during the sleeping state. However, normal ranges for the QT interval as measured by Holter methodology do not correspond quantitatively to those for standard ECGs such that data obtaining from the two methodologies are not suitable for direct comparison.

ANALYSIS OF ELECTROCARDIOGRAM DATA FROM CLINICAL TRIALS

Data should be provided for both the uncorrected and corrected QT interval, as well as the PR and QRS intervals.

Various alternative ECG repolarization parameters have been suggested, such as the T-end interval (the interval between the peak and end of the T wave), the JT interval (the difference between the QT and QRS intervals), and the QaT interval (the interval between the peaks of the Q- and T-waves), but clinical experience is presently inadequate to establish the prognostic value of these measurements.

QT Correction Formulae (1, 1A, 10)

As the QT interval has an inverse, curvilinear relationship to heart rate, QT intervals are typically corrected for the influence of heart rate using various correction formulae. Of these, the most widely-recognized are Bazett's correction and Fridericia's correction, which are based on the following formulae:

Bazett's correction

$$QTc = \frac{QT}{RR^{1/2}}$$

and Fridericia's correction

$$QTc = \frac{QT}{RR^{a}}$$

Bazett's formula has been more frequently used in medical literature than Fridericia's formula, such that most reported criteria for normal and abnormal values are derived from Bazett's formula (1):

Rating	Adult Male (msec)	Adult Female (msec)
normal	<430	<450
borderline	430-450	450-470
prolonged	>450	>470

However, some authorities believe that Fridericia's formula may be more accurate in subjects with extreme heart rate values, as Bazett's formula tends to undercorrect at low heart rates and overcorrect at high heart rates. Many pharmaceutical companies are electing to provide data from both of these correction formulae in all QT analyses contained in their study reports.

Correction formulae based on linear regression techniques are also in use:

e.g. Framingham formula: $QTc = QT + 1.54(1-RR)$

Heart rate correction on an individual patient basis can be achieved by applying linear regression techniques to QT interval data obtained from Holter ECG monitoring over a range of heart rates.

As the optimal choice of correction formula is a subject of controversy, data corrected by formulae other than Bazett's and Fridericia's correction are permissible for drug submission purposes if provided as auxiliary analyses to those performed using the well validated formulae. The sponsor should attempt to explain any discrepancy between the results obtained by application of different correction formulae. The correction formulae to be used should be specified *a priori* in the clinical trial protocols. Selection of a heart rate correction formula *post hoc*, based on the fact that it produces the most favourable results, is never acceptable.

Analysis of QTc Interval Data (10)

For clinical trials in which multiple ECG readings have been collected per patient, the QTc data may be analysed in terms of at least four different dependent variables:

- maximal QTc intervals
- maximal change from baseline
- time-averaged QTc intervals
- area under the QTc-time curve

Electrocardiogram data should always be presented both as group means for the test drug and placebo/active comparator treatments and the proportion of individual subjects in each treatment group experiencing abnormal values. An increase in the proportion of patients experiencing abnormal values should be considered a cause for concern, regardless of whether statistically significant differences are present between group mean values.

Categorical Analyses of QTc Interval Values (1A, 10, 11)

Categorical analyses of QT data are based on the number and percentage of patients meeting and/or exceeding some predefined upper limit value. Clinically notable QT interval signals may be defined in terms of absolute QTc interval or change relative to baseline (delta) values. Absolute interval signals are QT readings in excess of some specified threshold value and require at least a single ECG reading per subject. The major problem with absolute interval signals is the failure to take account of baseline drug-free QTc values. Although categorical analyses can be limited to treatment-emergent abnormal values, such analyses will not provide information on patients with aberrant baseline values that worsen during treatment.

