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Drug Report

Ranolazine: A novel therapeutic option in chronic stable angina

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Chronic stable angina (CSA) represents the largest cardiovascular disorder in the United States and is the initial clinical presentation of ischemic heart disease in 50% of patients.[1] CSA is the result of the progression of coronary atherosclerosis and becomes symptomatic once the luminal diameter of the vessel is occluded by >50%. Current medical therapy is targeted at reducing the frequency of anginal symptoms and improving exercise tolerance by increasing myocardial oxygen supply via arteriole dilation (i.e., dihydropyridine calcium channel blockers, nitrate therapy) and/or reducing myocardial oxygen demand by reducing heart rate and contractility (i.e., non-dihydropyridine calcium channel antagonists and β-adrenergic antagonists).[2] Combinations of these agents can induce profound reductions in blood pressure that limit the aggressive dosing needed in some CSA patients.[1]

In many patients receiving treatment with currently available antianginal drugs angina persists, illustrating the need for a drug with an anti-ischemic mechanism complementary and therefore potentially additive to those of the existing agents with out having the ill effects of reduction in blood pressure and heart rate as a limiting factor.[3]

Ranolazine is a drug that reduces angina symptoms, with a mechanism of action different from that of currently available pharmacological therapies. Ranolazine is approved by FDA for the treatment of patients with chronic angina who have not achieved an adequate response with other antianginal drugs.[4]

Chemistry

Ranolazine ([(+)*N*- (2,6-dimethylphenyl)-4(2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazine acetamide dihydrochloride]) is an active piperazine derivative.[5]

Pharmacokinetics

The immediate release ranolazine (not in current use) had an average terminal elimination half life ranging from 1.4 to 1.9 hours with a dosing of 240 to 400 mg three times per day.[6] Sustained release ranolazine has a prolonged absorption phase with maximal plasma concentration (C_{max}) typically seen 4 to 6 hours after administration. The average terminal elimination half life is ≈7 hours after multiple dosing to steady state and the peak trough difference is 1.6 fold with dosing of 500 to 1000mg twice daily.[7,8] Steady state is generally achieved within 3 days of twice daily dosing. Ranolazine plasma concentrations that are therapeutically effective for chronic angina is in the range of 2 to 6 μmol/L.[3,9]

Absorption of ranolazine is not affected by food. Oral bioavailability is in the range of 30-50%. Plasma protein binding (mainly to α1-acid glycoprotein) is >65%. The cytochromeP450 (CYP) 3A4- mediated pathway accounts for the majority of ranolazine biotransformation.[7,8] Clearance of ranolazine is reduced by renal insufficiency and moderate hepatic impairment.[7,10]

Mechanism of action and pharmacodynamics

The exact mechanism of action of ranolazine is unknown. Ranolazine was shown to have partial fatty acid oxidase inhibitor activity in preclinical investigations [11,12] and this was thought to be the mechanism behind its therapeutic efficacy. But this effect occurs at concentrations far above those achieved in recent clinical trials demonstrating therapeutic benefit. [4] Hence this is probably not the primary mechanism for clinical efficacy. Recent evidence supports an alternative mechanism that ranolazine exerts its action by improving dysfunctional sodium channels. It inhibits pathological increase in late Na+ current induced during myocardial ischemia. Calcium overload in the ischemic myocytes is reduced by Na+/Ca2+ coupling, thereby improving related diastolic function (i.e., more normal diastolic relaxation and decreased wall tension). Improved diastolic function decreases oxygen demand and increases coronary blood supply.[4,9,13]

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Ranolazine exhibits negligible affinity for alpha 1, beta 1, beta 2 adrenoreceptors, weak beta 1 and beta 2 antagonistic activity and a weak calcium channel antagonist activity.[14,15] Thus its mechanism of action as an antianginal drug is different from the currently available drug classes that affect heart rate, inotropic state, hemodynamic state or increase coronary blood flow. Further, at the dosage used in clinical trials, ranolazine does not have a clinically significant effect on resting or exercise heart rate or blood pressure.

Adverse drug reaction

Adverse drug reactions were limited among those patients who received ranolazine to headache (5.5%), dizziness (6.2%), constipation (4.5%), nausea (4.4%) being the most common.[16] Ranolazine has been associated with prolonging the QTc interval in a dose-related manner. Modest QT prolongation (mean 4 to 6 milliseconds), along with the associated risk of torsades de pointes, has been reported following use of ranolazine.[3,16]

Syncope (0.7%) and asthenia (0.5%) are occasional reactions that could occur with ranolazine. At higher plasma concentration (e.g. >8000ng/ml), ranolazine may cause nausea, vomiting, dizziness, vertigo, abnormal vision, confusion, postural hypotension and syncope.[3,16]

Ranolazine does not cause deleterious changes in laboratory parameters. Small mean increase in creatinine has been observed with no decline in glomerular filtration.[16] Further, a small mean decrease in haematocrit (1%) has been noted without evidence of red blood cell destruction or gastrointestinal blood loss. Mild transient eosinophilia has also been observed in a small number of patients.

