Indian Journal of Pharmacy and Pharmacology 2023;10(4):260–264

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Review Article

Ivabradine: Unraveling the intricacies of heart rate modulation in cardiovascular pathologies

Geeta Y Gupta[1]*, **Yogesh A Gupta**[2]

[1]*Dept. of Biological Sciences, Narnarayan Shastri Institute of Technology, Gujarat, India*
[2]*Dept. of Internal Medicine, Sterling Hospital, Ahmedabad, Gujarat, India*

ARTICLE INFO

Article history:
Received 26-11-2023
Accepted 08-12-2023
Available online 22-01-2024

Keywords:
Ivabradine
I funny (I f) channel
HCN Channel Blockers
Chronic stable angina
Acute coronary syndrome
Chronic heart failure
Multiorgan dysfunction syndrome
Cardiotonic drugs

ABSTRACT

Cardiac dysregulation, specifically perturbations in heart rate constitutes a pivotal factor influencing the morbidity and mortality associated with diverse pathological conditions including angina (chronic/stable), acute coronary syndrome, heart failure, renal failure, respiratory distress, chronic obstructive pulmonary disease, multiorgan dysfunction syndrome, mitral valve prolapse, and mitral stenosis. The pharmacological apparatus for heart rate control refined over decades encompasses various classes of agents each adhering to specific protocols. Among these Ivabradine has garnered attention as a non-inferior alternative to extant heart rate-reducing medications providing a subtle approach to cardiovascular therapeutics. [1]

1. Introduction

Elevation in heart rate irrespective of the underlying pathophysiological condition be it hypertension, normotension, or hypotension constitutes a prognostic indicator in numerous diseases. Consequently therapeutic interventions aimed at reducing heart rate concurrently influence blood pressure. [1–4] For first decade of its entry into heart rate control medicine Ivabradine remained solely used for indication related to cardiac disease per se. Multiple drugs in HCN channel blockers class are under study with good success rate. [5] As the research moved in right direction Ivabradine has placed itself as a novel pharmacological entity into various other speciality like critical care that distinguishes itself as the sole agent capable of reducing heart rate while maintaining blood pressure stability. This article seeks to explain the complex side of Ivabradine mechanism of action and describe its potential applications beyond mere bradycardia induction thereby contributing to a comprehensive understanding of its role in cardiovascular management in both cardiac and non-cardiac diseases.

1.1. Heart rate-reducing drugs classification

2. Cardioinhibitory Drugs [6,7]

Mechanism of Action:

These drugs primarily target

1. Beta-adreceptors (beta blockers),
2. Calcium channels (e.g., verapamil, diltiazem) or
3. Act centrally as sympatholytics (e.g., clonidine)

2.1. Effects

Cardioinhibitory drugs depress cardiac function by reducing heart rate, myocardial contractility and electrical conduction.

* *Corresponding author*.
E-mail address: geetaygupta@gmail.com (G. Y. Gupta).

https://doi.org/10.18231/j.ijpp.2023.045

3. Clinical Applications

Beta-blockers and calcium channel blockers (CCBs) are commonly used in conditions such as hypertension, angina, and myocardial infarction. Beta-blockers due to their impact on electrical conduction are also indicated in certain arrhythmias. Centrally acting sympatholytics like clonidine find utility in hypertension management.

3.1. Important consideration

While effective in reducing heart rate these drugs can also lead to a significant reduction in blood pressure.

