IVABRADINE: A PURE BRADYCARDIAC AGENT

Abstract

Ivabradine's therapeutic application has developed and is still developing along lines based on its mode of action.It works differently from other negative chronotropic drugs in that it specifically inhibits the wacky current (If) in sinoatrial nodal tissue of the myocardium, which lowers the rate of diastolic depolarization and, the heart rate. Ivabradine doesn't have any detrimental lusitropic or inotropic effects., thus retaining ventricular contractility, and does not change significant electrophysiological markers relating to heart rate. As a result, it has been tested and is currently being used in a small number of people who have systolic heart failure and persistent stable angina without causing clinically significant side effects. Even though it hasn't been licenced for other uses, ivabradine has showed potential in the treatment of unwarranted sinus tachycardia.In this article we discussed about the Dosing, Mechanism of action, Pharmacokinetics, Therapeutic application, Interactions, and Contraindications.

Keywords: Ivabradine, Chronotrophic, Depolarization, Ionotropic, Lusitropic

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I. INTRODUCTION

Congestive heart failure (CHF), sometimes referred to as heart failure (HF), is a syndrome, a collection of symptoms brought on by a decline in the heart's capacity to pump blood.. A significant global source of illness and mortality is heart failure.

Therefore One of the most crucial therapeutic approaches for the management of stable angina pectoris is lowering heart rate. Beta-blockers and several calcium channel antagonists have been shown to lower heart rate thus far., but side effects or contraindications may limit their use.

The sinoatrial node's electrical pacemaker activity, which is powered by the if current, regulates heart rate.. Ivabradine is a medication that reduces heart rate by shutting down the opening of If channels in the heart.

Ivabradine is primarily an electro-physiologically distinct medication, best known for its adverse chronotropic effects on the sinoatrial node.1 It slows the SA-node cells' diastolic depolarization slope and decreases HR both at rest and during exercise.

Since reducing heart rate will promote myocardial perfusion and reduce myocardial oxygen demand, patients with chronic stable angina should benefit from it.

Despite evidence-based -blocking therapy with ACEi (or) ARB.10, ivabradine remains a third-line therapy in heart failure (HF) for symptomatic patients with severe left ventricular systolic dysfunction (EF 35%) and a resting sinus rhythm of at least 70 bpm. [1,3,4,5]

II. IVABRRADINE-MECHANISM OF ACTION

The spontaneous depolarization current that regulates heart rhythm is produced by the pacemaker node cells of the heart by allowing action potentials to extend as far as they can. If channels in the heart's node, which regulate the depolarization's slope, aid in achieving this. [3]

The voltage, cyclical nucleotides, or nitric oxide variations can all cause this current, also known as the If current or funny current, to occur. Cyclic adsorption enhances the likelihood that the channel will open, allowing for both sympathetic and parasympathetic stimulation of the cell..[4]

Ivabridine decreases heart rate by selectively and precisely blocking the If ('funny') channels in a concentration-dependent manner. Without affecting blood pressure, ventricular repolarization, myocardial conduction, or myocardial contractility, it lowers heart rate. [3]

The flow of mixed sodium and potassium ions is stopped when ivabradine enters the If channel and connects to the intracellular side of the channel. This reduces the heart rate by stopping the gradual, spontaneous phase of diastolic blood depolarization. Consequently, ivabradine functions by opening the If channel when the heart is repolarized and closing it when it is depolarized. It is also more active when the heart rate is higher.[3]

III. PHARMACOKINETICS

Route of administration : It is consumed orally. The oral tablet form of ivabradine is offered.

