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Prediction of drug-related cardiac adverse effects in humans-B: Use of QSAR programs for early detection of drug-induced cardiac toxicities ☆

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ABSTRACT

This report describes the use of three quantitative structure–activity relationship (QSAR) programs to predict drug-related cardiac adverse effects (AEs), BioEpisteme™, MC4PC, and Leadscope Predictive Data Miner. QSAR models were constructed for 9 cardiac AE clusters affecting Purkinje nerve fibers (arrhythmia, bradycardia, conduction disorder, electrocardiogram, palpitations, QT prolongation, rate rhythm composite, tachycardia, and Torsades de pointes) and 5 clusters affecting the heart muscle (coronary artery disorders, heart failure, myocardial disorders, myocardial infarction, and valve disorders). The models were based on a database of post-marketing AEs linked to 1632 chemical structures, and identical training data sets were configured for three QSAR programs. Model performance was optimized and shown to be affected by the ratio of the number of active to inactive drugs. Results revealed that the three programs were complementary and predictive performances using any single positive, consensus two positives, or consensus three positives were as follows, respectively: 70.7%, 91.7%, and 98.0% specificity; 74.7%, 47.2%, and 21.0% sensitivity; and 138.2, 206.3, and 144.2 χ^2. In addition, a prospective study using AE data from the U.S. Food and Drug Administration's (FDA's) MedWatch Program showed 82.4% specificity and 94.3% sensitivity. Furthermore, an external validation study of 18 drugs with serious cardiotoxicity not considered in the models had 88.9% sensitivity.

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1. Introduction

The U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER), Informatics and Computational Safety Analysis Staff (ICSAS), is an applied research group that develops databases of animal toxicology studies and human clinical data for use in data mining and quantitative structure–activity relationship (QSAR) modeling. This is the second part of an investigation to identify structure–activity relationships for drug-related cardiac adverse effects (AEs) observed in humans (Matthews and Frid, 2010). This study describes the (1) creation of QSAR models to predict cardiac AEs of drugs using three different state-of-the-art global QSAR software programs and (2) methods that were employed to optimize the predictive performance of these models (Matthews et al., 2009a). The QSAR models permit the prediction of potential AEs of pharmaceutical molecules solely based on the molecular structures of pharmaceuticals. The first report describes the creation of an AE database that contains AE reporting data derived from two pharmaceutical post-market surveillance databases maintained by FDA—the Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS)—and published literature (Matthews and Frid, 2010). This report also correlates the drug-related cardiac AEs with four drug properties: the clinical indication (CI) for which the drug was prescribed; the therapeutic target (TT) for which the drug was designed to bind; the mechanism of action (MOA) by which the drug pharmacological activity is expressed; and the affinity coefficient (AC), which estimates how similar in structure a pharmaceutical test molecule is to drugs that are known to bind to a specific MOA receptor site.

Although substantial progress has been made in the application of *in silico* computational toxicology methods to predict toxicological activities of chemicals (Matthews et al., 2007a,b; Benz, 2007), the prediction of the AEs of pharmaceuticals in humans has not been fully realized (Johnson and Rodgers, 2006; Johnson et al., 2007; Matthews et al., 2004). A complete understanding of phar-

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Nomenclature

AC	affinity coefficient
Actives	subset of drugs that caused AEs in patients
AD	applicability domain (coverage of the QSAR models)
AE	adverse effect (of a pharmaceutical in humans)
AERS	FDA's Adverse Event Reporting System
A/I	ratio of actives to inactives
AU	activity unit (log normalized CASE units)
BioEpisteme™	software program from Prous Institute for Biomedical Research
BP	optimal break point to distinguish active drugs (with significant AEs) from inactive drugs
CDER	Center for Drug Evaluation and Research
CI	clinical indication
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
hERG	human ether-à-go-go-related gene
HLGT	MedDRA high level group term
HLT	MedDRA high-level term
ICSAS	Informatics and Computational Safety Analysis Staff
Inactives	subset of drugs that had no significant AEs
LFMA	Leadscope FDA Model Applier software (Leadscope, Inc.)
LMO	leave many out (statistical cross-validation method)
LOO	leave one out (statistical cross-validation method)
LPDM	Leadscope Predictive Data Miner software (Leadscope, Inc.)
MC4PC	Windows version of MCASE software (MultiCASE, Inc.)
MedDRA	Medical Dictionary for Regulatory Activities
MedWatch	FDA/CDER MedWatch program
MOA	mechanism of action (of a pharmaceutical)
OECD	Organization for Economic Co-operation and Development
PBPK	physiological-based pharmacokinetic and pharmacodynamic modeling
PRR	proportional reporting ratio
PT	MedDRA preferred term
QSAR	quantitative structure–activity relationship
QT interval	the time for both the heart ventricular depolarization and repolarization to occur
RCPP	rate of Change in the Predictive Performance; RCPP = (ΔSe/ΔFP)/(Δ%Act)
ROC	receiver operating characteristic intercept statistic; it is the ratio of the percentage of true positives to false positives
SMILES	simplified molecular input line entry system
SOC	MedDRA system organ class (term)
SRS	FDA's Spontaneous Reporting System
TT	therapeutic target
WoE	weight of evidence

