Usefulness of combining multi-ion-channel assays with the Langendorff assay in an assessment of proarrhythmic risks

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Introduction

Precise evaluation of cardiac safety in an early stage is essential for developing novel drugs. In particular, it is important to predict a possible risk for proarrhythmia in safety pharmacology testing. Prolongation of the QT interval, which is caused by blockade of the hERG channel, can lead to a life-threatening arrhythmia known as Torsades de Pointes (Tdp). Although risk predictions by in silico model have been promoted, the models seem to have room for further improvement. Recently, the QT prolongation associated with blockade of other ion channels has also been discussed. So, we attempted to predict the proarrhythmic risks more accurately by combining ion-channel assays with the Langendorff assay. In this study, we tested 6 drugs, which had been evaluated in clinical QT prolongation assessments by IQ-CSRC, using the manual patch-clamp technique and the Langendorff system.

Materials & Methods

Drugs: 6 drugs which were used in the IQ-CSRC study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tdp Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetilide</td>
<td>Known Risk of Tdp</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Conditional Risk of Tdp</td>
</tr>
<tr>
<td>Mosfloxacin</td>
<td></td>
</tr>
<tr>
<td>Dolasetron</td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>none</td>
</tr>
</tbody>
</table>

Patch Clamp—Whole cell mode

Cell Lines: 7 stable cell lines

- HEK-hNa1.5
- CHO-hCa,1.2/β1/δLα1
- CHO-hk,4.3
- CHO-hk,1.5
- HEK-hERG
- CHO-hk,LLQT1/mink
- CHO-hk,2.1

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Results

I<sub>Na</sub> inhibition: Strong → I<sub>K</sub> >> I<sub>Na</sub> → I<sub>Kr</sub>

- Dofetilide
- Ondansetron

I<sub>Na</sub> inhibition: Moderate → I<sub>Na</sub> > I<sub>Kr</sub> > I<sub>Na</sub>

- Mosfloxacin

I<sub>Na</sub> inhibition: None

- Quinine
- Levocetirizine

Conclusion

These results revealed that the proarrhythmic risks are highly predictable by combining ECG analysis in the Langendorff system with multi-ion-channel profiling. The present study provided an insight into usefulness of combining multi-ion-channel assay with Langendorff assay for an assessment of proarrhythmic risks. We concluded that this combination assays will greatly contribute to the drug discoveries and developments.

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