- Bioavailability : 40%
- Protein binding : 70% bound to plama proteins
- Dose : 5 mg should be used twice daily as the first dose.After two weeks, the dosage can be changed based on heart rate.
- 7.5 mg twice daily is the maximum dosage.
- The drop in heart rate is influenced by both the ivabradine dosage and the baseline heart rate.
- Half life t1/2 : 2 hours.
- Clearance: A little over 4% of the total clearance, which is around 400 ml/min, is eliminated unaltered in the urine. Renal clearance is about 70 ml/min.
- Route of elimination : Excreted via feces and urine.
- Toxicity : Ivabradine may cause fetal toxicity.
- Adverse effects : It may result in transient visual brightness, which is typically brought on by abrupt changes in light (luminous phenomena)
- Headache,
- Unusual tiredness,
- Pounding in the ears and etc.[4,5,6]

IV. DRUG INTERACTIONS

Ivabradine is interacting with most of the drugs like Atazanavir, Clarithromycin, Cobicistat, Conivaptan, Darunavir, elvitegravir/cobicistat/emtricitabine/tenofovirDF, Fosamprenavir, Idelalisibimatinib, Indinavir, Isoniazid, Itraconazole, Ketoconazole, Levoketoconazole, Lopinavir ,Nefazodone, Nelfinavir, Nicardipine, Nirmatrelvir/ritonavir, Posaconazole, Quinidine,ritonavir. With these drugs it causes many undesirable effects and also brings danger to the body which may reduce the heartrate and may also produce much more terrific adverse reactions.[5]

So, here we discussed the major drugs interaction like gastric proto pump inhibitors, phenytoin and carbamazepine.

1. **Ivabradine with Gastric Proto Pump Inhibitors:** An open-label, randomised, crossover, phase I pharmacokinetic interaction design was used to evaluate the effects of omeprazole and lansoprazole on the pharmacokinetics of ivabradine and its active metabolite S18982. Ivabradine's pharmacokinetic characteristics were not significantly altered by the administration of lansoprazole or omeprazole. The pharmacokinetics of a single dosage of ivabradine were not significantly impacted by the coadministration of either omeprazole or lansoprazole. There was no indication of a pharmacodynamic interaction or safety issues.[8]

2. **Ivabradine With Phenytoin :**The investigation looked at how ivabradine and phenytoin interacted pharmacologically in healthy volunteers. Following medication delivery for 12 hours, ivabradine plasma concentrations were assessed. Ivabradine's bioavailability was

reduced by around 70% when given alone or with phenytoin, with statistically significant variations seen for the drug's Cmax and AUC.[9]

3. **Ivabradine with Carbamazepine :** A research looked at how ivabradine and carbamazepine interacted pharmacologically in healthy individuals. When ivabradine was given in combination with carbamazepine, the results demonstrated a substantial difference in the peak plasma concentrations and the time it took to achieve C(max). According to the study's findings, ivabradine interacts with carbamazepine in healthy volunteers, reducing its bioavailability by around 80%, which is likely to have clinically relevant effects. The mean peak plasma values for ivabradine alone were 16–25 ng/mL and for ivabradine with carbamazepine pretreatment, they were 3–69 ng/mL. Given that it may alter how well ivabradine works to lower heart rate, this interaction is probably clinically relevant.[7]

This drug is not advised with grapefruit juice or eat grapefruits while taking this medication because altogether increment the blood levels and impacts of ivabradine, which might bring about unreasonable easing back of pulse or other conduction aggravations.

As for the drug interaction it is contraindicated in many drugs as it brings many undesirable effects to the body and it is advised not to take this medication with grapefruit.

V. CONTRAINDICATIONS

This drug is contraindicted in

- Abnormalities in the way the heart beats, such as sick sinus syndrome, sinoatrial block, or third-degree AV block, unless a pacemaker measures the heart rate.
- Heart failure with acute decompensation.
- Clinically severe hypotension, or a blood pressure of less than 90/50.
- Clinically severe bradycardia, defined as a resting heart rate of less than 60 prior to the start of treatment.
- Pacemaker dependence.
- Patients taking (CYP3A4) inhibitors.
- Severe liver impairment.[2,4,5]

