Early in silico assessment of the drug-induced proarrhythmic risk using the Drug Safety Suite

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BACKGROUND

The Comprehensive in vitro Proarrythmia Assay (CiPA) initiative was established to improve the accuracy of **torsadogenic risk** predictions by combining in vitro experiments of the dynamic and static interactions of compounds towards several ion channels with corresponding **in silico predictions** of their effects on the action potential of human cardiomyocytes. To this end, we launched the Drug Safety Suite, a collection of three web-, and cloud-based products (QT/TdP Risk Screen, CiPA In Silico, and STrhiPS), that performs an early screening assessment of pro-arrhythmic risk. This study illustrates how the Suite can complement in vitro testing**, improving the accuracy** of cardiac safety assessments.

RESULTS

Table 1. QT/TdP Risk Screen classification of the drugs at concentration Cmax.

	Cmax (nM)	QT/TdP risk screen
Astemizole	0.26	unsafe
Bepridil	33	unsafe
Chlorpromazine	38	probably unsafe
Cisapride	2.6	unsafe
Dofetilide	2	unsafe
Flecainide	1448	unsafe
Ranolazine	1948.2	unsafe
Verapamil	81	safe

QT/TdP Risk Screen

According to the CredibleMeds classification, all drugs are class 1 (unsafe) except for ranolazine (class 3 – probably safe) and verapamil (class 4 - safe). All drugs were correctly classified by QT/TdP Risk Screen except for chlorpromazine and ranolazine. The former was tested at a lower concentration than that reported in the CredibleMeds database. The latter was misclassified as explained in previous studies [4].

CiPA In Silico

qNet calculated with CiPA In Silico (Figure 1) correctly allocated the smallest values of qNet to bepridil and dofetilide, the two high risk drugs. The largest qNet value was obtained for the low-risk verapamil. For flecainide, qNet appeared to be overestimated (and risk underestimated), whereas for ranolazine, risk appeared to be overestimated.

STrhiPS

With the exception of ranolazine, the simulated impact on the safety biomarker ADP_{90} was in line with the CiPA and CredibleMeds TdP classification: ADP was prolonged in all unsafe drugs – particularly in the high-risk drug bepridil and flecainide – and it was shortened in the low-risk drug verapamil. Abnormalities were rarely observed at therapeutic concentrations (< 6% of cells in the population).

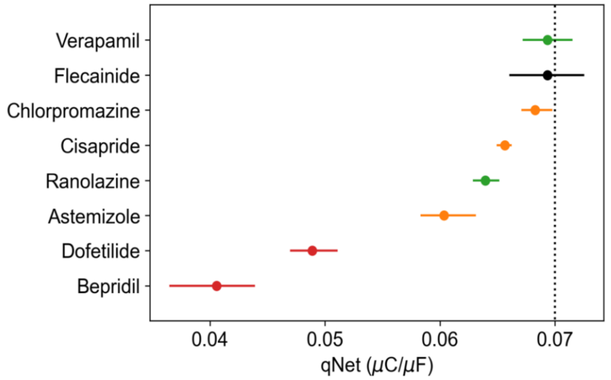

Figure 1. Safety marker qNet (median +/- CI) as calculated by CiPA In Silico for each of the 8 compounds. Colors according to CiPA classification [1,2] High risk (red), intermediate risk (orange), low risk (green), other (black).

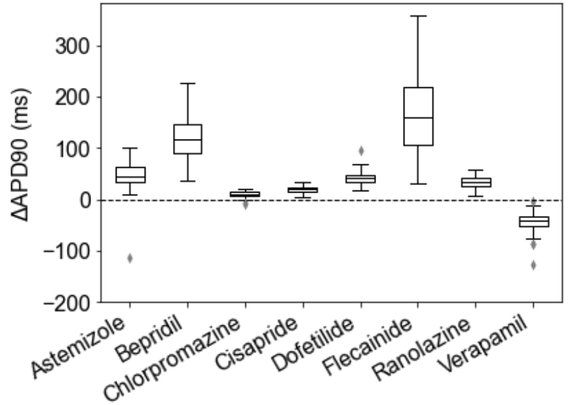

Figure 2. Difference in action potential duration (APD90) in absence and presence of drug computed by STrhiPS.

METHODS

- The Drug Safety Suite was applied to eight different compounds with known cardiac risk when administered at the therapeutic drug concentration, Cmax (see Table 1)
- For each compound, hERG kinetics data following the Milnes protocol and cardiac channel data for hERG, hCav1.2, and peak/late hNav1.5 were manually obtained at DSTC. These data were used as input parameters to run each product according to their requisites. As the original data for dofetilide were not sufficient to fit a Hill function, ion currents data for this drug were completed with the CiPA dataset [1,2].
- QT/TdP Risk Screen was used to classify each compound as safe or unsafe based on a model trained on the CredibleMeds database [3,4].
- CiPA In Silico was applied to derive the drug-specific safety marker qNet following FDA standards [1,2].
- STrhiPS was applied to simulate experiments on a population of 110 human induced pluripotent stem cells derived cardiomyocytes (hiPSC-CM). Action potential duration (APD) values were estimated in absence and presence of the drug, and drug-induced repolarization abnormalities were automatically detected [5,6].

DISCUSSION

- For this original data, QT/TdP Risk Screen, CiPA In Silico and STrhiPS classifications were generally in good agreement with the drug's known torsadogenic risk and previous publications, with misclassifications in only 1 (QT/TdP), 2 (CiPA in silico) and 1 (STrhiPS) cases.
- Ranolazine, which is a low-risk drug according to it's CiPA classification and a category 3 drug in the CredibleMeds database, is misclassified as an intermediate-high risk drug by all three tools. For QT/TdP Risk Screen, this is consistent with results previously discussed in the original publication [4]. For STrhiPS and CiPA In Silico, risk overestimation most likely resulted from some difference between the Hill parameters obtained in this study and the ones found in literature [1,4].
- In CiPA In Silico, flecainide was misclassified as safe (it has a well known high torsadogenic risk). Investigation of the parameter estimates showed the hERG data was not dynamic. This result might have been originated in a difference of data collection (voltage protocol, stimulation frequency, internal/external solution, and selection of peak or late Nav1).
- The combined use of the three tools can improve cardiac risk predictions. For instance, flecainide's qNet value was predicted by CiPA In Silico close to the discrimination threshold and with a degree of uncertainty that resulted in an inconclusive classification. Predictions obtained with the other two tools, confirmed flecainide as a high-risk drug.

CONCLUSIONS

The **three tools** performed well individually, but when **used in combination** complemented and strengthened each other's outcomes. This study has shown how the Drug Safety Suite can **complement in vitro experiments** to assess the potential pro-arrhythmic risk of compounds in early preclinical screening. The Suite is available on the secure and user-friendly InSilicoTrials.com platform. Runtime of the different products varies from seconds to few hours making the predictions in real time highly efficient.

References

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