Role of Ivabradine in Chronic Stable Angina

Satya Narayan Routray* Sasmita Swain
Department of Cardiology, S.C.B. Medical College, Odisha, India

ABSTRACT

Coronary Artery Disease (CAD) continue to remain as number one cause of death in most countries in the world. Chronic Stable Angina (CSA) also known as Chronic Angina (CA), is one important presenting feature in the disease spectrum. Angina occurs mainly due to a mismatch between oxygen requirement and availability. Heart Rate (HR) is the most variable and significant determinant of angina. Drugs like beta adrenergic receptor blockers and non-dihydropyridine type calcium channel blockers are in clinical use to lower the HR and play a crucial part in improvement of CA. There still remains a considerable gap in the management of such problem and Ivabradine, a funny channel blocker appears to be a suitable molecule to fill it by it's anti-ishaemic and anti anginal effects resulting from dose dependent reduction in rate pressure product. Evidences from different clinical trials are positive for use of Ivabradine in the management of angina pectoris as monotherapy or combination therapy with very good safety profile.

KEYWORDS
Ivabradine, Angina, Coronary disorder, Epidemiological change

*Corresponding Author:
Satya Narayan Routray, Department of Cardiology, S.C.B. Medical College, Odisha, India;
E-mail: drsnroutray@gmail.com

Sasmita Swain, Department of Obstetrics & Gynaecology, S.C.B. Medical College, Cuttack, Odisha, India.

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INTRODUCTION

Even in 21st century chronic stable angina or Chronic Angina (CA) has never failed to challenge doctors due to its complex pathogenesis, soul of which is an imbalance between myocardial oxygen requirement and availability. Heart rate is one of the main factors determining myocardial oxygen consumption.[1] Increase in heart rate results in reducing diastolic perfusion time and thus oxygen supply, due to short cardiac cycle length. Animal studies suggests that tachycardia may enhance the development of atherosclerosis, by increasing the exposure of the endothelium to shear stress. Thus an elevated heart rate plays an important role in the development of myocardial ischaemia leading to angina as a result of increased myocardial oxygen demand and a reduction in diastolic perfusion time, the latter being of particular importance considering that 90% of coronary flow occurs in diastole. As per latest available evidences current guidelines strongly recommend reduction in heart rate as an important strategy to prevent oxygen imbalance and improve angina symptoms.[2] To control heart rate and reduce symptoms, beta-blockers are mostly recommended as a first-line agent. However, in clinical practice, their use can be limited due to their broad mode of action resulting in many unfavourable side effects. Moreover, registry data have shown that many patients continue to remain symptomatic under beta-blocker therapy indicating the need for newer pharmacological interventions including combining heart rate reducing agents.[3]

LITERATURE REVIEW

Ivabradine-Mechanism of Action

Spontaneous diastolic depolarisation in the sino atrial node is caused by a mixed sodium-potassium current (I_f) across funny-channels. Ivabradine directly and selectively inhibits If channels, which results in reduced diastolic depolarisation rates and the slowing of heart rate.[4] Blockage of the I_f-channel occurs from the cytoplasmic side of the cell membrane, when the channel is in the open state. This blocking action reduces the rate of pacemaker activity of the heart, which is more intense at a higher firing rate. Ivabradine, therefore, is a specific heart rate-reducing drug. It's specificity for the I_f current ensures that this compound has no direct effects on myocardial function, ventricular repolarisation or cardiac conduction.[5] As such, Ivabradine's specific mode of action limits it's use to patients with sinus rhythm and excludes patients in atrial fibrillation or atrial flutter. Ivabradine reaches peak plasma levels in approximately 1 hour under fasting conditions and metabolised in both the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) enzyme. It is for this reason that ivabradine must not be co-prescribed with strong or moderate CYP3A4 inhibitors, such as diltiazem and verapamil. Ivabradine's main half-life is approximately two hours and its effective half-life around six hours.[6]

In humans, at the currently recommended doses, heart rate reduction is approximately 10 bpm-15 bpm both at rest and during exercise. Studies have shown ivabradine at a dose 7.5 mg twice daily demonstrated a significant reduction in heart rate over 24 hours, without affecting circadian heart rate patterns.[7] Intracardiac conduction, contractility or ventricular repolarisation or central aortic pressure (LV afterload) are not affected by Ivabradine. Studies have reported no effects of ivabradine on atrioventricular or intraventricular conduction times or corrected QT interval.