3.2. Antiarrhythmic drugs:[7,8]

Updated Vaughan Williams classification:

Class 0: HCN Channel Blockers: Ivabradine, Zatebradine, and Cilobradine

1. Class I: Voltage-gated Na+ channel blockers
   (a) Ia: Quinidine, disopyramide, procainamid
   (b) Ib: Lidocaine, mexiletine
   (c) Ic: Encainide, flecainide, propafenoneId: Ranolazine
2. Class II: Autonomic inhibitors/activators
   (a) IIa: Inhibitors: Pindolol, carvedilol, timolol, nadolol (non-selective βB); bisoprolol, atenolol, metoprolol, esmolol (selective β1 blocker)
   (b) Ib: Activators: Isoproterenol
   (c) IIc: Inhibitors: Atropine
   (d) IId: Activators: Carbacholine, methacholine, digoxin
   (e) IIe: Activators: Adenosine
3. Class III: K+ Channel Blockers/openers
   (a) a. IIIa: Voltage-dependent K+ channels
      i. K+ channels (non-selective) blockers: Amiodarone, dronedarone
      ii. iKv11.1 (rapid K+ current) blockers: Dofetilide, almokalant, ibutilide, sematilide, sotalol
      iii. Kv1.5 (ultra-rapid K+ current) blockers: Vernakalant
      IIIb: Metabolically dependent K+ channels blockers: Nicorandil, pinacidil
4. Class IV: Ca2+ handling modulators
   (a) IVa:
      i. Surface membrane non-selective Ca2+ channels blockers: Bepridil, falipamil
      ii. Surface membrane L-type Ca2+ channels blockers: Verapamil, diltiazem
      iii. IV: Intracellular Ca2+ channel blockers: Propafenone, flecainide
5. Class V Mechanosensitive channel blockers: Inhibitors: N-(p-amylcinnamoyl) anthranilic acid
6. Class VI: Gap junction channel blockers: Inhibitors: carbenoxolone
7. Class VII: Upstream target modulators
   (a) Omega-3 fatty acids: eicosapentaenoic acid, docosahexaenoic acid
   (b) Statins
   (c) ACE inhibitors: captopril, enalapril, ramipril, lisinopril; ARBs: losartan, telmisartan.

3.3. Purpose

Antiarrhythmic drugs are primarily used to convert arrhythmias into normal sinus rhythm or to prevent their occurrence.

Effects: These drugs may exhibit hypotensive effects but have no established roles in conditions such as angina, myocardial infarction, or sinus tachycardia.

3.4. Drug of interest

Cardiotonic drugs or hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels or Class O antiarrythmic drugs.[5,9]

Specific Target:

This novel class focuses on blocking the I_{funny} (I_f), or funny current I- funny (If), or funny current I (f) channel or funny channel current.

3.5. Clinical application

This class have few molecule of interest like Ivabradine, Zatebradine, and Cilobradine [9]. As of now Ivabradine is the sole drug in this class available for clinical use. This classification provides a comprehensive framework for understanding the diverse mechanisms and clinical applications of heart rate-reducing drugs from established categories like cardioinhibitory and antiarrhythmic drugs to emerging classes such as cardiotonic drugs.

3.6. Ivabradine:[2]

As a selective blocker of the I_{funny} (I_f), or funny current I- funny (If) channel colloquially referred to as "funny channels" Ivabradine's mechanism of action is underscored by its selectivity for open channels precluding severe bradycardia.[1–3] Originally identified in Sinoatrial Node (SAN) cells three decades ago these hyperpolarization-activated channels play a pivotal role in heart rate regulation modulated by the autonomic nervous system. Ivabradine's unique attribute encompasses a current-dependent and use-dependent effect exhibiting greater efficacy at higher heart rates thereby positioning it as a sophisticated therapeutic agent tailored to the intricacies of cardiovascular physiology.

4. Channels Characteristics

Type: The channels in question are hyperpolarization-activated.[1,2]

Current Type: They conduct a mixed Na^+-K^+ inward current[1,2]

5. Sensitivity to cAMP

Modulation by cAMP: The channels are sensitive to cyclic adenosine monophosphate (cAMP). This sensitivity makes them subject to modulation by the autonomic nervous system as neurotransmitters such as norepinephrine and acetylcholine can affect cAMP levels.[10]

6. Modulation by the Autonomic Nervous System

Autonomic influence: The autonomic nervous system specifically through its sympathetic and parasympathetic branches can modulate the activity of these channels. Sympathetic stimulation tends to increase cAMP levels leading to an enhanced (I_f) current while parasympathetic (vagal) stimulation may decrease cAMP levels reducing the current.[11]

In the context of the heart (I_f) current is particularly relevant in the sinoatrial (SA) node where it contributes to the pacemaker activity. This current plays a crucial role in the initiation of each cardiac cycle. Drugs like Ivabradine selectively inhibit the (I_f) current resulting in a reduction in heart rate. This is often desirable in certain cardiovascular conditions.[11]

Ivabradine acts as an open channel blocker, specifically targeting the (I_f) channel.

