World Journal of Pharmaceutical and Life Sciences
WJPLS

www.wjpls.org SJIF Impact Factor: 4.223

THE EFFECT OF IVABRADINE ON HIGH SENSITIVITY C-REACTIVE PROTEIN LEVELS AND SHORT TERM CLINICAL OUTCOME IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Article Received on 06/12/2016 Article Revised on 27/12/2016 Article Accepted on 16/01/2017

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ABSTRACT

Ivabradine is a new bradycardiac agent acting on the I_f current channels of sinoatrial nodal cells to decrease the rate of diastolic depolarization and thus the heart rate. Ivabradine has been shown to safely and effectively reduce heart rate without compromising cardiac function in patients with coronary artery disease and more recently in patients with heart failure and raised heart rate. The primary and principal cause of acute coronary syndrome in more than 90% of the patients is the rupture of an atheromatus plaque, endothelial dysfunction and inflammation and formation of fatty streaks are the core distributors to atherosclerotic plaque formation. C-reactive protein is a sensitive marker of inflammation. Increased levels of Hs-CRP are associated with endothelial dysfunction, vascular inflammation and in increase cardiovascular risk. The project aims to evaluate the effect of Ivabradine on high sensitivity C-reactive protein levels and its effect on ACS therapy.

KEYWORDS: ACS- C-reactive protein-Ivabradine-Heart rate.I_F current.

INTRODUCTION

C-reactive protein (CRP) is a specific biomarker for inflammation. Elevated serum levels of CRP using a high sensitivity assay (hsCRP) reflect subclinical inflammatory states such as

vascular inflammation. The value can identify the risk level for acute coronary syndrome (ACS). In patients with acute coronary syndromes (ACS), higher hsCRP levels are associated with adverse outcomes and subsequentvascular events.[1]

Ivabradine, a selective inhibitor of the funny current channel, reduces resting and exercise HR without affecting cardiac contractility or blood pressure.[1] Funny current channels (I_f), are activated during the resting potential stage and accelerate diastolic depolarization of the sinus node and thus its pacemaker function.[2] Ivabradine exerts antianginal and anti-ischemic effects in patients with coronary artery disease. Improved exercise tolerance, increased time to exercise-induced ischemia, and reduced frequency of ambient anginal attacks have been observed after funny current channel inhibition.[3]

C-reactive protein (CRP) is a substance produced by the liver in response to inflammation. High CRP levels can indicate that there is inflammation in the arteries of the heart, which can mean a higher risk for heart attack.[4] C-reactive protein is measured in milligrams of CRP per liter of blood (mg/L). CRP is traditionally measured down to concentrations of 3-5 mg/L, whereas hs-CRP measures down to concentrations around 0.3 mg/L. This improved sensitivity allows hs-CRP to be used to detect low levels of chronic inflammation. However, a desirable value is probably less than 1 mg/ml.[5]

Acute coronary syndromes (ACS) are responsible for a large number of cardiac-related hospital admissions with potentially high morbidity and mortality. They can be divided based on electrocardiogram (ECG) findings, into either ST elevation acute coronary syndromes (STE-ACS), or non-ST elevation acute coronary syndromes (NSTE-ACS).[6] The latter can be subdivided further into two closely related conditions, non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA) depending on the presence or absence of biochemical evidence of myocardial necrosis.[7]

The principal cause of acute coronary syndromes (ACS) in more than 90% of patients is the rupture of an atheromatous plaque. Endothelial dysfunction, inflammation, and the formation of fatty streaks are the core contributors to atherosclerotic plaquesformation.1 Heart rate is an independent risk predictor of the onset of acute coronary events. Many epidemiological and clinical studies aimed to explore the association between resting HR and outcomes in healthy and cardiovascular disease patients.

The anti-anginal and anti-ischemic efficacy of ivabradine–in monotherapy or in combination with a β-blocker–has been demonstrated by several clinical trials. As a consequence, the substance evolved as an alternative strategy particularly for patients in whom the use of β-blockers is contraindicated, intolerable or patients who remain symptomatic despite β -blockade.

Adel[8] et al (2012) conducted a study on 'CLINICAL STUDY EVALUATING THE EFFECT OF IVABRADINE ON INFLAMMATION IN PATIENTS WITH NON ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES.' This prospective, randomized, controlled, study recruited NSTE-ACS patients with HR ≥70beats per minutes. Each patient was randomly assigned to either control or ivabradine groups. The difference between the two groups was the addition of ivabradine (up to 7.5 mg bid) to the standard treatment of NSTE-ACS patients for 30 days in the ivabradine group. Levels of hsCRP were evaluated before and after the study period. In this study 45 patients were enrolled, twenty three of which received ivabradine. The decrease (%) in HR after treatment was significantly larger inivabradine group than in control group (23.8 (7.3 – 31) vs 4.7 (0 - 22.5) %, p = 0.014). The decrease in HR was positively correlated to hsCRP reduction, r = 0.445, p = 0.003. No significant difference between ivabradine and control groups in hsCRP reduction (80 (38 - 90.6) vs 61.3 (24 - 76.4) %, P = 0.057). Ivabradine was well-tolerated. The study concluded thatIvabradine effectively and safely decreased HR in NSTE-ACS patients. Reduction in HR was associated with hsCRP reduction. Larger studies are required to better demonstrate the anti-inflammatory effects of ivabradine in ACS.

