In Silico Analysis of a Human Cardiac Adverse Effects Data Set

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Abstract
Cardiotoxicity can be difficult to detect in current in vivo studies, and therefore may not be seen prior to the drug reaching a significant patient population. In silico models for the prediction of cardiotoxicity based on chemical structure may therefore play an important role in the early identification of potential toxicological concerns during the drug development process.

Previously, we have shown that structural alerts for the prediction of HERG channel inhibition can be developed from the results of in vitro studies. We were therefore interested to see if a similar methodology could also be applied to the derivation of predictive models from a data set of human cardiac post-marketing adverse effects data, containing information on 14 endpoints such as bradycardia and QT prolongation (provided through a Cooperative Research and Development Agreement between Lhasa Limited and the US Food and Drug Administration).

The data set of 1632 drug compounds was analysed and clustering software used to identify structurally similar chemicals. A total of 52 of the 250 clusters identified were found to be associated with at least one cardiac endpoint, although the majority of clusters were only associated with 1-3 endpoints. For the bradycardia endpoint, the resulting clusters were prioritised according to the number of active chemicals contained within the cluster and then, when appropriate, structure-activity relationships (SARs) were developed. These included SARs based on aryloxypropanolamine beta-blockers and N-alkyl-substituted piperidoxylidide local anaesthetics, such as esmolol and ropivacaine respectively.

Although initial results suggest that the structural alerts implemented based on human adverse effects data are more specific in scope than those derived from in vitro HERG channel inhibition assays, they nevertheless demonstrate that a knowledge-based approach may be successfully extended to the assessment of human in vivo cardiac effects. The correlation between the in vivo cardiotoxicity endpoints and existing in silico predictions has also been explored and indicates that predictions made for in vitro HERG channel inhibition correlate well with the effects of chemicals that induce both QT prolongation and torsades de pointes in vivo.

Method and Results
The data set used in this work was compiled by the Informatics and Computational Safety Analysis Staff (ICAS) group at the Center for Drug Evaluation and Research, US Food and Drug Administration and was made available through a Cooperative Research and Development Agreement. The data set contained 1632 drugs with scores describing activity (ADRs) for each compound and the estimated patient exposure to each compound. The proportion of active chemicals for each endpoint was low e.g. only 6.6% were associated with bradycardia. The process by which SARs were developed is illustrated in Figure 1 for the bradycardia endpoint and shows two of the eight SARs developed for this endpoint.

Conclusions
This work has demonstrated that SARs can be derived from an in vivo cardiac adverse effects data set. For bradycardia these include inclusion of aryloxypropanolamine beta-blockers such as esmolol1. The N-alkyl-substituted piperidoxylidide local anaesthetics, such as esmolol and ropivacaine respectively. Previously we had shown that SARs can be derived and structural alerts can be built from in vitro HERG channel inhibition data with good predictivity for HERG channel inhibition. The correlation between the in vivo cardiotoxicity endpoints and existing in silico predictions has also been explored and indicates that predictions made for in vitro HERG channel inhibition correlate well with the effects of chemicals that induce both QT prolongation and torsades de pointes in vivo. Thus, structural alerts show some promise for the prediction of a in vivo cardiac effects, and this may be achieved either directly (using in vivo data) or indirectly (using in vitro data).

References
2. Strichartz GR (editor), Handbook of Experimental Pharmacology (Local Anesthetics), 1987, 81, 187-212.

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