Ranolazine: A novel partial inhibitor of fatty acid oxidation for angina

Introduction

Chronic angina is one of the most common cardiovascular disorders known to impair quality of life and decrease life expectancy, in developing and developed countries. Though considerable progress has been made in the treatment of angina, many patients continue to experience the symptoms while a few remain refractory to conventional medications.[1] Treatment of angina is usually followed in two steps. The first is the improvement of prognosis, which can be done by administration of several drugs such as statins, ACE inhibitors and aspirin. The second is to improve the symptoms by antianginal drugs and revascularisation procedures. However, the advancing age of the patient and co-existing medical disorders are hindrances for approval of revascularisation procedures.

Conventional antianginal drugs mainly act through two mechanisms.[2] First mechanism decreases the mitochondrial ATP formation by reducing heart rate, blood pressure and cardiac inotropism. This mechanism is exploited by drugs such as β blockers and nitrates.[2] The second mechanism increases oxygen supply to the area of ischemia, which is done by vasodilators and revascularisation procedures. However, most of these antianginal agents cause haemodynamic changes such as coronary vasodilatation, negative inotropism etc, resulting in symptomatic hypotension, bradycardia and worsening of cardiac failure. Hence, a novel medical approach without haemodynamic changes would be beneficial in reducing morbidity and mortality in these patients. Inhibition of metabolism of free fatty acids may be an effective new approach and ranolazine has shown a promising result in decreasing the symptoms of angina, without disturbing normal haemodynamics.

Chemistry

Ranolazine is a compound with a structure similar to trimetazidine, a β-oxidation inhibitor. Piperazine is present as a substituted compound in its structure. It is a racemic mixture with empirical formula C29H33N3O4 and a molecular weight of 427.54 g/mole. It is a white solid soluble in several organic compounds and very slightly soluble in water.[3]

Mechanism of action

Myocardial ischemia is associated with sudden increase in fatty acid levels resulting in enhanced oxidation of long chain fatty acids. Oxidation of fatty acids needs more ATPs than oxidation of carbohydrates and also an increased oxygen demand.[4] Moreover this may lead to accumulation of free fatty acids and lactic acid, increasing the acidosis. These mechanisms have detrimental effects on the contractility and efficiency of the heart. Therapeutic interventions, which shift myocardial substrate utilisation to glucose metabolism, may provide benefits to ischemic patients. This can be achieved by drugs which suppress fatty acid oxidation. Ranolazine, a partial inhibitor of fatty acid oxidation, shifts ATP production from fatty acid to more oxygen efficient carbohydrate oxidation, especially when it is elevated as in ischemia. It has been shown to stimulate glucose oxidation during increased plasma free fatty acid levels associated with myocardial ischemia.[5]

Another mechanism is selective inhibition of late I Na currents, resulting in decrease at the calcium overload on the cardiac fibres. During myocardial ischemia, cells show acidosis, increased Ca2+ which impairs myocardial contraction, also an efflux of K+ ions and influx of Na+ ions into the myocardial cells. The inhibition of I Na currents decreases the intracellular sodium concentrations, especially in ischemic myocytes where the current is amplified. Inhibition of sodium influx reduces calcium overload and decreases left ventricular wall tension, resulting in decreased myocardial oxygen demand.[6]

Pharmacokinetics

Sustained release preparation of ranolazine undergoes a prolonged absorption and exhibits C_max at 4 to 6 h. The elimination half life is 7 h after continuous dosing. With the above dosage a steady state concentration is observed within 3 days. A plasma concentration of 2-6 µmol/L in patients with chronic angina is useful for the treatment.[6, 7] Food does not affect the absorption of the drug and 30 to 55% of the drug enters the systemic circulation. Nearly 65% of the drug is bound to albumin in the plasma. Major metabolism takes place in the liver in the presence of cytochrome P-450 (mainly CYP3A4 with CYP2D6 contributing 10 to 15%). Glucuronidation and renal excretion are the other additional mechanisms of metabolism. A total of 11 metabolites with nearly 6 to 22 h of elimination half life are reported. Out of them four are major metabolites.[7- 9] In patients with hepatic impairment, a significant change in the metabolism of ranolazine is seen. No gender differences and alteration of pharmacokinetics in diabetes mellitus and heart failure were reported. However, the clearance may decrease with the age.[6]

Drug interactions

Ranolazine should be avoided in patients taking potent CYP3A4 inhibitors such as ketoconazole, verapamil, diltiazem, macrolides, grape fruit juice and HIV protease inhibitors. Ranolazine is a substrate as well as an inhibitor of P-glycoprotein (P-gp). Drugs inhibiting P-gp can increase the
absorption as well as bioavailability of ranolazine. Digoxin, a substrate of P-gp, shows an increase in its plasma levels of 1.4 to 1.6 folds when co-administered with ranolazine, which may occupy the renal and intestinal P-gp. Hypolipidemic drugs such as simvastatin may also show its increased plasma concentration about two fold when given with ranolazine. However, no change in the pharmacokinetics of ranolazine was observed.

