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

Cristina Vaghi[1], Chiara Nicolo'[1], Fianne Sips [1], Hiroshi Matsukawa[2], Mao Yamaguchi[2], Koji Nakano[2], Masaru Tsuboi[2], Roberta Bursi[1]

[1]R&D Division, In SilicoTrials Technologies S.p.A.
[2]Higashimatsuyama Laboratories, Drug Safety Testing Center Co., Ltd. (DSTC)

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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 cloud-based products (QT/TdP Risk Screen, CiPA in Silico, and STrhiPS), that performs an early assessment of pro-arrhythmic risk. This study illustrates how the Suite can complement in vitro testing, **improving the accuracy** of cardiac safety assessments.

RESULTS

QT/TdP Risk Screen

According to the CredibleMeds classification, all tested drugs are Class 1 (unsafe) except for Ranolazine (Class 3 - probably safe) and Verapamil (Class 4 - safe). The tool has correctly classified all drugs except Chlorpromazine and Ranolazine. The former was tested at a different concentration than that reported in the CredibleMeds database. The latter was misclassified as discussed elsewhere [6].

	C_{max} (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

Table 1. QT/TdP Risk Screen classification at C_{max} therapeutic concentration.

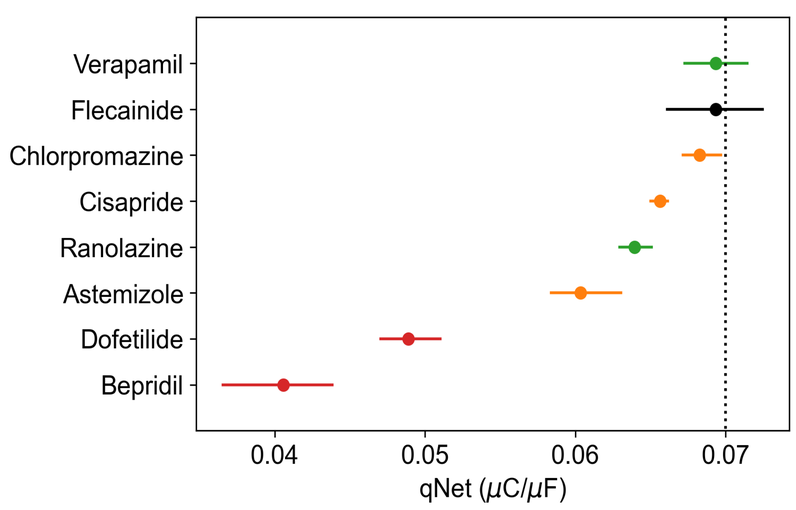

Figure 1. Safety marker qNet (median +/- CI) as calculated by CiPA In Silico. High-risk (red), intermediate-risk (orange), low-risk (green), major misclassification (black). Vertical dotted line: qNet no risk/risk threshold.

CiPA In Silico

qNet calculated with CiPA In Silico (Figure 1) correctly predicts lowest values of qNet for Bepridil and Dofetilide, two high-risk drugs; reduced qNet values for Astemizole, Cisapride and Chlorpromazine, three inter-mediate-risk drugs, and a qNet value at cut-off for Verapamil, a safe drug. For Flecainide and Ranolazine, both unsafe drugs, qNet values were overestimated and risk underestimated.

