ABSTRACT

Cardiac toxicity, manifested as compromised contractility or ischemic heart disease, comprises 26.9% of drugs removed after approval due to issues with contractility or ischemic heart disease. To address issues of attrition, safety and cost of drug development, there is a need to engage in more rigorous preclinical cardiac safety testing. The use of a multi-scale approach for assessing cardiac toxicity may detect signs and indicate mechanisms of toxicity that would otherwise go undetected by using traditional measures of cardiovascular function. The purpose of this research was to utilize the Langendorff isolated heart model to assess integrated parameters in response to drugs with known/unknown mechanisms of toxicity. We integrated ECG, contractility, energetic, and biomarker responses to assess the mechanisms of toxicity. We integrated ECG, contractility, energetic, and biomarker responses to assess the mechanisms of toxicity.

BACKGROUND

Challenges facing drug development
- Cardiac toxicity: 26.9% of drugs removed after approval are due to issues with contractility or ischemic heart disease
- Late toxicity: Several chemotherapies cause heart failure manifested as long as 10 years after treatment, difficult to detect in typical preclinical and clinical testing

Methods

Ex-vivo (Langendorff isolated heart):
- Sprague Dawley rats anesthetized with Sodium Pentobarbital (80 mg/kg). Hearts removed, perfused in Langendorff perfusion solution prior to perfusion with Isolated Heart Perfusion solution (HED-1, 1.8 KPi, 25 NaHCO3, 2.4 KCl, 1.17 NaH2PO4, 11 glucose, 1.2 HEPES, 14.2 CaCl2) in a Langendorff system (Enka, France)
- Water-filled balloon inflated in left ventricle to measure left ventricular pressure (pLV) parameters (dp/dt max, dp/dt min, developed pressure, and diastolic pressure), coronary flow rates, heart rate, and ECG waves were simultaneously recorded

RESULTS

Ex-vivo (Langendorff isolated heart):
- To assess the effects of drugs on cardiac toxicity, the Langendorff isolated heart was used.
- The effects of drugs on cardiac contractility were evaluated using the Langendorff isolated heart model.
- The drugs tested included doxorubicin, sorafenib, and verapamil.
- The effects of these drugs on cardiac contractility were observed over time.
- The results showed a significant decrease in contractility with doxorubicin and sorafenib, while verapamil had minimal effect.

CONCLUSIONS

Monitoring changes in contractility alone does not always predict toxicity.
- Early detection of contractility changes can provide better insight into potential toxicity and affected pathways.
- Combined multi-scale endpoints can provide better insight into potential toxicity and affected pathways.
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Next Steps
- Further analysis into drug induced cardiac immune response
- Additional cytokines
- Further investigation into cardiac reserve and in vivo translation

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