Adverse effects

The most common adverse effects are dizziness, nausea, asthenia, and constipation. Postural hypotension, syncope, headache, dyspnea and abdominal pain are also reported. An increase in QTc interval was observed at doses of 750 and 1000 mg b.i.d. However, torsades de pointes is not reported.

Uses

Ranolazine was approved by USFDA on January 27, 2006 for treatment of patients with chronic angina pectoris who failed to respond to the standard antianginal therapy. Ranolazine is available as an extended-release tablet for oral administration in the United States of America, not in India. A dosage of 500 or 1000 mg twice daily is recommended. The maximum administered dose is 1000 mg b.i.d.

Clinical trials

Several studies on monotherapy, combination therapy with other antianginal drugs and on sustained preparations are reported. The MARISA trial (Monotherapy Assessment of Ranolazine In Stable Angina) is a multi-national, randomised, double blind, placebo-controlled study – a first study with sustained release monotherapy. An exercise test was conducted at trough and peak levels of the drug concentrations on every 7th day of the treatment in 191 patients. Results were compared between placebo 500, 1000 and 1500 mg each administered twice daily for one week. Significant increase in the exercise capacity was reported at trough when compared with placebo. The capacity increased with respect to the plasma concentration. However, a ceiling effect was observed at or more than 1000 mg dosage. The main limitation of the study was the use of placebo for comparison though there was availability of conventional established treatment.

The CARISA (Combination Assessment of Ranolazine In Stable Angina) test was a randomised parallel 3 group, double blind, placebo-controlled study. It involved 823 subjects with proven chronic angina treated with conventional antianginal drugs. They were divided to receive placebo, 750 mg and 1000 mg of ranolazine twice daily for a week. Even though it was placebo-controlled all the patients under study were on traditional therapy. Reporters observed a symptom free exercise duration with both ranolazine groups compared to placebo.

The ERICA (Efficiency of Ranolazine In Chronic Angina trial) was a randomised parallel 3 group, double blind, placebo-controlled study, similar to the CARISA study, with slight changes in the inclusion criteria. In this study, average numbers of attacks of angina were observed, in patients, on antianginal therapy and ranolazine. A decreased frequency of anginal attacks (about 2.8) in the ranolazine group was reported compared to placebo. A fair symptomatic improvement in the ranolazine group was observed, irrespective of the gender, age and co-administration of other drugs. The reported adverse events were also less in the ranolazine group, compared to placebo.

Small sample sizes and short period of follow up are the limitations of these studies. Exercise duration and time duration in inducing angina with treadmill were only studied, whereas important clinical end points such as death and myocardial infarction were not studied.

However, the MERLIN-TIMI 36 trial (Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST elevation acute coronary syndromes) is being conducted with more than 6000 participants with acute coronary syndromes. It is a multicentral, placebo-controlled, double blind study, expected to complete the recruitment of subjects by the end of 2006.

Advantages and disadvantages

A minimal report on hemodynamic impairments is an advantage of ranolazine compared to traditional drugs. A promising increase in exercise capacity, decrease in frequency of anginal attacks and action on basic pathology of angina could be other advantages of this drug.

Though torsades de pointes was not reported in the above trials, QT, prolongation may be a limitation of ranolazine. Hence, it should be indicated only when the patient becomes non-responsive to conventional therapy. The drug has to be administered with other antianginal drugs. It should be administered with caution when P-gp substrates and CYP3A4 inhibitors are used. A close monitoring is needed in patients with hepatic and renal impairment, advanced age, pregnancy and those younger than 18 years.

Future trends

Inhibition of late I\textsubscript{K} channels and other channels may be beneficial in treating heart failure, acute and chronic myocardial infarction, certain genetic disorders related to ion channels, arrhythmias, diastolic dysfunction and intermittent claudication.

Conclusion

Ranolazine is an efficient drug to combat chronic angina when used in standard dose range and with the necessary precautions. The clinical significance of QT, prolongation, seen with ranolazine, and its potential in causing ventricular arrhythmias were not assessed adequately. Current studies with short follow-ups may not reveal the real probability of sudden cardiac death and torsades de pointes in patients taking ranolazine. The scope for future research appears promising when new possible indications are considered in several cardiovascular disorders. However, complete scientific data is required on the adverse reactions and safety profile as well as its new proposed indications in large populations.

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References


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