IVABRADINE: A PURE BRADYCARDIAC AGENT

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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 suppresses the funny current (If) in sinoatrial nodal tissue, which lowers the rate of diastolic depolarization and, the heart rate. Ivabradine has no negative inotropic or lusitropic effects, thus preserving ventricular contractility, and does not alter important electrophysiological parameters unrelated to heart rate. As a result, it has been tested and is currently being used in a small number of patients with chronic stable angina and systolic heart failure 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

INTRODUCTION

Heart failure (HF), also known as congestive heart failure (CHF), is a syndrome, a group of signs and symptoms caused by a decrease in the heart's ability to pump blood. A significant global source of illness and mortality is heart failure. Therefore, reducing the heart rate is one of the most important treatment methods in the treatment of stable angina pectoris. To date, beta-blockers and some calcium channel antagonists decrease heart rate, but side effects or contraindications may limit their use.

Heart rate is determined by spontaneous electrical pacemaker activity in the sinoatrial node driven by the If current. Ivabradine is a drug that lowers heart rate by blocking the heart's If channels in their open state.

Ivabradine is primarily an electro-physiologically distinct medication, best known for its adverse chronotropic effects on the sinoatrial node. It lowers heart rate both at rest and during exercise and delays the diastolic depolarization slope of SA-node cells. Patients with chronic stable angina should benefit from heart rate lowering since it will increase myocardial perfusion and decrease myocardial oxygen demand.

The use of ivabradine to reduce the risk of heart failure hospitalization or cardiovascular death in symptomatic patients with severe left ventricular systolic dysfunction (EF (Ejection Fraction) $\leqslant$ 35%) and a resting sinus rhythm of at least 70 bpm despite evidence-based β -blocking therapy with ACEI (Angiotensin-Converting Enzyme Inhibitors) or ARB (Angiotensin 2 receptor blockers). It remains a third-line therapy in HF. [1, 3, 4, 5]

IVABRRADINE-MECHANISM OF ACTION

The pacemaker node cells in the heart are responsible for creating the spontaneous depolarization current that sets the heart rate by letting action potentials go as far as they can. This is done with the help of If channels in the heart's node, which control the slope of depolarization [3].

It's called the If current or funny current, and it can be triggered by voltage, cyclical nucleotides, or nitric oxide changes. When cyclic adsorption molecules bind to c-AMP molecules, it increases the chances of opening the channel, so it can be stimulated both sympathetically and parasympathetically [4].

Ivabridine is a selective I_f ('funny') channel inhibiting drug which reduces the heart rate by selectively and specifically inhibiting the I_f channels in a concentration-dependent manner. It causes reduction of heart rate without any effects on blood pressure, myocardial contractility and relaxation, ventricular repolarization or myocardial conduction [3].

When ivabradine goes into the If channel, it attaches to the intracellular side of the channel, which stops the flow of mixed sodium and potassium ions. This stops the slow, spontaneous phase of depolarization in the diastolic blood, which lowers the heart rate. So, ivabradine works by opening the If channel when it's repolarized and closing it when it depolarizes, and it's more active when the heart rate is faster [3].

PHARMACOKINETICS

Route of administration: It is orally administered. Ivabradine is available as tablets to be taken by mouth.

Bioavailability: 40%

Protein binding: 70% bound to plasma proteins

Dose: The initial dose should be 5 mg, twice a day. (The dose can be adjusted after 2 weeks based on the heart rate).

The maximum dose is 7.5 mg, twice a day.

The reduction in heart rate depends on the baseline heart rate and the ivabradine dose.

Half-life t1/2: 2 hours.

Clearance: Total clearance is about 400ml/min; renal clearance is about 70ml/min and about 4% is excreted unchanged in urine.

Route of elimination: Excreted in faeces and urine.

Toxicity: Ivabradine may cause fetal toxicity when administered to pregnant women.

Adverse effects: It may cause temporary visual brightness, usually caused by sudden changes in light (luminous phenomena or phosphenes).

Headache,

Unusual tiredness,

Pounding in the ears and etc [4,5,6]

DRUG INTERACTIONS

Ivabradine is interacting with most of the drugs like Atazanavir, Clarithromycin, Cobicistat, Conivaptan, Darunavir, elvitegravir/cobicistat/emtricitabine/tenofovir DF, Fosamprenavir, Idelalisib, imatinib, 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.

