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Evaluation of Drug-Induced QT Interval Prolongation

Implications for Drug Approval and Labelling

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Abstract

Assessment of proarrhythmic toxicity of newly developed drugs attracts significant attention from drug developers and regulatory agencies. Although no guidelines exist for such assessment, the present experience allows several key suggestions to be made and an appropriate technology to be proposed.

Several different *in vitro* and *in vitro* preclinical models exist that, in many instances, correctly predict the clinical outcome. However, the correspondence between different preclinical models is not absolute. None of the available models has been demonstrated to be more predictive and/or superior to others. Generally, compounds that do not generate any adverse preclinical signal are less likely to lead to cardiac toxicity in humans. Nevertheless, differences in likelihood offer no guarantee compared with entities with a preclinical signal. Thus, the preclinical investigations lead to probabilistic answers with the possibility of both false positive and false negative findings.

Clinical assessment of drug-induced QT interval prolongation is crucially dependent on the quality of electrocardiographic data and the appropriateness of electrocardiographic analyses. An integral part of this is a precise heart rate correction of QT interval, which has been shown to require the assessment of QT/RR relationship in each study individual. The numbers of electrocardiograms required for such an assessment are larger than usually obtained in pharmacokinetic studies. Thus, cardiac safety considerations need to be an integral part of early phase I/II studies.

Once proarrhythmic safety has been established in phase I/II studies, large phase III studies and postmarketing surveillance can be limited to less strict designs. The incidence of torsade de pointes tachycardia varies from 1 to 5% with clearly proarrhythmic drugs (e.g. quinidine) to 1 in hundreds of thousands with drugs that are still considered unsafe (e.g. terfenadine, cisapride). Thus, not recording any torsade de pointes tachycardia during large phase III studies offers no guarantee, and the clinical premarketing evaluation has to rely on the assessment of QT interval changes. However, since QT interval prolongation is only an indirect surrogate of predisposition to the induction of torsade de pointes tachycardia, any conclusion that a drug is safe should be reserved until postmarketing surveillance data are reviewed.

The area of drug-related cardiac proarrhythmic toxicity is fast evolving. The academic perspective includes identification of markers more focused compared with simple QT interval measurement, as well as identification of individuals

with an increased risk of torsade de pointes. The regulatory perspective includes careful adaptation of new research findings.

Abnormalities of ventricular repolarisation are a serious cardiac risk factor. Repeated clinical studies have shown that patients with a prolonged QT interval, as well as patients with other repolarisation abnormalities such as shifts in the T wave axis, are at greater risk of cardiac mortality and malignant cardiac arrhythmias.[1-3] At present, experience is mostly limited to abnormal prolongation of the QT interval, although a consensus is emerging, supported by some initial data,[3,4] that the morphology of the T wave might be of equal, if not even greater, importance.

The processes of cardiac repolarisation are affected by a number of drugs. The most prominent example is drugs that have been developed for the particular purpose of changing cardiac repolarisation, the so-called class III antiarrhythmic agents. Generally, these drugs achieve their therapeutic effect by adjusting the properties of the potassium ion channels, thus reducing the net outward repolarising current and prolonging the action potential duration of cardiac myocytes. While these effects on cellular electrophysiological properties may regularise the repolarisation sequence within the myocardium, thus achieving an antiarrhythmic effect, these compounds may change the delicate balance of depolarisation, repolarisation and possible after-depolarisation in a deleterious way. Thus, the antiarrhythmic drugs that prolong cardiac repolarisation may induce a potentially fatal arrhythmia known as torsade de pointes.

When antiarrhythmic drugs were widely used for secondary prevention of malignant ventricular arrhythmias in ischaemic heart disease, their potential proarrhythmic effects probably did not outweigh their therapeutic achievements. However, following the development of the automatic implantable cardioverter defibrillator, antiarrhythmic drugs are no longer the method of choice for secondary prevention of malignant ventricular tachyarrhythmias because they are not as effective as once thought. Today, most antiarrhythmic drugs are used for (and many have been developed for) the conversion of atrial fibrillation and/or maintenance of sinus rhythm in patients with recurrent forms of atrial fibrillation. Generally, such patients are at low risk of potentially fatal ventricular arrhythmias and the possibility of ventricular proarrhythmic effects from the atrial antiarrhythmic therapy is of serious concern. Indeed, the incidence of torsade de pointes in patients treated with quinidine has been reported to be between 2.0 and 8.8%,[5-8] whereas in patients treated with sotalol an incidence between 1.8 and 4.8% was reported.[9-11]

It has been known for decades that other drugs, e.g. erythromycin[12] or other antibacterials[13,14] might also prolong the QT interval. Only more recently was it appreciated that noncardiac drugs may also have proarrhythmic properties such as torsade de pointes tachycardia.[15-17] Understandably, case reports linking torsade de pointes to noncardiac drugs have triggered substantial interest both from drug developers and from regulatory agencies responsible for the approval of new medicinal products. In this sense, the preapproval assessment of cardiac safety and the awareness of potential cardiac proarrhythmic toxicity of new drugs is a rather novel concept compared with other regulatory concerns such as haemo-, hepato- and nephrotoxicity.

The number of nonantiarrhythmic drugs implicated in proarrhythmic toxicity is increasing all the time, and reports exist listing as many as 50 clinically available or investigational noncardiovascular compounds and cardiovascular nonarrhythmic drugs as agents that may aggravate and/or provoke torsade de pointes.[18] A number of previously approved as well as newly developed compounds have been withdrawn from the market generally or at least in some countries (e.g. prenylamine, terodiline, sertindole, astemizole, terfenadine, cisapride) or had their labelling severely restricted.

In spite of the recognised importance of cardiac safety of newly developed compounds, the meth-

odology for the preclinical and clinical assessment of cardiac proarrhythmic toxicity is not at all straightforward. Parallel to the advancements made in the field, intense discussions continue between drug developers and regulatory agencies [e.g. the recent US Food and Drug Administration (FDA) hearing on ziprasidone].[19] Having this in mind, this article describes the present understanding of the cardiac proarrhythmic potential of newly developed drugs, the assessment of this risk, and its implications for drug labelling. Although some initial signals in respect of cardiac safety might be obtained from preclinical studies, their relationship to clinical findings is not very direct. Therefore, the preclinical assessment is discussed more briefly in this text than the clinical studies and their implications.

Proarrhythmia is only 1 form of cardiac toxicity, the other forms include myocarditis, cardiomyopathy (e.g. caused by the antipsychotic clozapine)[20] and heart failure (e.g. that attributable to chemotherapy).[21] Moreover, there are many forms of drug-induced proarrhythmia, including excessive slowing of conduction, sinus and/or atrioventricular (AV) nodal suppression, paradoxical acceleration of AV nodal conduction, as well as an increased frequency of monomorphic ventricular tachycardias. Despite this, our present text is concerned with the induction of torsade de pointes tachycardia. Therefore, when discussing proarrhythmic toxicity, we shall have mainly this type of proarrhythmia in mind.

1. QT Interval and Torsade de Pointes Tachycardia

The electrocardiographic T wave is a composite recording of currents between individual ventricular myocytes that appear at different levels of repolarisation. The orientation and shape of the T wave is determined by the transmural and apex to base distribution of action potential durations that exist because of heterogeneity in the density of the various ion channels that determine ventricular repolarisation. Uniform as well as heterogeneous changes in the duration of the action potential therefore translate into changes of the shape of the T wave and of the duration of the QT interval. Although specific pathologies are linked to shortening of the QT interval,[22] drug-related changes of repolarisation ion channels generally lead to QT interval prolongation.

It can be deduced from the ionic basis of the ventricular action potential that reduction of outward currents and/or enhancement of inward currents during phase II and III of the action potential will prolong its overall duration. Blocks or activation of individual ionic channels have different effects on the action potential duration of different cell types. Namely, Purkinje fibres, subendocardial myocytes, mid-myocardial M cells and subepicardial myocytes (and several different populations of atrial myocytes)[23,24] have a different distribution and/or proportion of the various ion channels that determine repolarisation. For preclinical studies, it is also important to note that there are substantial differences between currents involved in these cell types among different species. For instance, in isolated guinea pig, sheep and dog myocardium, both I_{Kr} and I_{Ks} are present, whereas in cat, rabbit and humans I_{Kr} has been reported to be the dominant current,[25] although discussions continue on these findings. Differences in the composition of the individual currents also exist between male and female, and also between healthy and diseased hearts.

The reduction in net outward current and/or increase in inward current may facilitate the development of early after-depolarisations. Preferentially, early after-depolarisations occur in M cells and Purkinje fibres. When the occurrence of early after-depolarisations in these tissue types coincides with increased transmural heterogeneity of ventricular repolarisation, the early after-depolarisation may lead to slowly propagating extrasystoles that trigger torsade de pointes tachycardia.[26-29]

The likelihood of inducing torsade de pointes increases with increased heterogeneity of repolarisation (i.e. with an overall increase in repolarisation abnormality) as well as with the increased probability of early after-depolarisations. From this

point of view, there are clearly differences between different compounds. However, there also appear to be important differences in susceptibility between different individuals. Recently, it has been demonstrated that in patients who developed torsade de pointes secondary to class III antiarrhythmics, drug-induced QT prolongation was more marked than in patients without the tachycardia and, surprisingly, it was not related to the dose of the drug.[30] Thus, some patients appear to be more susceptible to cardiac toxicity of a particular compound than others.

2. Preclinical Studies

The potential risk of cardiac proarrhythmic toxicity clearly calls for an early detection of the effects that any new pharmacological compound may have on ventricular repolarisation. Not surprisingly, however, the precision of *in vitro* and *in vivo* animal models to predict QT interval prolongation and torsade de pointes induction in humans is far from perfect. Drugs exist that have been reported to block the I_{Kr} channel and have other preclinical markers *in vitro* but not prolong the QT interval in humans. For instance, cetirizine has been reported to block the I_{Kr} channel (although at rather high concentrations),[31] to prolong action potential duration in rabbit Purkinje fibres[32] and to cause mild biphasic QT interval prolongation and early after-depolarisations in Langendorff-perfused rabbit ventricles.[33] However, it does not prolong the QT interval clinically[34] or in laboratory animals,[35] most probably because of its very low lipophilicity.[36] Thus, preclinical studies are mainly useful in the initial screening of new chemical entities. Having a choice of several different compounds for further development, it is probably not too unreasonable to concentrate first on those with negative preclinical tests.