Contraindications for the use of the drug includes concurrent use of potent and moderately potent CYP3A inhibitors which may increase ranolazine levels as well as use of QT prolonging drugs and hepatic impairment (Child-Pugh Classes A, B or C). The use of the drug is contraindicated in those patients with pre-existing QT prolongation, including congenital long QT syndrome and uncorrected hypokalemia. Further, precautions for the use of the drug include patients with severe renal impairment; increase blood pressure and those with known history of ventricular tachycardia. [16]

Ranolazine belongs to USFDA pregnancy category C. Due to lack of human safety information, ranolazine should be used during pregnancy only if the potential benefit to the mother overweighs the potential risk to the foetus. [16]

Use and approved indications

Ranolazine is approved by FDA for the treatment of chronic angina pectoris. It should be used in addition to amlodipine, beta-blockers or nitrates (rather than in place of these agents) at an initial dose of 500 mg orally twice daily; increased to the maximum recommended dose of 1000 mg orally twice daily as needed based on clinical symptoms. Due to its ability to prolong QT interval, ranolazine should be reserved for patients who have not achieved an adequate response with other antianginal therapies.[3] When combined with standard antianginal therapy, ranolazine demonstrated benefits with minimal effects on blood pressure and heart rate, thus alleviating the concerns for its use in combination with other antianginal medications. Ranolazine may thus be well suited for patients with lower blood pressure or heart rate, in whom the institution or upward titration of antianginal drugs with important hemodynamic effects may not be tolerated.[3]

Clinical Trials

The major completed trials which evaluated the efficacy and safety of controlled release ranolazine in the management of chronic angina includes The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) [9], Combination Assessment of Ranolazine in Stable Angina (CARISA) [3] and Efficacy of Ranolazine In Chronic Angina (ERICA) [17] trials. MARISA and CARISA trials enrolled patients with chronic effort angina for at least 3 months who had reproducible treadmill-induced exercise-induced angina and ST-segment depression at low exercise workloads at baseline. Primary efficacy endpoints included symptom limited exercise duration at trough plasma concentrations approximately 12 hours after dosing.

MARISA was a 4-week, double blind, 4-group, cross over, placebo controlled (n=191) study that tested a 3-fold dose range (500, 1000 or 1500 mg) of ranolazine. Significant increase in exercise duration at trough compared with placebo in a dose-dependent fashion was observed with all 3 doses. Ranolazine had negligible effects on heart rate and blood pressure. One year survival rate combining data from the MARISA trial and its open-label follow-on study was 96.3 ± 1.7%.

CARISA was a 12-week, phase 3 double blind, placebo-controlled clinical trial enrolling 823 patients with refractory angina who were receiving standard therapy with atenolol, diltiazem, or amlodipine who

were randomized to placebo, ranolazine at 750 mg or 1000 mg twice daily. After 12 weeks, patients receiving ranolazine arms had a 26% increase in total exercise time and a decrease in the number of anginal episodes per week. The time to onset of 1 mm of ST-segment depression during exercise testing did not change. These improvements did not depend on changes in blood pressure, heart rate, or background antianginal therapy and persisted throughout 12 weeks of therapy. Survival of 750 patients taking ranolazine during the CARISA trial or its associated long- term open-label study was 98.4% in the first year and 95.9% in the second year.

ERICA trial had average number of angina attacks per week as the primary efficacy variable. During the 6-week treatment phase, the mean number of angina episodes per week decreased to 3.2 in the placebo group and 2.8 in the ranolazine group. Mean nitroglycerin use per week decreased to 2.6 in the placebo group and 2.0 in the ranolazine group without a significant change in heart rate or blood pressure.

Ranolazine is currently being tested in a large >6000 patients multinational acute coronary syndrome trial; the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome (MERLIN TIMI 36) [18] study to determine its impact on death and ischemic events. The study is expected to complete enrolment in 2006 and make a suitable contribution to the knowledge on the expanded potentials of ranolazine.

Comparing the effects of ranolazine with atenolol, Rousseau et al [6] investigated whether ranolazine therapy (400mg of immediate-release ranolazine 3 times daily) improves exercise-induced angina pectoris and myocardial ischemia compared with placebo or with standard doses of atenolol (100 mg/day of atenolol) each administered for 1 week in patients who had chronic angina and evaluated the effects on haemodynamics at rest and during exercise in 158 patients. Ranolazine therapy prolonged exercise duration and decreased exercise-induced ischemia and angina with quantitative effects equal to or greater than those with atenolol. Unlike atenolol, the anti-ischemic and antianginal effects of ranolazine occurred without decreases in blood pressure, heart rate, or rate—pressure product.

Conclusion

Ranolazine affords additional anti anginal and anti-ischemic efficacy in patients with severe chronic angina who remain symptomatic while taking standard doses of atenolol, amlodipine, or diltiazem, with minimal hemodynamic effects. It is of significant use in patients who cannot tolerate the initiation or upward titration of currently available antianginal drugs because of their depressive effects on blood pressure and heart rate.

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