Ivabradine with gastric proto pump inhibitors: The effects of omeprazole and lansoprazole on the pharmacokinetics of ivabradine and its active metabolite S18982 were assessed in an open-label, randomized, crossover, phase I, pharmacokinetic interaction design. Pharmacokinetic parameters for ivabradine did not vary significantly after omeprazole or lansoprazole administration. Co-administration of either omeprazole or lansoprazole did not significantly affect the pharmacokinetics of a single dose of ivabradine. No pharmacodynamic interaction or safety concerns were evidenced [8].

Ivabradine with phenytoin: The study evaluated the pharmacokinetic interaction between ivabradine and phenytoin in healthy subjects. Plasma concentrations of ivabradine were determined during a 12-hour period following drug administration. Statistically significant differences were observed for the C_{max} and AUC (Area under the curve) of ivabradine when administered alone or with phenytoin, reducing its bioavailability by approximately 70% [9].

Ivabradine with carbamazepine: A study evaluated the pharmacokinetic interaction between ivabradine and carbamazepine in healthy volunteers. Results showed significant differences in peak plasma concentrations and time taken to reach Cmax when ivabradine was administered with carbamazepine. The study concluded that carbamazepine interacts with ivabradine in healthy volunteers, lowering its bioavailability by about 80%, which is likely to be clinically significant. The mean peak plasma concentrations were 16-25 ng/mL (ivabradine alone) and 3-69 ng/mL (ivabradine after pretreatment with carbamazepine). This interaction is likely to be clinically significant, as it may affect the effectiveness of ivabradine in reducing heart rate [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.

CONTRAINDICATIONS

This drug is contraindicated in

- Conduction abnormalities, e.g., sick sinus syndrome, sinoatrial block, or third-degree AV block, unless a pacemaker determines the heart rate.
- Acute decompensated heart failure.
- Clinically significant hypotension (Blood pressure less than 90/50).
- Clinically significant bradycardia (Resting heart rate less than 60 before therapy initiation).
- Severe hepatic impairment.
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker).
- Patients taking cytochrome P450 3A4 (CYP3A4) inhibitors.
- Severe liver impairment [2,4,5].

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 (Atrioventricular) block and do not have a working demand pacemaker [4].
- Furthermore, it is not advisable in patients who have a demand pacemaker set to a rate of more than 60 beats per minute [4].
- It is not advised during pregnancy and lactation [4].

THERAPEUTIC APPLICATIONS

- Ivabradine is recommended as a second-line treatment for angina relief because it is well-tolerated and effective [2].
- Ivabradine, by reducing I_F current, suppresses the abnormal automaticity and it potentially reduces the trigger for ventricular arrhythmias [4].
- It helps 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].

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 (Left ventricular) dysfunction, or the cardiac conduction system. Also, after ivabradine treatment, neither rebound goods after medicine termination nor pharmacological forbearance have been noted.

Cases with natural sinoatrial knot illness (similar as sick sinus pattern), for which impediments are contraindicated due to their mode of action, were from ivabradine trials. The effectiveness of ivabradine monotherapy in individualities with stable angina has been assessed. In a clinical programme comprising further than 5000 cases, the anti-anginal and anti-ischaemic impact of ivabradine, both alone and in combination with other specifics, as well as its forbearance, have been evaluated.

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**.**

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In a group of cases with characteristic angina, the study revealed advanced situations of characteristic bradycardia and a statistically significant increase in the combined threat of cardiovascular death or nonfatal heart attack. these findings urged an EMA review of the medicine, which nearly clearly had an impact on its defining. One study suggests that only 9.3 of cases with habitual HF and systolic impairment were suitable for ivabradine at 12- month follow up, once the complaint had been meetly optimised with blockers and ACEI.

CONCLUSION

Clinicians consider ivabradine to be the second-line treatment in systolic hypertension and stable chronic angina pectoris. Pure heart-rate lowering is clinically feasible via If (funny current) inhibition and can prevent angina with tolerable tolerability. On the other hand, ivabradine prevents angina and simultaneously reduces ischaemia. Currently, only ivabradine has been shown clinically to lower heart rate without negative inotropism or conduction or contractility effects. It plays a role in the treatment of IST (Inappropriate Sinus Tachycardia) and other electrophysiology disorders, but is not well-supported by large-scale studies and currently remains an unapproved indication. 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, decompensated heart failure and etc. 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.

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