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REVIEW

Strategies to reduce the risk of drug-induced QT interval prolongation: a pharmaceutical company perspective

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Drug-induced prolongation of the QT interval is having a significant impact on the ability of the pharmaceutical industry to develop new drugs. The development implications for a compound causing a significant effect in the 'Thorough QT/QTc Study'—as defined in the clinical regulatory guidance (ICH E14)—are substantial. In view of this, and the fact that QT interval prolongation is linked to direct inhibition of the hERG channel, in the early stages of drug discovery the focus is on testing for and screening out hERG activity. This has led to understanding of how to produce low potency hERG blockers whilst retaining desirable properties. Despite this, a number of factors mean that when an integrated risk assessment is generated towards the end of the discovery phase (by conducting at least an *in vivo* QT assessment) a QT interval prolongation risk is still often apparent; inhibition of hERG channel trafficking and partitioning into cardiac tissue are just two confounding factors. However, emerging information suggests that hERG safety margins have high predictive value and that when hERG and *in vivo* non-clinical data are combined, their predictive value to man, whilst not perfect, is >80%. Although understanding the anomalies is important and is being addressed, of greater importance is developing a better understanding of TdP, with the aim of being able to predict TdP rather than using an imperfect surrogate marker (QT interval prolongation). Without an understanding of how to predict TdP risk, high-benefit drugs for serious indications may never be marketed.
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Abbreviations: hERG, human ether-a-go-go-related gene; TdP, Torsades de Pointes; TQTS, Thorough QT/QTc Study

Introduction

Some drug-induced sudden deaths are associated with the development of a cardiac arrhythmia called Torsades de Pointes (TdP). The most likely primary event underlying this arrhythmia is inhibition of the potassium current known as I_{Kr}. Active compounds bind to the pore-forming α-subunits of the channel protein carrying this current—subunits that are encoded by the human ether-a-go-go-related gene (hERG). Because I_{Kr} plays a key role in repolarization of the cardiac action potential, selective inhibition of this current prolongs the action potential, and this is manifested as a prolongation of the QT interval on the electrocardiogram (see Vandenberg *et al*., 2001). Although drug-induced QT interval prolongation is not a safety concern *per se*, in a small percentage of people it has been associated with TdP, which either spontaneously terminates or degenerates into ventricular fibrillation. It is also true to say that QT interval prolongation is associated with an increased death rate (Straus *et al*., 2005) whether there is a proven link to TdP or not.

Bearing in mind this background biology, compared with other safety-related issues facing the pharmaceutical industry, predicting the risk of drug-induced delayed cardiac repolarization in man should be relatively simple. Importantly, the effect is strongly linked to inhibition of a known and testable molecular entity (the hERG channel). In addition, *in vitro* action potential assays and *in vivo* non-clinical tests have been developed (McMahon *et al*., 2007). The resulting data can be combined into an integrated risk assessment, and the generic nature of the issue implies that there should be a well-populated database of non-clinical and clinical information to determine concordance between the two. In this review, we describe the degree to which this simplistic view is correct and highlight areas where further insights are required.

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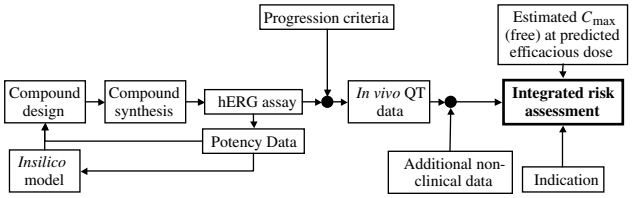

Figure 1 A generic, non-clinical strategy to reduce QT interval prolongation risk in man. Following compound design and synthesis, testing in a human ether-a-go-go-related gene (hERG) assay is the first step. A critical factor is feeding back potency data to medicinal chemists in a time frame short enough to influence compound design, hence, the need for a hERG assay with good throughput. The structure of each compound tested and its hERG potency data are ideally also used to feed *in silico* models of hERG activity to aid the compound design step. Compounds are categorized as candidates for further evaluation if their hERG potency exceeds predefined criteria. If the hERG profile and other attributes of a compound make it a potential candidate drug, an *in vivo* QT assessment is made. Depending on the *in vivo* outcome, additional non-clinical data may be collected, for example, data from an *in vitro* action potential assay. These data can then be collated on a single plot of free drugs levels against effects. The integrated risk assessment can then be completed by factoring in an estimate of the highest free drug levels in the plasma to give clinical efficacy along with an appreciation of the intended indication. The box in bold is to emphasize the integration of all relevant data.