From 1964, Propranolol was only approved beta blocker for the management of patients with CSA till calcium channel blockers became available in 1975. Being first line pharmacological agents as per guidelines, for the control of heart rate and symptomatic relief of angina these agents stood the test of time.[8-10] Ivabradine based on its negative chronotropic property has been evaluated in a large number of randomized studies as an anti-ischemic drug for CA (CSA) patients. Some of these important studies are discussed below.[11]

DISCUSSION

As Monotherapy for Angin

In a study by Borer et al TST (Time to 1 mm ST depression) increased by 32.0 s and 44.1 s with ivabradine 2.5 mg and 5 mg twice daily respectively versus 9.0 s with placebo (P=0.016 for 5 mg twice daily dose *vs* placebo).[12] TLA (Time to Limiting Angina) increased by 22.5 s and 27.2 s with ivabradine 2.5 and 5 mg twice daily respectively versus 12.7 s with placebo. Both resting and exercise HR decreased significantly with ivabradine 2.5 mg and 5 mg twice daily (both P<0.05 vs placebo).[13] The initiative study revealed that after 16 weeks of treatment, patients in the ivabradine group (receiving 7.5 mg twice daily) and those receiving atenolol (100 mg/day) had similar beneficial effects on total exercise duration and the number of angina attacks per week (−2.2 ± 4.3 *vs* -2.7 ± 12.3); proving the non-inferiorty of ivabradine to atenolol.[14-16] Data at 4 months of follow-up showed that all stress test variables, including time to limiting angina, time to angina onset and time to 1 mm ST-segment depression, showed a tendency to a larger improvement with ivabradine compared with atenolol, though statistically not significant.

In a small study by Skalidiset al. Ivabradine 5 mg twice daily improved hyperaemic coronary flow velocity and reserve in patients with stable CAD. Resting-APV (17.0 ± 5.5 *vs* 19.7 ± 7.6, P=0.003) and augmentation of hyperaemia-APV (57.9 ± 17.8 *vs* 53.5 ± 21.4, P=0.009) led to improvement in CFR (3.51 ± 0.81 *vs* 2.78 ± 0.61, P<0.001).[17]

In Mix Treatment in Patients with Angina

Associate study randomised patients to receive in addition to atenolol 50 mg, placebo or ivabradine 5 mg twice daily for 2 months, which was then increased to 7.5 mg twice daily for two further months. Patients underwent exercise testing at 2 months and 4 months of follow-up.[18] Patients in the ivabradine group showed a significant increase in total exercise time and all other exercise test criteria such as time to limiting angina, time to angina onset and time to 1 mm ST-segment depression (P<0.001) compared with patients receiving placebo.[19]

In additions trial recruited patients with stable angina pectoris who were receiving beta-blockers and initiated treatment with ivabradine 5 mg or 7.5 mg twice daily. Additions showed that combined therapy with ivabradine and a beta-blocking agent reduced heart rate (from 85 bpm to 65.6 bpm), angina attacks per week (from 1.7 to 0.3) and nitrate consumption from 2.3 to 0.4 per week (all P<0.0001). The addition of ivabradine was associated with improved QOL, as assessed by EQ-5D index scores (P<0.0001).[20]

In a recent clinical trial adding ivabradine to maximally tolerated beta blocker demonstrated detectable reduction in

myocardial ischaemia by myocardial perfusion scan after 3 months of treatment. In view of the above safety and efficacy this drug has been endorsed for the treatment of stable angina pectoris for patients in sinus rhythm and a pulse of 70 bpm or more inspite of adequate beta blockers and who can't endure beta-blockers or have contraindications for the utilization of beta-blockers.

Anti-Anginal Activity Post Pci (Per Cutaneus Coronary Intervention)

In a post hoc analysis from additions in patients with angina and history of PCI treated with ivabradine 5.0 mg or 7.5 mg twice daily for 4 months, the frequency of angina was reduced from 1.9 ± 2.4 per week to 0.5 ± 1.5 per week and nitrate consumption fell from 2.7 ± 3.7 per week to 1.0 ± 1.9 per week (P<0.0001).[21-23]

In Stable Patients with Normal LV Function and No Clinical Heart Failure)

Signify trial assessed the efficacy of ivabradine given on top of standard antianginal therapy, involving 19102 patients without clinically apparent heart failure and a baseline heart rate ≥ 70 bpm. After 27.8 months (median follow-up), there was no significant difference in the primary endpoint (6.8% and 6.4%, respectively; HR 1.08; 95% CI 0.96 to 1.20; P=0.20) as well as no significant difference in the incidence of death from cardiovascular causes or non-fatal myocardial infarction.[24]

