Risk Assessment by Combined Three−Dimensional Human Cardiac Microtissues and Pharmacokinetic Modeling

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Authors(s):

Mark C Daley, Graduate Student, Brown University. Dept of Biomedical Engineering
Majory Moreau, associate director, Scitovation. Dept of Computational Toxicology
Jeffrey Fisher, senior research fellow, Scitovation. Dept of Computational Toxicology
Ulrike Mende, Professor, Rhode Island Hospital. Dept of Medicine
Bum−Rak Choi, Associate Professor, Rhode Island Hospital. Dept of Medicine
Patrick Mcmullen, Director of Computational Toxicology, Scitovation. Dept of Computational Toxicology
Kareen L. K. Coulombe, Associate Professor, Brown University. Center for Biomedical Engineering

Abstract

Background & Aim: Adverse cardiovascular events, particularly arrhythmias, remain among the most frequent cardiotoxic responses to chemicals and a primary reason for safety−related withdrawal of pharmaceuticals. Current safety assessment relies on labor−intensive in vivo models that are limited by species−specific electrophysiology and single−target in vitro assays that capture one arrhythmogenic mechanism.

Methods: To address these limitations, we combined concentration−response data from human in vitro cardiac microtissues with a physiologically based pharmacokinetic (PBPK) model to predict human equivalent exposures of compounds with known cardiotoxicities. Self−assembled microtissues were formed by combining metabolically purified human induced−pluripotent stem cell−derived ventricular cardiomyocytes (= 70% pure) and primary cardiac fibroblasts in a 95:5 ratio into agarose molds with 800−µm−diameter round−bottom wells.

Results: After one week, action potentials (APs) were recorded using the voltage sensitive dye di−4−ANEPPS at 0.5 Hz pacing. AP duration (APD) and AP triangulation were measured at baseline and after six sequential 10−minute chemical exposures at half−log increasing concentrations. Points−of−departure (PoDs) were estimated using spline meta−regression fitting of concentration−response curves and identification of the point of maximum curvature. Illustrative examples include cisapride, the use of which is limited due to APD prolongation and arrythmia generation, and ranolazine, which is still prescribed despite potential APD prolongation. Our model estimated median PoDs of 0.27 and 10 µM, respectively, and reverse dosimetry using a PBPK model identified exposure levels consistent with these tissue concentrations (0.127 and 33.6 mg/kg/day). Corresponding margins of exposure were between 0.5−2 and 2.7−7.3, reflecting observed clinical risk.

Conclusion: Thus, we demonstrate the ability to differentiate human−relevant exposures via integrated new approach methodologies to better inform next−generation cardiotoxicity assessment.

Clinical Implications: