Quantitative Structure-Activity Relationship Model to Predict Cardiac Adverse Effects

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Abstract

Drug-induced cardiotoxicity represents one of the most common causes of attrition of drug candidates in preclinical and clinical development. Evaluation of cardiac toxicity is essential during drug development and regulatory review. Previous efforts to develop predictive cardiac toxicity models have been challenging, due in part to a low number of positives (i.e., cardiotoxic events) described in the public domain. As a result, these models show high specificity but low sensitivity in their predictive performance, indicating that while making reliable positive predictions they may overlook important safety signals in some instances. In the present study, 73,166 drug-induced adverse event combinations from the FDA Adverse Event Reporting System (FAERS) were extracted for 2088 drugs using 243 cardiac toxicity-related preferred terms (PTs). The 243 PTs were combined into 12 groups based on their clinical relevance and optimal classification was determined by Empirical Bayes Geometric Mean (EBGM), drug label, published literature, and clinical data. The new training set was expanded to include 515 new drugs containing functional groups such as allene, amidines, dithiocarbamate, hydrazides, nitroso, quinones and sulfonyl groups. A hierarchical clustering analysis of the final training set showed representation of an additional 71 structural clusters over which the models can make a prediction. The cross-validated performance for the new models reached up to 81% sensitivity and 79% negative predictivity. These new models covering a wide range of cardiac endpoints will provide a fast, reliable, and comprehensive predictions of potential cardiotoxic compounds in drug discovery and regulatory safety assessment.

Introduction

- Drug-induced cardiotoxicity represents one of the most common causes of attrition of drug candidates in preclinical and clinical development
- FDA maintains Adverse Event Reporting System (FAERS) of post marketing surveillance and risk assessment to identify adverse events that may not have been detected during drug approval process.
- Adverse events are coded in FAERS using Medical Dictionary for Regulatory Activities (MedDRA) where a preferred term (PT) is one of the five levels used to describe medical conditions.
- Disproportionality methods such as Proportional Reporting Ratio (PRR) and Empirical Bayesian Geometric Mean (EBGM), can be used to identify statistical associations between drug products and events in their respective databases of safety reports [1]. Various commercially available software programs generate PRR and/or EBGM scores (eg, Empirica Signal™, PV Analyser™, Molecular Health EFFECT [MH EFFECT™], and Statistical Analysis Systems™ [SAS™]).
- EBGM calculation is conceptually similar to PRR; however, it incorporates Bayesian “shrinkage” and stratification to produce disproportionality scores toward the null, especially when there are limited data and small numbers of cases.
- Quantitative Structure-Activity Relationship (QSAR) modeling uses computational algorithms to identify correlations between chemical structural features and biological activity (or toxicity) in large data sets [2].
- QSAR modeling techniques can be utilized here to identify substructural features associated with and predictive of cardiac toxicity using a data set of post-market AEs.

Objectives

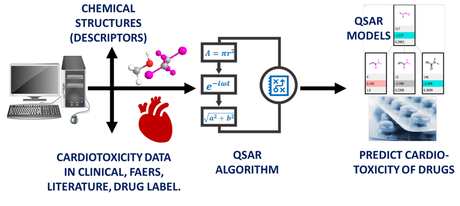
To develop training sets using post market surveillance data

To construct and optimize QSAR models

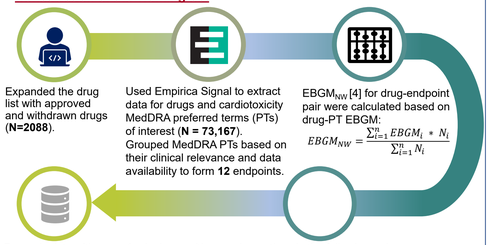
To assess the performance of models

Materials and Methods

Overall Workflow



Construction of the Training Set



Expanded the drug list with approved and withdrawn drugs (**N=2088**).

Used Empirica Signal to extract data for drugs and cardiotoxicity MedDRA preferred terms (PTs) of interest (**N = 73,167**). Grouped MedDRA PTs based on their clinical relevance and data availability to form **12** endpoints.

