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Full Length Research Paper

Ivabradine for Treatment of Stable Angina and Heart Failure

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A significant number of industrial professionals and pharmacists have revealed that ivabradine is extremely suitable drug, which can be used for inhibiting sinus-node. This medicine has enough capability to reduce the risk of various cardiovascular diseases. Therefore, ivabradine is helpful for the governmental authorities and hospital administration to reduce the mortality and morbidity rates of cardiac conditions. During the presence of angina, this drug can be easily used for improving exercise capacity. Sinus tachycardia can be easily controlled with the help of this pharmaceutical agent. Conversely, this medicine is not associated with decreased mortality rates of coronary artery deisease. Therefore, it is extremely necessary for current investigators to identify advanced knowledge in relation with ivabradine.

Keyword: Angina, cornonary artery disease, drug evaluation, ivabradine, heart failure

INTRODUCTION

Ivabradine refers to a very common pharmaceutical agent, which is mostly used in the clinical settings for inhibiting sinus node. Various research studies and peer reviewed articles have focused on the importance and consequences of ivabradine. The symptoms of stable angina pectoris can be easily treated with the help of this medicine.

Ivabrdaine has been evaluated by certain studies that ivabradine can easily reduce heart rate by inhibiting funny channel. Funny channel is also known as funny current (f_I), which refers to the current of the heart. Calcium channel blocker and beta blocker are two significant categories of medicines, which are also used for reducing heart rate. However, both of these pharmaceutical agents have no effects on the funny channel.

Ivabradine binds with the intracellular side of the pacemaker cells for carrying out desired outcomes (DiFrancesco and Borer, 2007). It has been evaluated by certain studies that this action or mechanism of ivabradine is extremely different from the other drugs, which are usually used for reducing heart rate. It is also a fact that reduced heart rate is a very common benefit of ivabradine. Therefore, this medicine is extensively used in various different cases of cardiac conditions. At the same time, various different approaches and strategies are used along with this medicine (Swedberg et al., 2010). However, it is also a fact that this medicine has replaced numerous secondary techniques effectively. A very common example is related to monotherapy. Monotherapy is a common approach, which is used for reducing heart rate. However, the use of ivabradine is a very common alternative of monotherapy. Thus, this drug can be also used for the cases of ischemic heart deisease (IHD) conditions and congestive heart faiure (CHF) (Mosterd and Hoes, 2007; Mosterd et al., 1999).
It has been evaluated by various studies that ivabradine is useful for the patients, having IHD and CHF.

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It is a fact that ischemic heart disease will boost up the heart rate of an individual to the extensive levels. The administration of ivabradine will certainly result in the deprived heart rate without developing any complication. It is also a fact that the cases of IHD and CHF is continuously increasing due to sedentary life style, inappropriate dietary plans, and existence of chronic medical conditions. Increased rates of mortality and morbidity are directly associated with the condition of CHF. The incidence rate of CHF is around 1% to 2% among the western countries (Mosterd and Hoes, 2007; Mosterd et al., 1999). However, the condition of IHD is responsible for causing 1/3 of all deaths among USA population . Some of the studies have mentioned that these rates have a close association with the wellness and wellbeing of the individuals.

The incidence rate of IHD within Saudi Arabia is around 5.5% (Mansour et al., 2004). Therefore, it is said that the population of Arab countries are extremely prominent to the increased risk of IHD and CHF in the upcoming years. It is also a fact that life quality of patients, having IHD or CHF, is poor and deprived (Khunti et al., 2002). The reason behind this statement is that the symptoms of IHD and CHF will affect the major systems and organs of the human body. At the same time, both of these conditions will also make a direct impact over the physical and professional performance. Therefore, proper management is tremendously required for the patients of IHD and CHF for improved general health status (Flather et al., 2000).

Data Sources and Selection

Search Strategy

The process of searching literature and appropriate data was developed by a professional librarian. The librarian used electronic materials as the basic part of search strategy. English articles between years 1990 and 2010 were selected for the study. Databases of Cochrane, PubMed, and Embase were used for the collection of authenticated data.

