Vascular Health and Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Extended-release ranolazine: critical evaluation of its use in stable angina

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
24 August 2011
Number of times this article has been viewed

Adriano AM Truffa
L Kristin Newby
Chiara Melloni

Duke Clinical Research Institute and Department of Medicine, Duke University Medical Center, Durham, NC, USA

Abstract: Coronary heart disease is the major cause of morbidity and mortality throughout the world, and is responsible for approximately one of every six deaths in the US. Angina pectoris is a clinical syndrome characterized by discomfort, typically in the chest, neck, chin, or left arm, induced by physical exertion, emotional stress, or cold, and relieved by rest or nitroglycerin. The main goals of treatment of stable angina pectoris are to improve quality of life by reducing the severity and/or frequency of symptoms, to increase functional capacity, and to improve prognosis. Ranolazine is a recently developed antianginal with unique methods of action. In this paper, we review the pharmacology of ranolazine, clinical trials supporting its approval for clinical use, and studies of its quality of life benefits. We conclude that ranolazine has been shown to be a reasonable and safe option for patients who have refractory ischemic symptoms despite the use of standard medications (for example, nitrates, beta-adrenergic receptor antagonists, and calcium channel antagonists) for treatment of anginal symptoms, and also provides a modestly improved quality of life.

Keywords: ranolazine, coronary heart disease, angina, treatment

Introduction

Coronary heart disease is the major cause of morbidity and mortality throughout the world.[1] About 16.3 million people in the US have coronary heart disease and an estimated 8.9 million people have chronic stable angina.[2,3] Coronary heart disease is responsible for approximately one of every six deaths in the US,[3] and based on data from 2007, the estimated direct and indirect cost of coronary heart disease in the US annually exceeds $177.5 billion.[3,4]

Angina pectoris is a clinical syndrome characterized by discomfort, typically in the chest, neck, chin, or left arm, induced by physical exertion, emotional stress, or cold, and is relieved by rest or nitroglycerin.[2] It is present symptomatically in only 18% of coronary artery disease.[3] Chronic stable angina is usually caused by partial but flow-limiting obstruction of at least one of the major coronary arteries or its branches by atheromatous plaque, resulting in myocardial ischemia as a result of a mismatch between myocardial oxygen demand and supply.[5]

The general management of chronic stable angina is directed at medical therapy to reduce coronary heart disease progression, as well as therapies and lifestyle modification to control or eliminate coronary heart disease risk factors (smoking, high blood pressure, diabetes mellitus, hyperlipidemia, physical inactivity, weight management, and influenza vaccination).[2,6]

Correspondence: Chiara Melloni
2400 Pratt St, Durham,
NC, USA 27705
Tel +1 919 668 8646
Fax +1 919 668 7057
Email mello004@mc.duke.edu

The treatment of chronic stable angina aims to increase myocardial oxygen supply by vasodilation (eg, nitrates, calcium channel blockers), to reduce coronary artery obstruction (eg, percutaneous coronary intervention or coronary artery bypass grafting), and to decrease myocardial oxygen demand (eg, beta-adrenergic receptor blockers, calcium channel blockers).[7–9] The goals of such treatment are to improve quality of life by reducing the severity and/or frequency of symptoms, to increase functional capacity, and to improve the prognosis of the patient, by preventing myocardial infarction and death.

Medical management, aimed at preventing future clinical events, is pivotal in all patients with coronary artery disease and includes antiplatelet agents (aspirin and clopidogrel), beta-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors and/or renin-angiotensin-aldosterone system blockers, nitrates, calcium channel antagonists, and lipid-lowering agents.[6,10] In addition, specific treatment may be needed to control angina symptoms. Antianginal drug treatment should be tailored to the needs of each patient and should be monitored individually. Short-acting nitrate therapy should be prescribed for all patients for immediate relief of acute symptoms as tolerated. Although different drugs have been shown to have additive antianginal effects in clinical trials, this may not necessarily be so in an individual patient.

Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) is also an option for the relief of angina when medical therapy fails,[11] but as demonstrated in the COURAGE trial, when used on the background of optimal medical therapy, does not reduce death or myocardial infarction compared with optimal medical therapy alone.[6,10,12] Still, despite management with existing medical and revascularization options, millions of patients experience acute and chronic anginal symptoms. It is known, for example, that more than 25% of patients after revascularization, even if on optimal medical therapy, can develop a new ischemic symptom in five years.[7,13] This observation underpins the ongoing need to develop new antianginal drugs. Most recently, ranolazine has been developed as one such option.

Ranolazine

Pharmacology and antianginal effects

Ranolazine is a novel antianginal agent, with a different mechanism of action from the common agents, that reduces ischemia in patients with chronic angina.[14,15] Although it has weak alpha-adrenergic and beta-adrenergic antagonist properties, under normal physiological conditions, these properties are dominated by its effects on the autonomic nervous system.[16–18] Therefore, it is not classified as a beta-adrenergic receptor blocker, calcium channel antagonist, or a vasodilator.[19] Ranolazine preferentially blocks the cardiac late sodium current at concentrations that do not inhibit the peak transient current.[20] This novel mechanism of action is postulated to reduce angina symptoms by avoiding ischemia-induced sodium and overload in cardiac myocytes during ischemia.[7,15,21] Ranolazine is also believed to inhibit partially fatty acid oxidation,[22] resulting in a shift in substrate metabolism towards glucose during ischemia that may also contribute to reduction in angina symptoms.

Regardless of the postulated mechanism, based on its ability to improve exercise performance, increase the time until angina recurs, and reduce angina frequency (alone and on top of other standard antianginal agents),[9,19,22] ranolazine was approved by the US Food and Drug Administration in 2006[23] for use in patients with chronic stable angina. Importantly, in the trials that led to its approval, ranolazine did not appear to affect heart rate or blood pressure, and was generally well tolerated. The primary safety concern was prolongation of the rate-corrected QT interval (QTc) with ranolazine treatment, without clinical cases of torsades de pointes. This safety signal was later addressed in the MERLIN-TIMI (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes) 36 trial discussed later.[8]

Metabolism

Several routes for elimination of ranolazine have been identified. It is metabolized both in the liver through the cytochrome P450 3A enzyme pathway and in the intestine,[21,24,25] and more than 70% of the drug is excreted as metabolites in the urine.[21] Clearance of ranolazine is reduced by renal insufficiency and moderate hepatic impairment; therefore, careful dose adjustment is required in patients with mild to moderate renal insufficiency or hepatic impairment. Ranolazine is contraindicated in patients with severe renal insufficiency or moderate to severe hepatic impairment.[15,26]

Many drugs are also known to interact with its metabolism and affect its clearance, increasing ranolazine plasma concentrations, including ketoconazole, diltiazem, and verapamil. Concomitant use of ranolazine can increase the plasma concentration of simvastatin and digoxin.[15,21]

Randomized clinical trials

In the last decade, several randomized clinical trials have been conducted in patients with chronic stable angina

investigating the efficacy of ranolazine to improve angina relief and exercise performance and duration. MARISA (Monotherapy Assessment of Ranolazine In Stable Angina), a double blind, placebo-controlled study, investigated the effect of three different doses of ranolazine (500, 1000 or 1500 mg, each administered twice daily) on total exercise duration in 191 patients with angina-limited exercise. All doses of ranolazine were well tolerated and effective in reducing angina frequency and increasing exercise duration (by 94, 103 and 116 seconds, $P < 0.005$ compared with placebo) when used as monotherapy.[19]

The ERICA (Antianginal Efficacy of Ranolazine When Added to Treatment With Amlodipine) trial addressed whether ranolazine decreased the symptoms of angina in stable coronary patients who had persistent symptoms even with the use of maximum recommended doses of amlodipine. The population in this study consisted of 565 stable patients with known coronary disease taking maximal amlodipine doses and having three or more anginal attacks per week. Patients were randomized to ranolazine 1000 mg versus placebo twice daily for six weeks. The results showed that ranolazine in combination with amlodipine reduced the frequency of angina compared with amlodipine alone (mean anginal attacks per week 2.88 versus 3.31, $P = 0.028$; average weekly nitroglycerin consumption 2.03 versus 2.68, $P = 0.014$).[9]