Strategy overview

The sequence of events outlined below encompasses what might be considered a generic non-clinical strategy aiming to minimize QT interval prolongation risk in man and is summarized in Figure 1.

Designing out hERG activity

Owing to the withdrawal of a number of medicines from the market because of TdP (Shah, 2005), pharmaceutical companies were already acutely aware of the need to minimize the QT interval prolongation risk of potential new drugs. The content of the final clinical regulatory guidance (ICH E14; ICH, 2005a) will intensify the focus on this topic. Specifically, the consequences for development of a compound found to be 'positive' in the so-called 'thorough QT/QTc study' (TQTS) further increases the pressure to ensure that new chemical entities are free of this problem. In practical terms, in the early phases of drug discovery, this means testing for and designing out the effect of compounds on the hERG channel. For compound supply, throughput and ethical reasons, testing *in vivo* or using native cardiac tissues is not feasible at this stage. A number of factors have combined to allow companies to make some progress in terms of screening out hERG activity. A variety of assay types have evolved that indirectly aim to assess the potency of test compounds in a time frame short enough to influence chemical design (Finlayson *et al*., 2001; Tang *et al*., 2001; Angelo *et al*., 2003; Netzer *et al*., 2003; Wang *et al*., 2003; Chiu *et al*., 2004; Sorota *et al*., 2005; Wible *et al*., 2005). Advances in technology have also facilitated the generation of electrophysiology-based assays that directly assess effects on hERG channel function with significantly higher throughput than via conventional means (Kiss *et al*., 2003; Guo and Guthrie, 2005). Tangible evidence of this progress is publications showing chemical strategies for how hERG liability can be reduced while retaining desirable properties (Collins *et al*., 1998; Bell *et al*., 2001; Potet *et al*., 2001; Rowley *et al*., 2001; Fletcher *et al*., 2002; Friesen *et al*., 2003; Bilodeau *et al*., 2004; Edmondson *et al*., 2004). In addition, *in silico* methods are evolving that may add to the armoury of the medicinal chemist (Cavalli *et al*., 2002; Roche *et al*., 2002; Ekins, 2003; Pearlstein *et al*., 2003b; Aronov and Goldman, 2004; Gavaghan *et al*., 2007). Despite some success, the battle against hERG activity is far from over as the channel is pharmacologically very promiscuous. This probably relates to the presence of amino acids in the putative drug-binding cavity that have aromatic side chains (in contrast to other potassium channel types where the amino acids in equivalent positions have aliphatic side chains) (Mitcheson and Perry, 2003). The chemical insights gained so far relate more to physical chemistry properties than to a detailed understanding of the structure–activity relationships; and *in silico* models are not necessarily optimal, owing to the variability of the methodology used to generate the data on which they are based (Pearlstein *et al*., 2003a). On a more optimistic note, site-directed mutagenesis of the major drug-binding site may lead to a more precise understanding of how compounds bind (for example, Mitcheson *et al*., 2000 and Fernandez *et al*., 2004).

Although the hERG safety margin concept does not appear in the final non-clinical regulatory guidance (ICH S7B; ICH, 2005b), for internal decision making, companies have necessarily required an estimated target for the extent to which hERG potency must be reduced and used this criterion as the basis for whether to progress a given compound for further evaluation. A number of retrospective, literature-based exercises have provided some indication of the required margin between the maximum free plasma exposure required for clinical efficacy and hERG potency (usually IC_{50}) (Kang *et al*., 2001; Webster *et al*., 2002; Redfern *et al*., 2003; De Bruin *et al*., 2005). Overall, these reports suggest that a minimum safety margin of 30-fold is required. These hERG-related data demonstrate a high degree of predictive value to man and support the safety margin concept. The fact that there is a good degree of concordance between the findings has been very useful to quantify the challenge for drug discovery projects. However, the safety margins need to be applied with care for two reasons: they are based on measured C_{max} (free) values for efficacy, whereas drug discovery projects usually only have predicted estimates of this figure that are notoriously difficult to define with any certainty. The clinical end point in these reviews of hERG safety margin is TdP, not QT interval prolongation. Although TdP is the relevant index, the TQTS defined in ICH E14 (ICH, 2005a) effectively means that QT interval prolongation is the dominant index for judging risk. The effect of this on non-clinical decisions about suitable safety margins is unclear, but the disparity between the statistical power of the TQTS (which aims to detect QT interval increases in the region of 2.5%) and that achievable to detect significant effects in *in vivo* non-clinical assays (conventionally around 10%; Hammond *et al*., 2001; Tattersall *et al*., 2006) has obvious

implications (that is, *in vivo* non-clinical studies are likely to underestimate the risk of a 'positive' TQTS).

