RANOLAZINE AND IVABRADINE - THEIR CURRENT USE

ABSTRACT
Chronic stable angina is a debilitating illness affecting millions worldwide. Considerable progress has been made over the last 30 years in understanding its pathogenesis. Conventional anti-anginal drugs such as nitrates, β-blockers and calcium channel blockers effect heart rate, blood pressure, pre-load and contractility and thus reduce the oxygen demand. Ranolazine is a new anti-anginal drug approved by the US-FDA for use either as an add-on therapy and now even as a monotherapy. It inhibits the late sodium currents, thereby maintaining sodium – calcium homeostasis and preventing ischaemia induced diastolic dysfunction. Ranolazine does not affect the heart rate, BP and ionotropic state. Anti-anginal benefits of Ranolazine have been confirmed by various trials (MARISA, CARISA, ERICA, MERLINTIMI 36 etc.) in addition it exerts anti-arrhythmic effect in acute NSTEMI. Although it prolongs QT, interval but no case of Torsade de pointes has been observed. It significantly lowers HbA1C in diabetics, which represents potential for clinical benefit.

Ivabradine is a pure heart rate lowering agent acting by inhibiting the funny current (I) in the SA node. It doesn’t affect blood pressure, myocardial contractility, intra cardiac conduction or ventricular repolarisation. Clinical trials (BEAUTIFUL, ASSOCIATE etc.) endorse the concept of pure heart rate lowering as a strategy for improving exercise capacity in patients with stable angina, and possibly improving the prognosis of coronary artery disease and chronic heart failure. Ivabradine is an agent that effectively prevents myocardial ischaemia and treats symptoms in patients with chronic stable angina pectoris.

INTRODUCTION
Chronic stable angina is a debilitating illness affecting millions worldwide. Considerable progress has been made over the last 30 years in the understanding of the pathogenesis of angina pectoris. Over the period, number of pharmacological measures such as nitrates, beta-Blockers, calcium channel blockers and revascularisation strategies such as Coronary Artery Bypass Grafting (CABG) and Coronary Angioplasty have been introduced but still many patients continue to experience Angina despite being on optimal medical therapy. In addition there are a number of patients particularly elderly patients who are unsuitable for revascularisation procedures or they do not tolerate higher doses of conventional anti-anginal drugs. In such cases a novel medical treatment with different mechanism of action would be particularly beneficial in relieving the symptoms.

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Fig. 1 : Sites of Action of Anti-Ischemia Medication
Conventional anti-ischaemic drugs such as Nitrates, β-Blockers and Ca Channel Blockers effect the heart rate, blood pressure, preload and contractility and thus reduce the oxygen demand. Recently certain new anti-anginal drugs have been introduced that exert primarily a metabolic action and have little or no effect on coronary haemodynamics. These drugs have considerable potential as adjunctive therapy for angina, particularly in patients refractory to standard therapies and maybe a primary therapeutic option in certain circumstances. They generally do not adversely effect blood pressure, pulse rate or left ventricular systolic function.

**RANOLAZINE**

Ranolazine is a unique anti-ischaemic drug that was initially thought to act purely through metabolic mechanisms. However, it has recently been shown to be capable of inhibiting the late sodium current, thereby maintaining sodium and calcium homeostasis and preventing ischaemia-induced diastolic dysfunction. In chronic stable angina, ischaemia is due to increased oxygen demand, which is marked by increased heart rate, blood pressure, loading conditions of the heart, or contractility. Ischaemia leads to an increase in late sodium current and, eventually, calcium overload. The consequences are electrical instability and myocardial dysfunction, both systolic and diastolic, because of increased diastolic stiffness. This latter condition results in compression of nutritive blood vessels, leading to a decreased oxygen supply and worsening of the ischaemia. In this situation, conventional anti-ischaemic drugs, such as beta-blockers, nitrates, and calcium channel inhibitors, all work on the factors leading to increased oxygen demand (i.e. heart rate, loading conditions, and contractility). Ranolazine has a unique mechanism: by decreasing the late sodium current, it decreases calcium overload and thereby diastolic stiffness. This in turn improves myocardial perfusion. The anti-ischaemic properties of ranolazine have been shown to be exerted without significant modifications in heart rate, blood pressure, and inotropic state.