CARISA (Combination Assessment of Ranolazine In Stable Angina), a randomized three-group parallel, double-blind placebo-controlled study, had the primary aim of comparing the effects of ranolazine 750 mg or 1000 mg versus placebo on treadmill exercise duration in 823 patients with persistent symptoms of chronic angina despite use of maximum doses of atenolol, amlodipine, or diltiazem. This trial demonstrated the ability of ranolazine to improve exercise capacity (exercise duration increased by 115.6 seconds from baseline in both ranolazine groups versus 91.7 seconds in the placebo group, $P = 0.01$) and increase time to the onset of angina on the back drop of these standard antianginal medications.[22]

The most recent investigation, the MERLIN-TIMI 36 trial, evaluated the efficacy and safety of ranolazine in 6560 patients with non-ST segment elevation acute coronary syndromes. Although the primary endpoint of the study was not met (reduction of a composite of cardiovascular death, myocardial infarction, and recurrent ischemia in the ranolazine arm compared with standard treatment) the incidence of recurrent ischemia was significantly lower in the ranolazine group compared with standard treatment (13.9% versus 16.1%; hazards ratio 0.8, 95% confidence interval 0.76–0.99).[7]

Overall, ranolazine has been well tolerated in the studies of patients with chronic stable angina and acute coronary syndromes. The most common side effects of ranolazine consistently observed across these trials, in particular with higher doses, were constipation, dizziness, nausea, headache, asthenia, and peripheral edema.[9,19,22]

However, in the MARISA and CARISA trials, ranolazine was shown to increase the QTc, but without evidence of effect on QT dispersion or torsades de pointes.[19,22] The larger MERLIN trial in patients with acute coronary syndrome confirmed the safety of ranolazine in a higher-risk ischemic population, showing no increase in torsades de pointes or other life-threatening arrhythmias.[8] Syncope and postural hypotension have occurred in patients taking high doses (up to 2000 mg) of ranolazine.[19,22] However, Holter monitoring during the first seven days of treatment in the MERLIN trial showed no evidence of arrhythmias associated with these side effects, and in fact revealed a reduction in both tachyarrhythmias and bradyarrhythmias in the ranolazine treatment arm.[8] In general, most side effects from ranolazine treatment can be avoided by starting ranolazine with the lowest available dose and titrating the dose upward based on efficacy and tolerability.

Although the MERLIN-TIMI 36 trial does not support the use of ranolazine in patients with acute coronary syndrome to reduce subsequent death or myocardial infarction during follow-up, data from the trial confirmed the safety profile and tolerability of ranolazine and provided additional support for ranolazine as an antianginal drug in chronic angina. Ranolazine offers a second option for intensification of antianginal therapy in case first-line agents fail.[7,13]

Quality of life and economic impact

Despite advances in medical and interventional technologies, millions of people continue to experience angina symptoms. This not only translates into a dramatic worsening in their quality of life, but also represents a major public health problem.[27,28] Thus, patient-centered health status assessment that measures patient symptoms and function, as well as quality of life, is becoming an increasingly common outcome measure.[27,28]

Different health status/quality of life indicators have been used in recent studies of ranolazine,[7,9] among them, the Seattle Angina Questionnaire, the Rose dyspnea scale, the Medical Outcomes Study 12-item Short Form (SF)-12, and the EuroQol-5D questionnaire.[28] The Seattle Angina Questionnaire surveys patients on 19 items that measure five clinically important dimensions about health in patients with coronary artery disease, ie, angina frequency, angina stability,

physical limitations, treatment satisfaction, and disease perception/quality of life. The Rose dyspnea scale has four items to assess the level of a patient's dyspnea with common activities. The SF-12 is used to assess general health status using the physical and mental components of a larger scale called the SF-36. Finally, the EuroQol-5D is a questionnaire with five items assessing mobility, self-care, usual activities, pain and discomfort, and anxiety/depression.[28]

Using data from the MERLIN trial, Arnold et al demonstrated that compared with patients without angina, patients with daily angina had at least a two-fold increase in resource utilization, with an incremental cost of $4000 after eight months of follow-up.[27]

