Prediction of pro-arrhythmic activity in humans with the use of physiologically based pharmacokinetics and pharmacodynamics modelling

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Abstract

Drug induced cardiac arrhythmia, especially occurrence of Torsade de Pointes (TdP), has been a leading cause of attrition and post-approval re-labelling and withdrawal of many drugs. TdP is a multifactorial event, reflecting more than just drug-induced cardiac ion channel inhibition and QT interval prolongation. A drug that is well tolerated in most patients can cause TdP in a particular individual under certain clinical situations e.g. disease or co-medications or electrolyte imbalance. Moreover, assessment of the TdP liability of a drug based only on the parent moiety and the hERG (**h**uman ***E****ther-à-go-go*-**R**elated **G**ene) centric evaluations could be misleading since many drugs such as citalopram affect not only rapidly activating delayed rectifier potassium current (I_{Kr}) but also other ionic currents and may have electro-physiologically active metabolites. Testing all probable hypotheses in clinical and/or animal studies may be practically, ethically and economically unfeasible. In addition relating findings from animal studies to humans can be flawed due to species-specific differences in pharmacokinetics (PK) and toxicological response. These present a translational gap in extrapolating preclinical cardiac safety assessment to estimate human TdP risk reliably, especially when the drug of interest is used in combination with other QT prolonging drugs for treatment or has active metabolites. Thus, novel translational tools that allow prediction of clinical cardiac toxicity risk and expected clinical QT prolongation response are greatly needed. One such set of tools are physiologically based, biophysically detailed models of cardiac physiology that can characterize the contributions of multiple ion channel inhibition on the electrophysiology of human cardiomyocytes incorporated in the physical model of ventricular wall as string of cells arranged from inside to outside of ventricular wall. As part of this thesis, it was demonstrated with case examples how such mechanistic approach can be used from early discovery to late stage drug development and post marketing surveillance safety assessment where the model in enriched as more knowledge about the PK and safety of the drug becomes available. In early discovery, such Quantitative Systems Toxicology and Safety (QSTS) models can be run with properties predicted from chemical structure to aid high throughput virtual screening or prioritization of promising molecules and as more *in vitro* and clinical data becomes available, the models can be further verified, refined and enriched by "predict-learn-confirm" process. Prior simulations of clinical thorough QT trial for example could help reduce, refine or optimize the clinical study design to reach meaningful endpoint and help reduce the chance of study failure. With the case studies of moxifloxacin, citalopram and tolterodine, the utility of such QSTS approach to build and test hypothesis was demonstrated, such as (1) assessing the role of plasma versus heart tissue concentration in driving the cardiac response; (2) assessing the contribution of electro-physiologically active metabolite; (3) understanding impact of population variability such as genetic polymorphism on the cardiac safety profile of drugs: (4) impact of drug effect on cardiac ion channels other than hERG on cardiac safety of drug and (5) personalized safety assessment by simulating "virtual twin" of a real patient *in silico*. Adoption of such QSTS modelling strategies from early stages of drug discovery and development and enrichment of model and information along with drug product life cycle could allow bridging translational gap in clinical cardiac safety assessment.