Building an integrated risk assessment

Much as those trying to discover and develop new pharmaceuticals, particularly irascible medicinal chemists, would like judging the QT interval prolongation risk in man to be condensed into a single parameter—potency at the hERG channel—this is clearly not realistic given the true complexity of the underlying biology. Starting towards the end of the discovery phase, therefore, hERG data are generally added to by at least a non-rodent *in vivo* QT assessment and, until recently, also with data from an *in vitro* cardiac action potential assay. In effect, companies have tended to generate data for the integrated risk assessment as described in the final non-clinical guidance document (ICH S7B; Guth *et al*., 2004; ICH, 2005b). It is at this point where the QT-related data forming the integrated risk assessment have to be put into the context of the likely indication and the QT liability of any competitor compounds. So, to use extreme examples, it is very unlikely that a potential rhinitis treatment showing hERG activity and QT interval prolongation *in vivo* with small safety margins will get progressed, but the same profile for an oncology compound with promising non-clinical efficacy may be worthy of further study. The latter case is at the core of the issue in terms of assessing proarrhythmic risk rather than QT interval prolongation risk.

It is only when data for the integrated risk assessment are collated that the true complexity of the issue is revealed. Although simplistically a compound might be expected to block hERG, prolong APD *in vitro* and prolong QT at similar free drug concentrations, this outcome is likely to be seen only in a minority of cases. This reflects the fact that, for example, some hERG blockers are equally active at channels carrying inward current like the L-type calcium channel, leading to hERG blockers that do not prolong APD (Martin *et al*., 2004). The technology advances (Priest *et al*., 2007) that have led to 10- to 100-fold higher throughput for electrophysiology-based hERG assays, could also be applied to, for example, cardiac calcium and sodium channels to get an earlier indication of such mixed ion channel blocking profiles. There are, of course, a variety of other reasons for surprise outcomes *in vivo* that reflect complicating factors only manifested in an animal model. The obvious example being the influence of metabolites on cardiac electrophysiology, leading to a situation where the parent drug has low hERG activity but produces QT interval prolongation at low plasma exposures in a dog model. This apparent 'false-negative' scenario can be further compounded if there are active, human-specific metabolites, leading to bad news quite late in the development process. Another factor is partitioning of the parent drug or active metabolites into cardiac tissue, as reported by Titier *et al*. (2004). This is an important factor because to plot the integrated risk assessment in concentration–effect terms, *in vivo* QT data are plotted relative to plasma drug levels; so the pharmacokinetic data are from the plasma whereas the pharmacodynamic data are from the heart. Finally, if a drug is eventually given to patients on clinical trials or post marketing, there are then a host of potential drug–drug interactions and differences in genetic background that could produce effects on the QT interval despite an excellent non-clinical profile. For all these reasons, it would be prudent to select drug candidates with the largest possible safety margins to hERG IC_{50} and effects in other non-clinical models because in the long-term these margins may be prone to collapse.

Predictive value to man of the non-clinical integrated risk assessment

Having expended significant effort in terms of time, money, and animal and human resources, the key question is to what extent the integrated risk assessment approach has accurately identified QT interval prolongation in man. Early indications are that the non-clinical data are largely but not absolutely predictive of the clinical outcome. For example, work has been initiated that aimed to retrospectively test the predictivity of non-clinical assays using compounds known to prolong or have no effect on the QT interval in man. The two studies of this type (ILSI/HESI and PRODACT; Ando *et al*., 2005; Miyazaki *et al*., 2005) used the same kind of assays (hERG, *in vitro* cardiac action potential and *in vivo* QT assessment) and suggested that by forming an integrated risk assessment there was a good level of predictivity. In isolation, the outcome of these initiatives is not definitive, particularly given concerns over the quality of the ILSI/HESI work (Cavero and Crumb, 2005), but the conclusions have been bolstered by additional information from individual companies and the Food and Drug Administration (FDA) (Cavero and Crumb, 2005). An internal review of AstraZeneca data indicated that in five out of six cases (four positive and two negative cases in man), the non-clinical data were predictive; the outlier compound was without effect in several QT-related non-clinical assays yet prolonged the corrected QT interval in man (Valentin *et al*., 2006). The picture is the same for a more extensive data set from Pfizer (UK; R Wallis, personal communication). If hERG and *in vivo* data are combined, only 1 out of 17 compounds (10 positive (including 5 standards) and 7 negative cases in man) were not correctly predicted—the outlier was again negative non-clinically but positive in man. The FDA have carried out a similar exercise and reported that 8 out of 10 clinically positive drugs were identified as positives non-clinically (based on either hERG and/or *in vivo* data being positive).

