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Review Article

Ivabradine: a novel drug for angina pectoris

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ABSTRACT

Angina pectoris is one of the leading cardiovascular diseases responsible for morbidity and mortality world over. Nitrates, beta blockers and calcium channel blockers (CCB) are used in the management of this condition. Studies have confirmed that tachycardia has a negative prognostic factor in subjects with angina and heart failure. In view of this a new drug Ivabradine, with a novel mechanism for reducing heart rate is approved for use in angina pectoris. It blocks If channels (f-funny) which is responsible for spontaneous diastolic depolarisation of Sino Atrial node. This block reduces the heart rate resulting in decreased myocardial oxygen demand, thus improving the clinical situation. It can be used as an alternative in patients with intolerance or contraindication to beta blockers.

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1. Introduction

The most prevalent cardiovascular disease is the coronary artery obstruction which decreases the myocardial oxygen supply causing ischemia of the myocardium. The coronary blood flow occurs during the diastole, so decreasing the heart rate allows more time for left ventricular filling and coronary perfusion, and thus maintains the oxygen balance. Tachycardia decreases duration of diastole, accelerates atherosclerosis , disrupts the coronary plaques and increases the occurrence of sudden cardiac death.[1] In angina, beta blockers and calcium channel blockers are used to decrease heart rate, but they are associated with adverse effects like hypotension, negative inotropism, bradycardia and AV conduction disturbances, reflex tachycardia and peripheral edema.[1] In view of this, a novel heart rate lowering drug, ivabradine with an activity on the sinoatrial (SA) node, can be used.

2. Mechanism Of Action And Pharmacological Effects

SA node is the pacemaker of the heart. The pacemaker myocytes have the capacity to spontaneously generate slow diastolic depolarisation which drives the threshold level required for initiating an action potential. This spontaneous diastolic depolarisation is due to ionic currents. One such is the If current (f-funny) with unusual properties when compared to other currents at the time of its discovery.[2] It is a mixed sodium and potassium inward current, activated during the hyperpolarised state of the cell. During hyperpolarisation, the intracellular cyclic adenosine monophosphate (cAMP) increase and phosphorylates the If channels resulting in opening of the ion channel. This increases the rate of diastolic depolarisation and increase in heart rate without affecting the duration of action potential. This If channel is modulated by the autonomic nervous system by altering the levels of cAMP, for instance, beta adrenergic agonists activate adenylate cyclase which increases cAMP levels and thus a rise in heart rate. Ivabradine, the novel heart rate lowering anti-anginal drug selectively blocks the pacemaker cells with If channels in a dose dependant manner. It enters the ion channel pore and blocks it from the intracellular side. Thus it blocks the channels only when it is open, thus reducing the firing rate of SA node and decrease the heart rate. The magnitude of inhibition is directly proportional to the frequency of channel opening, i.e, more effective at higher heart rates. It has no effects on other ionic currents at therapeutic dose.[3]

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3. Pharmacokinetics

On oral administration, 90% gets absorbed with a bioavailability of 40%. Food delays the absorption by 1 hour. Peak plasma concentration is attained after 45-90 minutes and steady state concentration (10ng/ml) is achieved within 1 day. The volume of distribution is 100 L with 70% bound to plasma proteins.[4] The half life is 2 hours. It undergoes metabolism by oxidation and hydroxylation involving cytochrome (CYP) 3A4 only. The N-desmethylated metabolite S18982 is active, contributing to pharmacological effect and 70-75% is bound to plasma proteins. It is also metabolised by CYP3A4 with same half life. 4% of ivabradine gets excreted unchanged in urine. The rest appears as metabolites in faeces and urine. [5]

3.1. Drug Interactions

Ivabradine does not inhibit or induce CYP3A4 or other isoenzymes of P450, but CYP3A4 enzyme inhibitors like ketoconazole, verapamil, diltiazem, lacidipine, grape fruit juice increase the plasma levels of ivabradine and its metabolites. St John's wort decreases its levels by CYP3A4 induction. [4] Studies show additive effect of decrease in heart rate when atenolol is combined with ivabradine. [4] No clinically significant interactions observed when administered concomitantly with digoxin, aspirin, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), diuretics, statins, nitrates, CCB, fibrates and oral antidiabetic drugs. [4] QTc prolongation was not seen when ivabradine was combined with amiodarone or thioridazine. [4]