All drugs that have been so far shown to cause torsade de pointes tachycardia cause a substantial degree of I_{Kr} channel blockade, for instance quinidine,[37] flecainide,[37] astemizole,[38] terfenadine,[39] cisapride,[40] bepridil,[41] haloperidol[42] and others.[18] Cardiac proarrhythmic toxicity solely attributable to alterations of other ion channels has not been noticed. This does not, however, mean that such a possibility can be excluded. Probably, chemical entities exist and will occur in the future that cause cardiac toxicity because of different mechanisms. Similarly, drugs that cause QT prolongation because of other effects than I_{Kr} blockade may not be proarrhythmic. A possible example of such a drug is the combined potassium and calcium antagonist verapamil. QT interval prolongation with verapamil is linearly correlated to the plasma concentrations[43] but there are no described cases of verapamil-induced torsade de pointes.

2.1 *In Vitro* Models

Broadly, there are 4 categories of *in vitro* models that can be used to study cardiac toxicity: heterologous expression systems, disaggregated cells, isolated tissues and isolated intact hearts.

Heterologous expression systems have been mainly used to study drug effects on the I_{Kr} channel. Various expression systems are available. A well established method is the microinjection of ion channel RNA into *Xenopus laevis* oocytes.[44,45] Because of some limitations of this model,[46] mammalian recombinant expression systems are increasingly used. Most studies have used human embryonic kidney cells, mouse fibroblasts and Chinese hamster ovary cells.

Although these models allow the investigation of channel blockade under different concentrations ranging over several magnitudes, their results should not be over-estimated. Drugs in which cardiac toxicity is attributable to ionic changes other than I_{Kr} blockade would not be detected as a potential proarrhythmic risk. In addition, not only the parent compound but also all its metabolites need to be tested; hence all potential metabolites need to be precisely identified. Effects on other channels, some opposing, some exacerbating the effect on I_{Kr}, may also coexist. For instance, it has been proposed that simultaneous calcium and potassium channel blockade makes the proarrhythmic effects of QT prolongation much less likely.[47] Although whole panels of ion channels need to be investi-

gated, the net result depends differentially on the drug concentration and the heart rate, and it is difficult to predict the effect on more integrated electrophysiology systems. Thus, only approximate results may be drawn from the isolated channel studies.

Isolated tissue studies serve an important purpose of studying the effects on all the ionic channels in combination. It is important to select species for which sufficient data exist demonstrating a similarity with human myocardium. The tissues from dog, rabbit and guinea pig have been most used. The variability of ventricular myocytes requires endocardial, epicardial and M cell muscle regions to be studied to ensure that the potential for heterogeneous effects is well explored. Even with these studies, the relationship between the results of channel studies on one hand, and clinical observations in humans on the other hand, is far from direct. For instance, risperidone is usually considered clinically safer than sertindole, which is believed (perhaps based on data of questionable quality) to prolong the QT interval in humans more and to be less safe than risperidone. However, although risperidone was reported to cause substantial changes of action potentials of rabbit Purkinje fibres, including triggered after-depolarisation activity, the changes with sertindole were truly minimal.[48]

For screening a large number of compounds, the Langendorff perfused guinea pig or rabbit heart, which allows electrocardiogram (ECG) and/or monophasic action potential recordings, has been reported to give consistent information on I_{Kr} blocking drugs when compared with other compounds. However, precision of such a consistency is not absolute. An example might be the comparison of fluoroquinolone antibacterials that have been investigated in terms of both I_{Kr} channel blockade and prolongation of action potential of Purkinje fibres. When investigating the effects on the human ether-a-go-go related gene (HERG) K^+ channel (cloned from a human neuroblastoma cell line), IC_{50} values [95% confidence intervals (CIs) in parentheses] of 18 (13 to 26), 50 (37 to 66), 129 (99 to 167) and 996 (562 to 1670) μmol/L were found for sparfloxacin, grepafloxacin, moxifloxacin and ciprofloxacin, respectively.[49] Thus, an obvious sequence of potency of sparfloxacin > grepafloxacin > moxifloxacin > ciprofloxacin was found. When concentrations required to produce 15% prolongation of canine Purkinje fibres were measured (at a stimulation frequency of 1Hz), values of 4.2 ± 0.7, 9.3 ± 0.9, 9.9 ± 1.6 and 72.8 ± 26.4 mg/L were found for sparfloxacin, grepafloxacin, moxifloxacin and ciprofloxacin, respectively.[50] Thus, the potency sequence of sparfloxacin > grepafloxacin = moxifloxacin > ciprofloxacin was found, confirming the extremes of sparfloxacin and ciprofloxacin but not the difference between grepafloxacin and moxifloxacin, which seemed to be substantial for I_{Kr} channel blockade.

Even with the Purkinje fibre model, a failure to see excess in action potential prolongation does not provide complete security of excluding proarrhythmic toxicity in humans and the risk of torsade de pointes. This is not only because of the potential toxicity of metabolites but also because of differences between and within species (including humans). For instance, in agreement with the previous example but contrary to the usual clinical perception, risperidone was found significantly more potent than sertindole in prolonging the QT interval of the perfused feline heart.[51]

2.2 *In Vivo* Animal Models

Multilead ECGs may be recorded in conscious or anaesthetised guinea pigs, rabbits, dogs or pigs.[52-54] Studies of serial drug-induced changes in repolarisation require baseline stability of the model that is frequently difficult to achieve, especially with dogs in which the T wave morphology is highly variable. Drugs that change not only the repolarisation but also affect the heart rate lead to an additional problem of appropriate heart rate correction. Methods that are frequently used in humans to correct the QT interval for heart rate have been reported not to be applicable to animals, and although some data on heart rate correction in different species exist,[55] the extrapolation of results

for the prediction of effects in humans may be problematic.

Canine models with AV block have been described.[56-58] The AV block allows different pacing modes to be used to mimic the sequences of the short-long-short intervals that are typically observed in the initiation of torsade de pointes in patients with the acquired or congenital long QT interval syndrome. Experiments involving these models have been reported that seem to correlate with established clinical findings of drugs with known cardiac proarrhythmic toxicity.[58] However, it has also been reported that the chronic AV block induces ventricular hypertrophy.[59] Since hypertrophy causes modifications of the transmural and apex-based heterogeneity of repolarisation properties of myocardial cells, the model might be suitable for predicting cardiac toxicity in cardiac patients with myocardial hypertrophy but potentially less suited to forecast proarrhythmic danger in normal hearts. A variety of other experimental models of torsade de pointes have also been developed, but none is universally applicable.[60]

2.3 Value of Preclinical Studies

In many instances, preclinical data accurately predicted the clinical outcome. However, for all the reasons described in the previous sections, it is important not to rely on any single preclinical model when making decisions on the further development of a new chemical entity. Different models also serve different purpose. For instance, the *in vitro* models using potassium channels are helpful to 'screen' new compounds for the potential effects although, for example, the dog heart block model is used to investigate the mechanisms of potassium channel-induced proarrhythmia. Despite all the efforts and significant achievements in this area, none of the available preclinical models has been demonstrated to be more predictive and/or superior to others. Hence, the preclinical investigations lead to probabilistic rather than absolute answers. Even with carefully conducted *in vivo* animal models, a possibility exists of metabolites specific to humans that must be investigated separately after they have been identified. Thus, the possibility of false negative conclusions of preclinical studies cannot be excluded. Likewise, factors such as differences in drug concentrations in clinical and preclinical studies, interactions between I_{Kr} and non-I_{Kr} channel effects[61] and different levels of human cardiac binding may lead to false positive conclusions. A good example is the nonsedating antihistamine ebastine, which has been reported to block the mammalian potassium channels.[62] In spite of this preclinical signal, recent detailed analyses of clinical data have shown that the drug does not prolong the QT interval in humans.[63]

Hence, the only conclusion that can be drawn from preclinical studies is that those compounds that have not generated any adverse preclinical signal are less likely to lead to cardiac toxicity in humans compared with those entities for which a preclinical signal exists. Nevertheless, differences in likelihood do not offer any guarantee. After all, in order to investigate the effects on the human heart *in situ*, there is nothing better than to study the human heart *in situ*.

3. Clinical Studies

Cardiac safety considerations need to be an integral part of the early phase I and phase II studies of every investigational drug. Even with chemical entities that are safe on their own, increased cardiac proarrhythmic toxicity may occur in interactions with other drugs, e.g. those that change or delay the metabolism of the new compound. Therefore, interaction studies are needed that concentrate especially on those interactions which may appear clinically. Once proarrhythmic safety of a new drug has been established in phase I and phase II studies, large phase III studies and postmarketing surveillance can be limited to less strict designs and less laborious investigations (e.g. a smaller number of ECGs involved in patient monitoring, less precise approaches to heart rate correction, etc.)

3.1 Phase I/II Studies

Questions most frequently appearing when designing cardiac safety investigations within phase

I and phase II studies are: (i) how frequently should ECGs be recorded; (ii) how should the QT interval be measured; (iii) how should the QT interval be corrected for heart rate, which is especially important with drugs that change heart rate but also relevant to all others; and (iv) what are the permissible increases of the corrected and uncorrected versions of the QT interval.

As already discussed, different patients are likely to be differently susceptible to cardiac toxicity and these differences are likely to translate into different degrees of QT interval prolongation. It is therefore imperative to study not only the whole population of patients enrolled into phase I or phase II studies, but also to investigate carefully every single individual. In other words, it is essential not only to establish the mean change in the heart rate-corrected QT interval, but also to identify individuals who appear to be outliers to the general trend. Most recently, it has been recognised that this outlier analysis can be substantially misleading if improper data handling, especially inappropriate heart rate correction, is used. The correct adjustment of the QT interval for heart rate has important implications for the design for phase I/II studies. Therefore, the most appropriate method to correct the QT interval for heart rate will be discussed prior to the general design of the studies.

3.1.1 Heart Rate Correction

A change in heart rate may occur in participants in phase I/II studies not only because of the direct effects of the compound on the sinus node but also because of indirect therapeutic effects (e.g. anti-inflammatory effects when studying an antibacterial), autonomic conditioning of the participants during the study or a simple psychological placebo effect. As discussed in detail in section 3.1.2, diurnal variation of the QT interval (corrected or otherwise) is very substantial. Considerations of proper heart rate corrections are therefore important in all phase I/II studies.