Delta signals occur when the change from baseline in the absolute QTc interval is greater than some predefined value. Accordingly, delta signals require a minimum of two measurements, the first of which is performed under drug-free circumstances. Interpretation of delta signals is complicated by regression toward the mean. Regression toward the mean is a measuring phenomenon, resulting from imperfect correlation between the first and second measurements, such that individuals having baseline QTc intervals that are above the mean will tend to have smaller delta values than those having baseline QTc intervals below the mean. This phenomenon is occasionally exploited inappropriately as apparent evidence that individuals with high baseline QTc intervals are less susceptible to drug-induced QT prolongation than those with lower baseline values. The effects of regression toward the mean can be minimized by using baseline values that are calculated from multiple measurements, rather than single readings. To avoid the confounding influences of circadian variation, baseline and treatment measurements should ideally be performed at the same time of day.

Consensus within the scientific community concerning the choice of upper limit values for absolute interval signals and change from baseline signals has remained elusive. While lower limits increase the false-positive rate, higher limits increase the risk of failing to detect a signal. Unfortunately, there is no well recognized threshold below which a prolongation of the QT interval is considered to be free of arrhythmogenic risk. Multiple analyses using different signal values are a reasonable approach to this controversy:

Absolute QTc Interval Signals

QTc • 450 msec
QTc • 480 msec
QTc • 500 msec

Change from Baseline (Delta) Signals

QTc increases from baseline • 30 msec
QTc increases from baseline • 60 msec
QTc change from baseline • 15%
QTc change from baseline • 25%

If a QT-prolonging effect is suspected or has not been definitively dismissed, subjects having baseline QTc intervals in excess of 450 msec should normally be excluded from clinical trials, unless the efficacy of the drug and the seriousness of the disease or disorder undergoing treatment are considered to justify the risk of an arrhythmic event. Discontinuation of a subject from a clinical trial should be considered if a treatment-emergent absolute QTc interval or a change in QTc interval exceeds a pre-determined upper limit, which may be in the range of 450-480 msec for absolute interval signal values and 30-60 msec for change from baseline signals. The choice of upper limit within these ranges will be dependent on the risk-tolerance level considered appropriate for the indication and patient group in question.

Continuous Interval Analyses of QTc Data (1A, 10, 11)

Continuous interval analyses of QTc data typically provide the mean change from the pre-therapy baseline in either the maximal or the time-averaged QTc, together with the standard deviation. The maximal QTc interval (highest on-therapy QTc interval for an individual) is considered to be a more robust statistic than the time-averaged QTc (average of all on-therapy QTc intervals for an individual). Time averaging of QT intervals assumes that within subject variation is attributable only to random noise, thus ignoring the influence of concentration-effect relationships and circadian variations. Time-averaged values thus have a tendency to underestimate the magnitude of a drug effect on the QT interval, so diminishing the power to detect significant prolongation.

A small mean increase in the QTc interval, which appears not to be clinically significant in itself, may nonetheless signal an enhanced risk with the test drug, if not matched by a corresponding change in the placebo control group.

Another approach is to calculate the area under the QTc interval time curves (AUCs) for on-therapy versus pre-therapy measurements. Successful use of the AUC as the dependent variable necessitates the collection of multiple data points for each subject and synchronization of the ECG measurement schedule for both the baseline and treatment phases. AUC values have the advantage of being univariate summary measures that integrate effect over time relationships and are relatively stable to random fluctuations. However, published experience with this approach is limited and interpretation of QTc AUC values is complicated by the absence of well recognized criteria for distinguishing clinically

relevant absolute or delta values. Therefore, use of AUC computations in drug submissions is permissible only as an auxiliary to more established data analyses.

Mean changes from baseline derived from time-averaged or maximal QTc data may mask the presence of outliers having extreme QTc interval changes. As the absence of statistically or clinically significant differences in mean changes between the test drug and comparator groups does not preclude the possibility of marked QTc prolongation occurring in individual patients, summary statistics must always be accompanied by appropriate categorical analyses.

Choice of Baseline (10)

Use of baseline values representing single readings is a practice to be discouraged. Baseline ECG measurements for a given subject should be computed as the mean or median of multiple measurements in order to reduce the effects of regression toward the mean and enhance the precision between measurements.