7. Selective Binding to Open Channels

This means that the drug binds to the (I_f) channel when it is in the open state and unbinds when the channel is closed. This specificity is important for the drug's action.[11]

8. Heart Rate Dependence (above 60)

The drug's action is related to heart rate and it seems that the (I_f) channel generally opens when the heart rate is above 60. This implies that the drug's effects are more pronounced at heart rates above 60 beats per minute.[11]

9. Avoidance of Severe Bradycardia

Since the drug affects the (I_f) channel and this channel generally opens at heart rates above 60, the drug does not cause severe bradycardia (slow heart rate).[11]

9.1. Current and use dependence

The drug's effect on the (I_f), channel is both current-dependent and use-dependent. Current dependence means that the drug's action is influenced by the current flowing through the channel. Use dependence implies that the drug's effect is more prominent with increased channel activity such as at higher heart rates.[11]

9.2. More effect at higher heart rates

The drug's impact on the (I_f) channel is greater at higher heart rates. This could be advantageous in situations where there is a need to reduce heart rate without causing excessive slowing at normal or lower heart rates.[11]

Ivabradine is known to selectively inhibit the (I_f) current in the sinoatrial (SA) node reducing heart rate without significant negative effects on myocardial contractility or conduction. It is often used in conditions where lowering heart rate is beneficial such as in certain cases of heart failure or angina.[11]

Ivabradine's negative time dependent chronotropic effects translate into diminished myocardial oxygen demands an augmented redistribution of transmural blood flow.[11] Crucially it lacks adverse ionotropic and lusitropic effects rendering it superior to beta blockers in specific contexts.[11] Moreover its benign influence on coronary vasomotion owing to the absence of the (I_f) current in vascular smooth cells further differentiates it from traditional agents. Noteworthy is its purported facilitation of ventricular relaxation attributed to altered Na^+ and Ca^{++} flux at the sarcolemmal Na^+ Ca^+ exchanger level contributing to positive effects on left ventricular remodelling.[12]

9.3. Bradycardic drugs and Ivabradine

So-called bradycardic drugs exemplified by relatively selective (I_f) sodium channel blockers such as Ivabradine exert their primary action by inhibiting the hyperpolarization-activated sodium channel in the sinoatrial node. This mechanism results in a reduction in cardiac rate without significant hemodynamic effects reported beyond the heart.[2,11]

9.4. Clinical applications of Ivabradine

Ivabradine demonstrates a broad spectrum of clinical applications encompassing chronic stable angina, acute coronary syndrome, chronic heart failure, and multiorgan dysfunction syndrome. In clinical scenarios where beta blockers pose contraindications or are poorly tolerated, Ivabradine emerges as a pivotal therapeutic option.[9]

9.5. Versatility across conditions

Chronic stable angina: Ivabradine proves effective in the management of chronic stable angina contributing to symptom relief by selectively reducing heart rate.[2]

Acute coronary syndrome: Its role extends to acute coronary syndrome, providing a targeted approach to heart rate modulation in critical cardiovascular events.[2,9]

Chronic heart failure: It demonstrates efficacy in chronic heart failure offering a unique mechanism to optimize cardiac function by specifically inhibiting the (I_f) current in the sinoatrial node.[4]

9.6. Indispensability in contraindications to beta blockers

In scenarios where beta blockers are contraindicated or poorly tolerated Ivabradine stands out as an indispensable therapeutic option. Its mechanism of action distinct from beta blockers provides an alternative strategy for heart rate control.

