A Literature Review of Ivabradine and Delayed Rectifier Potassium Current

Amarpal Singh Karamjit Singh[1], Dominic Chow[2]
[1]Cardiology Research, Northern Health Epping, [2]University of Melbourne, Victoria, Australia

Northern Health

RESEARCH WEEK
20-24 OCTOBER 2025
INSPIRED RESEARCHERS
Northern Health

Introduction

- Ivabradine primarily acts on the hyperpolarization-activated cyclic nucleotide gated (HCN) channel. Emerging evidence shows that ivabradine also prolongs phase 3 repolarization in ventricular tissues by inhibiting the rapid component of delayed rectifier potassium current (IKr) mediated by the ether-à-go-go related gene (hERG) channel.
- A literature review was done and focused on current knowledge of the unique inhibitory effect of ivabradine on IKr by analyzing current preclinical studies, human trials, and clinical observations.
- This review aims to look beyond bradycardia mediated Torsades de Pointes (TdP) to suggest an additional driver of TdP, mediated by inhibition of the hERG channel.

Methods:

OVID Medline and PubMed were searched from 2015 up until 2025.

Inclusion/exclusion criteria: Studies that were focused on bench-top experiments, animal studies, post-marketing case reports and randomized controlled trials (RCTs) where included in our study. Review articles and conference abstracts were excluded

Keywords: Ivabradine, hERG, IKr, torsades de pointes

Our literature review includes studies that measures current clamp with Ivabradine at 1µM (1 Iva) and 10µM (10 Iva) on iPSC-derived human cardiomyocytes

Results

Of 22 articles that were retrieved 13 articles were included in our study (**Figure 1**)

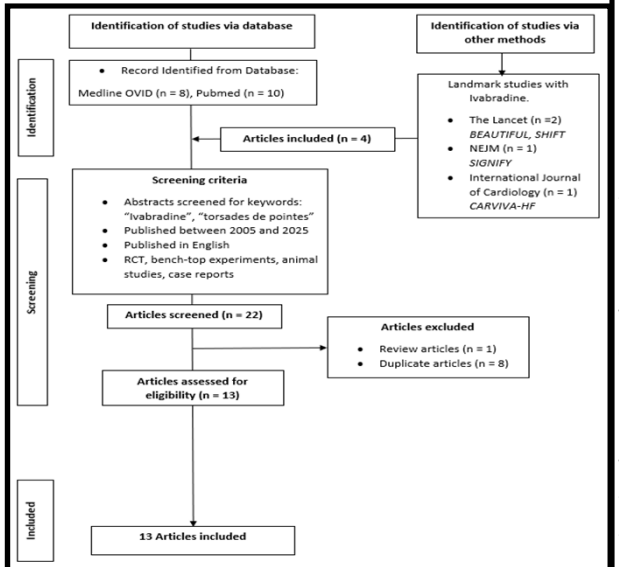

Figure1: Study flowchart

Clinical Implications

Interaction between Ivabradine and Class III Anti-arrhythmics

Despite limited case reports, Ivabradine and class III anti-arrhythmic agents have been proven to inhibit hERG channel[1-5] and may lead to exaggerated inhibition of IKr, significant prolongation of action potential, and eventually to the development of TdP.

Interaction between Ivabradine and beta-blockers

No safety concerns were reported when ivabradine was introduced with beta-blocker therapy in BEAUTIFUL trial[6] 87% of participants were receiving concurrent ivabradine and beta-blockers. Meanwhile, out of 87% of individuals receiving concurrent ivabradine and beta-blocker therapy in SIGNIFIY Trial[7], severe ventricular arrhythmia occurred in 0.7% (n=7, p value = 0.39).

Interaction between Ivabradine and Macrolides

One case report details the development of TdP in a man in his 60's, five days after receiving azithromycin for the treatment of sinusitis while already receiving ivabradine (7.5 mg)[8]. However, baseline QTc was already prolonged (between 490 and 560 ms)

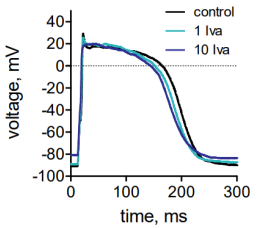

Figure2: Effect of ventricular action potential with Ivabradine as measure with current clamp at 1µM (1 Iva) anc 10µM (10 Iva) on iPSC-derived humar cardiomyocytes

Highlight of bench top studies:

(1) The molecular inhibitory properties of hERG channels are concentration dependent[1-4].

(2) Supratherapeutic plasma levels of Ivabradine, from overdose or co-administration of medications that inhibit CYP3A, can lead to toxic accumulation of plasma levels of Ivabradine, inhibiting hERG channels, and leading to torsades de pointes.

Conclusion

Current bench top studies show that the inhibitory concentration of ivabradine required to inhibit hERG channel and prolong action potential appears to be higher in human induced pluripotent stem cells than in animal cardiomyocytes[1-4]. In clinical practice, this translates into a supratherapeutic plasma concentration of Ivabradine that is needed to prolong phase 3 repolarization[1-4].

References: 1. doi.org/10.1124/mol.118.115642, 2. doi.org/10.1016/j.yjmcc.2015.05.009, 3. doi.org/10.33594/0000001194, 4. doi.org/10.1161/jaha.115.001813, 5.doi.org/10.1016/j.vascn.2016.03.009, 6. doi.org/10.1159/000112412, 7. doi.org/10.1056/nejmoa1406430, 8. doi.org/10.1007/s12012-014-9274-y