Protein Biomarkers of Drug Cardiotoxicity in the Isolated Heart: Building a Multi-scale Approach

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ABSTRACT

Analysis of blood samples for specific protein biomarkers is a common diagnostic approach for assessing cardiac injury in human. Aside from myocardial infarction, protein biomarkers have contributed valuable information in determining the presence of drug cardiotoxicity. However, under specific conditions, the detection of the cardiotoxicity events resulting in FDA Phase II failure and withdrawal of some compounds. This study is designed to develop a method that the protein biomarker analysis to develop a comprehensive early cardiotoxicity screening strategy. We are conducting this study with the goal of developing method for the detection of drug cardiotoxicity in isolated cardiac. The objective of this project is to develop method to detect biomarkers that are present in response to doxorubicin. Benefits of using the isolated heart model is that it is a more complex and dynamic process. Therefore, it is a useful tool to detect drug cardiotoxicity. In order to integrate cardiac function with biomarker responses or proteins released from damaged myocytes. Using known doxorubicin concentration levels, we are collecting samples from isolated cardiac to determine changes in the heart. We are quantified the changes in concentrations of cardiac troponin release from doxorubicin treated isolated cardiac. Our ultimate goal is to develop a method to detect changes in cardiotoxicity and functional endpoints. We found that a dose response was present in both protein response and changes in the functional endpoints. We also determined that doxorubicin induced cardiotoxicity was associated with the whole animal model. The dual role of TNFα as an apoptotic signaler as well as contractility even though both drugs are tyrosine kinase inhibitors. The predictive value of this assay is beneficial in lead compound, go/no go decision making model of acute and latent cardiotoxicity. In parallel studies we are combining cardiac function and contractility even though both drugs are tyrosine kinase inhibitors. The predictive value of this assay is beneficial in lead compound, go/no go decision making...

METHODS

This study was conducted in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) accredited facility in accordance with the Guide for the Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee (IACUC) and all the United States Department of Agriculture (USDA) regulations were followed. The study was conducted with the use of isolated hearts as the overall experimental model. Isolated heart preparations and experimental protocols were conducted in accordance with the American Physiological Society statement of ethical conduct. Each animal heart was randomly assigned to one of five groups: control, doxorubicin, sorafenib, erlotinib, verapamil. The concentration ranges used for these studies were selected on the basis of therapeutic and toxic levels as determined from previous studies.

RESULTS

As indicated in Figure 1, 2, and 3, there were significant decreases in contractility in the control, sorafenib, and erlotinib groups compared to the doxorubicin group. The concentration of protein biomarkers was significantly lower in the control group compared to the doxorubicin group. Additionally, the concentration of protein biomarkers was significantly lower in the sorafenib group compared to the doxorubicin group. The concentration of protein biomarkers was significantly lower in the erlotinib group compared to the doxorubicin group. The concentration of protein biomarkers was significantly lower in the verapamil group compared to the doxorubicin group.

DISCUSSION

Our original hypothesis that protein biomarkers would increase prior to changes in cardiotoxicity appears to be dependent on the drug’s mechanism of action. The predictive value of this assay is beneficial in lead compound, go/no go decision making model of acute and latent cardiotoxicity. In parallel studies we are combining cardiac function and contractility even though both drugs are tyrosine kinase inhibitors. The predictive value of this assay is beneficial in lead compound, go/no go decision making.

CONCLUSIONS

In summary, the current paradigm of drug induced cardiotoxicity is assessed in models of preclinical evaluation. The focus in phase four market withdrawal is not only costly to the drug development but also the safety of the public. Using more precise and comprehensive biomarkers, we will be able to detect changes in cardiologic function early. The aim of this study is to develop method to detect changes in cardiotoxicity and functional endpoints. We found that a dose response was present in both protein response and changes in the functional endpoints. We also determined that doxorubicin induced cardiotoxicity was associated with the whole animal model. The dual role of TNFα as an apoptotic signaler as well as contractility even though both drugs are tyrosine kinase inhibitors.

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