The fact that the non-clinical data are not 100% predictive of the outcome in man is not surprising but is obviously of concern given that, based on the limited data available, there are several examples of non-clinical false-negatives. The challenge is to try to understand the mechanistic basis of the effect caused by these compounds and determine whether viable non-clinical assays can be put in place to detect them. For example, there is evidence that some compounds indirectly decrease total current flow through hERG channels by reducing trafficking of the channel protein to the plasma membrane (Ficker *et al*., 2004; Cordes *et al*., 2005; Eckhardt *et al*., 2005; Kuryshev *et al*., 2005), but simple assays can be

devised to measure this (Wible *et al*., 2005). Drugs that affect autonomic tone may also lead to conflicting data: the complex relationship between QT and RR intervals could change depending on the prevailing autonomic tone (Fossa *et al*., 2005). If the nature of this effect was species specific, then a compound could be without effect non-clinically but there could be an apparent change in the QT interval in clinical studies even using individual QT–RR plots to derive corrected values.

Determining the predictive value of non-clinical data in 'yes/no' semiquantitative terms is clearly not ideal, particularly because it is difficult to define one set of criteria for a positive or negative outcome in each study type that are suitable for every scenario. However, bearing in mind the number of factors involved, a more quantitative approach based around an overlay of the all the non-clinical and clinical concentration–effect curves is not a realistic aspiration at the moment. Nevertheless, as more compounds go through the TQTS there may be enough clinical data generated using similar designs to assess predictive value in these terms; although for the full value of this data to be realised, there would need to be a more open cross-company dialogue to produce a large database.

Are we measuring the wrong end point?

The integrated approach described above is focused on predicting the risk that a new chemical entity will prolong the QT interval. Implicit in this is the assumption that QT interval prolongation automatically carries a TdP risk. However, there is a groundswell of opinion that the two may not necessarily be linked, and this has led to the development of non-clinical models aiming to predict TdP (see Lawrence *et al*., 2005, 2008). In pragmatic terms, a focus on estimating QT interval prolongation risk is the right thing to do, because it is a positive signal in the TQTS study that will significantly affect new chemical entity progression in the development phase. However, to avoid disadvantaging promising new treatments that do not actually carry a significant proarrhythmic risk relative to potential benefit, there needs to be scope for further dialogue with regulators as the science of understanding and predicting TdP risk matures.

Conclusion

Drug discovery and development is by its very nature a complex exercise. Simplicity is therefore a desirable (though often unattainable) characteristic in all aspects of the process. With this in mind, in the QT interval prolongation/TdP area, designing out hERG activity is critical. Even though mechanisms other than direct hERG block may occasionally lead to unexpected outcomes *in vivo*, the available data suggest that in the majority of cases a compound that is inactive at hERG will not be classed as active in the TQTS study. The number of surprise outcomes *in vivo* will also diminish as more is understood about the mechanistic basis for these effects (for example, inhibition of hERG channel trafficking) and simple assays are devised that can detect them.

When the hERG data are added to in the form of an integrated risk assessment, there is good evidence that the data largely predict the clinical outcome. Even then, however, there will be compounds where the non-clinical data do not accurately estimate risk, but the possible basis for some of these examples is emerging (for example, modulation of autonomic tone).

Providing the non-clinical to clinical correlation data set can be strengthened, avoiding the TQTS in man may be justified for compounds that have a negative profile in a comprehensive non-clinical package providing the kind of technology described by Dota *et al*. (2002) is available to conduct a high-quality ECG assessment in early clinical trials.

Despite of all the effort described above, there will still be compounds that prolong the QT interval in the TQTS study but have great potential benefit for patients with serious illnesses. Devising non-clinical or early clinical methods that can reliably predict which compound will lead to TdP and which will not, may be the last item in the drug company tool kit required to combat this problem. Indeed, it is imperative that this distinction can be made; otherwise, there is a serious risk of losing high-benefit compounds or causing companies to embark on unnecessary Phase 3 evaluations solely on the basis of QT interval prolongation.

Conflict of interest

The authors state no conflict of interest.

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