Cardiovascular toxicity has been highlighted as one of the leading reasons for compound attrition all along the development pipeline over a number of years. Input into models is IC$\text{}_{50}$ data for three ion channels (hERG, hNav1.5, hCav1.2) from a single publication by ChanTest$^\text{®}$. Revised Redfern categories describe the number of reported incidences of TdeP:

1. Class 1a and III antiarrhythmics; generally associated with a large, but acceptable, risk of TdeP. Drugs that have been withdrawn from the market (by at least one major regulatory authority) due to unacceptable TdeP risk.
2. Drugs with a measurable incidence of TdeP, or for which numerous case reports exist.
3. Drugs for which there have been isolated case reports of TdeP.
4. Drugs for which there have been no published reports of TdeP.

Categories 1 and 2 from Redfern et al are grouped together as the degree of propensity is the same, only the indications are different$^5$.

Methods

Input into models is IC$\text{}_{50}$ [EFTPC], where [EFTPC] is the mean effective therapeutic concentration for plasma protein binding. Output from each model is a single value fed into a classifier.

Models tested via a leave one out cross validation were:

1. Physiomics Model
3. Competitor 2: linear combination of ratios
4. Competitor 3: dog model$^4$ highlighted as a predictive model for AP changes in dog$^6$
5. Competitor 4: human model$^4$ highlighted as a predictive model for QT changes in human$^6$

Results

Figures show the error in classification: 0 - correct, 1 - one away, 2 - two away and 3 – three away.

1. Physiomics proprietary model is better than any current literature models.
2. Measuring more than hERG improves predictivity.

Conclusion

Physiomics has developed a cardiac toxicity prediction service using high-throughput screening data that is more predictive when assessed against published literature models. The model highlights that measuring more than hERG is important to assess torsadogenic risk. In addition to the TdeP prediction service we have also developed a dog toxicity prediction service. Finally, the service we are providing could be part of a much larger framework to assess what additional information would be needed in addition to QTc prolongation to provide a more thorough qualitative assessment of a TQT study.

References