3.2. Dose

The starting dose is 5mg twice daily with meals, may be increased to 7.5 mg twice daily after 3-4 weeks. [5] Ivabradine is available in India as Ivabrad(pinnacle-lupin) and Ivabid (Piramal) for 5 mg and 7.5mg strengths. 10 tablets cost 116.55 Rs. for 5 mg and 155 Rs. for 7.5 mg.

3.3. Uses

It is used in exertional angina, heart failure, and mitral stenosis. In all these conditions, the main objective is to decrease the heart rate and has been shown to be non inferior to atenolol and amlodipine in treatment of angina pectoris. [2, 5]

3.4. Adverse Effects

1. Luminous phenomenon (phosphenes)- 14.5%, transient enhanced brightness in a limited area of the visual field, mild to moderate in intensity which occurs within first 2 months of treatment and can also recur.[5] This may be due to blockade of Ih channels in retina which is similar to If channels.

2. Bradycardia (2-5%), AV block, ventricular extra systoles.

3. Headache, dizziness and blurred vision [4].

4. Increase in the QT interval with ivabradine has not exceeded 2 ms, which was below the limit of 5 ms for torsadogenicity. Ivabradine does not appear to have any direct proarrhythmic effect.[6]

3.5. Contraindications

Sick sinus syndrome, moderate to severe hepatic failure, severe renal impairment, patients with congenital long QT syndrome and long QT interval due to other QT-prolonging drugs. [4]

4. Clinical Studies

Ivabradine was comparable to atenolol (4 months study-50 and 100mg once daily) and amlodipine (3 months study) in the dose range of 5 to 7.5 mg twice daily in reducing the frequency of anginal attacks per week, time to angina onset, improving exercise tolerance test and consumption of short acting nitrates. Heart rate and oxygen consumption is reduced by ivabradine compared to atenolol and amlodipine. [8,9] In a long term study (1 year), ivabradine when added to a dihydropyridine and long acting nitrates significantly reduced the number of anginal attacks from baseline.[9]

Ivabradine reduced the rates of admission to hospital for acute myocardial infarction and coronary revascularization as per this study Ivabradine can be safely used in Coronary artery disease (CAD) patients and it can also be used in combination with beta blockers. In CAD patients with heart rate more than 70 beats per minute (bpm) or more, the outcome was better.[10] The subgroup analysis from the BEAUTIFUL study shows that ivabradine reduces the risk of cardiovascular death, hospitalization for myocardial infarction, and heart failure by 24% in patients with limiting angina and has a maximum effect on myocardial infarction with a 42% risk reduction.[11] Ivabradine by reducing heart rate has reduced the hospital admissions in patients with worsening heart failure with heart rate more than 70 bpm and deaths..[12]

5.Advantages

Not associated with development of pharmacological tolerance
No rebound phenomenon after abrupt discontinuation
No change in glucose and lipid metabolism
No negative inotropic and intracardiac conduction effects
Can be safely combined with beta blockers for the treatment of angina. [5]

Useful in patients with bronchial asthma, peripheral arterial disease, diabetes mellitus (beta blockers are contraindicated). [1] Beta blockers and calcium channel blockers are not used in patients with heart failure or with atrioventricular node dysfunction or in hypotension. Ivabradine is useful in the above situations.[1]

6. Conclusion

It is FDA approved for the treatment of chronic stable angina in patients with normal sinus rhythm. By decreasing heart rate it reduces the number of attacks, improves exercise capacity and thereby decreases the incidence of coronary artery disease. It can be used as an alternative in patients with intolerance or contraindication to beta blockers. Currently it is undergoing clinical trials to establish its effect on C reactive protein in acute coronary syndrome. [13] Ivabradine is currently the sole agent to lower heart rate without negative inotropic and dromotropic effect.

CONFLICT OF INTEREST- there is no conflict of interest .
SOURCE OF SUPPORT –nil
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