QT Dispersion (1A, 7)

QT dispersion is defined as the difference between the shortest and the longest QT intervals measured on the 12-lead ECG and has thus been considered to provide a reflection of the regional heterogeneity of cardiac repolarization. Normal values are typically in the range of 40-60 msec. Absolute values of • 100 msec and changes from baseline of >100% have been suggested as clinically notable signals for categorical analyses. The role of QT dispersion as a parameter in the evaluation of the cardiotoxic risk of a drug is a subject of debate, as the predictive value of this parameter has yet to be consistently demonstrated. Analyses of QT dispersion may be used to supplement, but not replace, standard analyses of QTc interval duration.

Morphological Analyses (11)

The following analyses of morphological changes should be provided:

• incidence of morphological changes (predetermined definitions) versus control group

• incidence of morphological changes from baseline categorized as worsened, unchanged, or improved

• incidence of morphological changes characterized as clinically significant or insignificant

Attention should be directed to changes in T wave morphology and the occurrence of U waves as these phenomena may precede *torsades de pointes*.' T wave alternans (beat-to-beat variability in the amplitude and/or morphology of the T wave) is associated with an increased likelihood of ventricular tachyarrhythmias. Other T wave abnormalities reflective of delayed repolarization include double humps ("notched" T wave), wide bases, indistinct terminations (TU complex), delayed inscription (prolonged isoelectric ST segment), and sinusoidal oscillations (13).

U waves are considered abnormal when they reach an amplitude of • 25% of the T wave in any lead.

Integrated Analyses and Meta-Analyses

Integrated analyses and meta-analyses may provide useful information on the adequacy of the safety database in terms of the total number of patients receiving ECG recordings, as well as overall estimates of effect size and incidence of clinically notable events. Analyses of pooled ECG data from several clinical trials may increase the power to detect a significant drug effect. However, the clinical trials used in the generation of such analyses should be clearly identified and their inclusion justified. The data from certain trials may be inappropriate for pooling if the study conditions under which they were attained were not representative of the proposed clinical use. For example, if the pooling results in the inclusion of data from many patients receiving sub-therapeutic doses of the drug, the calculated means and incidence values may under-estimate the magnitude and frequency of the QT prolonging effect at the recommended therapeutic doses.

Subset Analyses

The availability of subset analyses for sex, age (e.g. <18 yrs, • 65 yrs), cardiac co-morbidities, hepatic impairment, renal impairment, and other special patient populations is recommended. Particular attention should be directed to subset analyses for sex, as female gender is recognized to be a predisposing factor for drug-induced QT prolongation and *torsades de pointes*. Many cardiac co-morbidities are also considered to be risk factors. Such subset analyses should be provided for both continuous interval and categorical analyses.

Statistical Analyses (10)

Clinical trials which investigate the QT-prolongation potential of a drug should be of sufficient power to detect significant differences between treatment groups.

The comparative merits of ANOVA and ANCOVA models for the testing of between group

differences in QT data should be considered. While both approaches test the hypothesis that no difference exists between the mean values among treatment groups, the ANOVA assumes homogenous baselines among subjects randomised to the various dose groups, while the ANCOVA model is based on the assumption that the regression coefficient relating baseline to observed QT is homogeneous among all subjects in the trial. ANCOVA analyses are usually preferred over ANOVA analyses for the testing of between group differences in QT data.

A possible disadvantage of the ANCOVA model is the assumption of a linear relationship between the covariate and dependent variable. In many instances, the relationship between dose/ concentration and pharmacodynamic effect may be nonlinear or exhibit hysteresis. Appropriate approaches to the statistical analysis of nonlinear relationships and hysteresis include the use of nonlinear mixed-effect software programs such as NONMEM or P-Pharm.