Previously the simple application of one or several 'universal' heart rate correction formulae (e.g. the Bazett[64] or Fridericia[65] formula) has been advocated despite the wide-ranging appreciation that these formulae might substantially overcorrect or undercorrect the QT interval, particularly when heart rate strays beyond narrow physiological confines.[66]

The fact that the duration of cardiac systole depends on heart rate was appreciated even before the invention of electrocardiography.[67] The concept of the Bazett and Fridericia formulae appeared in 1920 and, since then, a large number of other formulae have been proposed to replace the most frequently used Bazett formula.[68-77] However, none of these suggestions has been particularly successful in achieving its aim. Each of the new proposals was based on an assumption that a 'physiological' pattern of the QT/RR relationship exists that might be approximated by pooling the data of different individuals. In this assumption, it is overlooked that if a universal 'physiological' pattern of QT/RR relationship existed, the various studies reporting different heart rate correction formulae would not have led to such conflicting results.

The use of a universal heart rate correction formula in a phase I/II study is based on the assumption that the mathematical curve corresponding to the formula provides a reasonable fit not only to the pooled drug-free data of the whole group but also to the drug-free data of each individual participant. Such an assumption must be satisfied in order to obtain corrected QT (QTc) interval values that are truly independent of heart rate; QTc interval data need to be independent of heart rate because the comparison of on- and off-treatment recordings might otherwise be influenced by changes in heart rate and both false positive and false negative conclusions might be reached (dependent on the change of heart rate on-treatment and on the overcorrection or undercorrection of the formula used). If any of these assumptions are not satisfied, a drug that changes heart rate (directly or indirectly) might be artificially reported to change (or not change) the QTc interval purely because of over- or undercorrection by the use of an inappropriate formula.

Surprisingly, although the problems of Bazett correction with drugs that change heart rate are well

known and are frequently discussed when a drug that accelerates heart rate leads to artificial QTc (Bazett) prolongation, some regulators seem not to be fully aware of the opposite possibility. For instance, Bazett correction leads to substantial and highly significant (and artificial) shortening of the QTc interval on β-blockers.[78] Thus, Bazett correction may easily mask a substantial QT interval prolongation and signs of proarrhythmic toxicity with drugs that slow heart rate. Moreover, since bradycardia is one of the predisposing factors of torsade de pointes initiation,[79] this potential regulatory oversight may eventually have serious consequences.

Previously proposed universal heart rate correction formulae have been derived from population data, and the large differences between these formulae suggest that the QT/RR relationship has not been found reproducible from study to study. It is therefore unreasonable to expect that a general formula selected from those previously published will satisfy the drug-free QT/RR relationship for the data of a given study. For this reason, it has been proposed that the drug-free data of each new study might be used to develop a heart rate correction formula that will fit the need of the particular data in hand. Linear as well as nonlinear regression modelling of the QT and RR interval data points have been proposed. Indeed, a log/log linear formula $QT = \beta \times RR^{\alpha}$, where β and α are parameters determining slope and curvature, respectively, leads to a very simple heart rate correction in the form of $QTc = QT/RR^{\alpha}$. Thus, all the drug-free QT/RR interval data of a given study might be subjected to log/log linear modelling and a simple study-specific correction formula derived from the model. Thus, the exact form of the formula clearly depends on the distribution of the drug-free data. Although it has been reported that the formula $QTc = RR^{0.37}$ satisfies different data sets,[66,80] this observation has not been reproduced in more recent investigations.[81,82]

The concept of pooled regression analysis improves the heart rate correction by ensuring that in the pooled data of a study, the QTc intervals are statistically independent of the RR intervals. For instance, pooled regression analysis (restricted to linear QT/RR regression models) was recently used in the evaluation of the ziprasidone study.[19] However, the concept of the pooled regression is based on the assumption that the QT/RR relationship is equivalent in all participants in the study (the same assumption is made when applying any pooled formula, irrespective of whether universal or data-specific).

Only very recently has it become possible to record very frequent serial 12-lead ECGs in the same individual. Studies utilising this technology have suggested that the concept of a 'physiological' QT/RR relationship that is identical in every healthy individual is inherently flawed.

Most recently, a study was conducted at St George's Hospital Medical School in London[83,84] recording serial 12-lead ECGs in 22 healthy volunteers. Each of the participants underwent repeated ambulatory 12-lead monitoring using the SEER MC recorders by GE Marquette Medical Systems. The recorders were programmed to obtain a 10-sec 12-lead ECG every 30 sec for the whole duration of a nominal 24-hour period. In each individual, the recording was repeated after 1 day, 1 week and 1 month so that, in total, 4 sets of 24-hour data were obtained in each individual. The separate 12-lead ECGs were subsequently processed using the QT Guard system by GE Marquette to obtain an automatic reading of heart rate and of the median duration of QT interval of all the 12 ECG leads (i.e. the median value of all measurable leads was used). Although, as acknowledged later in this text (section 3.1.3), automatic measurement of the QT interval in 12-lead ECGs is potentially problematic, this study utilised automatic readings purely because of the sheer volume of ECGs to be processed. The data from this study showed that while the QT/RR pattern was stable in each individual, it differed substantially between individuals (fig. 1). In addition to the visual observations, a nonlinear regression $QT = \beta \times RR^{\alpha}$ was obtained between the QT and RR interval data points of each 24-hour recording. The values of the parameters β and α of

individual patients differed considerably, but remained relatively stable in each individual. Thus, the QT/RR relationship exhibits a high intraindividual stability with a high interindividual variability.[83,84]

This study (which has been confirmed in independent data) shows that even in a population of healthy individuals, no single mathematical formula can be obtained that will describe the QT/RR relationship satisfactorily in all individuals.

Moreover, it has been noticed in subsequent published[63] and unpublished (M. Malik, unpublished observations) studies that in a particular population of individuals, the curvatures of the QT/RR relationship of separate individuals might be on average flatter than their pooled composition (i.e., the average of individual α values was significantly lower than the value from the pooled regression). This means that even a formula derived from a pooled regression of all drug-free data of the study might systematically over- or undercorrect when applied to separate individuals. For these reasons, the drug-free pattern of the QT/RR relationship should be examined in each participant in a phase I/II study so that no methodological inaccuracy in heart rate correction is introduced. It seems that only in this way is meaningful outlier analysis possible.[63]

The concept of heart rate correction ignores the dynamicity of QT/RR relationship. Since the QT interval is under an autonomic influence,[85] different modes of heart rate changes, e.g. heart rate acceleration due to parasympathetic withdrawal, sympathetic overdrive and pacing, lead to different direct and reflex effects on QT interval adaptation. All these reflexes are likely to change differently on drugs that alter repolarisation.[86,87] Thus, assessment of the individual changes between the off- and on-treatment patterns of QT/RR relationship, e.g. by nonlinear dynamic modelling, offers many advantages compared with heart rate correction. Although simple comparisons of QT/RR regressions before and after treatment have been made in pooled population data,[88] individual nonlinear models of on-treatment data, which would allow for the incorporation of plasma concentrations and the modes of QT/RR adaptation, have not yet been used much. At present, however, these approaches seem to be restricted mainly to academic research work since the very large number of ECGs that are needed in each individual makes the studies rather expensive. Nevertheless, as discussed in section 3.1.3, once the problems of automated QT interval measurement are solved, studies of individual QT/RR dynamics will offer a powerful and possibly more focused tool for the assessment of drug-induced repolarisation abnormalities.

3.1.2 Study Design

The need to establish an individualised heart rate correction formula for each study participant requires the number of drug-free ECGs available from each individual to be substantially larger than usually obtained in clinical pharmacology studies. There is insufficient experience to gauge the number of ECGs necessary in each individual to construct the specific QT/RR relationship with a sufficient confidence. This number depends on the range of heart rates covered by the serial ECGs. It has to be noted that because of the autonomic influence on QT interval and the time lag that it takes for the QT interval to adapt to changes in heart rate, it is not appropriate to use provocative manoeuvres such as exercise to increase the range of heart rates covered. A balance between a sufficient number of ECGs available for the construction of the individual QT/RR relationship and the practicality of their measurement needs to be found. Preliminary experience suggests that approximately 50 to 100 ECGs per individual might be sufficient, providing that their heart rates range sufficiently so that no extrapolation beyond the data will be needed when assessing the QT interval in the on-treatment ECGs[63] (M. Malik, unpublished observations). Although this number might sound particularly large, the 12-lead Holter technology allows a very large number of 12-lead ECGs to be obtained without much technical difficulty.

The need for individualised heart rate correction also dictates that the studies of cardiac safety should be of crossover rather than of parallel design, be-

