

The hERG Inhibition Assay

Assay

Rapid delayed rectifying potassium (IKr) current inhibition assay

Tissue or cell line

HEK293 or CHO cells stably transfected with the human ERG (hERG) gene

Technique

Manual or automated (PatchXpress) patch-clamp, whole-cell configuration

GLP Compliance

Pre-IND (GLP-compliant) or exploratory designs (non-GLP compliant) available

Rationale

Part of the core battery of Safety Pharmacology tests required for IND submission

Whole-cell current amplitude and kinetics measurements verify the result of potential interactions of a test article with the product of the hERG gene, a human ion channel responsible for the IKr repolarizing current. IKr current inhibition has been shown to elongate the cardiac action potential, a phenomenon associated with increased risk of arrhythmia. IKr current inhibition accounts for the vast majority of known cases of drug-induced QT-prolongation.

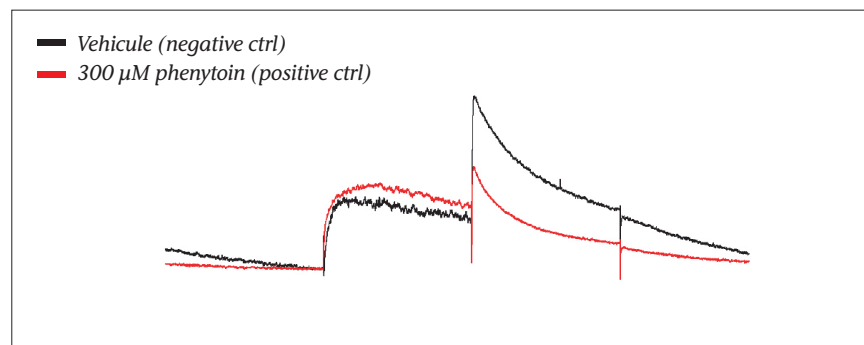


Figure 1. Inhibition of IKr current in hERG-expressing HEK-293 cells using 300 μ M phenytoin

Protocol outline

Number of cells analyzed : 7 (screens : 3)

Number of concentration of the test article per cell : 4 (screens : 3)

Method of test article exposure : Standing medium or continuous perfusion

Voltage steps: -15, -5, 5, 15, 25mV

Positive controls commonly used : E-4031, dofetilide, d,l-sotalol, or terfenadine

Study outcome

- A quantitative assessment of IKr current inhibition on 7 cells in the presence of 4 rising concentrations of the test article
- Determination of the IC50 value (if applicable)
- FDA-ready hard-copy and e-report for electronic IND submission
- Holistic interpretation of a positive signal, considering all other data generated

Recommended readings

1. Shah RR., Drug-induced QT interval prolongation--regulatory guidance and perspectives on hERG channel studies., Novartis Foundation Symposium 266:251-80, 2005.

2. Sanguinetti MC. Mitcheson JS., Predicting drug-hERG channel interactions that cause acquired long QT syndrome., Trends in Pharmacological Sciences 26(3):119-24, 2005.

Contact us:

info@ipstherapeutique.com
(P) 819.564.5391
(F) 819.820.6831