ADVERSE EXPERIENCES POSSIBLY RELATED TO QT PROLONGATION

Premature Discontinuations or Dosage Reductions

Attention should be directed to subjects or patients discontinuing clinical trials due to QT prolongation. Information should be provided on the basis for premature termination of the patient (e.g. a QTc value in excess of a protocol-defined upper limit, occurrence of QTc prolongation in association with symptoms of arrhythmia) as well as the dose and duration of treatment, plasma levels if available, demographic characteristics, and possible risk factors.

Dosage reductions prompted by QT interval prolongation should also be documented.

Clinical Trial Adverse Experience Reports

Impairment of cardiac repolarization may result in a range of adverse experiences including the following (3, 13, 14):

- dizziness
- palpitations
- syncope
- ventricular tachycardia
- *torsades de pointes*
- ventricular fibrillation
- seizures (due to cerebral ischaemia resulting from arrhythmia)

- cardiac arrest
- arrhythmias (not otherwise specified)
- serious cardiac adverse events
- sudden cardiac death

Any excess in the incidence of such events in the investigational drug treatment group as compared with the placebo and/or active control groups is justification for concern. Detailed patient narratives should be provided for all serious cardiac adverse events. In assessing the possible causal relationship of drug-induced QT prolongation, attention should be directed to considerations such as temporal relationship, dose-dependency, evidence of positive dechallenge or rechallenge, corroborative non-clinical findings, and ECG results, preferably collected at the time of the event. As the QTc interval is a parameter subject to considerable fluctuation, a possible role for QT prolongation cannot be definitively dismissed on the basis of on-therapy ECG measurements performed prior or subsequent to the adverse event. Potential relationships between the occurrence of the adverse events and patient age, gender, pre-existing cardiac disease, electrolyte disturbances, obesity, concomitant medications, and other risk factors should be explored.

In evaluating the safety database of a new drug, consideration should be given to the extent to which the inclusion and exclusion criteria for patient eligibility may have influenced the study population with respect to the risk of QT prolongation and associated adverse events (e.g. exclusion of patients with cardiac co-morbidities or renal/hepatic impairment, prohibition of diuretics as concomitant medications). Ideally, the phase II and III studies should include an adequate representation of female and elderly patients.

Standard criteria should be specified in the clinical trial protocol for defining what constitutes an adverse event with respect to QT recordings. If symptoms or ECG findings suggestive of an arrhythmia are experienced by a subject during a clinical trial, an urgent specialist assessment should be arranged. Immediate discontinuation of the suspect drug may be appropriate. If the investigational drug is to be continued in the affected subject, Holter monitoring should be instituted.

As the incidence of *torsades de pointes* and sudden cardiac death is expected to be quite low with many QT prolonging drugs, the failure to observe these events over the course of the typical clinical trial programme should not be a sufficient basis for dismissing the possible arrhythmogenic risks of a drug when these are suspected on the basis of ECG data. Owing to their rarity, serious ventricular arrhythmias with a QTc prolonging drug are often not reported until large populations of patients have received the agent in post-marketing settings.

Post-Marketing Adverse Experience Reports

If the drug is licensed for sale in other countries, the post-marketing adverse experience data should be examined for events of QT prolongation, cardiac arrest, sudden cardiac death, and ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, and *torsades de pointes*.

REGULATORY IMPLICATIONS AND RISK MANAGEMENT STRATEGIES

QT prolongation, with or without documented arrhythmias, may be the basis for non-approval of a drug or discontinuation of its clinical development. Failure to perform an adequate non-clinical and clinical assessment of the potential QT prolonging properties of a drug may likewise be adequate justification to delay or deny marketing authorization.

Drugs that prolong the QT interval at recommended therapeutic doses should not be candidates for clinical development and license approval unless they provide important benefits for serious diseases or disorders not amenable to treatment with safer drugs or have demonstrated efficacy in patients refractory or intolerant to the alternative drugs. Exceptions may be granted for drugs having large margins of safety (i.e. a drug that results in QT prolongation only in situations of excessive overdosage).

