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# Preclinical Torsades-de-Pointes Screens: Advantages and limitations of surrogate and direct approaches in evaluating proarrhythmic risk

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ABSTRACT

The successful development of novel drugs requires the ability to detect (and avoid) compounds that may provoke Torsades-de-Pointes (TdeP) arrhythmia while endorsing those compounds with minimal torsadogenic risk. As TdeP is a rare arrhythmia not readily observed during clinical or post-marketing studies, numerous preclinical models are employed to assess delayed or altered ventricular repolarization (surrogate markers linked to enhanced proarrhythmic risk). This review evaluates the advantages and limitations of selected preclinical models (ranging from the simplest cellular hERG current assay to the more complex in vitro perfused ventricular wedge and Langendorff heart preparations and in vivo chronic atrio-ventricular (AV)-node block model). Specific attention is paid to the utility of concentration–response relationships and "risk signatures" derived from these studies, with the intention of moving beyond predicting clinical QT prolongation and towards prediction of TdeP risk. While the more complex proarrhythmia models may be suited to addressing questionable or conflicting proarrhythmic signals obtained with simpler preclinical assays, further benchmarking of proarrhythmia models is required for their use in the robust evaluation of safety margins. In the future, these models may be able to reduce unwarranted attrition of evolving compounds while becoming pivotal in the balanced integrated risk assessment of advancing compounds.



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## 1. Introduction

The pharmaceutical industry and regulators are under increasing pressure to quickly develop novel, effective, and safe therapeutics. One vexing problem that plagues drug development is that of avoiding compounds with a propensity of eliciting Torsades-de-Pointes (TdeP), a rare arrhythmia that can lead to ventricular fibrillation and sudden cardiac death. Since becoming a prominent safety issue with such drugs as the antianginal agent prenylamine and the antihistamine terfenadine in the late 1980's and early 1990's, at least ten drugs have been removed from the market, with warnings added to the product labels of others due to issues of cardiac proarrhythmia. Such actions demonstrate the urgent need to avoid this safety hurdle while producing novel therapeutic agents.

TdeP is a rare arrhythmia not readily observed during clinical trials or post-marketing surveillance with most drugs. For example, the

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estimated incidence of adverse cardiac events with cisapride is about 1 in 111,000 prescriptions (Malik & Camm, 2001). Most drugs linked to TdeP are associated with delayed or altered repolarization, manifest clinically as prolongation of the QT interval on the surface ECG. Consequently, regulatory guidances (such as the E14-Guidance, (E-14 Guidance for Industry (2005a))) expect a rigorous clinical study to evaluate the ability of drug candidates to prolong the QT interval in humans (a so-called thorough QT study). Such studies are designed to provide robust and precise estimates of QT prolongation with therapeutic (and supratherapeutic) drug exposures. These studies are also expensive in terms of resources and additional development time. Despite the key role they have assumed in drug development, it is recognized that QT prolongation remains a surrogate marker for proarrhythmia. Preclinical and clinical data suggest that there is no fixed relation between the extent of QT prolongation and the risk of TdeP (see Belardinelli et al., 2003; Roden, 2004; Shah, 2005a, 2005b, 2005c).

The purpose of this article is to provide perspectives on the strengths and limitations of selected preclinical proarrhythmia models used to evaluate torsadogenic risk. For comparison purposes, we start first with a discussion of the simplest in vitro surrogate marker of delayed repolarization, namely the hERG current assay. Subsequently, increasingly complex in vitro models are introduced, including the in vitro ventricular wedge and Langendorff-perfused rabbit heart preparations, and the in vivo chronic AV-node blocked model. Specific attention is provided to discerning the utility of quantitative (concentration–response) relationships to guide drug discovery and avoid TdeP risk. This review is limited to studies of acute electrophysiologic drug effects, and does not consider drugs that may have more long-term effects on repolarization, such as those that alter hERG channel trafficking and channel density (see Kuryshev et al., 2005; Dennis et al., 2007). Available data suggests that the more complex proarrhythmia models are presently most useful to resolve conflicting or questionable proarrhythmic signals generated in simpler assays. Further benchmarking of proarrhythmic models (required for more precise estimates of model sensitivity and specificity) may support their role in reducing attrition of advancing compounds and a place in the integrated risk assessment for cardiac safety.