maceutical AEs at the cellular level in humans is very complex. It requires: (1) physiological-based pharmacokinetic and pharmacodynamic (PBPK) modeling; (2) understanding of human and organ-specific metabolism, (3) examination of possible drug–drug interactions; (4) knowledge of all possible pharmacological targets to which the drug might bind; and (5) consideration of the CI and health status of the patients being treated. In the past decade, substantial progress has been made in the application of QSARs to PBPK modeling of pharmaceuticals (Reisfeld et al., 2007), the prediction of cytochrome P450 metabolism of xenobiotics in humans and across mammalian species, and providing a plausible understanding of bioactivation and elimination of pharmaceuticals (de Graaf et al., 2005; Ekins, 2007). In contrast, the application of QSARs to predict ligand binding to all possible pharmaceutical TTs has lagged behind. Current QSARs are designed specifically for predicting binding to androgen, estrogen, and thyroid endocrine organ receptors (Lill and Vedani, 2007), and potassium, sodium, and calcium ion channels (Aronov et al., 2007). The most thoroughly investigated TT is that coded by Kv11.1, the human ether-à-go-go-related gene (hERG). hERG QSARs now have been successfully used to predict potential cardiac toxicity associated with QT prolongation (Curren et al., 1995).

1.1. Investigation objectives

The first objective of this investigation was to devise a generalized, *in silico* methodology that could unambiguously discriminate a subset of drugs associated with unexpected and serious cardiac AEs in patients (hereafter called actives) from a subset of drugs that had produced no significant AEs (hereafter called inactives). The reasons for selecting cardiac AEs are summarized in the companion report (Matthews and Frid, 2010). ICSAS's goal was to construct a battery of QSAR models that could be used to predict drug-related injury to the heart in humans. The second objective was to rigorously test the relative reliability of this QSAR methodology using three different types of validation experiments. The first test would employ internal cross-validation experiments in which 10% of the training data set was randomly left out and predicted by the remaining 90% of the training data set (i.e., leave many out (LMO) validation). The second test was a prospective study that used the most recent (posted June 2006 through August 2008) pharmaceutical AE data warnings in FDA's MedWatch Program (http://www.fda.gov/medwatch/). (MedWatch is an Internet gateway for timely safety information on drugs and other medical products that FDA regulates.) These MedWatch data were compiled and predicted with QSAR models that employed AE data compiled through May 2006. The third test was an external validation study that used drugs with known serious cardiotoxicity that had not been considered in the QSAR models when they were constructed.

ICSAS's operating hypothesis in this investigation was that the active drugs represented the highest risk of causing serious heart failure because they had caused more than one type of AE. Furthermore, the multiple AEs presumably were related to different mechanisms by which the drug injured the heart, and it was postulated that these active drugs might share chemical molecular properties that could be recognized by QSAR software programs. Our hypothesis was inspired by the observations of Hyman Zimmerman (1978, 1999), who reported that drugs causing drug-induced liver injury by two different mechanisms in the same patient (i.e., an increase in a liver enzyme such as alanine or aspartate aminotransferase and also jaundice) are most likely to cause serious human liver toxicity in that patient. Our strategy for testing this hypothesis previous has been described (Ursem et al., 2009; Matthews et al., 2009a,b). The strategy involves separation of active and inactive drugs using two independent experimental parameters: (1) identification of clusters of toxicologically related AE endpoints and (2) identification of clusters of active drugs that shared molecular properties that QSAR software programs recognize.

1.2. Why employ three QSAR programs?

The decision to use more than one QSAR software program to model cardiac AEs was influenced by ICSAS's experience in using