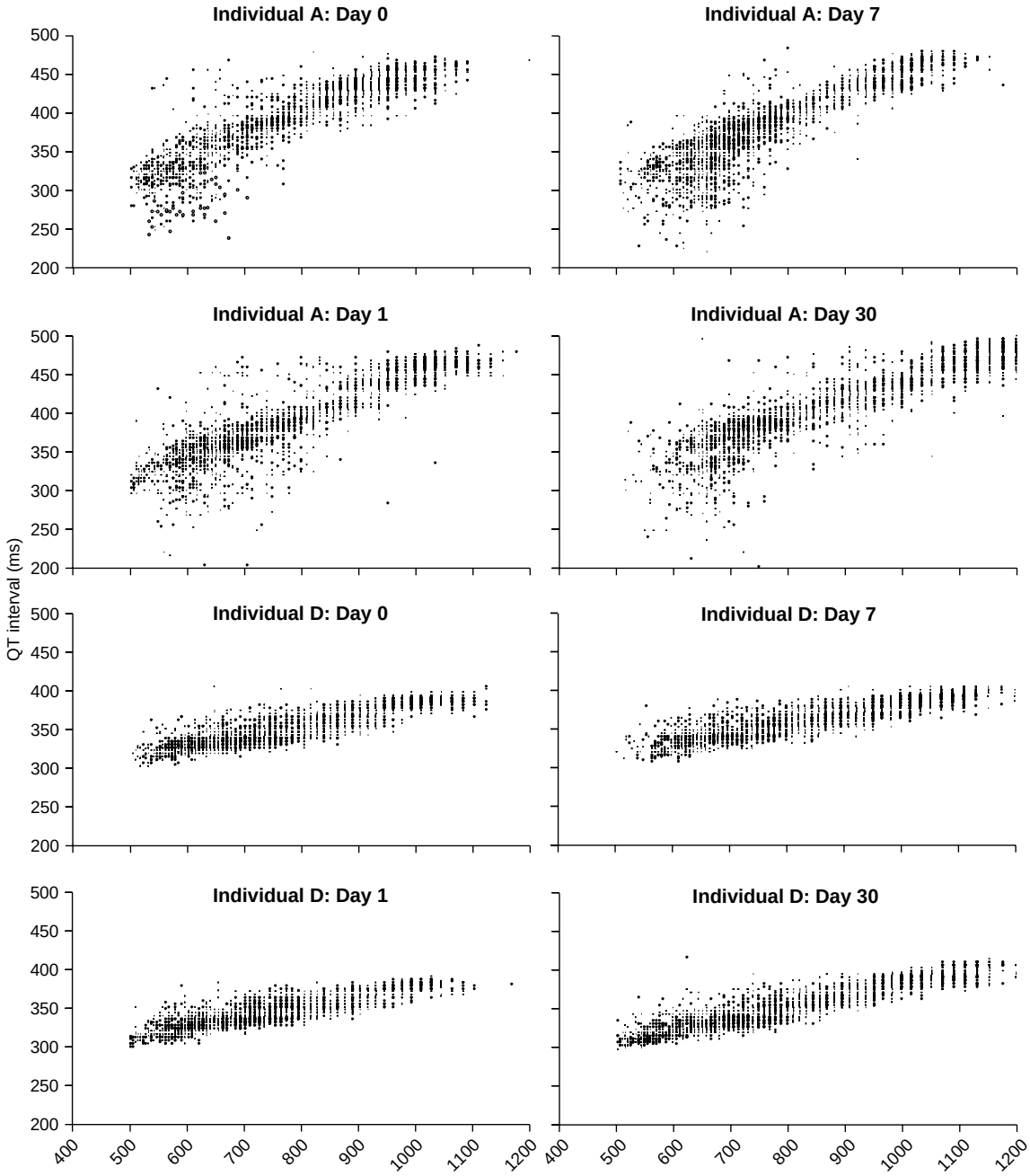

Fig. 1. Examples of the QT/RR relationship in 2 different healthy volunteers recorded 4 times each. Note that while the pattern of QT/RR data exhibits a high intraindividual stability, it also shows substantial interindividual variability. Note also that since these data were generated by fully automatic QT interval measurement in serial 12-lead electrocardiograms, outliers attributable to technical imprecision of the measurement exist. The heart rate was measured in beats/min, which resulted in clustering of points on the horizontal axes.

cause only in crossover design will sensible comparisons of QTc values be possible.

As discussed in the previous section, although it is ideally preferable to compare the full QT/RR relationship on- and off- treatment, the number of ECGs required for such an analysis may not necessarily be practical (especially because of the need for precise measurement). Therefore, once the individualised and drug-free QT/RR relationship has been found in each individual, a specific heart rate correction formula can be constructed. Application of such an individualised heart rate correction formula allows the recording of the usual number of ECGs during the separate on-treatment days (e.g. 10 to 15 ECGs during each day together with the plasma concentrations of the investigated drug and of its principal metabolites).

Once the problems of the QT interval measurement in a large number of ECGs have been satisfactorily solved (as discussed in section 3.1.3), continuous or nearly continuous monitoring with 12 lead Holter recorders will become the method of choice for phase I/II studies together with the studies of QT/RR dynamics. At present, the possibility of recording multiple ECGs at each study point (e.g. 3 to 5 sequential recordings within a 2 to 5 minute period) is worth considering in order to increase the precision of QT interval measurement. The effect of short term autonomic modulations of the QT interval and QT/RR relationship, which may exceed 20ms (fig. 2), may be filtered out by averaging the sequential measurements.[89]

Previously, the diurnal and other variability of the QTc interval has been studied using mainly the Bazett correction, which might have influenced the results.[90-93] However, circadian patterns of QTc interval and of QT/RR relationship have been confirmed with both regression modelling[92,93] and individualised heart rate correction.[94] Thus, the circadian pattern of the QT interval must be accounted for in the design and evaluation of phase I/II studies. Not only should the on- and off-treatment recordings be obtained at the same time of the day, the circadian pattern should also be considered when evaluating individual relationships between QTc changes and plasma concentration. Thus, in addition to establishing the QT/RR profile for the purposes of individualised heart rate correction, the circadian variability specific to each study participant must be assessed.

Because the QT interval adapts to the changes in heart rate rather slowly (90% of the adaptation requires approximately 2 minutes),[95] it is important to ensure that no ECGs are recorded when the heart rate is rising or falling. Specifically, if ECGs are recorded while the heart rate is increasing and the QT interval is not adapted to the faster heart rate, an artificially prolonged QTc interval will result because of the mismatch between the RR and QT intervals (QT/RR hysteresis).

Finally, phase I studies should be designed and organised to exclude volunteers who might be suspected of alcoholism and/or recreational drug abuse. Both chronic alcoholism[96,97] and cocaine abuse[98,99] are known to prolong QT interval. The use of vagrants is both ethically and practically unwise, since marked outlier changes of the QT interval in response to study medication often justifies consideration of 're-challenge', a process which is virtually impossible with homeless people, who may be here today and gone tomorrow.

3.1.3 Measurement of the QT Interval

Although most modern electrocardiographs report an automatic measurement of the QT interval, these automatically obtained values are usually correct only in normal noise-free ECGs in which the pattern of the T wave is well defined. Morphological abnormalities of the T wave, noise in the signal as well as confusion between the T and U wave may easily invalidate automatic measurements (fig. 3). For this reason, no automatic algorithm can be suggested as sufficiently precise and robust to satisfy the precision required in the assessment of drug cardiac safety. Although, as discussed later in this section, some combinations of manual and automatic measurements are permissible when subjected to advanced quality control, it is safer to use manual measurements taken by experienced personnel.

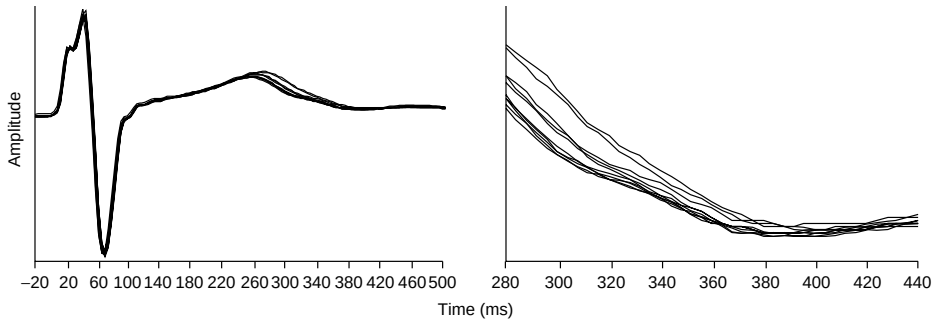

Fig. 2. Median complex of lead V_2 in 10 serial electrocardiograms recorded in a healthy volunteer (male, 35 years). All the recordings were obtained in a supine resting condition within a period of <3 minutes during which he was motionless and his heart rate was stable. The left panel shows complete recordings of QRS/TU complexes, the right panel is a zoom into the terminal portion of the T wave. The horizontal axes show the time of the recording in milliseconds relative to Q wave onset. Note that, dependent on the method for QT interval measurement, an intraindividual variability of up to 25ms may occur.

A particular problem of QT interval measurement is linked to the distinction between T and U waves, the origin of which remains disputed. Theories that attributed the U wave to the repolarisation of the Purkinje fibres[100] or to a mechano-electrical mechanism[101] were superseded by the M cell theory of Antzelevich et al.[102] However, later experiments by the same group showed that a 'pathologically augmented U wave' or 'T-U complex' is in fact a prolonged biphasic T wave with an interrupted ascending or descending limb.[103] Measurement is even less reliable for certain T-U patterns, e.g. when the T wave is flat or inverted and the U wave augmented. A substantial variability of the measurement often results from complex morphology repolarisation patterns being classified differently by different observers.[104] Probably, electrophysiological mechanisms responsible for usual 'physiological' U waves are different from those leading to abnormal U waves, e.g. those seen in acquired long QT syndrome. It seems reasonable to propose that all electrocardiographic signals originating from repolarisation of the ventricular myocardium should belong to the T wave. In this sense, the concept of biphasic and other unusually shaped T waves is more appropriate than a distinction between the T wave and an augmented U wave that may lead to serious underestimation of the QT interval. Augmented pathological U waves may be the only sign of adverse repolarisation changes, e.g. in recordings in patients taking mibefradil.[105] However, a pattern resembling an augmented U wave may also originate from slow after-depolarisation. Distinction of such patterns from bizarre T waves may be very difficult. At the same time, the signs of after-depolarisation also indicate the same proarrhythmic danger as do bizarre T wave shapes and/or a prolonged QT interval. Thus, in all cases that are difficult to reconcile, augmented U waves should be preferably included into the T wave. The U wave should probably not be incorporated in the QT measurement when there is a clear distinction between the T wave and an obviously 'physiological' U wave of small amplitude. Such U waves probably have no pathological significance and can be safely ignored. In 1952, Lepeschkin and Surawicz[106] described and classified various patterns of T and U wave merging and suggested methods for determining the end of the T wave when 'buried' within the U wave. They showed that, depending on the pattern of T-U wave amalgamation, either the intersection of the tangent to the steepest downslope of the T wave with the isoelectric line, or the nadir between the T and the U waves is closest to the 'real' T wave end. This article is clearly less often read than quoted, since the tangent method was proposed merely as 'an attempt to determine the true end of the T wave in cases of partial merg-