On 27th January, 2006, Ranolazine was approved in the USA – FDA for use in patients with chronic angina who continue to be symptomatic on β-Blockers, Ca antagonists or Nitrates. Based on its success and efficacy as an Anti-Anginal agent on 26th November, 2008 Ranolazine was approved as a First Line Anti-Anginal drug.

**Anti-Ischaemic properties of Ranolazine**

Roysseau et al in 2005 tested immediate release Ranolazine 400mg T.I.D. in patients with chronic stable angina vs Atenolol or placebo - Time to 1mm ST depression and exercise duration on TMT were both improved by Ranolazine when compared with placebo. In addition exercise duration was significantly longer with Ranolazine than with either Atenolol or Placebo (Figure 2).

The **MARISA (Monotherapy Assessment of Ranolazine In Stable Angina)** trial aimed to establish the dose–response relationship of sustained-release ranolazine in a population of 191 high-risk patients with angina/limited exercise capacity, washed out from previous therapy. Exercise stress tests were carried out at 4 and 12 h after administration of 500, 1000, or 1500 mg sustained-release ranolazine b.i.d. (peak and trough levels).
Improvements in exercise duration and efficacy parameters were observed at all doses of the drugs, but the improvement was greater at higher doses (Figure 3). This improvement was obtained without significant differences in heart rate and blood pressure at rest and during exercise between the three doses of ranolazine and placebo. Minor blood pressure depression was observed with 1000 and 1500 mg of ranolazine, in particular during exercise, but it is fair to say that the anti-ischaemic effect was obtained without any major modification of heart rate or blood pressure.

In summary, sustained-release ranolazine administered twice daily significantly improves exercise performance and delays occurrence of symptoms and signs of ischaemia, at doses ranging from 500 to 1500 mg, without significant haemodynamic effects. In the CARISA (Combination Assessment of Ranolazine in Stable Angina) trial, two doses of sustained-release ranolazine (750 or 1000 mg b.i.d.) were used in combination with diltiazem, amlodipine, or atenolol in patients with chronic stable angina.38 The cohort was quite large, with more than 800 patients included. Treadmill exercise was carried out at 12 h after administration and at 2, 6, and 12 weeks treatment in three parallel groups, according to a double-blind, placebo-controlled design. Again, all three efficacy parameters (exercise duration, time to angina, and time to 1 mm ST-depression) were improved, but without clear dose related changes. During the 12-week duration of the trial, the frequency of anginal attacks and consumption of nitroglycerin were significantly reduced in ranolazine-treated patients (Figure 4). From this trial, it is clear that sustained-release Ranolazine offers additional anti-anginal effect and anti-ischaemic efficacy in patients receiving standard doses of anti-ischaemic agents such as atenolol, amlodipine, or diltiazem, without significant haemodynamic changes at rest or during exercise. It is worth mentioning that in this trial, 480 patients received Ranolazine for 1 year, whereas 173 patients received the drug for 2 years. There were no significant safety concerns in this trial.

Evaluation of Ranolazine In Chronic Angina (ERICA) was a clinical randomized trial in patients with continuing anginal attacks (more than three attacks per week) already treated with amlodipine at a dose of 10 mg daily, with or without long-acting nitrates. Ranolazine was administered at a dose of 500 mg b.i.d. vs. Placebo for a week, then titrated to 1000 mg b.i.d. for 6 weeks (Figure 5). The primary endpoint was angina frequency during the last 6 weeks, and the secondary endpoints were safety, tolerability, nitroglycerin consumption, and quality of life, according to the Seattle Angina questionnaire. Of 567 patients randomized, 25% were female, 40% were elderly, and 45% were on long-acting nitrates. The results of this study showed a significant reduction in anginal attacks, with excellent tolerability, without syncope or torsade de pointes.
Effect of Ranolazine in Diabetes Mellitus:

Timmis et al. compared the anti-anginal efficacy and safety of Ranolazine in diabetic and non-diabetic patients included in the CARISA trial. Glycaemic control was also assessed in CARISA and its long term open label extension study. They concluded that anti-anginal safety of Ranolazine for angina were similar between diabetic and non-diabetic patients. Ranolazine significantly improved the glycaemic control and lowered HbA1C by 0.5% - 0.7% in diabetic patients. The significant response in HbA1C that was observed with Ranolazine was equivalent to that expected with oral hypoglycaemic agents and thus represents a considerable potential for clinical benefit.