VI. PRECAUTIONS

- It is strongly advised to abstain from use in patients who have experienced a decrease in blood pressure or liver function, as well as other heart-related issues (e.g., Sick Sinus Syndrome, Heart Block, Slow/Irregular Heartbeats, Pacemaker Use).[5]
- Additionally, it is not recommended in patients who have suffered a second degree AV block and do not have a working demand pacemaker. [4]
- Patients with demand pacemakers set at a rate higher than 60 beats per minute should also avoid it. [4]
- It is not advised during pregnancy and lactation..[4]

VII. THERAPEUTIC APPLICATIONS

- Due to its effectiveness and tolerability, ivabradine is suggested as a second-line medication for angina relief.[2].
- By lowering the IF current, ivabradine controls aberrant automaticity and may lessen the trigger for ventricular arrhythmias. [4]
- It help to keep heart failure from getting any worse and requiring hospital treatment. It is likewise utilized by children who have cardiovascular breakdown because of enlarged heart (expanded/ dilated cardiomyopathy).[4]
- When used with other heart failure medications, ivabradine may slowdown the worsening heart failure. It improves the heart failure symptoms.[5]
- Vasodilation can be facilitated by ivabradine by enhancing both endothelium-dependent and endothelium-independent vascular relaxation.[2]
- This drug also exhibits analgesic effects against inflammatory pain.[5]

VIII. FUTURE ASPECTS

Ivabradine remedial boluses are presumably well permitted in clinical use, according to preclinical and clinical examinations. Ivabradine doesn't evoke supplemental vasodilation at these situations, have an adverse inotropic effect on healthy levies, cases with LV dysfunction, or the cardiac conduction system. also, after ivabradine treatment, neither rebound goods after medicine termination nor pharmacological forbearance have been noted. [1]

Trials with ivabradine included patients with natural sinoatrial knot disease (a condition similar to sick sinus pattern), for whom impediments are contraindicated because of how they work.[2]

Individuals with stable angina have been studied to determine the efficacy of ivabradine monotherapy.

The anti-anginal and anti-ischaemic impact of ivabradine, both alone and in combination with other drugs, as well as its forbearance, have been investigated in a clinical programme including more over 5000 patients..[2]

Ivabradine continues to be a third- line drug in HF since entering FDA blessing for use in HF in 2015 and EMA blessing in 2012. Since ivabradine defining rates aren't included in the crucial performance pointers for epidemiological studies, similar as the UK National Heart Failure inspection, they are not regularly measured. also, it appears that new specifics like valsartan/ sacubitril are plying increased pressure on this metric**.** [3]

Ivabradine's failure is substantially allowed to be the result of worries brought up by the SIGNIFY study.[3]

The investigation found advanced instances of typical bradycardia and a statistically significant rise in the combined risk of cardiovascular mortality or nonfatal heart attack in a group of individuals with distinctive angina. These findings prompted an EMA evaluation of the drug, which very certainly had an effect on its definition. [2]

After the complaint had been well addressed with blockers and ACEi, one research indicated that only 9.3 of individuals with habitual HF and systolic impairment were appropriate for ivabradine at 12-month follow up.[5]

IX. CONCLUSION

Clinicians consider ivabradine to be the second-line treatment in systolic hypertension and stable chronic angina pectoris. Utilising If (funny current) inhibition, pure heart-rate decrease is clinically possible and can effectively avoid angina. On the other hand, ivabradine concurrently lowers ischaemia while preventing angina[1]. At this time, only ivabradine has been clinically demonstrated to reduce heart rate without causing adverse inotropism, conduction, or contractility effects. It is used to treat IST and other electrophysiological conditions, but is not well-supported by large-scale studies and currently remains an unapproved indication. [2]As for the drug interaction it is contraindicated in many drugs as it brings many undesirable effects to the body and it is advised not to take this medication with grapefruit and it is also contraindicated in the treatment like sick sinus syndrome, decompensted heart failure and etc.[5] Ivabradine's failure is substantially allowed to be the result of worries brought up by the SIGNIFY study. So by the future advancements these worries can be reduced and can be more potential drug in cardiovascular diseases.[1]

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