Search Terms

Different types of keywords were used by the investigators for conducting search strategy effectively. Ivabradine, cardiac failure, heart failure left sided, myocardial diseases, right sided heart failure, congestive heart failure and decompensation heart failure were certain common keywords for searching articles.

Eligibility Criteria

Peer reviewed journal articles and scholarly journal articles have been selected by this project in relation with the benefits and consequences of ivrabradine. Review articles, letters and magazine articles were excluded from this study due to their unauthenticated nature.

Data Synthesis

Data was collected from the studies regarding population, designs, participants, follow-up, inclusion, exclusion criteria, and the primary outcome. The information about these categories were placed in a table for making appropriate presentation.

Pharmacology

Ivabradine is considered as a cardiogenic drug, which has the capability to inhibit the f_I in the cardiac structures. This drug is mostly used in the clinical settings for reducing heart rate by inhibiting f_I of sinus node. This drug is also helpful for the professionals to increase diastolicdepolarization.

Additionally, diastolic depolarization will also increase the timing in relation with action potential and will result in the lower firing process. This state of the body will certainly result in the reduced heart rate. This process has clearly mentioned that ivabradine will be significant for the cardiac patients to control the problem of tachycardia or increased heart rate (DiFrancesco and Borer, 2007; Borer, 2006).

Pharmacokinetics

The chemical formula of Ivabradine is " 3-(3-({((7S)-3,4-Dimethoxybicyclo (4.2.0) octa-1,3,5-trien-7-yl)methyl} methylamino) propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one" (Micromedex, 2012). This chemical formula is mainly used in the industries and pharmaceutical companies for manufacturing ivabradine. It has been evaluated that ivabradine has potential to absorb completely with the bioavailability of 40%. The concentration of peak plasma in the fasting state is achieved within one hour. Concentration can be delayed by 1 hour, which will certainly result in the increased extent of absorption by 20% to 30%. Enhanced metabolism will also occur because of CYP450 isoenzyme CYP3A4 to its main active metabolic N-desmethyl-ivarbradine. The half life of this drug is 11 hours (Micromedex, 2012).

Place in Therapy

Approved Labeling

Approved level can be easily attained with the help of symptomatic therapy of angina in the individuals, having natural sinus rhythm. It is also a fact that intolerance towards beta-blockers is required among the patients (Micromedex, 2012).

Dosage and Administration

Ivabradine is mostly introduced in the human body from oral route. The standard dosage of this drug is 5 mg, two times in a day. Initially, the dose of 5mg was given to the patients. The dose was increased after four weeks to 7.5mg. However, the dose was condensed to 2.5mg in the presence of bradycardia. Consistent bradycardia resulted in the discontinuation of treatment. Starting dose in older patients was 2.5mg, two times a day (Micromedex, 2012; Lexi, 2012).

Warning and Precaution

The risk of angina, cardiogenic shock, and myocardial infarction is significantly high among the patients having extensive bradycardia. The treatment would be stopped in the case of constant bradycardia (Micromedex, 2012; Lexi, 2012).

Contraindications

Common contraindications for this drug are severe hypotension, severe hepatic impairment, atrial fibrillation, and cardiac arrhythmias. Ivabradine has embryotoxic and teratogenic nature, and has the capability to distribute in breast milk (Micromedex, 2012; Lexi, 2012).

Drug Interaction

The drugs, which have wide-ranging QT, can cause serious complications among population after interacting with ivabradine. Combination of ivabradine and HIV-protease inhibitors will also cause certain complications. Additionally, this drug must not be used with the inhibitors of macrolide antibacterials, ketoconazole, and itraconazole. Similarly, interaction of ivabradine with CYP3A4 inhibitors, diltiazem and verapamil, will cause extensive bradycardia (Micromedex, 2012; Lexi, 2012).