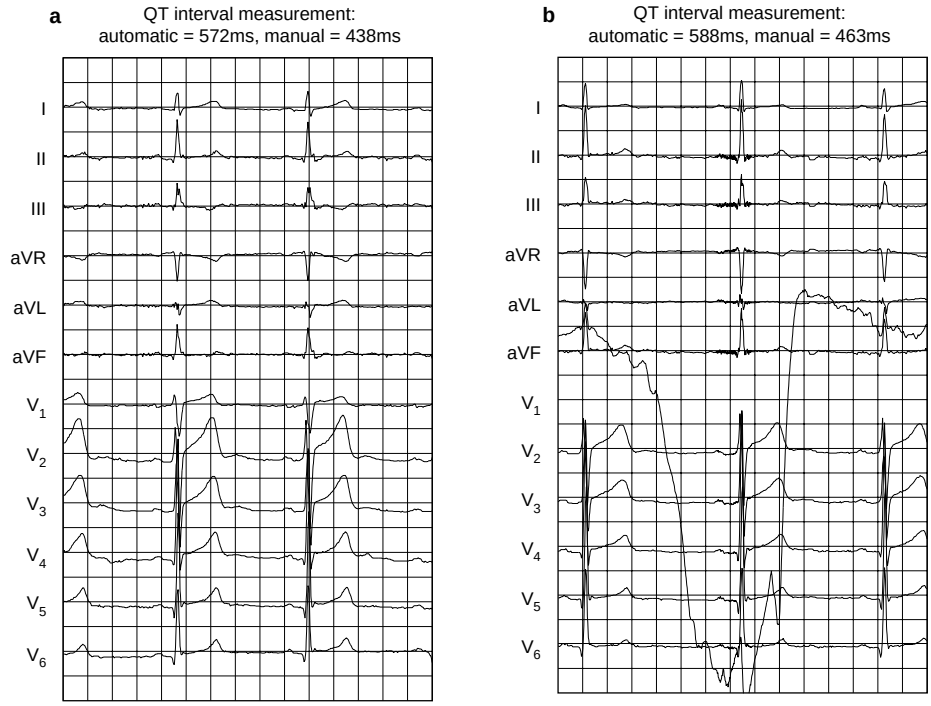

Fig. 3. Two examples of errors in computer measurement of the QT interval in 12-lead electrocardiograms (ECGs). The automatic readings of both ECGs were obtained from the ECG Research Workstation by Marquette GE, which is one of the leading technical systems for ECG processing. In the ECG in panel (**a**), the computer program was probably confused by the physiological U waves (note lead V_2). The manual reading of the QT interval was 438ms, whereas the automatic reading showed 572ms. In panel (**b**), the noise in the limb leads and loss of signal in V_1 probably contributed to the erroneous automatic reading of 588ms, while the manual reading was 463ms. Each square of the display corresponds to 200ms/500μV.

ing of T and U',[106] rather than as a universal method for determining the end of the T wave.

Recording technology plays an important role for the precision of QT interval measurement. In the past, ECGs were normally recorded only on paper using most frequently the standard 25 mm/s paper speed and 10 mm/mV gain. In ECGs recorded in this way, the QT interval was sometimes measured using procedures of questionable precision, including even hand held callipers. More recently, paper printed ECGs have been measured on a digitising board in the belief that the technical precision of the digitising equipment can be matched by human operators. Unfortunately, such beliefs are not justified and measurement of paper printed ECGs using digitising boards may lead to very substantial errors.[107,108] Errors of up to 3mm (that is, 120 msec at 25 mm/sec) in repeated measurements were reported.[107]

With advances in electrocardiographic equipment, the possibility occurred of recording 12-lead ECGs digitally. Digital recordings may be displayed on computer screens with a substantial magnification (up to 10 times the paper display) and measured with computer-driven on-screen callipers, the precision of which corresponds to the sampling frequency of the ECGs (usually 500Hz, i.e. 1 sample every 2ms, leading to a theoretical

measurement precision of ± 1ms). Even more importantly, the on-screen measurement allows the whole history of the measurement to be stored: not only is the duration of QT interval reported but also the precise positions of the Q-onset and T-offset are localised within the ECGs. Because of these advantages, on-screen measurement is also frequently considered with scanned paper-recorded ECGs. Systems also exist for conversion of scanned paper-recorded signals into digital ECGs.[109] However, scanning paper records should be restricted only to evaluation of previously recorded data that do not exist in another form, or perhaps to those phase III/IV studies that are organised in too many centres to make the handling of digital electrocardiographic files practical. (Recently, ECG transmission via the Internet became possible and, in the foreseeable future, independent of the number of centres, the collection of large numbers of digital recordings should be practical.)

Moreover, as discussed in section 5, new approaches emerge allowing advanced ECG processing (potentially relevant to drug studies) well beyond the simple measurement of the QT interval. All these new approaches require digital electrocardiographic signals. For all these reasons, the sponsors of future drug studies, especially phase I/II, should insist on high quality ECGs to be obtained and measured in a digital form.

Different concepts have been proposed as to which leads of the 12-lead ECG should be measured. Some advocate, mainly to reduce the cost of the measurement, that only lead II should be measured since the longest QT interval is frequently found in lead II. Unfortunately, lead II contains the longest QT interval only in approximately 60% of normal ECGs and in substantially fewer cases with T wave abnormalities (fig. 4). Hence, while limiting measurement to lead II might be permissible in large phase III studies where a compromised precision of the QT interval assessment might be acceptable, restricting the measurement to only one lead is clearly inappropriate in phase I/II studies. Allowing an alternate lead, such as V_2, when lead II is unreadable, is also inadequate in formal phase II studies because a drug that affects the T wave may render one or other lead unreadable, allowing only an inappropriate comparison of different leads before and after drug administration.

It is also advocated that the so-called quasi-orthogonal system, i.e. the measurement of the QT interval from the earliest Q wave onset in quasi-orthogonal leads I, aVF and V_2, to the latest T wave offset in these 3 leads, might provide a more comprehensive assessment of the QT interval irrespective of the morphology of the vectorcardiographic loop of the T wave. Others argue that the quasi-orthogonal system is not necessarily truly orthogonal under all circumstances and that changes in the cardiac axis and in ventricular gradient may distort the results of the quasi-orthogonal measurement.

In healthy hearts, it is reasonable to expect that the drug effect on ventricular repolarisation will be similar in all myocardial regions. In such a case, measuring the QT interval in all 12 leads of the complete ECGs and taking the median duration of all the measurable leads seems to be a safe and robust approach. When dealing with phase II studies in cardiac patients, it might be safer to replace the median duration of the QT interval in all measurable leads by the maximum QT interval. This will account for the possibility that the drug-related abnormalities of the T wave loop might make the QT interval prolongation visible only in some of the ECG leads. However, little knowledge exists on the possibility of 'regional' QT interval prolongation and the assessment of the maximum QT interval among all measurable leads has clearly poor data precision properties compared with the median of all measurable leads. Data stability is the reason for advocating the median QT approach to the assessment of QT interval prolongation in noncardiac patients.

As already discussed, the localisation of the end of the T wave is known to be problematic. For this reason, measurement of 1 single cardiac beat is clearly insufficient. Rather, multiple beats (e.g. 3 to 5) should be measured in each ECG lead and the results of these measurements averaged. The selec-

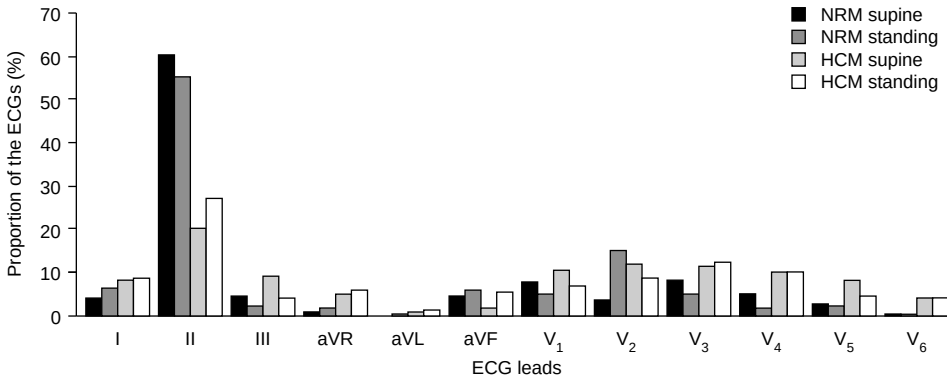

Fig. 4. Distribution of the maximum QT interval among 12 leads in electrocardiograms (ECGs) recorded in 70 healthy volunteers (NRM) and 65 patients with hypertrophic cardiomyopathy (HCM). Note that in supine recordings, approximately 60% of NRM ECGs had the maximum QT in lead II, whereas this was the case with only 20% of HCM ECGs in which T wave abnormalities occurred.

tion of the beats to be measured needs to be performed carefully. For instance, beats following the compensatory pause of an atrial or ventricular premature beat should be avoided because the T wave is known to be frequently abnormal in these beats.

Who should measure the ECGs is controversial. The European Committee for Proprietary Medicinal Products (CPMP) 'Points to Consider' document[110] clearly states that the measurement of the QT interval should be performed by electrocardiographically trained cardiologists. The pharmaceutical industry frequently argues that this requirement is particularly harsh because it is both impractical and expensive to follow. Unfortunately, there are good reasons for the CPMP requirement. When the T wave morphology is normal and when the T wave is clearly visible in a noise-free ECG, the measurement of the QT interval does not require any particular skill. However, proarrhythmic toxicity is frequently manifested by the appearance of abnormal T wave patterns including pathological U waves. Distinction between pathological and physiological U waves that should or should not be included in the measurement of the QT interval requires electrophysiological expertise and clinical experience with reading the ECGs lead by lead. A competence of this kind is difficult to achieve with superficially trained personnel or technicians without a more fundamental understanding of cardiac electrophysiology. Even when the ECGs are read by qualified electrocardiologists, quality control should be incorporated. In particular, the power calculation of the study should include the expected precision in QT interval measurement that should be verified. For such an assessment, 2 independent observers should measure a substantial proportion of the ECGs. A general precision of ECG reading quoted by a clinical research organisations is frequently of little meaning because the precision depends substantially on the quality of the ECGs and on drug-induced changes in the morphology of the T wave that differ compound by compound and study by study.

