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LITERATURE REVIEW

Overview of Ivabradine Drug: Use and History

Melviana Lubis

Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara

Corresponding email: melvianalubis@umsu.ac.id

Abstract: Despite significant advances in management and prevention, heart failure continues to be a leading cause of death and morbidity. Ivabradine, a medication in the class of hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers, is one example of a "new drug" used to treat heart failure with a low ejection fraction. The history and use of ivabradine are intriguing because they can help us understand cardiovascular pathophysiology. In the future, there may be additional indications for ivabradine use.

Keywords: ivabradine, If channel blocker

INTRODUCTION

Despite significant advances in management and prevention, heart failure continues to be a leading cause of death and morbidity. Scientists and researchers are still fighting and working hard to reduce the numbers. New treatment targets are still being investigated, and new drugs are being developed regularly. Ivabradine, a medication in the class of hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers, is an example of a "new drug" used to treat heart failure.[1,2] This paper discusses the history of its discovery, mechanism of action, indications, and potential side effects.

Ivabradine History, Study & Trial

The discovery of ivabradine cannot be separated from the discovery of If current in pacemaker cells by F (Funny channels) in 1979.[3] Unlike the other channels and currents (T and L type Ca2+ channels and K+ channels), the F or 'funny' channel is so named because of its unique character. Most ion channels are activated by depolarisation, but the If channel's current is activated by hyperpolarisation.

Suppose the wind is an influx of Na-K ions that simultaneously initiates the sinoatrial node (SAN) action potential (See Figures 1 and 2). Since then, scientists have been studying and characterising the funny channel, making it a natural target for drugs aimed at pharmacologically controlling heart rate.[4]

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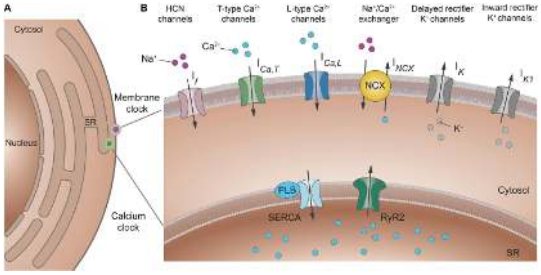

Figure 1. Ion channel in SAN[5]

(A) Schematic representation of a SAN cell containing the nucleus, cytosol, and sarcoplasmic reticulum (SR) (B) Different ion channels localised in the plasma membrane, including the If channel (HCN channel).

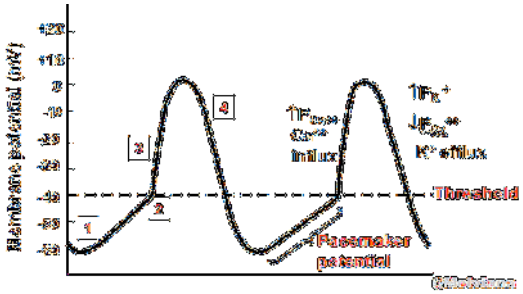

Figure 2. Pacemaker Potential[6]

1. Funny channel (If channels) are open (↑P Na^+) and closing K^+ channels
2. Transient (T type) Ca^{2+} channels open, pushing the membrane potential to the threshold
3. Long-lasting (L type) Ca^{2+} channels open, giving rise to the action potential
4. Opening of K^+ channels (↑P K^+) and closing of L-type Ca^{2+} channels, hyperpolarising the cell

Experts have long recognised that heart rate influences myocardial metabolic demand.[2,7] The higher the heart rate, the greater the myocardial oxygen consumption. This became the hypothesis for the first ivabradine RCT clinical trial, which was conducted in 2002.[7] For two weeks, 360 patients with chronic stable angina pectoris were divided into groups that received 2.5 mg, 5 mg, 10 mg ivabradine, or placebo. Then, in an open-label study, all patients were given ivabradine 10 mg for 2-3 months and no other antianginal drugs other than short-acting nitrates. Patients were then randomly assigned to continue on 10 mg twice daily ivabradine or withdraw to placebo for one week, followed by an exercise tolerance test. The result was a worsening exercise tolerance test parameters in patients who received a placebo during the drug discontinuation process but not in the Ivabradine group.