If QT prolongation is a shared feature of the drugs of a particular therapeutic class, a QT prolonging drug may be acceptable if the sponsor has investigated the magnitude and frequency of the QT changes caused by the new drug and demonstrated these to be not worse than the effects of its comparators. Special considerations may also apply if the therapeutic alternative poses a substantial risk of one or more serious adverse reactions (e.g. aplastic anemia, fulminant hepatic failure) which are considered to represent a safety hazard equal to or greater than that presented by the QT prolonging drug. The selected comparators should be drugs currently recognized as first line therapies for the disorder in question, unless the company is seeking a claim for efficacy in refractory patients.

Documentation of QT prolongation in the Product Monograph in the form of contraindications, warnings, precautions, and descriptions of ECG changes and related adverse events may not be considered adequate as a risk management measure if the number of risk factors and the complexity of screening and monitoring procedures are judged to be impractical from a clinical use perspective.

A susceptibility to clinically important drug-drug or drug-food interactions (3A) that increase the cardiotoxicity of the drug would be expected to have a negative impact on the risk-benefit profile (e.g. metabolic deactivation of sensitive CYP3A4 substrates such as terfenadine, astemizole, and cisapride is inhibited by azole antifungals, macrolide antibiotics, and grapefruit juice, resulting in an exaggerated QT

prolongation effect). Characteristics that would result in a QT prolonging drug being considered a high risk candidate for metabolic drug interactions include a steep concentration-effect relationship or elimination that is primarily dependent upon a single metabolic pathway. Moreover, drugs having a low oral bioavailability due to extensive first pass metabolism or active extrusion by the P-glycoprotein transporter may be subject to abrupt, dramatic increases in plasma levels if their metabolism or efflux is inhibited.

If a drug is to be approved in spite of concerns regarding QT prolongation potential, the Product Monograph should contain the following information:

- If safer therapeutic options are available for the indication in question, the QT prolonging drug should be restricted to patients who are refractory or intolerant to other treatment modalities.

- The QT prolonging effects of the drug should be quantified in terms of both the mean change from baseline in the maximal on-therapy QTc interval and the percentage of patients with on-therapy QTc readings in excess of defined, clinically notable, upper limit values. The number of patients who were subjected to ECG evaluations in clinical trials should be specified.

- The use of the drug should be contraindicated in patients having diseases or disorders that increase the possibility of arrhythmic events. Risk factors for drug-induced arrhythmias secondary to QT interval prolongation include, but are not limited to, the following (2, 3, 13, 14):

    - congenital or acquired long QT syndrome (e.g. Romano-Ward syndrome, Jervell and Lange-Nielson syndrome)
    - ischemic heart disease or infarction
    - congestive heart failure
    - left ventricular hypertrophy
    - impaired left ventricular function
    - positive history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation)
    - cardiomyopathy
    - bradycardia
    - myocarditis
    - cardiac tumours
    - mitral valve prolapse
    - rheumatic fever
    - bundle branch block
    - sinus node dysfunction
    - increased vagal tone

- severe hepatic or renal dysfunction (for drugs eliminated principally by these routes)
- electrolyte imbalance (e.g. hypokalemia, hypomagnesemia, hypocalcemia, acidosis, intracellular Ca^{2+} loading) or conditions predisposing the patient to electrolyte imbalances (e.g. chronic vomiting, anorexia nervosa, bulimia nervosa)
- concomitant treatment with other drugs or foods that inhibit the metabolism of the QT prolonging drug (3A)
- concomitant treatment with digoxin
- concomitant treatment with drugs that affect the electrolyte balance (e.g. diuretics)
- hypothyroidism, hyperparathyroidism, pheochromocytoma
- head injury
- stroke
- subarachnoid hemorrhage
- hypothermia
- nutritional deficits (e.g. eating disorders, liquid protein diets)
- alcoholism

If the medical condition for which the drug is intended is associated with a degree of morbidity or mortality that exceeds the potential danger of arrhythmogenic effects, the risk factors listed above may be presented as warnings rather than contraindications.