Ranolazine as an Anti-Arrhythmic:

**MERLIN TIMI 36** was a randomised placebo controlled trial. 6560 patients hospitalised with NSTEMI were 1:1 randomised to Ranolazine and placebo in addition to standard therapy.

Treatment with Ranolazine resulted in significant lower incidence of ventricular tachycardia, supra-ventricular tachycardia and significant ventricular pauses in addition to its anti-anginal efficacy.

Safety and Side-effects:

On long term follow up study varying from 1-3 years few side effects have been noticed. Main side effects reported are dizziness (6.2%), headache (5.5%), constipation (4.5%), nausea (4.4%) and asthenia.

QT interval and Ranolazine:

Although in CARISA & other trials average increase in QTc was 6.1ms and 9.2ms at the Ranolazine doses of 750mg and 1000mg twice daily but no cases of Torsade de pointes have been seen in patients who received Ranolazine in clinical trials to date. Ranolazine does not cause ‘Early after-depolarisation’ as well does not cause ‘increased dispersion of ventricular repolarisation’, the
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CONCLUSION

Ranolazine is a novel anti-anginal medication recently approved by the FDA for management of refractory angina. It affords additional anti-anginal and anti-ischaemic efficacy in patients with severe chronic angina who remain symptomatic while taking standard doses of β-blockers, nitrates or calcium channel blockers with minimal haemodynamic effects and without evident long term adverse effects. It may be particularly useful in patients who cannot tolerate the initiation or upward titration of currently available anti-anginal medication because of their depressive effects on blood pressure and heart rate. In addition to its anti-anginal property, Ranolazine has a favourable effect on lowering the incidence of arrhythmias in acute NSTEMI and HbA1c levels in diabetic patients.

IVABRADINE

Resting heart rate is associated with cardiovascular as well as all-cause mortality, and the mortality benefit of some cardiovascular drugs seems to be related in part to their heart rate-lowering effects. Since it is difficult to separate the benefit of heart rate lowering from other actions with currently available drugs, a ‘pure’ heart rate-lowering drug would be of great interest in establishing the benefit of heart rate reduction per se. Heart rate is determined by spontaneous electrical pacemaker activity in the sinoatrial node. Cardiac pacemaker cells generate the spontaneous slow diastolic depolarisation that drives the membrane voltage away from a hyperpolarised level towards the threshold level for initiating a subsequent action potential, generating rhythmic action potentials that propagate through the heart and trigger myocardial contraction. The If current is an ionic current that determines the slope of the diastolic depolarisation, which in turn controls the heart rate.

Ivabradine is the first specific heart rate-lowering agent to have completed clinical development for stable angina pectoris. Ivabradine specifically blocks cardiac pacemaker cell f-channels by entering and binding to a site in the channel pore from the intracellular side. Ivabradine is selective for the If current and exerts significant inhibition of this current and heart rate reduction at concentrations that do not affect other cardiac ionic currents. This activity translates into specific heart rate reduction, which reduces myocardial oxygen demand and simultaneously improves oxygen supply, by prolonging diastole and thus allowing increased coronary flow and myocardial perfusion. Ivabradine lowers heart rate without any negative inotropic or lusitropic effect, thus preserving ventricular contractility.

In isolated rabbit sinoatrial node, the spontaneous firing rate of the pacemaker cells was reduced by Ivabradine. Over the large range of concentrations tested (0.3–10 μmol/L), the slope of slow diastolic depolarisation was reduced, while maximum diastolic potential or threshold potential of activation remained unaffected.

Anti-Anginal efficacy of Ivabradine:

Ivabradine is a specific inhibitor of the If current in the sinoatrial node. As a result, it is a pure heart-rate-lowering agent in patients with sinus rhythm. Ivabradine does not affect blood pressure, myocardial contractility, intra-cardiac conduction, or ventricular repolarisation. Treatment with ivabradine therefore provides an opportunity to assess the effects of lowering heart rate without directly altering other aspects of cardiac function. Ivabradine is an agent that effectively prevents myocardial ischaemia and treats symptoms in patients with chronic stable angina pectoris.