9.7. Trials and positive impact

1. Till now Ivabradine is approved for use in patients with symptoms due to stable heart failure and an ejection fraction of 35% or less to reduce their risk of hospital admission for worsening heart failure. It is also indicated in chronic stable angina. Over the years it has being studied for various indication and found to be effective.[2]
   (a) SHIFT trial proved its effect in reducing hospitalisation in patients with symptomatic heart failure with ejection fraction of 30% or less and with sinus tachycardia.[2]
   (b) The BEAUTIFUL trial was done to prove the ability of Ivabradine in reducing heart rate that affected cardiovascular morbidity and mortality in patients with coronary artery disease and EF less than 40%.[2]
   (c) The SIGNIFY trial was done to see effect of addition of Ivabradine with standard angina treatment.[2]
2. Ongoing projects to evaluate Ivabradine in diverse clinical settings.
   (a) Ivabradine use in association with anti arrhythmic drug to maintain sinus rhythm is studied.[13]
   (b) Ivabradine use in post cardiac bypass surgery for the maintainence of sinus rhythm is being studied.[13]
   (c) Ivabradine is also studied for heart rate control in cases of persistent or permanent Atrial fibrillation and who are on beta blockers.[13]
   (d) BRAKE-AF study is going on at present to see how Ivabradine will provide rate lowering effect in patients with permanent atrial fibrillation. (The IvaBRAdine blocK of Funny Current for Heart Rate Control in permanEnt Atrial Fibrillation)[13]
   (e) Ivabradine is also studied in cases of Postural orthostatic tachycardia syndrome (POTS). This disease have patients with increase heart rate with postural changes with arterial hypotension.[13]
   (f) Ivabradine is also studied in controlling heart rate in patients with atrial tachycardia[13]
   (g) In cases of septic shock where increased heart rate is an independent indicator of increased mortality and morbidity Ivabradine use is being studied. The most important aspect of this group is the presence of hypotension.[14]
   (h) Apart from the use the increased incidence of use of Ivabradine in various approved category has increased incidence of migraine with aura. This is believed to be because of release of substance migraine like phosphenes.[15]
   (i) Ivabradine is being studied for control of sinus tachycardia in patient suppfering from Normotensive or Hypotensive Mitral valve prolapse.[16]

9.8. Adverse effects[2]

Despite its efficacy Ivabradine is not devoid of adverse effects mentioned below:

1. Looking to its heart rate controlling effect the notable side effects are bradycardia, heart block and symptoms of syncope giddiness.
2. It has led to increase in atrial fibrillation.
3. Visual luminous phenomena recognized as phosphenes and bradycardia are observed in a subset of patients.
4. Ivabradine is metabolized by CYP3A4. When it is used with drugs which are CYP3A4 inhibitors like verapamil or diliazem then it can cause increases in risk of bradycardia.
5. Ancillary effects encompass dizziness, palpitations, hypereosinophilia, and hyperuricemia, necessitating meticulous consideration in clinical decision-making.

10. Conclusion

In recognizing the autonomy of heart rate as a pivotal prognostic marker across critical and chronic conditions Ivabradine emerges as a transformative force in cardiovascular care embodying a nuanced approach to treatment. Its distinctive pharmacological profile coupled with a growing body of clinical evidence and global medical expertise positions Ivabradine as a therapeutic agent transcending disciplinary boundaries. It significantly contributes to the evolving discourse on contemporary cardiovascular therapeutics.

As research endeavours and clinical experiences continue to expand Ivabradine stands poised to solidify its status as a quintessential therapeutic adjunct across

diverse medical disciplines. This heralds a new era in the holistic management of cardiovascular disorders where Ivabradine's unique mechanism of action offers novel avenues for optimizing patient outcomes. The ongoing trajectory of Ivabradine's influence underscores its potential to shape the landscape of cardiovascular medicine marking a profound advancement in the comprehensive care of individuals with cardiovascular conditions.

11. Source of Funding

None.