Ivabradine improves exercise tolerance and reduces the time it takes for ischemia to develop during exercise. [7,8,9]

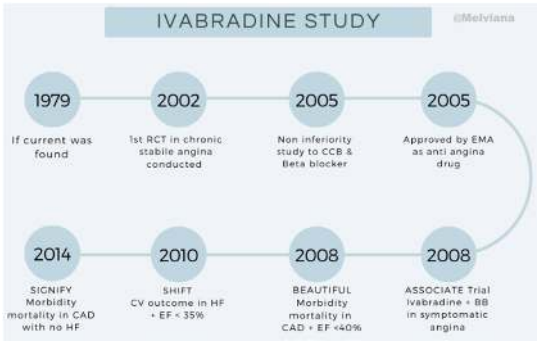

Figure 3. Ivabradine study and trials

There were also several randomised controlled trials (RCTs) on Ivabradine's effect on stable angina pectoris, including non-inferiority studies and those comparing it to standard drugs (atenolol or amlodipine).[10] Those studies lead us to conclude that ivabradine improves exercise parameters, reduces the number of weekly attacks, and lowers short-term nitrate consumption in angina patients. Ivabradine is as effective as recommended medications like amlodipine (Ca channel blocker) and atenolol (β-blocker). The European Medicines Agency (EMA) approved ivabradine as a treatment for angina pectoris based on these findings in 2005.[8,9,10]

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It continued; in 2005, a multicentred RCT was carried out. It is known as ASSOCIATE research ("evaluation of the Antianginal efficacy and Safety of the Association of the Current Inhibitor ivabradine with a betablocker").[8] This study examined the anti-ischemic and anti-anginal effects of adding ivabradine to atenolol-treated symptomatic angina patients. As a result, the group that received ivabradine had better exercise results and clinical parameters than the group that received only atenolol plus placebo.[8,10]

These results prompted the EMA in 2015 to expand the indication of ivabradine as an angina pectoris drug in patients still symptomatic after β-blocker treatment and has more than 60-time beat per minute or as a treatment in patients who cannot tolerate or have a contraindication to β blocker.

A research group funded by Sevier, France, also investigated the benefits of ivabradine. This study was designed to test the hypothesis that lowering heart rate without affecting other cardiac functions could reduce CV-related mortality and morbidity in patients with CAD and left ventricular dysfunction.[11] BEAUTIFUL study (morbidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) was conducted from 2004 to 2006 to evaluate the benefit of administering ivabradine in 10,917 patients with coronary heart disease (CAD) and ejection fraction < 40%, against endpoint outcomes such as cardiovascular death, episodes of hospitalisation due to acute myocardial infarction and new attack or worsening heart failure.[10,11] Although there was no difference in morbidity or mortality outcomes, ivabradine administration reduced the incidence of fatal and non-fatal myocardial infarction (hazard ratio of 0.64) and coronary revascularisation (hazard ratio of 0.70) in a subgroup with a heart rate of 70 beats per minute.[10,11]

An elevated resting heart rate is a risk factor for cardiovascular outcomes in chronic heart failure. SHIFT study was held in 2010 based on this hypothesis. SHIFT (the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial) compared the benefits of giving ivabradine to 6,558 heart failure patients with reduced cardiac function, ejection fraction 35%, and heart rate greater than 70 beats per minute to the outcomes of cardiovascular events: cardiovascular death or hospitalisation due to worsening heart failure. The study successfully demonstrated a decrease in cardiovascular events (24% in the ivabradine group vs 29% in the non-ivabradine group).[12]

SIGNIFY (A study assessing the morbidity-mortality benefits of ivabradine in patients with coronary artery disease) was published in 2014. This study evaluated 19,102 patients with coronary artery disease (CAD) without signs of heart failure and a pulse rate of 70 beats per minute for the benefit of adding ivabradine. The findings revealed no significant difference in the occurrence of cardiac death or myocardial infarction between the ivabradine and placebo groups in this group. Furthermore, the ivabradine group had more bradycardia (18% ivabradine vs 2.3% placebo).[10,13]

Even though the results were not as expected and differed from the satisfactory results found in the SHIFT study, they