- The concomitant use of two or more QT-prolonging drugs should be contraindicated. Drugs with QT-prolonging effects include, but are not limited to, the following:

  - class IA antiarrhythmics (e.g. quinidine, procainamide, disopyramide)
  - class III antiarrhythmics (e.g. amiodarone, sotalol, bretylium, ibutilide)
  - class IC antiarrhythmics (e.g. flecainide)
  - bepridil
  - phenothiazine antipsychotics (e.g. thioridazine, mesoridazine, chlorpromazine)
  - pimozide
  - risperidone
  - tricyclic antidepressants (e.g. amitriptyline, imipramine, desipramine, doxepin)
  - venlafaxine
  - maprotiline
  - lithium
  - macrolide antibiotics (e.g. erythromycin, clarithromycin)
  - fluoroquinolone antibiotics (e.g. moxifloxacin)
  - pentamidine
  - antimalarials (e.g. halofantrine, quinine, chloroquine, mefloquine)

- probucol
- astemizole
- terfenadine
- droperidol
- dolasetron
- cisapride
- tamoxifen
- tacrolimus

The above list is not comprehensive. Current medical literature should be consulted for newly approved QT-prolonging drugs or older drugs for which QT-prolonging effects have recently been established.

- Screening ECGs should be performed prior to the initiation of treatment. Treatment with a QT-prolonging drug should not be initiated in patients with abnormally long baseline QTc intervals. Monitoring of the QT interval during treatment may be advisable, particularly during the initial stages of treatment or after a dosage increase. However, owing to intra-individual variability of the QT interval, conventional ECG screening and monitoring are not considered to be highly effective approaches to identifying patients at risk for arrhythmias related to drug-induced QT prolongation.

- Patients reporting signs and symptoms suggestive of arrhythmias (e.g. dizziness, palpitations, syncope) should receive ECG evaluations and specialist assessments.

- Serum potassium, calcium, and magnesium levels should be monitored during treatment with prompt correction and/or discontinuation of the QT prolonging drug in the event of an electrolyte abnormality. Patients should be advised of drugs and medical conditions that may lead to electrolyte abnormalities (e.g. use of diuretics, severe dehydration, vomiting, eating disorders).

- Discontinuation of the drug should be recommended if an arrhythmic event occurs or if the ECG shows a QTc interval above an upper limit that is considered to represent an appropriate risk-tolerance level for the indication in question (e.g. 450-480 msec).

- The dose-/concentration-dependency of the QT prolongation effect should be described in the Product Monograph. Dosage recommendations should encourage the use of the lowest effective dose of the drug and specify a maximum recommended dose which should not be exceeded.

- For an intravenously administered QT prolonging drug, limitations on the infusion rate may be critical.

- The occurrence of *torsades de pointes* during treatment with a QT prolonging drug requires emergency medical care, including urgent specialist assessment. The suspect drug(s) should be immediately discontinued. Infusion of magnesium may terminate *torsades de pointes* arrhythmia even in patients with normal magnesium levels. Electrolyte abnormalities such as hypokalemia should be corrected. Control of the arrhythmia may be achieved through accelerating the heart rate by means of cardiac pacing. Increasing the heart rate shortens the QT interval and prevents the lengthy post-ectopic pauses that favour the development of *torsades de pointes*. Degeneration of *torsades de pointes* into ventricular fibrillation may necessitate treatment with electrical cardioversion or defibrillation. Strategies for control of the arrhythmia must be maintained until the drug and/or its cardiotoxic metabolites have been eliminated (2, 3, 15).

- The "Information for the Consumer" section of the Product Monograph should explain in lay language the effect of the drug on the electrical activity of the heart and the relationship between this ECG effect and the theoretical or demonstrated risk of arrhythmias. Patients should also be alerted to symptoms of possible arrhythmia such as dizziness, palpitations, and fainting and instructed to seek immediate medical attention if these develop.

Prior to the launch of a QT prolonging drug, a letter should be issued to health care professionals advising them of the cardiotoxic risks associated with the new agent and appropriate risk management strategies.

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