12. Conflict of Interest

None.

References

1. Ide T, Ohtani K, Higo T, Tanaka M, Kawasaki Y, Tsutsui H. Ivabradine for the treatment of cardiovascular diseases. *Circ J Internet*. 2019;83(2):252–60.
2. Reed M, Kerndt CC, Ivabradine ND. StatPearls Publishing. 2023.
3. Riccioni G. Focus on Ivabradine: a new heart rate-controlling drug. *Expert Rev Cardiovasc Ther*. 2009;7(2):107–20.
4. Kim Y, Boucher M, Ottawa AC. ON): Canadian Agency for Drugs and Technologies in Health, CADTH Issues in Emerging Health Technologies; 2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK378971/#:~:text=Issues%20in%20Emerging%20Health%20Technologies%2C%20now%20renamed%20to%20Horizon%20Scans,next%20six%20to%2018%20months..
5. Scicchitano P, Carbonara S, Ricci G, Mandurino C, Locorotondo M, Bulzis G. HCN channels and heart rate. *Molecules*. 2012;17(4):4225–60.
6. Bauer M. Cardiovascular anatomy and Pharmacology. Springer International Publishing; 2018. p. 195–228.
7. Treatment with antihypertensive drugs. In: and others, editor. Hypertens Res . vol. 32; 2009. p. 33–42.
8. King GS, Goyal A, Grigorova Y. Antiarrhythmic Medications. vol. 2023. StatPearls Publishing; 2023.
9. Mengesha HG, Tafesse TB, Bule MH. If channel as an emerging therapeutic target for cardiovascular diseases: A review of current evidence and controversies. *Front Pharmacol*. 2017;8:847. Available from: http://dx.doi.org/10.3389/fphar.2017.00874.
10. Sartiani L, Mannaioni G, Masi A, Romanelli N, Cerbai M. The hyperpolarization-activated cyclic nucleotide-gated channels: From biophysics to pharmacology of a unique family of ion channels. *Pharmacol Rev*. 2017;69(4):354–95.
11. Kamisah Y, Hassan C. Therapeutic use and molecular aspects of Ivabradine in cardiac remodeling: A review. *Int J Mol Sci*. 2023;24(3):2801. doi:10.3390/ijms24032801.
12. Zuo G, Ren X, Qian X, Ye P, Luo J, Gao X. Inhibition of JNK and p38 MAPK-mediated inflammation and apoptosis by Ivabradine improves cardiac function in streptozotocin-induced diabetic cardiomyopathy. *J Cell Physiol*. 2019;234(2):1925–61.
13. Abdelnabi M, Ahmed A, Almaghraby A, Saleh Y, Badran H. Ivabradine and AF: Coincidence, correlation or a new treatment. *Arrhythm Electrophysiol Rev*. 2020;8(4):300–3.
14. Datta PK, Rewari V, Ramachandran R, Singh PM, Ray BR, Aravindan A. Effectiveness of enteral Ivabradine for heart rate control in septic shock: A randomised controlled trial, Anaesth Intensive Care. *Anaesth Intensive Care*. 2021;49(5):366–78.
15. Sprenger T, Supronsinchai W, Goadsby PJ. New onset migraine with aura after treatment initiation with Ivabradine. *J Headache Pain*. 2013;14(1):45.
16. Çiçek D. Effects of a Novel I(f) Inhibitor; Ivabradine, on the Biochemical, Hemodynamic, and Electrophysiological Parameters in Symptomatic Patients with Mitral Valve Prolapse. *Acta Cardiologica Sinica*. 2010;26(4):253–61.

Author biography

Geeta Y Gupta, Assistant Professor Forensic Science https://orcid.org/0009-0009-7043-8597

Yogesh A Gupta, Head of Geriatrics

Cite this article: Gupta GY, Gupta YA. Ivabradine: Unraveling the intricacies of heart rate modulation in cardiovascular pathologies. *Indian J Pharm Pharmacol* 2023;10(4):260-264.