There was likewise a critical cooperation between the impacts of ivabradine and the presence of angina (CCS class II) at standard. In that subgroup, ivabradine expanded the outright gamble of the essential composite endpoint of death from cardiovascular causes or non-lethal myocardial localized necrosis by 1.1%. These surprising discoveries were in all probability the consequence of the utilization of bigger than suggested ivabradine measurements and blend treatment with other pulse bringing down medications like verapamil.[25]

In Stable Patients with LV Systolic Dysfunction or Clinical Heart Failure

Beautiful study assessed the effects of ivabradine-given in addition to standard antianginal treatment-in 10917 patients with CAD and LV ejection fraction (LVEF) <40%.[19,20] The primary endpoint was a composite of cardiovascular death, hospitalisation for acute myocardial infarction or new-onset or worsening heart failure. The incidence of the primary endpoint did not differ in the ivabradine group compared with the placebo group.[26]

A post hoc examination of the of the beautiful trial in patients whose restricting side effect at gauge was angina (n=1507) showed that ivabradine decreased the essential composite endpoint by 24% (HR 0.76; 95% CI 0.58 to 1.00; P=0.05) and the pace of hospitalization for myocardial dead tissue by 42% (HR 0.58; 95% CI 0.37 to 0.92; P=0.021).

Shift trial investigated the effects of ivabradine (initiated at 5 mg twice daily and titrated to a maximum of 7.5 mg twice daily) when added to current guideline-based therapy with 6558 patients with symptomatic Chronic Heart Failure (CHF), LV systolic dysfunction (LVEF ≤ 35%) and a heartrate of 70 bpmor higher. Ivabradinesignificantly reduced the risk of cardiovascular deathand hospitalisation due to worsening heart failureby 18% (29% *vs* 24%; HR 0.82; 95% CI 0.75 to 0.90; P<0.0001), compared with placebo.

A post hoc analysis of SHIFT carried out in 2220 stable angina patients with CHF showed that ivabradine improved on cardiovascular outcomes in the angina subgroup.

Side effects

The most well-known ivabradine-related antagonistic responses incorporate phosphenes (glowing visual peculiarities) and bradycardia, the two of which are dose related.[27]

Phosphenes-normally of gentle to direct force-have been accounted for in 14.5% of patients and are typically set off by abrupt varieties in light power. They for the most part happen in something like 2 months of treatment commencement, after which they might happen over and over.

Extreme bradycardia was accounted for by 3.3% of patients, especially during the initial 2-3 months of treatment.

In mean, atrial fibrillation was seen in 5.3% of patients taking ivabradine, contrasted and 3.8% in placebo arm.

Contraindications

Ivabradine is contraindicated in decompensated HF, hypotension (systolic BP under 90/50 mm Hg), conduction irregularities (SSS, sinus bradycardia, sino atrial block or third degree heart block) and liver failure.[28]

Ivabradine in pregnancy and breast feeding

Basing on lack of human data and adverse outcome in animal studies ivabradine is contraindicated in pregnancy. An observational study from German embryotox database reported 38 pregnancies with ivabradine exposure, 32 had life births, 3 had spontaneous abortion and 3 were terminated electively. One neonate was detected to have cleft palate with atrial septal defect. Ivabradine was discontinued in 33 of 38 women once pregnancy was diagnosed, 5 women continued the drug throughout pregnancy. In addition one case of tracheal atresia was reported amongst 3 retrospectively reported pregnancies. If there is inadvertent exposure during pregnancy, monitoring the fetus with ultrasound for structural anomalies and growth restriction is warranted.

Ivabradine is excreted in milk. As there is no adequate data regarding the infant risk during breast feeding, potential benefit should be weighed against risk before starting ivabradine during this period.[29]

CONCLUSION

Ivabradine has been studied in a large number of clinical trials involving more than 50000 participants and is currently indicated for the symptomatic treatment of CSA in adults who are in sinus rhythm and with a baseline heart rate ≥70 bpm with optimal beta blockade.

Ivabradine is also indicated in adults with angina pectoris who cannot take beta-blockers, because of side effects or contraindications.

Treatment with ivabradine may be particularly beneficial in angina patients with concomitant CHF (New York heart association class II–IV CHF with systolic dysfunction, patients in sinus rhythm with a heart rate ≥ 70 bpm, in combination with standard treatment.

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