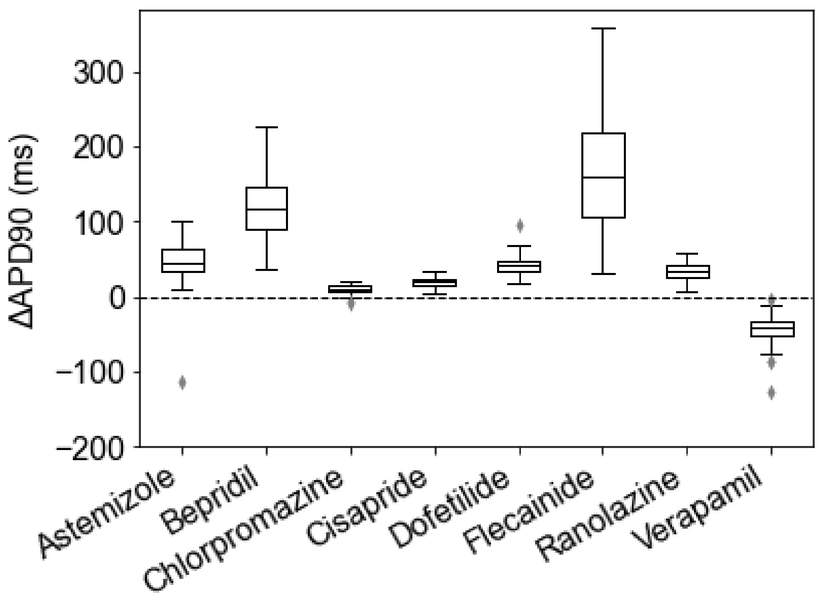

Figure 2. Simulated difference in Action Potential Duration at 90% repolarization (APD_{90}) in absence and presence of drug in a population of 110 cells.

STrhiPS

Except for Ranolazine, the simulated drug effects on the ADP_{90} safety markers were in line with CiPA and CredibleMeds classifications. ADP_{90} was prolonged in all unsafe drugs – particularly in the high-risk drugs Bepridil and Flecainide - and it was shortened in the safe drug Verapamil. In all simulations, abnormalities were rarely observed at the simulated therapeutic concentrations (<6% of cells in the population).

METHODS

- The Drug Safety Suite was tested on eight different compounds with known cardiac risk at C_{max} of the therapeutic drug concentration (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 the Drug Safety Testing Center. As the original data for Dofetilide were not sufficient to fit a Hill function, ion currents data for this drug were completed with data from the CiPA dataset [1].
- QT/TdP Risk Screen is a tool built on a combination of mechanistic-based and Machine Learning-based approaches and it predicts clinical risk of Torsade de Pointes in line with the CredibleMeds classification [2].
- CiPA in Silico is a tool that simulates drug-ion channel dynamic (hERG) and static (six other channels) interactions, and it estimates the safety marker qNet following FDA recommendations [1, 3].
- STrhiPS is a tool that generates populations of human induced pluripotential stem cells derived cardiomyocytes (hiPSC-CM) and it estimates drug-induced potential effects on safety markers like the Action Potential Duration at 90% repolarization (APD_{90}) [4, 5]. It is based on a hiPSC-CM action potential model that has been calibrated with a genetic algorithm.

DISCUSSION

- Based on original experimental data, QT/TdP Risk Screen, CiPA In Silico and STrhiPS results were mostly in good agreement with the drugs' known torsadogenic risks and previous publications, with misclassifications in only 1 (QT/TdP Risk Screen), 2 (CiPA In Silico) and 1 (STrhiPS) cases, respectively.
- Ranolazine, which is a low-risk drug according to it's CiPA classification and a Class 3 drug in the CredibleMeds database, is classified as an intermediate-high risk drug by all three tools. For QT/TdP Risk Screen, this is consistent with previous observations [6]. For STrhiPS and CiPA In Silico, overestimation of the effect most likely originates from differences in Hill coefficient values obtained in this study and in the literature [1, 6].
- In CiPA In Silico, Flecainide is classified as safe, whereas it has a known high torsadogenic risk. Investigation of the parameter estimates suggested that the hERG data might not have fully displayed the dynamic effect and therefore might not have contained sufficient information for high quality parameter estimates.
- The combined use of the three tools enables outcomes cross-validation and consequently can improve accuracy of cardiac risk predictions.

CONCLUSIONS

This case 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. Runtimes of the different products vary from seconds to few hours making the predictions in real time highly efficient.

References

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