$EBGM_{NW}$ [4] for drug-endpoint pair were calculated based on drug-PT EBGM:

$$EBGM_{NW} = \frac{\sum_{i=1}^{n} EBGM_i * N_i}{\sum_{i=1}^{n} N_i}$$

For endpoints with unbalanced training set, construct balanced training set using down-sampling technique based on similarity clustering.

Assigning positives and negatives in the following order:

1. Excluded drugs with related indication to each endpoint using RxNorm [3].
2. Drugs with safety signals in clinical studies, literature, and drugs labels -> pos.
3. Drugs with $EBGM_{NW}$ and N larger than optimized threshold -> pos.
4. Drugs approved on or before 2016, with $EBGM_{NW}$ and N smaller than optimized threshold, -> neg.

	Endpoints	Number of PTs	# Drug-AE pairs (P)	# Reports (N)	N/P	positives[1]	negatives[1]
	General Cardiac Toxicity	32[1]	27,509	1,152,174	42	844	564
	Cardiac Ischemia	32	10,415	304,691	29	419	1227
	Heart Failure	37	11,393	224,439	20	514	1077
	Cardiac Valve Disease	38	6,108	55,221	9	238	1443
	Myocardial Disease	11	1,399	10,112	7	190	1599
	Pericardial Disease	13	2,563	46,795	18	246	1571
	Structural Heart Disease	39	7,716	68,295	9	456	1177
	Arrhythmia	68	30,521	781,713	26	827	651
Arrhythmia subsets	Torsade de Pointes	1	686	13,795	20	223	1628
Arrhythmia subsets	Long QT synd. + TdP	2	1,089	16,979	16	288	1526
Arrhythmia subsets	Atrial Fibrillation	1	1,284	86,605	67	299	1501
Arrhythmia subsets	VA_CA[2]	13	6,670	219,534	33	548	1104

Table 1. Total number of PTs, Drug AE pairs and reports for each endpoint. [1]Total number of positive, intermediate and negative before down-sampling. [2]VA_CA indicates ventricular arrhythmia and cardiac arrest.

QSAR Modeling

Commercial QSAR software programs were used for model building and testing:

- Leadscope Enterprise v3.9.2-1
- MultiCASE CASE Ultra v1.8.1.6.

Results and Discussion

QSAR Predictive Performance

	Endpoints	Positives	Negatives	Leadscope Enterprise[1] Sensitivity	Specificity	Concordance	Positive Predictivity	Negative Predictivity	CASE Ultra[1] Sensitivity	Specificity	Concordance	Positive Predictivity	Negative Predictivity	ROC-AUC
	General Cardiac Toxicity	844	564	73%	72%	73%	73%	72%	64%	63%	63%	72%	54%	0.663
	Cardiac Ischemia	419	460	76%	71%	73%	72%	74%	63%	57%	60%	57%	63%	0.613
	Heart Failure	514	514	74%	74%	74%	74%	75%	65%	58%	62%	61%	62%	0.644
	Cardiac Valve Disease	238	238	79%	76%	78%	77%	78%	70%	67%	70%	68%	70%	0.696
	Myocardial Disease	190	209	75%	80%	78%	79%	76%	69%	71%	70%	69%	71%	0.713
	Pericardial Disease	246	270	76%	76%	76%	77%	75%	70%	68%	68%	68%	70%	0.722
	Structural Heart Disease	456	456	72%	77%	74%	76%	73%	68%	60%	64%	64%	64%	0.662
	Arrhythmia	827	651	75%	72%	74%	73%	74%	65%	62%	64%	68%	69%	0.656
Arrhythmia subsets	Torsade de Pointes	223	245	80%	82%	81%	82%	80%	74%	70%	73%	70%	72%	0.756
Arrhythmia subsets	Long QT synd. + TdP	288	288	78%	77%	78%	77%	78%	69%	70%	70%	71%	69%	0.726
Arrhythmia subsets	Atrial Fibrillation	299	299	75%	75%	75%	76%	75%	60%	66%	66%	65%	64%	0.669
Arrhythmia subsets	VA_CA[2]	548	548	73%	74%	73%	74%	73%	65%	60%	62%	61%	63%	0.647

Table 2. Cross-validation performance for newly constructed QSAR models using Leadscope Enterprise and CASE Ultra. [1]Each QSAR modeling software uses different cross-validation methodologies and statistics are not directly comparable. [2]VA_CA indicates ventricular arrhythmia and cardiac arrest.