Adverse Events

Adverse effect is considered as another very important aspect of any pharmaceutical agent. It is a fact that proper concentration should be given to the adverse effects and events, in relation with ivabradine. It is a fact that poor concentration on adverse effects can increase the risk of death. Common side effects of ivabradine are blurred vision, constipation, nausea, luminous phenomena in the visual field (phosphenes), radycardia, diarrhea, headache, cardiac arrhythmias, dizziness, muscle cramps, and dyspnoea. Eosinophilia, elevated blood-creatinine concentrations, and Hyperuricaemia are also common adverse effects (Micromedex, 2012; Lexi, 2012; Tardif, 2007).

Clinical Studies of Efficacy

This study has selected six randomized control trials for deriving out effective knowledge and information. All of the selected studies appraised the effects of ivabradine in reducing mortality rates and hospital admission for heart failure.

SHIFT trail has indicated that ivabradine is directly associated with reduced mortality rates because of cardiovascular conditions. Sarullo et al. (2010) described that ivabradine will influence over life quality, gas exchange, functional aspects, modulation of hormones, and exercise capacity. BEAUTIFUL trail further investigated that ivabradine will not make any impact over the mortality rates of cardiac conditions, heart failure and myocardial infarction. This study has also mentioned that further approaches can be used along with ivabradine for reducing mortality rates. Tardif et al. (2009) has also describe that ivabradine will progress the duration of exercises as compared with those patients, who had received beta-blocker therapy. Ruzyllo et al. (2007) has revealed that ivabradine is also helpful for improving exercise duration as compared with patients, receiving amlodipine.

On the other hand, REDUCTION trail has shown that the use of ivabradine will certainly result in the reduced heart rate, reduced attacks of angina, and reduced consumption of nitrate among patients. Borer el al. (2003) has mentioned that ivabradine will also develop positive outcomes in relation with exercise tolerance (ET) and aggravation of ischemia, this study has clearly identified that ischemic heart diseases can be controlled with the help of this drug. Jean-Claude Tardif et al. (2005) proved that ivabradine is much better than atenolol for making positive improvements in ET among patients of angina. This study has also indicated that the condition of angina can be easily treated after using ivabradine. Table 1 and table 2 are representing complete details about the trials and selected research studies.

Table 1. Studies done on Heart Failure patients

Authors	Study name	Type of study	Patients	Results
Filippo M. Sarullo et al 2010	Impact of off-label use of Ivabradine on Exercise Capacity, Gas Exchange, Functional Class, Quality of Life and Neurohormonal Modulation in Patients With Ischemic CHF	Randomized prospective approach used for project. Ivabradine versus Placebo Total of 60 Patients. 30 pateints placebo and 30 pateints ivabradine were used with the dose of 5mg bid, then 7.5mg.	**Inclusion** Patients having symptoms of heart failure (HF), EF, NYHA class II and III, and Heart rate (HR) >70 bpm included in the study. **Exclusion** Patients having unstable angina, acute myocardial infarction (MI), CHF, valvular heart disease, and arrhythmias were excluded from the study. **Primary endpoint** Positive impacts of ivabradine on gas exchange, life quality, exercise capability, modulation of hormones, and functional class was observed among patients. **Median follow-up** 3 month	Capacity of exercise was augmented from 14.8 $\pm$2.5 to 28.2 $\pm$ 3.5 min. The P value was <0.0001. The utilization of oxygen enhanced from by 17.9 $\pm$ 2.4 mL/kg in a minute. At anaerobic threshold, the oxygen level utilization was improved by 15.3 $\pm$ 1.4 mL/kg in a minute. Conversely, NT pro BNP level dwindled to 1434 $\pm$ 1273 pg/mL. Similarly, no difference was identified in control group.
Karl Swedberg et al. 2010	Ivabradine and outcomes in chronic heart failure (SHIFT)	General type of placebo controlled and randomized study was used for this study. 6505 patients were matched up with 3264 placebo. 3241 ivabradine were used with the initial dose of 5mg and then 7.5mg, BID.	**Inclusion** Patients having symptomatic heart failure, EF < 35%, and HR > 70 bpm included in the study. **Exclusion** Patients having MI, arythemia, and symptomatic hypotension excluded from the study. **Primary Endpoint** Increased admissions within hospitals due to worsened HF and cardiovascular death (CV) deaths. **Median follow-up** 22.9 month	The results declared that 29% placebo and 24% Ivabradine group had chief endpoint incident. (HR 0.82, 95% CI 0.75-0.90, p<0.0001)