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provided valuable insights. Positive results with lowering the heart rate in patients with heart failure but not in those with stable coronary artery disease may reflect that elevated heart rates in these conditions had different pathophysiological mechanisms. Neurohormonal activation occurs in heart failure, leading to ventricular remodelling, further left ventricular dysfunction, and a downward spiral. No neurohormonal activation exists in stable coronary artery disease without left ventricular dysfunction. There were also some theories that the unexpected results were due to the ivabradine dose being higher than in other studies, so ivabradine may have lowered the heart rate too much or had unintended effects that negated other beneficial effects.[9,10,13,14]

The cardiology community in Europe has only used Ivabradine since its inception. Based on the findings of the SHIFT study, the FDA approved the use of ivabradine for indications of heart failure with reduced EF in 2015. The FDA, unlike the EMA, has not approved the use of ivabradine in angina.[14,15]

Ivabradine's benefits and applications are still a hot topic. An RCT was recently conducted in 22 patients with hyperadrenergic postural orthostatic tachycardia syndrome (POTS). The study found that ivabradine is both safe and effective in improving heart rate and quality of life in patients with hyperadrenergic POTS.[16]

Ivabradine Drug Mechanism

Ivabradine is a benzo cycloalkane derivative that acts on HCN (hyperpolarization-activated cyclic nucleotide-gated) F channels.

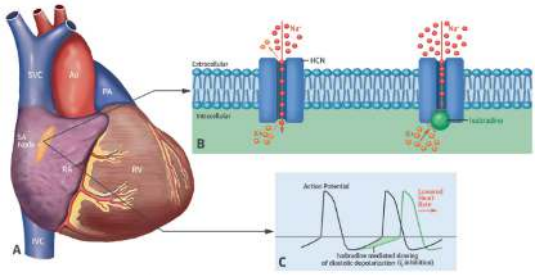

Figure 4. Mechanism of Action of Ivabradine[9]
(A) Ivabradine acts on the SAN, which is located primarily subepicardial at the junction of the superior vena cava (SVC) and the right atrium (RA). (B) In the open state, ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) transmembrane channel responsible for the transport of sodium (Na+) and potassium (K+) ions across the cell membrane. This inhibits the inward funny current (If), activated specifically at hyperpolarised membrane potentials. (C) Selective inhibition decreases the slope of the pacemaker action potential's diastolic depolarisation (shaded region) and increases diastole duration without affecting other phases of the action potential. This causes a decrease in heart rate.

HCN channel isoforms include HCN1, HCN2, HCN3, and HCN4. Ivabradine blocks HCN4 channels in an open state and inhibits HCN1 channels in a closed state in human embryonic kidney cells (HEK 293), which already contain the rat HCN1 and human HCN4 genes.[17,18]

Ivabradine selectively inhibits If channels and is dose-dependent. When the drain is blocked, the inflow of Na+ and K+ to the SA node decreases, causing phase 4 to slope and the heart rate to slow. Ivabradine's inhibitory effect on the If channel depends on the excitation state. Because ivabradine inhibits HCN4 when activated, patients with higher initial heart

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rates will experience a more significant decrease in heart rate.[17,18]

The slower heart rate allows blood flow to the heart muscle longer than usual. They are inhibiting If channels lower myocardial demand. As a result, it is beneficial in treating angina and CHF. Because blockers and Ca channel blockers both reduce heart contractility, this mechanism of action is not found in heart rate control drugs. Ivabradine is thus beneficial in CHF with a low ejection fraction. Or in cases where blocker drugs are not tolerated. [9,10,14]

The Food and Drug Administration (FDA) has also approved the use of ivabradine in paediatric patients aged six months and older who are in sinus rhythm with an elevated heart rate for the treatment of stable symptomatic heart failure (HF) due to dilated cardiomyopathy (DCM). The EMA had previously approved 19 Ivabradine for angina pectoris. [8,9,10]

Ivabradine's indications may expand. In recent years, several studies using ivabradine have yielded promising results. A case series demonstrated that ivabradine effectively treats paediatric tachyarrhythmias and CHD.[20] Ivabradine is also frequently used in treating SVT.[21,22] However, its official use necessitates larger-scale clinical trials with more patients.