In the BEAUTIFUL study (multicentric double blind study), efficacy of Ivabradine was studied for patients with coronary artery disease. They concluded that Ivabradine can be given safely to patients with coronary artery disease and impaired left-ventricular systolic function, and that it can be used in conjunction with β blockers. Furthermore, a combination of Ivabradine with β blockade was not only safe, but it also improved coronary artery disease outcomes in patients with heart rates of 70 bpm or more.

The efficacy of Ivabradine was studied in a randomised, placebo controlled, dose ranging study in 360 patients with stable angina and documented coronary artery disease. All enrolled patients were randomly assigned to receive placebo or one of the three oral doses of Ivabradine (2.5, 5 or 10mg BID) for a period of 2 weeks. The results of the study demonstrated that Ivabradine produced dose dependent decrease in the heart rate at rest and exercise. Moreover, no rebound or tolerance effects were
observed among the study patients.

Stag and Tchetche 17 2006 also studied long term safety and efficacy of Ivabradine in stable angina and documented coronary artery disease. Patients were assigned to receive either Ivabradine 5 or 7.5mg BID for 12 months. They found that both doses were effective in reducing heart rate and the number of angina attacks and the drug was safe and well tolerated.

Anti-anginal efficacy of Ivabradine has also been compared with that of other anti-anginal drugs like Atenolol 18 and Amlodipine 19 and the authors have observed that Ivabradine has comparable efficacy to Atenolol and Amlodipine in improving exercise tolerance and is safe.

**ASSOCIATE study**20 published in Jan 2009 studied the effect of addition of Ivabradine 5mg BID to patients of Ischaemic Heart Disease receiving Atenolol 50mg/day on exercise duration. Total exercise duration increased by 24.3±65.3 sec. Ivabradine in combination with Atenolol was well tolerated. Only 1.1% patients withdrew because of bradychardia in Ivabradine group.

**Haemodynamic effects of Ivabradine in patients with advanced Heart Failure:**

Ferrari etal21 evaluated the haemodynamic effects of Ivabradine in patients with advanced HF and markedly depressed left ventricular function. The study enrolled 10 patients with class III New York Heart Association (NYHA) (50±12 years, LV ejection fraction 21±7%) who underwent 24hr haemodynamic monitoring. All enrolled patients were infused with Ivabradine. The results of the study found that the Ivabradine significantly reduced the HR by a maximum of 27% at 4hr without decreasing cardiac index. Moreover, Ivabradine increased the stroke volume and LV systolic work by a maximum of 51% and 53% at 4hr respectively. Furthermore, the study did not report any serious adverse events.

1. Current Inhibition and Arrhythmias in Failing Hearts:

Owing to QT lengthening, bradycardia is found to be an important risk factor for ventricular tachyarrhythmias, particularly Torcades de pointes. Even in the presence of significant bradycardia, Ivabradine therapy was not associated with an excess of ventricular proarrythmias. The incidence of ventricular premature beats noted during 24hr ambulatory Holter monitoring or during an exercise stress test, recorded on the 12-lead ECG did not differ in patients receiving Ivabradine treatment, Amlodipine, Atenolol or placebo (2.8%, 2.7% 1.2% and 1.3% respectively). Moreover patients who are at risk for drug induced ventricular proarrythmias, that is, female gender, old age, LV hypertrophy, congestive heart failure and hypokalemia did not appear to have increased ventricular arrhythmias with Ivabradine than Atenolol or Amlodipine.

**CONCLUSION**

Clinical trials endorse the concept of pure heart rate lowering as a strategy for improving exercise capacity in patients with stable angina, and possibly improving the prognosis of coronary artery disease and chronic heart failure. Ivabradine is currently the only agent shown to clinically lower the heart rate with no other cardiac effect (especially on conduction and contractility) and the experience acquired to date strongly suggests that it may be possible to achieve many of the potential advantages of pure heart rate lowering in a range of cardiovascular conditions.

**REFERENCES**

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