Table 2. Studies done on Ischemic Heart Disease

Authors	Study name	Type of study	Patients	Results
Kim Fox et al. 2009	Morbidity-Mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL)	Randomized, double-blind, parallel, and placebo-controlled approaches were used. 10917 patients selected with 5438 placeb and 5479 ivabradine used in the study.	**Inclusion** Patients having narrowed coronary arteries, HR < 60 bpm at the stage of resting, sinus rhythm, and coronary artery disease (CAD) were incorporated in the study. **Exclusion** Patients having stroke, CABG, sinoatrial block, vulvular disease, AV block, congenital QT, hypertension, and severe HF excluded from the project. **Primary End Point** Amalgamation of cardiac and vascular deaths, hospital admission due to MI and HF were observed. **Median follow-up** 19 month	This drug did not influence on endpoint of composite (HR = 1.00, (95% CI 0.91–1.1), p=0.94). The treatment with ivabradine did not show any on composite outcomes among patients (hazard ratio 0.91, 95% CI 0.81–1.04, P = 0.17).
Jean-Claude Tardif et al. 2009	Efficacy of the If current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy	Placebo-controlled and randomized trial was used. 866 patients were chosen; 440 were placebo and 449 ivabradine were used with dosage of 5mg bid for 2 month, then 7.5mg for 2 month.	**Inclusion** Patients having sinus rhythm, and treatment with atenolol and beta blocker were incorporated in the study. **Exclusion** Patients having angina at rest, NYHA, bradycardia, HF, prinzmetal angina, and hypotension were excluded from the study. **Primary end point** Modification was pragmatic in exercise duration throughout the therapy. **Median follow-up** 4 months	The length of total exercise was around 4 months, which improved in ivabradine group by 24.3 $\pm$ 65.3 in a comparison with 7.7 $\pm$ 63.8 among placebo. The group of Ivabradine was better as compared to placebo group after 4 and 2 months (P-values between < 0.001 and 0.018).

