Early prediction of proarrhythmic cardiotoxicity in the drug development process

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This editorial refers to 'Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk' by G.R. Mirams et al., pp. 53–61, this issue.

Drug-induced QT interval prolongation and the appearance of life-threatening Torsade de Pointes (TdP) arrhythmia are potential risks during treatment with a variety of drug compounds, including anti-arrhythmics and non-cardiovascular drugs.1–3 Because of this cardiotoxic side effect, a number of non-cardiovascular drugs have been withdrawn from the market, and the development of several compounds has been aborted in the late phases of the development programmes.3–6 The late detection of cardiotoxic side effects induced by compounds of pharmacological interest can significantly obstruct drug discovery and development projects and increase their cost. Consequently, it is desirable to identify the potential proarrhythmic cardiotoxicity of compounds at an early stage of drug development.

In the majority of cases, drugs that prolong the QT interval preferentially inhibit the rapid component of the delayed rectifier potassium current \(I_{Kr}\) (or hERG, the \(\alpha\)-subunit of \(I_{Kr}\) channels). It is the major repolarizing current of the cardiac action potential that is exceptionally susceptible to blockade by many different compounds. Drugs that block \(I_{Kr}\) prolong the action potential duration and may induce TdP. Therefore, testing the ability of new compounds to interact with \(I_{Kr}\) is important, and the hERG IC50 value can be used as the earliest predictor of future torsadogenic risk. However, there are examples showing the absence of a direct association between hERG block and TdP: some hERG inhibitors do not cause TdP and vice versa, there are drugs that are weak hERG inhibitors but cause TdP. To enhance confidence in the prediction of drug safety, Redfern et al.4 proposed a 30-fold margin between the effective free therapeutic plasma concentration (EFTPC) of a drug and its hERG IC50. In fact, a drug that demonstrates signs of hERG inhibition at concentrations at least 30-fold higher than therapeutic plasma concentration is unlikely to induce TdP. However, because there are clinically used drugs with much smaller margins that are not associated with TdP, the 30-fold margin rule seems too restrictive. As a result, an investigation of a promising novel agent demonstrating a high activity against a chosen target could be falsely terminated. Thus, a correct go/no-go decision cannot be made solely on a compound’s interaction with \(I_{Kr}\) channels.

The study by Mirams et al.7 is an attempt to improve the reliability of early prediction of potential proarrhythmic side effects of new compounds by taking into account their interaction not only with \(I_{Kr}\) but also with other ion channels. Interactions with other cardiac ion channels can either mitigate or exacerbate the prolongation of repolarization induced by \(I_{Kr}\) block. As the first step, drug effects on fast sodium channel and the L-type calcium channel were included in the study in addition to their effects on hERG channel. Thirty-one clinically used drugs for which EFTPC and the clinical risk of TdP had been reported were analysed. IC50 values for three channel types for each compound were either gathered from the literature or determined experimentally. To integrate the information on multi-channel block, simulation studies with mathematical models of ventricular action potential were performed. The results demonstrate that simulation of action potential prolongation provides improved prediction of the TdP risk associated with a compound, above that provided by existing markers. The study confirms that consideration of only hERG block is not sufficient to predict torsadogenic risk. Importantly, compound effects on magnitudes of the currents only are necessary to make a prediction. Most of these data can be obtained using heterologous expression systems. These experiments do not require much time and are not very expensive, which is essential for early safety testing.

Preclinical prediction of drug safety becomes more complicated because even in vivo assessment of drug effects on the QT interval in large animals (which has low throughput and is extremely labour-intensive) does not have a high predictive value: there is no conclusive evidence to show that drug-induced prolongation of the QT interval inevitably leads to TdP. The link between QT interval prolongation and TdP is very complex and affected by many factors, including age, gender, electrolyte imbalance, disease states, and concomitant medication.8,9 Modelling of these clinical conditions in animals is very complicated, if at all possible. It is

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therefore important that no assumptions about the mechanisms leading to TdP are needed to show the predictive power of the method of Mirams et al.: it is based simply on a correlation between the results of a simulation study and the clinically recorded incidence of TdP.

In further work, to improve prediction of the model, the authors plan to add more drugs to the data set, including effects of compounds on other ionic currents contributing to repolarization (late sodium and \( I_{\text{Ks}} \)), and long-term drug-induced changes (membrane protein trafficking and expression). In fact, the more drugs are included in the data set, the stronger and more substantiated the conclusions made will be. With regard to addition of more ion channels and especially data about trafficking and expression, these experiments require more time and are more expensive and labour intensive than those currently used in the model. Therefore, it will be very important to test whether inclusion of these data can significantly improve the reliability of early prediction of a proarrhythmic potential of new drugs.

Currently, the research and development cost to bring a new molecular entity to market is approximately US $1.8 billion, and preclinical drug discovery accounts for almost one-third of this. Thus, any new method that can simplify and accelerate the studies assessing cardiac safety of new compounds could increase the number of new and innovative drugs available in the future and decrease their cost. The approach of Mirams et al. shows that the use of computational modelling and simulation in combination with experimental techniques could be a powerful and inexpensive tool for early assessment of drug safety.

References