- Newly constructed models show good sensitivity and negative predictivity (Table 2).
- Negative predictivity and sensitivity (**highlighted**) are critical parameters for safety assessment of drug products.

Development of Enhanced Leadscope Enterprise Models

Figure 1. Coverage across selected functional groups.

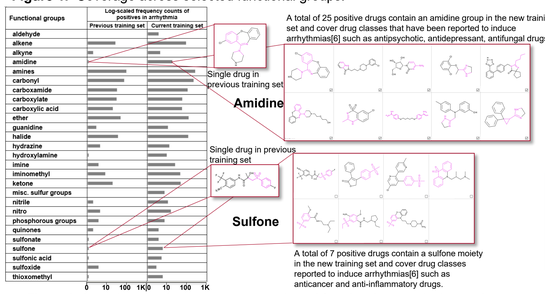
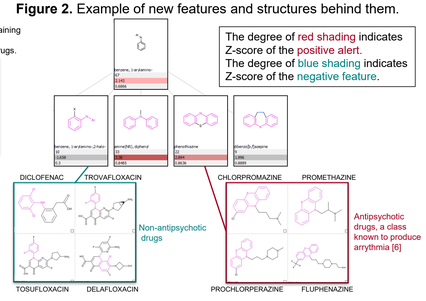


Figure 2. Example of new features and structures behind them.



- Figure 1 shows improved coverage across selected functional groups in the newly constructed arrhythmia training set as compared to the previous model [5].
- Figure 2 shows selected alerts and deactivating features that are in the new model, and training set structures behind these alerts.

Development of Enhanced CASE Ultra Models

Figure 3. ROC plots from cross-validation experiments using CASE Ultra.

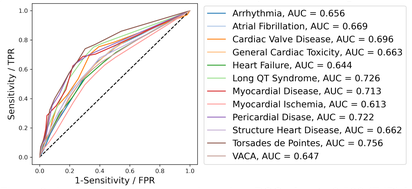
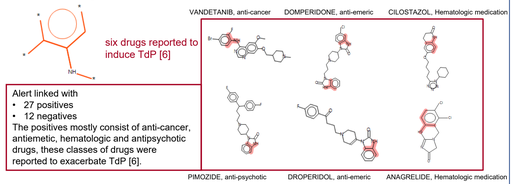


Figure 4. Example of an alert feature in the Torsade de Pointes model.



- Figure 3 shows good performance based on ROC of up to 0.736 (TdP) for the new QSAR models.
- Figure 4 shows selected alert feature and training set structures behind this alert in the Heart Failure model.

Conclusion

- New cardiotoxicity training sets have been enhanced with (1) newly approved pharmaceuticals; (2) up-to-date information from clinical data, alerting publications, and drug labels relating to cardiac toxicity; and (3) the use of EBGM scored FAERS data.
- Newly constructed models cover a variety of cardiac adverse effects including cardiac ischemia, heart failure, cardiac valve disease, myocardial disease, pericardial disease, structural heart disease and arrhythmia.
- Overall, new models showed higher sensitivity (up to 81%) and negative predictivity (up to 79%) over the last generation while maintaining good specificity (up to 75%).
- Furthermore, new models provide sufficient transparency and interpretability for the application of expert knowledge, which has been previously shown to enhance the overall accuracy of predictions by providing a rationale to supersede a positive or a negative prediction and maximize confidence in the overall prediction.
- These new models will provide a fast and more effective evaluation of potential drug candidates.

Ongoing Research

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

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