Table 2 continue

Witold Ruzyllo et al. 2007	Antianginal Efficacy and Safety of Ivabradine Compared with Amlodipine in Patients with Stable Effort Angina Pectoris	Random, non inferiority and double blind approach were used. 1195 patients selected with 404 were dependent upon amlodipine 10mg, daily. 400 patients were using ivabradine 7mg twice. 391 patients were dependent upon 10mg.	**Inclusion** Patients having coronary artery diseases, positive exercise test, short acting nitrates, and angina history were included in the study. **Exclusion** Patients having HF, indwelling pacemaker, unstable angina, and hypertension excluded from the study. **Primary end point** The modification occured in length of exercise after 3 months of therapy **Median follow-up** 3 months	The length of exercise was increased to 27.6 ± 91.7sec in using ivabradine 7.5mg. 21.7 ± 94.5sec were identified, using ivabradine 10mg and 31.2 ± 92.0 sec were seen after using amlodipine10mg. Proper progresses have been observed in exercise length.
Ralf Koster et al. 2009	Treatment of stable angina pectoris by ivabradine in every day practice: The REDUCTION Study	Open label, non- interventional and prospective methods were used. 4954 patients used ivabradine 5 mg, two times in a day. After 4 weeks, 7.5 mg dosage was used among the selected patients.	**Inclusion** Patients taking therapy angina were integrated in the study **Primary end point** The concluding endpoints were angina attacks, heart rate, and nitrate consumption. **Median follow-up** 4 months	Reduced HR was identified with the figure of 12.4 ± 12.2 beat/min. The attack of angina abridged to 0.4 ± 1.5 per week. The nitrate utilization condensed to 0.6 ± 1.6 U/wk ($P < 0.0001$).
Jean-Claude Tardif et al, 2005	Efficacy of ivabradine, a new selective f_I inhibitor, compared with atenolol in patients with chronic stable angina	Double blinded and random methods were used. 939 patients of angina were selected. Patients received ivabradine 5 mg, two times a day at least 4 weeks. Then, the dose was increased by 7.5 or 10 mg, two time in a single day for 12 weeks. As an alternative, atenolol was also used for 4 weeks on the dose of 50 mg once a day. This dosage was followed by 10 mg of the drug for the time frame of 12 weeks.	**Inclusion** 18 years old individuals, who had CAD, MI, angina, and coronary angioplasty were selected. **Exclusion** Patients having CHF, AV block, pacemakers, hypotension, heart diseases, and flutter excluded from the study. **Primary Endpoint** Alteration in the duration of exercise (TED) **Median follow-up** 16 weeks	The length of exercise was augmented after 16 weeks of the therapy. The TED was 86.8 ± 129.0 s and 91.7 ± 118.8 after using ivabradine on the dose of 7.5 and 10 mg. The TED was 78.8 ± 133.4 s after using atenolol on the dose of 100 mg.

Table 2 continue

Jeffrey S. Borer et al, 2003	Antianginal and Antiischemic Effects of Ivabradine, an f_I Inhibitor, in Stable Angina	Double-blind random multi-centered and placebo-controlled methods used. 360 patients were chosen randomly, and received ivabradine for 2 weeks. This was followed through open label for 3 months extension.	**Inclusion** Age18 years, with $\geq$ 3months history of Chronic stable angina, relieved by nitroglycerin or rest , plus catheterization documented coronary artery illness or last myocardial infarction 3months prior tocasualtask; all people required to manifest positive exercise tolerance tests (ETT) (with both limiting angina and S.T segment depression 1 mm Than rest). **Exclusion** Un-stable angina, Prinzmetal angina or Micro-vascular angina," important valvular illness, atrial fibrillation, in-dwelling pace-maker or flutter, second andthird atrio-ventricular block, or in-ability to carry out ETT. **Primary Endpoint** Modifications in time by 1mm depression and time for reducing angina during test. **Median follow-up** 3 months	Time in relation with 1-mm ST segment depression enlarged after administrating 5 and 10 mg of the drug, bid. The factor of time was also augmented with limiting angina among the users of 10 mg. ETT parameters occurred among patients, who had received proper placebo. Not a single phenomenon was identified due to ceased treatment.

DISCUSSION

Ivabradine is a lone selective sinus node inhibitor. It has significant effect on reducing cardiovascular mortality and morbidity in the patients with symptomatic heart-failure having low fraction of ejection and with HR >70, also it has excellent effect in improving exercise capacity in angina patients comparing with calcium channel blocker as well as placebo. But doesn`t have effect on mortality on coronary artery disease. Also it used in several cases of sinus tachycardia and showed a good result. Still researcher is looking for more studies to prove the influence of ivabtadine in cardiac patients with or without systolic heart-failure.

CONCLUSION

Ivabradine is an extremely significant pharmaceutical agent, which is mostly used for reducing heart rates among patients. It is a fact that ivabradine will influence over the sinus node for inhibiting its functions. This medicine is frequently used in the clinical settings for reduced HR, reduced risk of cardiac conditions, improved exercise capacity, and reduced mortality rates of cardiovascular conditions. Nonetheless, the results have shown that this drug will not influence over the death rates in relation with CAD. Therefore, it can be concluded that advanced investigation and explorations are necessary for ruling out authenticated information in relation with ivabradine

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