In experimental animals, ivabradine caused bradycardia, hypoxia, organ malformation, and embryonic death. As a result, ivabradine is currently prohibited during pregnancy.[23] Nonetheless, off-label use for supraventricular tachycardia was daily in childbearing women. A prospective cohort study of 38 pregnancies with ivabradine exposure and completed follow-up revealed that 32 were live births, three had spontaneous abortions, and three were terminated electively. In the case of accidental ivabradine exposure or the absence of other treatment options, the study recommended fetal ultrasound for structural anomalies and growth restriction.[21]

After oral administration, ivabradine absorption is nearly complete, with peak plasma levels reached in about 1 hour. Because of the first-pass effect in the gut and liver, it has approximately 40% bioavailability. The heart and liver metabolise ivabradine via CYP450 3A4.

The primary active metabolite is the N-demethylated derivative (S 18982), which has about 40% of the parent compound's exposure. In plasma, the main half-life is 2 hours (70-75% of the AUC), and the effective half-life is 11 hours. The total clearance is approximately 400 ml/min, and the renal clearance is about 70 ml/min. Metabolites are excreted to a similar extent through faeces and urine.

About 4% of an oral dose is excreted unchanged in the urine. Bradycardia, atrial fibrillation, high blood pressure, and phosphenes have all been reported as side effects of ivabradine therapy. The visual effects (phosphenes) are thought to be caused by ivabradine's inhibition of the retina's I (h) current. Visible symptoms are usually transient, non-serious, and completely reversible.[24,25]

CONCLUSIONS

We already knew about ivabradine's long journey from discovery to widespread use for various indications. We also gained

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a new understanding of the role of heart rate in CV pathophysiology by combining our knowledge of If channel inhibitors with the results of population-based clinical studies. In the future, we may see some research on the benefits of using ivabradine in cases where the pathophysiology is still associated with increased heart rate, such as arrhythmia.

ACKNOWLEDGMENTS

In the future, we may see some research on the benefits of using ivabradine in cases where the pathophysiology, such as arrhythmia, is still associated with an increase in heart rate.

REFERENCES

1. Psotka, M. A., & Teerlink, J. R. (2016). Ivabradine: Role in the chronic heart failure armamentarium. *Circulation*, *133*(21), 2066–2075.
2. Badu-Boateng, C., Jennings, R., & Hammersley, D. (2018). The therapeutic role of ivabradine in heart failure. In *Therapeutic Advances in Chronic Disease* (Vol. 9, Issue 11, pp. 199–207). SAGE Publications Ltd.
3. Baruscotti, M., Bucchi, A., & DiFrancesco, D. (2005). Physiology and pharmacology of the cardiac pacemaker ("funny") current. In *Pharmacology and Therapeutics* (Vol. 107, Issue 1, pp. 59–79).
4. Vilaine, J. P. (2006). The discovery of the selective If current inhibitor ivabradine. A new therapeutic approach to ischemic heart disease. *Pharmacological Research*, *53*(5), 424–434.
5. Hennis, K., Rötzer, R. D., Piantoni, C., Biel, M., Wahl-Schott, C., & Fenske, S. (2021). Speeding Up the Heart? Traditional and New Perspectives on HCN4 Function. In *Frontiers in Physiology* (Vol. 12). Frontiers Media S.A.
6. Irvine S. Pacemaker Potential. [Image on the internet]. 2012 [cited 2022 December 20]. Available from: https://dundeemedstudentnotes.wordpress.com/2012/06/09/pacemaker-potential/
7. Borer, J. S., Fox, K., Jaillon, P., & Lerebours, G. (2003). Antianginal and antiischemic effects of ivabradine, an If inhibitor, in stable angina: A randomised, double-blind, multicentered, placebo-controlled trial. *Circulation*, *107*(6), 817–823.
8. Tardif, J.-C., Ponikowski, P., & Kahan, T. (2009). Efficacy of the If current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomised, placebo-controlled trial. *European Heart Journal*, *30*(5), 540–548.
9. Koruth, J. S., Lala, A., Pinney, S., Reddy, V. Y., & Dukkipati, S. R. (2017). The Clinical Use of Ivabradine. *Journal of the American College of Cardiology*, *70*(14), 1777–1784.
10. Ferrari, R. (2015). The ivabradine journey. *European Heart Journal, Supplement*, *17*, G1–G9.
11. Fox, K., Ford, I., Steg, G., Tendera, M., & Ferrari, R. (2008). Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a

E-ISSN: 2528-410X

randomised, double-blind, placebo-controlled trial. *Www.Thelancet.Com*, *372*.