Gordan F.Rushworth[9] et al (2011) conducted a study on 'Ivabradine: a new rate-limiting therapy for coronary artery disease and heart failure'.This study was first tested for efficacy in a cohort of 360 patients with stable angina. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial.A subgroup analysis has shown that ivabradine improves mortality in patients with an initial heart rate greater than 70 bpm and because it can limit heart rate at rest and during exercise, it is particularly useful for treating ambulatory angina pectoris.Ivabradine should currently be used as a second-line agent for managing angina, or as first-line treatment if the patient is intolerant to β-blockers or there are contraindications.

Ferrai[10] et al(2008) conducted a study on 'randomized trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction - baseline characteristics of the study population'. Ivabradine is a selective heart rate-lowering agent that acts by inhibiting the pacemaker current If in sinoatrial node cells. Patients with coronary artery disease and left ventricular dysfunction are at high risk of death and cardiac events, and the BEAUTIFUL study was designed to evaluate the effects of ivabradine on outcome in such patients receiving optimal medical therapy. This report describes the study population at baseline. BEAUTIFUL is an international, multicentre, randomized, double-blind trial to compare ivabradine with placebo in reducing mortality and cardiovascular events in patients with stable coronary artery disease and left ventricular systolic dysfunction (ejection fraction <40%).

Fox k[11] et al(2009) conducted a study on **'**Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial'. BEAUTIFUL found no impact of ivabradine on outcomes in patients with stable coronary artery disease (CAD) and left ventricular systolic dysfunction (LVSD). We performed a post hoc analysis of the effect of ivabradine in BEAUTIFUL patients whose limiting symptom at baseline was angina, particularly in terms of coronary outcomes. Our analyses raises the possibility that ivabradine may be helpful to reduce major cardiovascular events in patients with stable CAD and LVSD who present with limiting angina. However, a large-scale clinical trial is ongoing, which will formally test this hypothesis.

Mohammad salem[12] et al;(2015) conducted a study on 'Safety and efficacy of Ivabradine in patients with acute ST-segment elevation myocardial infarction (STEMI)'. ST segment elevation myocardial infarction (STEMI) is commonly induced by thrombus formation leading to complete occlusion of a major epicardial coronary vessel. We aimed to explore safety and efficacy of Ivabradine in patients with STEMI associated with left ventricular dysfunction. 200 consecutive patients with STEMI were included in this controlled study. All patients had successful reperfusion and LVEF less than 50%. 100 patients received 5 mg ivabradine twice a day in addition to the conventional treatment, while 100 patients received the conventional treatment only. Composite end point of death, re-infarction, overt heart failure, or need for revascularization was reported at 30 days. Ivabradine when added to the conventional treatment reduced the heart rate significantly compared to the conventional

treatment alone. However it did not affect incidence of primary end point. Ivabradine didn't show a significant impact on major adverse cardiac events when added to conventional treatment.

K K Adile[13] et al(2012) conducted a study on 'Safety and efficacy of oral ivabradine as a heart rate-reducing agent in patients undergoing CT coronary angiography.' To investigate the role of oral ivabradine as a heart rate reducing agent in patients undergoing CT coronary angiography (CTCA). Despite the routine use of beta-blockers prior to CTCA studies, it is not uncommon to have patients with heart rates persistently above the target range of 65 bpm. Ivabradine is a selective inhibitor of the If current, which primarily contributes to sinus node pacemaker activity, and has no significant direct cardiovascular effects such as reduction of blood pressure, cardiac contractility or impairment of cardiac conduction. Ivabradine is a potentially attractive alternative to currently used drugs for reduction of heart rate in patients undergoing CTCA.

CONCLUSION

Procoralan tablets contain the active ingredient ivabradine, which is a type of medicine called a selective If current inhibitor. It helps to lower the heart rate, which can be helpful in treating both angina and heart failure. Ivabradine works by inhibiting the electrical current produced in the pacemaker of the heart that controls the heart rate. It does this by binding to 'If-channels' that are found in the pacemaker. These If-channels are responsible for generating an electrical impulse that spreads through the heart, causing it to contract so that blood can be pumped to the lungs and the rest of the body. By binding to the If-channels, ivabradine slows the rate at which the heart beats.

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