Unfortunately, some clinical research organisations involved in ECG measurements for the assessment of cardiac drug safety are not very competent and substantial measurement errors occur. Figure 5 shows examples of 2 cases in which inappropriate measurement of ECGs led to difficulties in the evaluation of phase I studies. The cases represent very poor work by clinical research organisations, which is difficult to correct. When remeasuring those ECGs that appear to be outliers in a database of a phase I/II study, every regulator will reasonably argue that the measurement proved to be imprecise and that false positive cases have been

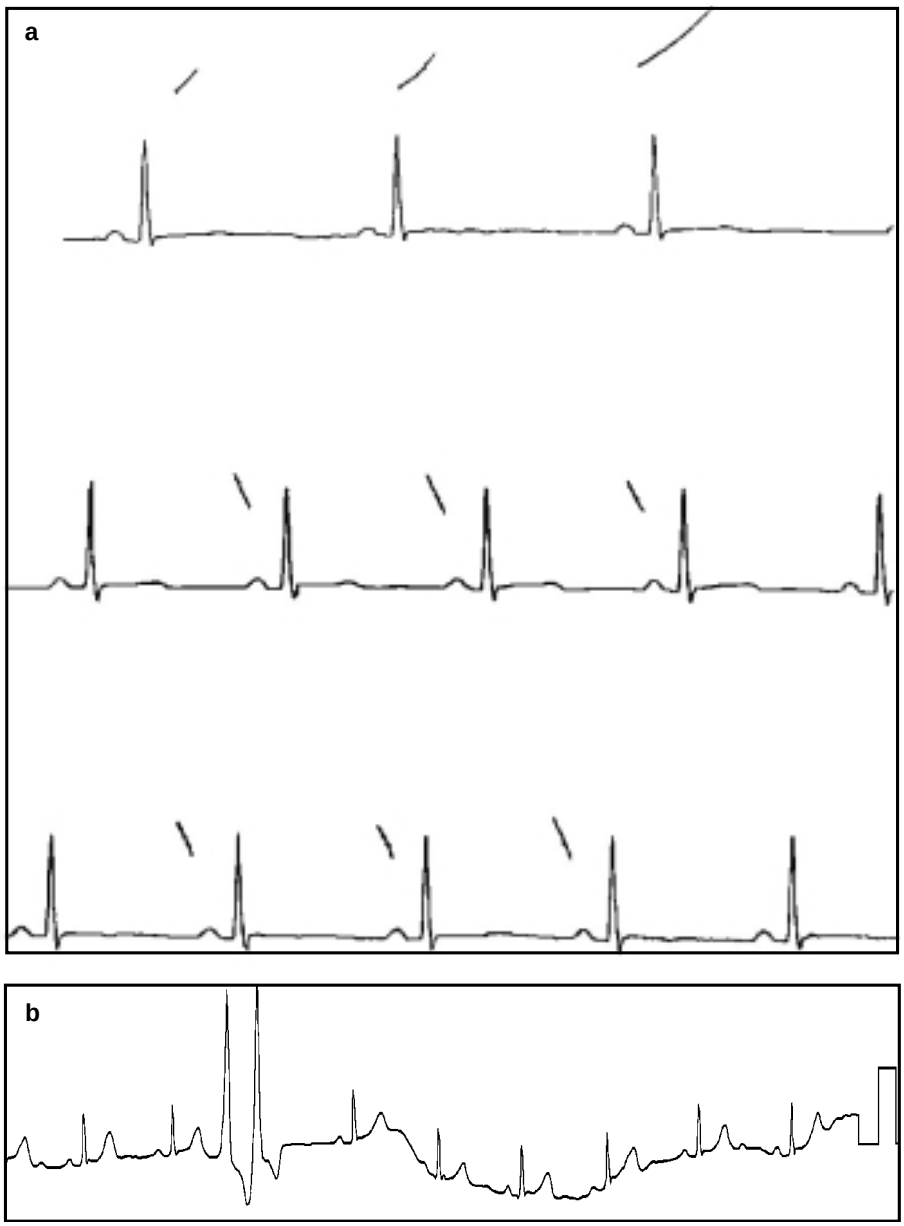

Fig. 5. Two examples of poor quality of manual QT interval measurement. The tracings in panel (**a**) are of lead II from serial electrocardiograms of the same individual recorded during a phase I study. In each of these leads, the QT intervals in 3 cardiac complexes should have been measured. The ticks were made by an operator identifying complexes that he/she measured. Note that these include cardiac cycles in which no T wave could have been identified. In the tracing from a different phase I study shown in panel (**b**), the QT interval was measured correctly but the operator included the couplet of extrasystoles into the calculation of heart rate (dividing the interval between the first and last sinus rhythm QRS complex by 9 RR intervals). This led to overestimation of heart rate and to an artificially prolonged corrected QT (QTc) interval. In both cases, the reported QT and RR values were recorded in the study database and subsequently consituted substantial outliers with a considerable QTc interval prolongation.

removed while possible false negative cases ignored. Thus, the only solution is to re-measure all ECGs, which involves both increased cost and delay. Moreover, any attempt to re-read ECGs for the purposes of using a superior measurement should show that it is really superior mainly in terms of consistency. This may be achieved by quality control of repeated reading of >10 to 15% of recordings. Only if the re-read shows tighter correlation or better correspondence between the 2 sets of readings should it be used to replace the original study database. The proportion of ECGs that should be measured repeatedly depends on both cost and practicality. A larger proportion of up to 100% will probably be appropriate for a small set of recordings, with a smaller proportion for a large set.

For these reasons, it is preferable to follow the suggestions by CPMP and to require a measurement by cardiologists, including an appropriate quality control. As an example, the Department of Cardiological Sciences at St George's Hospital Medical School in London developed a standard of practice involving digital on-screen measurements of ECGs with simultaneously recorded 12 leads. In each ECG, 5 suitable cardiac cycles are identified and the QT interval is measured in all leads of all 5 cycles by 2 (or 3, if a higher precision is required) mutually independent cardiologists. The measurement of the QT interval includes morphological classification of repolarisation patterns and categories of T/U amalgamation.[104,111] Those electrocardiographic leads are identified for which the observers differed by more than an agreed limit (e.g. 25ms) or for which they disagreed on the morphological T/U classification (this usually concerns approximately 20 to 30% of all leads). These leads are returned to the same cardiologists for a second blinded and independent measurement and, if a disagreement still exists, the measurement and morphological classification is reconciled by 2 of the most senior cardiologists of the Department (this usually concerns approximately 5 to 10% of all leads). In each lead, the QT intervals measured in separate cardiac cycles are averaged and lead-specific QT interval durations are obtained. From the QT interval durations in all leads that were found measurable, either the median (and/or maximum) QT interval is derived and used to express the QT duration in the given ECG. These QT interval values are corrected for heart rate using the mean of all sinus rhythm P-P intervals that appear in the complete recording (usually 10 sec). Recordings that contain arrhythmia are generally discarded; although some part of the recording may be usable, the data may be too difficult to interpret.

At present, there are few alternatives to such extensive measurement approaches short of accepting the possibility of substantial errors that may badly backfire in the regulatory review of phase I/II studies. At the same time, the situation is likely to change in the foreseeable future with the advances of automatic QT interval measurement. Some practical advances have already been made. The advanced automatic algorithms for QT interval measurement permit many different alternatives and/or parameter settings that have a substantial effect on the result.[112] Dependent on the particular morphology of the T/U complex, different measurement algorithms are more or less precise in different ECGs and leads. By processing an ECG using a comprehensive spectrum of automatic algorithms, an automatic method may be identified which reproduces the precise manual measurement for the given T/U morphology. Because of the dependence on the T/U morphology, such an optimum algorithmic method is both individual- and electrocardiographic lead-specific, but does not change in serial ECGs in the same individual providing no drug-induced changes are introduced (M. Malik, unpublished observations). Hence, only a small representative number of 12-lead ECGs from each off- and on-treatment 24-hour recording must be measured manually to identify the correct mode of automatic measurement. Such a mode may be subsequently applied (under an automatic control of morphological stability) to all ECGs of the full 24-hour record. A similar concept may also be applied to serial ECGs obtained at different study time points, allowing a very precise measurement of the QT interval at each instant, e.g.

in relation to the maximum plasma concentration. In this way, the cost of the measurement may be decreased substantially without compromising the quality.

It has been also advocated[110] that in addition to QT interval duration, the measurement should include so-called QT dispersion, that is the range of QT intervals in measurable leads of the standard 12-lead ECG.[113] Although reports exist showing that QT dispersion assessment may, in some cases, distinguish between less and more proarrhythmic QT interval prolongation,[114] it has been more recently recognised that the assessment of QT dispersion is subject to a substantial measurement error,[115,116] that normal limits have not been properly established and that the methodology is not adequately developed.[117-119] Only very large values of QT dispersion (e.g. >100ms) may have an auxiliary role in the assessment of drug-induced QT interval changes because they are indicative of gross repolarisation abnormalities, such as morphological changes that may be independent of the QT interval duration.[119]

3.1.4 How Much QT Prolongation Is Bad?

As already discussed, there is a relationship between the degree of QT interval prolongation and the incidence of torsade de pointes tachycardia. Hence, a drug that prolongs QT interval substantially more than another is probably more dangerous, although exceptions exist (e.g. amiodarone and verapamil). At the same time, studies of some drugs that have been subsequently found clinically unacceptable because of their proarrhythmic danger have often reported only minor QTc interval changes. For instance, a review of 14 studies of QTc interval prolongation with terfenadine[120-133] showed that on the drug alone without metabolic inhibition, 2 studies did not find any QTc interval prolongation, 4 studies reported QTc interval increases no greater than 5ms, 7 studies reported QTc interval increases between 8 and 18ms, and only 1 study reported a QTc interval prolongation of 24ms. Only when investigating a decrease in drug elimination caused by inhibition of the cytochrome P450 3A4 (CYP3A4) isoenzyme system by ketoconazole was a substantial QTc prolongation of 82ms reported.[120] This was in agreement with clinical observations that all or almost all adverse cardiac events occurred with metabolic saturation because of overdose or enzyme inhibition.

Similarly, in a study of healthy adult volunteers, administration of cisapride was associated with QTc prolongations of 6 to 18ms.[134,135] Only when the metabolic path was blocked by a CYP3A4 inhibitor did the average QTc increase by 25ms,[134] when it was associated with a 3-fold increase of plasma cisapride concentration. In retrospect, although these results might have been (and probably were) affected by poor data handling, mostly by the use of the Bazett formula, this observation of a small QT interval prolongation should have been a warning signal.

Because of this experience, it is very difficult to propose a safety limit of QTc interval prolongation. Rather, the change of the QT interval should be seen as an epiphenomenon suggesting a potential cardiac safety problem. Hence, in this setting QTc prolongation is more a marker than a mechanism of proarrhythmia. Once it has been established beyond reasonable doubt that the investigational drug prolongs the QTc interval, an adverse signal in respect of cardiac safety must be considered, while the magnitude of the QTc interval prolongation is an approximate guide to the severity of the signal. The judgement of the severity of the signal based on QTc interval prolongation is controversial. Many argue that small QTc increase, such as <10 msec, is acceptable if there is no metabolic problem and little likelihood of attempted suicide. This argument is based on the observation that although terfenadine leads to small QTc interval prolongation on its own, without metabolic saturation the drug appears to be harmless. Others argue that since QTc increase is a marker rather than a mechanism, the extent of the increase is irrelevant and once it has been established, an adverse signal exists.