12. Swedberg, K., Komajda, M., Böhm, M., Rey, J., Borer, S., Ford, I., Dubost-Brama, A., Lerebours, G., & Tavazzi, L. (2010). Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *The Lancet*, *376*, 875–885.
13. Fox, K., Ford, I., Steg, P. G., Tardif, J.-C., Tendera, M., & Ferrari, R. (2014). Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure. *New England Journal of Medicine*, *371*(12), 1091–1099.
14. Böhm, M., Bewarder, Y., Kindermann, I., Slawik, J., Wintrich, J., & Werner, C. (2020). Optimisation of Heart Failure Treatment by Heart Rate Reduction. *International Journal of Heart Failure*, *2*(1), 1.
15. Fala, L. (2016). *Ivabradine: A New Oral Option for Treating Heart Failure Corlanor (Ivabradine), First HCN Channel Blocker, FDA Approved for Treating Patients with Heart Failure*. www.AHDBonline.com
16. Taub, P. R., Zadourian, A., Lo, H. C., Ormiston, C. K., Golshan, S., & Hsu, J. C. (2021). Randomised Trial of Ivabradine in Patients With Hyperadrenergic Postural Orthostatic Tachycardia Syndrome. *Journal of the American College of Cardiology*, *77*(7), 861–871.
17. Bucchi, A., Tognati, A., Milanesi, R., Baruscotti, M., & DiFrancesco, D. (2006). Properties of an ivabradine-induced block of HCN1 and HCN4 pacemaker channels. *Journal of Physiology*, *572*(2), 335–346.
18. Bucchi, A., Baruscotti, M., Nardini, M., Barbuti, A., Micheloni, S., Bolognesi, M., & DiFrancesco, D. (2013). Identification of the Molecular Site of Ivabradine Binding to HCN4 Channels. *PLoS ONE*, *8*(1).
19. Bonnet, D., Berger, F., Jokinen, E., Kantor, P. F., & Daubeney, P. E. F. (2017). Ivabradine in Children With Dilated Cardiomyopathy and Symptomatic Chronic Heart Failure. *Journal of the American College of Cardiology*, *70*(10), 1262–1272.
20. Janson, C. M., Tan, R. B., Iyer, V. R., Vogel, R. L., Vetter, V. L., & Shah, M. J. (2019). Ivabradine for treatment of tachyarrhythmias in children and young adults. *Heart Rhythm Case Reports*, *5*(6), 333–337.
21. Hoeltzenbein, M., Lehmann, M.-L., Beck, E., Dathe, K., Schaefer, C., & De, C. S. (2021). Ivabradine use in pregnant women-treatment indications and pregnancy outcome: an evaluation of the German Embryotox database. *European Journal of Clinical Pharmacology*, *77*, 1029–1037.
22. Younis, N. K., Abi-Saleh, B., al Amin, F., el Sedawi, O., Tayeh, C., Bitar, F., & Arabi, M. (2021). Ivabradine: A Potential Therapeutic for Children With Refractory SVT. *Frontiers in Cardiovascular Medicine*, *8*, 1–14.
23. Ritchie, H. E., Telenius, C., Gustaffson, E., & Webster, W. S. (2019). The effects of nifedipine and ivabradine on the functionality of the early rat embryonic heart. Are these drugs a risk

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in early human pregnancy? *Birth Defects Research*, *111*(5), 281–288.

24. Choudhary, P., Ansari, M. D. E., & Kamal, M. (2021). Role of ivabradine in paediatrics: A review article. *Progress in Pediatric Cardiology*, *63*, 1–5.
25. Amgen Inc. Thousand Oaks, CA. Ivabradine (Corlanor) package insert. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2019/209964lbl.pdf. Accessed January 7, 2023.