Zhongyu Mou\textsuperscript{1}, Rebecca Racz\textsuperscript{1}, Kevin Cross\textsuperscript{2}, Mounika Girreddy\textsuperscript{3}, Suman Chakravarti\textsuperscript{3}, and Lidiya Stavitskaya\textsuperscript{1}

\textsuperscript{1}FDA Center for Drug Evaluation and Research (CDER), Silver Spring, MD; \textsuperscript{2}Instem, Columbus, OH; \textsuperscript{3}MultiCASE, Inc., Beachwood, OH

Abstract

Drug-induced cardiotoxicity remains a fundamental concern in drug discovery and development. The ability to predict cardiac toxicity during drug development, and in regulatory review, will likely be improved by new QSAR models. The objective of this study was to develop quantitative structure-activity relationship (QSAR) models for predicting potential cardiotoxic compounds in drug discovery and regulatory review. We used a combination of computational algorithms to identify correlations between chemical descriptors and cardiac toxicity. The geometric mean (EBGM) and drug label, published literature, and clinical data. The cross-validated performance for the new models reached up to 0.72

Introduction

New models offer an opportunity to identify a wider variety of cardiac adverse effects, including cardiac diseases, heart failure, cardiac valve disease, myocardial disease, and cardiotoxicity. Overall, new models showed higher sensitivity (up to 81%) and negative predictivity (up to 75%) compared to the best general linear model with an overall sensitivity of 68% and specificity of up to 75%.

Results and Discussion

Several cardiac toxicity classes had positive predictive values of over 75%, including heart failure (82%) and myocardial ischemia (80%), with sensitivity of 76% and 76%, respectively. The new models provide an opportunity to identify drug classes and functional groups that are associated with cardiac toxicities and facilitate safety assessment of new drugs.

Conclusion

New models provide the opportunity to identify drug classes and functional groups that are associated with cardiac toxicities and facilitate safety assessment of new drugs. The new models offer an opportunity to identify a wider variety of cardiac adverse effects, including cardiac diseases, heart failure, cardiac valve disease, myocardial disease, and cardiotoxicity. Overall, new models showed higher sensitivity (up to 81%) and negative predictivity (up to 75%) compared to the best general linear model with an overall sensitivity of 68% and specificity of up to 75%.

Ongoing Research

The assessment of newly constructed QSAR models on external validation sets based on clinical data of investigational drugs is currently under way.

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References