In addition to the heart rate-corrected QTc interval, the duration of the uncorrected QT interval should be considered. Based on clinical experience, a consensus exists that irrespective of the heart rate,

a QT interval duration >500ms is a marker of substantial repolarisation abnormality.[110] Although an outlier analysis of the on-treatment QT interval duration should always be performed based on this upper threshold, statistical comparisons of uncorrected QT interval between on- and off-treatment recordings are meaningless unless the heart rate did not change at all (e.g. was kept practically constant by atrial pacing or some other design feature).

Establishing beyond reasonable doubt that a drug prolongs the QT interval remains a problem. A small change may occur because of pure chance and may appear to be statistically significant. Experience shows that, even with accurate measurement and heart rate correction, a statistically significant difference of about 5ms may exist on placebo treatment.[63] The design of each study should therefore allow for the assessment of the natural variability of the individual ECGs so that the power of the study to detect small changes of the QT interval might be properly assessed.

These considerations are applicable to the changes in the mean QT interval in the total study. Outlier analysis may generate an adverse signal even when no mean QT interval prolongation has been found. The CPMP document[110] suggests that every participant in whom the QTc interval has been prolonged by more than 30ms should be considered as a potential adverse effect, while a QTc prolongation in excess of 60ms is a definite adverse effect. The precision of ECG reading in interpreting these data is of paramount importance (see examples in figure 5). The presently available experience suggests that these limits set by CPMP are probably realistic and practical. When averaging the QT interval measured in several ECGs recorded during an on-treatment day or when calculating an area under the QTc curve (and expressing it per unit of time), the outliers on placebo usually do not exceed a 20ms difference. Single ECG comparisons (either single predose or single postdose (or both), poorly measured data sets, or inappropriately 'corrected' intervals often throw up bizarre and inconsistent measurements that exceed these categorical limits.

In addition to the investigations of simple QTc interval changes on treatment, the relationship of QTc changes to plasma concentrations of the investigational drug and its metabolites is of importance. However, the concentrations of drug in the myocardium do not necessarily follow the plasma concentrations (e.g. distribution hysteresis or myocardial accumulation). Hence, the relationship of the QT interval prolongation to plasma concentrations is of lesser importance in studies reaching steady state in which the area under the QTc curve or an average of QTc values from different timepoints has better measurement stability. For similar reasons, the finding that QTc prolongation is not related to plasma concentrations, especially in small studies with inadequate methodology and sampling, is not a good reason for dismissing the adverse signal. Some mechanisms of QT prolongation might be saturable at relatively low drug concentrations, in which case it may be impossible to show a concentration-effect relationship.

Finally, it should be noted that exceptions to the general rule also exist. For example, amiodarone, a class III antiarrhythmic with multiple mechanisms of action (inhibition of the fast sodium current, calcium current and potassium currents, I_{Kr} and I_{Ks}),[136] frequently prolongs the QT interval considerably but has a low incidence of torsade de pointes and of cardiac arrest.[11] The reasons for this exception are poorly understood but could relate to the manifold actions of the drug. Many drugs, including the old and new antiarrhythmics and some of the new cardiac entities, also block or activate multiple channels. Presumably, such diverse effects, which may oppose or augment each other, may also be concentration- and heart rate-dependent, thus rendering the result of QT prolongation highly uncertain. (This is one of the problems that may be addressed using the dynamic modelling of QT/RR/concentration relationships rather than by simple comparisons of QTc values.)

3.1.5 Special Challenges

Table I lists several features/conditions that lead to increased susceptibility to drug-induced prolongation of the QT interval. It is a reasonable regula-

tory requirement to investigate the effects of a new drug, which has a potential to prolong the QT interval, in some special patient groups with these characteristics. Most importantly, women should not be excluded from phase I/II studies.[137,138] Similarly, interaction studies are needed to investigate the potential of proarrhythmic toxicity under extreme clinical circumstances.

In addition to the general conditions increasing the proarrhythmic risk listed in table I, conditions specific to the investigational drug have to be addressed. These mainly include overdose, metabolic interactions and combinations with other drugs known to prolong QT interval. Metabolic interactions with inhibition of relevant cytochromes are of particular importance. Experience has shown that in the case of many drugs that eventually proved to be problematic, the strongest signals came from studies of metabolic interactions.

Regulatory authorities frequently require investigation of proarrhythmic safety in high risk patients. Indeed, the concept of phase II studies in high risk patients given standard clinical doses of the drug has a substantial appeal since it may offer more definite assurance of cardiac safety. Unfortunately, attempts to undertake such studies often lead to substantial ethical and practical difficulties. Frequently, the conflict between the goal of the study and the clinical ethics leads to inclusion and exclusion criteria that are too tight to make the study practical.

Table I. Some of the factors prolonging the QT interval

Electrolyte disturbances, e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia
Hypoglycaemia
Myocardial ischaemia, myocardial infarction and cardiomyopathy
Hypertension
Diabetes mellitus, hypothyroidism and pituitary insufficiency
Stroke and trauma, tumour and infection of the CNS
Obesity and bodyweight gain
Alcoholism and cocaine abuse
Liquid protein diet
Female gender
Increased age
Meal intake
Sleep
Congenital long QT interval syndrome

3.2 Phase III Studies

If the findings from phase I/II studies are positive or borderline, indicating a potential proarrhythmic risk, recording ECGs and measuring the on- and off-treatment QT interval in all patients in phase III studies should be strongly considered. Cardiac safety of the drug during its postmarketing clinical use will be better characterised in this way. However, phase III studies are usually efficacy-oriented, and their results might be strongly influenced by inclusion and exclusion criteria. It is therefore very important to consider how the clinical trial population represents the ultimate target population of clinical practice. Thus, if practically and clinically appropriate, phase III studies should include patients with common clinical cardiac disorders, e.g. patients with coronary artery disease, hypertension and congestive heart failure. Similarly, the inclusion of patients with other comorbidities and comedications should be considered.

Because of the reasons described previously, heart rate correction is particularly problematic in phase III studies. Providing the population of the study is reasonably homogenous and large, a heart rate correction based on the pooled drug-free data of all study participants, although not ideal, is clearly practical and preferable to the use of any general heart rate correction formula. Optimising the heart rate correction in a phase III study is particularly important when the drug changes the heart rate directly or indirectly. If the population of the study is not homogeneous, optimisation of heart rate correction should be performed separately in well-defined subgroups. Although an imprecision of the correction may be introduced by using pooled data, there are no practical alternatives, short of recording a large number of ECGs in each study participant, which is not practical in large phase III studies.

3.3 Postmarketing Surveillance

Any conclusion that the drug is free from proarrhythmic cardiac toxicity should be reserved

until postmarketing surveillance data are reviewed. Only when large numbers of patients are treated, many of whom will probably be taking multiple medications, have different comorbidities, and be subject to other conditions that were not represented in the clinical trials, will adverse effects manifest that would have otherwise not been recognised or even considered. As discussed subsequently in this text, the recent advances in human genotyping may soon offer the possibility of conducting phase I/II studies in specific groups of volunteers and patients with a high susceptibility to torsade de pointes induction. While waiting for such a possibility, individuals with high susceptibility will only be found with a large exposure.

The same considerations as with phase III studies apply to postmarketing randomised phase IV studies which may involve tens of thousands of patients. In studies of this size, the cost of recording and measuring ECGs is considerable and may limit the value of such studies. This problem may also be solved by reliable automatic ECG analysis.

4. Regulatory Concerns

The awareness of cardiac proarrhythmic toxicity, especially that related to noncardiovascular or cardiovascular nonantiarrhythmic drugs, is rather novel. Sufficient experience does not exist in the interpretation of mild and borderline signals from preclinical and clinical studies. Academic expert consensus is frequently lacking, including a consensus on some of the most essential issues. At the same time, regulatory decisions must be made. It is therefore not surprising that the regulatory agencies have adopted a safe approach and are possibly overcautious in a number of cases. Thus, the regulatory agencies have sometimes been accused of conducting 'witch hunts' and of not adopting consistent and coherent approaches to the approval of different compounds. However, it is much easier to be critical of regulatory agencies than to propose a credible alternative. It seems reasonable to anticipate that once further advances in the understanding of the signals of cardiac toxicity have been made, the requirements for regulatory approval will become more focused and more precisely defined.

Under the present circumstances, there are a number of questions that need to be addressed during the discussions with regulators. Amongst others, the ability of studies/trials to provide data that allow the distinction between drug-induced and natural QT interval prolongation must be addressed. A crossover design is helpful in this setting and should include not only placebo but also negative control arms, involving a compound with similar therapeutic efficacy that is known to have no or very little cardiac toxicity. Treatment/placebo effects as well as patient conditioning, known for instance in psychiatric patients but probably present in many others, might be highlighted in this way. Equally importantly, the precision of the assessment needs to be demonstrated. Careful audit and quality control of ECG measurement is essential. Crossover arms involving a positive control with a drug of known cardiac toxicity may help to demonstrate the power of the study to detect statistically significant QT interval prolongations, but such studies also raise considerable ethical issues. Of course, the crossover design also lead to well recognised practical problems. Such studies take a longer time to organise and complete and potentially have a higher withdrawal rate than a parallel study. Carry-over effects continue to taunt regulators, but in most instances it is easily possible to include sufficient delay between study arms to eliminate this problem. In the QT context, the comparability of data and the consequent advantages of data analysis offered by crossover designs generally overwhelm their practical disadvantage. If properly designed and if combined with precise ECG measurement, the power of crossover studies may be increased, allowing far fewer participants to be studied.

Even when a positive signal is found in preclinical investigations and/or clinical phase I/II studies, the regulators might be satisfied that it does not constitute a practical problem if it can be demonstrated that a QT interval prolongation occurs only in situations that are very unlikely to be reproduced

in a clinical setting. For instance, QT interval prolongation might be found only with dosages that are well above the potential clinical range even when considering slow or modified metabolism. It is true that almost every chemical entity has been used in suicide attempts, but if it can be demonstrated that even with doses that might be expected under such circumstances, the QT interval is not prolonged very drastically (e.g. <50ms) while it remains unchanged with lesser doses that are still above the standard clinical range, the issue of cardiac proarrhythmic toxicity might be sidelined.

The fact that no torsade de pointes tachycardia was documented during the development and subsequent postmarketing surveillance of a particular drug is not very helpful in establishing the safety of the drug. Torsade de pointes may masquerade as syncope, fainting, palpitations, ventricular tachycardia or sudden death. These surrogates are very nonspecific and often the true diagnosis remains obscure until the chance recording of an episode of torsade de pointes. Although with some drugs an incidence of torsade de pointes tachycardia of more than 1% of patients treated has been reported,[5-11] the incidence is less than 1 in 100 000 with other drugs that are also considered unsafe.