## 2. General considerations (and limitations) of using surrogate markers to evaluate proarrhythmic risk

It is instructive to consider screening assays for TdeP based on the endpoints acquired with the different models, namely, either surrogate (or indirect) markers of TdeP or direct measures of the incidence of TdeP (see Table 1). Examples of surrogate endpoints used to evaluate drug effects range from the deceptively simple $IC_{50}$ value for hERG current block to characterizing changes in the duration and shape of the cardiac action potential (from tissues or multiple cardiac regions) to changes in the configuration of T waves from ECG (or ECG-like) recordings. Only more complex models can be used to directly measure the incidence of TdeP, as one cannot elicit TdeP using a single channel expression system, myocytes, or (arguably) a wedge of ventricular tissue. As would be expected, more complex assays provide for greater numbers of surrogate markers for evaluation (ion channel < myocytes < tissue < organ < animal). Multiple surrogate endpoints complicate the evaluation of torsadogenic risk, as weighting factors must be assigned to the different markers in order to provide "risk signatures" that match preclinical and clinical perceptions. The relative clinical risk of TdeP is also difficult to discern, due to the rare incidence of TdeP. In addition, multiple additional factors (for example, drug–drug interactions that may prominently increase drug concentrations) may contribute to the perceived clinical risk independent of direct effects on myocardium. Finally, different definitions of TdeP are often used with comparing TdeP in preclinical models with the clinical experience. For example, a clinical definition of TdeP cited by Napolitano et al. (1994) ("progressive twisting of QRS axis around an imaginary baseline, complete 180 degree twist, and markedly prolonged QT interval in the last sinus beat preceding the onset of arrhythmia" (Drugs)) is very different than that cited for ventricular wedge preparations by Shimizu and Antzelevitch (1998) ("programmed electrical stimulation-induced polymorphic ventricular tachycardia displaying characteristics of TdeP"(Circ )). Together, these above considerations make quantitative comparisons of concentration–response relationships across preclinical and clinical studies difficult, and highlight the need for wide safety margins derived from preclinical studies.

It is generally accepted that TdeP results from the culmination of multiple factors acting synergistically to initiate (and sustain) this arrhythmia. TdeP was initially considered an idiosyncratic drug reaction (that is, an adverse drug reaction that does not occur in most people at doses used clinically), and undoubtedly some cases of drug-induced Torsades are likely idiosyncratic (for example, those involving genetic mutations affecting cardiac potassium channels). However, most cases can be attributed to the contributions of multiple risk factors that include a drug (pharmacodynamic) effect (Roden, 1998; Zeltser et al., 2003; DeBruin et al., 2005). Consequently, it would be expected that the most useful surrogate marker(s) to interrogate would be those most frequently linked to TdeP and that also play a key role in the initiation of TdeP, with other markers assuming lesser (but still important) roles. Given that multiple risk factors are recognized to play a role in the initiation of TdeP (female gender, bradycardia, hypokalemia, hypomagnesia, and structural heart disease), it is not surprising that simple surrogate markers do not provide 100% sensitivity or specificity with regards to predictability of clinical outcome (TdeP). Thus, in order to provide a robust quantitative (concentration–response relationship) of the TdeP risk, it is imperative to understand 1) the role and limitations of each surrogate marker, and 2) the influence (which may be dynamic and nonlinear) of contributing risk factors on the predictability of the surrogate marker under study. The identification of discrepancies between preclinical "signals" and clinical findings, while highlighting less than perfect assay sensitivity or specificity, represents an important first step towards understanding the limitations of any surrogate marker.

**Table 1**
Summary of parameters typically evaluated in preclinical "QT" models

| Model | Parameters measured or emphasized | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Preparation | Curr. | Repolariz. | EADs | Triang. | Reverse use-dep. | Instability/variability | Disper. | Pseudo-ECG-QT | ECGQT | QTMorph. | TdeP(like) |
| hERG | Channel | X | | | | | | | | | | |
| APD Repolarization | Tissue | | APD | X | X | X | | | | | | |
| QT measures | Animals | | | | | | | | | X | | |
| Wedge | Tissue slice | | APD | X | | | | X | X | | X | X |
| Langendorff | Organ (Hearts) | | MAPD | X | X | X | X | X | X | | | X |
| Chronic AV-block | Animals | | MAPD | X | | | X | X | | X | | X |

Models are arranged according to increasing complexity. Measures of the incidence of TdeP (rightmost column) is only one of eleven parameters evaluated in the six selected assays. Repolariz. = repolarization; EADs = early afterdepolarizations, Triang. = triangulation, QT Morph. = QT morphology (Tpeak–Tend), MAPD = monophasic action potential duration, Disper. = APD dispersion, ADP = transmembrane action potential, TdeP = Torsades-de-Pointes.