The prescription database of postmarketing surveillance of cisapride involved 36 743 patients treated mainly for gastro-oesophageal reflux and disorders of gastrointestinal motility. The analysis of the database did not show any association between the use of cisapride and serious disorders of cardiac rhythm: with adjustment for clinical history, use of CYP3A4 inhibitors and use of drugs that prolong the QT interval, the odds ratio for cisapride and cardiac outcomes was 1.0 (95% CI between 0.3 and 3.7).[139] However, since the launch of cisapride in 1993, over 30 million prescriptions have been written in the US and 270 adverse events including torsade de pointes, and 70 fatalities, were reported to the FDA between July 1993 and May 1999.[140,141] Therefore, 1 adverse event was reported for approximately every 111 000 prescriptions and 1 fatality for approximately every 430 000 prescriptions (on average each patient was prescribed the drug on about 3 occasions). Hence, clinical studies would have to be truly enormous to claim drug safety on the basis of the absence of torsade de pointes tachycardia.

As already discussed, investigations need to be performed not only with the new drug alone but also in combination with compounds that may modify its metabolism or that might contribute to cardiac proarrhythmic toxicity. Since modifications of ion channels may also occur because of synergy of 2 or more completely innocent and individually harmless compounds, comprehensive models lead to an endless number of possibilities that might theoretically need investigation. However, the scale of public health problems resulting from such interactions is rather insignificant, although probably not zero (cases of torsade de pointes attributable to insecticide poisoning are known,[142] and even a case of fatal arrhythmia attributable to intoxication with floor polish has been recorded[143]). It is therefore not surprising that only the cases of established metabolic interactions are being normally investigated.

Some populations might be at an increased risk of proarrhythmic toxicity. This applies to the elderly, who frequently receive multiple drugs with the potential for interaction, including those that have not been previously appreciated. Similarly, patients with cardiac, renal, hepatic and other predisposing diseases that may increase the risk of abnormal drug elimination and/or modified metabolism have the potential for increased susceptibility to proarrhythmia. Patients with myocardial hypertrophy and/or heart failure, including those without apparent repolarisation abnormalities, also constitute a group with increased proarrhythmic danger. However, phase II studies in patients at particular risk may not be practical (section 3.1.5).

Finally, the results of studies addressing the potential of cardiac proarrhythmic toxicity have to be considered within the overall frame of risk-benefit assessment of a new drug. The outcome of such an assessment depends on the frequency, magnitude and variety of the QT changes observed and on their potential relationship to adverse events de-

tected in the clinical programme, on the safety risks presented by the new drug relative to its therapeutic potential, and also on the availability of clinically effective alternatives with a more favourable safety profile. A good example is the withdrawal of terfenadine from the US market after fexofenadine (the active metabolite of terfenadine with a much safer profile,[144] despite 1 report to the contrary[145]) became available. Although halofantrine blocks the HERG channel,[146] resulting in substantial QT prolongation,[147] and may well induce torsade de pointes and sudden death,[148,149] its overall risk is minuscule in view of its value for the treatment of otherwise resistant malaria. However, since research on new antimalarial drugs continues,[150,151] the risk-benefit ratio of halofantrine may need re-evaluating in the future if an equally effective replacement is found with a substantially lower propensity to cardiac proarrhythmic toxicity.

The labelling implications of the risk-benefit assessment for a drug that prolongs QT interval may be considerable. Most frequently, drugs with borderline potential for cardiac toxicity have restrictions imposed and included in their summary of product characteristics (prescribing information). Limitations imposed range from general warnings to contraindications, which might be specific or broad, and are generally aimed at reducing the exposure of patients who are likely to be more susceptible to the proarrhythmic effects. As with other noncardiac safety concerns, biochemical monitoring may be required. This mostly concerns the levels of serum potassium, since hypokalaemia is a predisposing factor (see table I). Means and procedures for electrocardiographic monitoring have also been considered, and imposed in some cases, although it is questionable whether any of these restrictions are practical with noncardiovascular drugs. Some regulators argue that if the judgement of QT interval prolongation and/or T wave morphological changes is left to physicians without special cardiac training, the precision of the assessment is not guaranteed. In practice, physicians frequently rely on automatic QT interval reading provided by commercial electrocardiographs, which may be misleading (although figure 3 shows cases when automatic reading led to QT interval overestimation, substantial underestimation is equally possible). Similarly, it is questionable whether small noncardiological practices have the capability of recording ECGs with a sufficient degree of technical precision. This is a very relevant consideration with respect to antipsychotic medications, where it is often quite impossible to perform an ECG, let alone interpret the recording, with sufficient safety and alacrity to provide the urgent treatment that is necessary. Similarly, antimalarial treatment may be urgently needed in circumstances where an ECG recording is quite impossible.

All these regulatory restrictions are only a part of the safety management of a new drug. In clinical reality, whether or not a patient will benefit from detailed prescribing information depends both on the patient and the prescribing physician. The compliance of physicians with prescribing restrictions and monitoring requirements is poor. In published surveys on terfenadine and cisapride, there was a significant number of inappropriate prescriptions of these drugs to patients at increased risk.[152-154] Monitoring requirements such as baseline and/or periodic ECGs have been frequently ignored. These realisations have made regulatory agencies aware of the fact that prescribing restrictions might not offer the safety net for which they are intended. Some agencies therefore argue that rather than relying on complex and significant prescribing restrictions of a drug that is not otherwise essential, it is better not to approve the new compound at all.

Other parts of the safety management of a new drug include patient information sheets and booklets, pharmacy training, healthcare lectures, etc. All these may help until the cardiac safety of a new drug is verified through substantial exposure. It is essential to counsel patients about any risk they face when accepting pharmaceutical therapy. It is our practice to provide all patients at proarrhythmic risk from drug-induced QT prolongation with an information leaflet, which they are encouraged

to read and show to their doctors, pharmacists and friends.

5. Academic Perspective

Presently, despite numerous attempts,[155-164] no automatic method for QT interval measurement is reliable enough to be used in studies of drug-induced QT interval prolongation. Even with technologies supplied by leading manufacturers of electrocardiographic equipment, substantial discrepancies appear between automatic and manual measurement by a trained cardiologist.[165] Thus, the most immediate challenge to academia is the development of more advanced automatic measurement techniques. Although the simple graphical manipulations of T wave patterns, e.g. various threshold and tangent methods, seem to be remote from the target, some of the new theoretical concepts[166,167] may offer a hope that the problem will not take very long to solve.

The duration of the QT interval is only one of the possible measures of cardiac repolarisation. At times when ECGs were solely recorded on paper, other measures such as areas under the T wave in different ECG leads were not practical. At present, however, ECGs are recorded mostly digitally and the digital signals can be easily subjected to complex computer processing. A consensus is now emerging that abnormalities of the morphology of the T wave, which are normally hidden within the clinical diagnosis of 'nonspecific T wave changes', are potentially more important than the length of the QT interval. Indeed, the cases of gross QT interval prolongation by drugs with known cardiac toxicity are mostly accompanied by substantial modifications of T wave morphology which is perhaps less easy to miss than the changes of the QT interval duration and which, pending the development of appropriate technology, might be detected with a substantially better accuracy. Academia is therefore facing a substantial challenge of developing both appropriate technical tools for T wave morphology assessment as well as relevant physiological and pathophysiological models in order to understand the meaning of the new repolarisation characteristics. Early indications show that morphological assessment of the T wave is likely to be more potent than the sole measurement of the QT interval.[168,169] It can be expected that this stream of research will have substantial implications for the assessment of cardiac proarrhythmic toxicity and of drug-induced repolarisation abnormalities. The measurement of the QT interval is not particularly precise and the association of a prolonged QT interval with proarrhythmic effects is not direct. Therefore, it is likely that in the future the measurement of the interval will no longer be used for the assessment of drug safety. The morphological descriptors have a potential for not only detecting subtle warnings of cardiac toxicity but also of classifying patients into those more or less susceptible to adverse proarrhythmic effects.[170]

The detection and classification of individual susceptibility in addition to the detection of proarrhythmic danger of a new compound is another academic challenge. It is now generally accepted that patients who develop torsade de pointes tachycardia on a proarrhythmic drug are those who have a special predisposition to such an adverse reaction. Such a tendency is likely to be multifactorial, including genetic predisposition[171,172] such as the nonpenetrating penetrant gene abnormality of the congenital long QT interval syndrome or other gene abnormality of cardiac ion channels.[173,174] In this sense, the differences between less or more cardiotoxic drugs might be related to the degree of predisposing abnormality required for proarrhythmia manifestation. Hence, a complete spectrum might exist between cardiac toxicity that manifests by triggering torsade de pointes tachycardia even in individuals with a very mild repolarisation abnormality and cases of cardiac toxicity with which a rare gene abnormality or other combinations of predisposing factors are more to blame than the drug itself. It seems plausible to speculate that electrocardiographic testing, perhaps combined with special electrophysiological (e.g. pacing-induced long-short-long sequences) or other challenges,[175] might be capable of detecting different spectra of diminished repolarisation 'safety net', thus identi-

fying individuals in whom the cardiac toxicity of a particular compound is more likely to manifest. (A fitting term, 'repolarisation reserve', has been proposed to express the variable responses in repolarisation adaptation to various challenges.) If successful, detection of nonpenetrant gene abnormalities might offer the advantage of classifying cardiac safety for individuals rather than for the general population.

6. Conclusion

Assessment of cardiac proarrhythmic toxicity must be an integral part of the development of every new drug. As we have discussed, while preliminary signs and signals of potential cardiac toxicity may be obtained from preclinical studies, more definite (although not absolute) answers are acquired from clinical investigations, mainly phase I and phase II studies. In such investigations, the quality of data is of paramount importance. Therefore, not only the evaluation but also the design and conduct of phase I/II studies should reflect the need for the assessment of cardiac toxicity. Although some aspects of the assessment of cardiac safety suffer from lack of standardised methodology, and although the mutual understanding between the drug developers and regulators is sometimes insufficient, the whole area of cardiac drug safety is now understood much more than it was in the past, when the awareness of the problem was very novel.

Unfortunately, the problems of the pharmaceutical industry are sometimes self-inflicted. Not infrequently, a potential signal of QT interval prolongation comes from a study that was poorly designed for the assessment of cardiac safety. Thus, involvement of specialists in the field comes never too early.

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