Secondary analyses from the same trial showed that overall there was only a small difference in quality of life between patients treated and not treated with ranolazine, and the greatest benefits of this medication were observed for angina frequency, overall quality of life, and treatment satisfaction on the Seattle Angina Questionnaire among those who had angina prior to the acute coronary syndrome event. Smaller benefits were observed in the SF-12 physical and mental component scores, Rose dyspnea score, and EuroQol-5D measures.[28]

In another study, a graded relationship was observed between higher angina frequency and health care costs, with costs more than twice as high among patients with daily angina compared with those without angina. No differences in overall medication costs were observed between the angina frequency groups, perhaps because patients with higher angina frequency used more antianginal medications than statins and clopidogrel.[27]

Conclusion

The main goals of treatment of stable angina pectoris are to improve quality of life by reducing the severity and/or frequency of symptoms, to increase functional capacity, and to improve prognosis. Ranolazine has been shown to be a reasonable and safe option for patients who have refractory ischemic symptoms despite the use of usual medications for treatment of angina symptoms, and also provides slightly improved quality of life.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Aslam S, Gray D. Ranolazine (Ranexa) in the treatment of chronic stable angina. *Adv Ther*. 2010;27(4):193–201.
2. Trujillo TC, Dobesh PP. Traditional management of chronic stable angina. *Pharmacotherapy*. 2007;27(12):1677–1692.
3. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics – 2011 update: A report from the American Heart Association. *Circulation*. 2011;123(4):e18–e209.
4. Vadnais DS, Wenger NK. Emerging clinical role of ranolazine in the management of angina. *Ther Clin Risk Manag*. 2010;6:517–530.
5. Norton C, Georgiopoulou V, Kalogeropoulos A, Butler J. Chronic stable angina: Pathophysiology and innovations in treatment. *J Cardiovasc Med (Hagerstown)*. 2011;12(3):218–219.
6. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113(19):2363–2372.
7. Melloni C, Newby LK. Metabolic efficiency with ranolazine for less ischemia in non-ST elevation acute coronary syndromes (MERLIN TIMI-36) study. *Expert Rev Cardiovasc Ther*. 2008;6(1):9–16.
8. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Skene A, McCabe CH, Braunwald E. Evaluation of a novel anti-ischemic agent in acute coronary syndromes: Design and rationale for the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes (MERLIN)-TIMI 36 trial. *Am Heart J*. 2006;151(6):e1181–e1189.
9. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L. Antianginal efficacy of ranolazine when added to treatment with amlodipine: The ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol*. 2006;48(3):566–575.
10. Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol*. 2007;50(23):2264–2274.
11. Coronary angioplasty versus medical therapy for angina: The second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet*. 1997;350(9076):461–468.
12. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356(15):1503–1516.
13. Newby LK, Peterson ED. Does ranolazine have a place in the treatment of acute coronary syndromes? *JAMA*. 2007;297(16):1823–1825.
14. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: The MERLIN-TIMI 36 randomized trial. *JAMA*. 2007;297(16):1775–1783.
15. Dobesh PP, Trujillo TC. Ranolazine: A new option in the management of chronic stable angina. *Pharmacotherapy*. 2007;27(12):1659–1676.
16. Letienne R, Vie B, Puech A, Vieu S, Le Grand B, John GW. Evidence that ranolazine behaves as a weak beta1- and beta2-adrenoceptor antagonist in the cat cardiovascular system. *Naunyn Schmiedebergs Arch Pharmacol*. 2001;363(4):464–471.
17. Allely MC, Brown CM, Kenny BA, Kilpatrick AT, Martin A, Spedding M. Modulation of alpha 1-adrenoceptors in rat left ventricle by ischaemia and acyl carnitines: Protection by ranolazine. *J Cardiovasc Pharmacol*. 1993;21(6):869–873.
18. Zhao G, Walsh E, Shryock JC, et al. Antiadrenergic and hemodynamic effects of ranolazine in conscious dogs. *J Cardiovasc Pharmacol*. 2011;57(6):639–647.
19. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004;43(8):1375–1382.
20. Estacion M, Waxman SG, Dib-Hajj SD. Effects of ranolazine on wild-type and mutant hNav1.7 channels and on DRG neuron excitability. *Mol Pain*. 2010;6:35.
21. Siddiqui MA, Keam SJ. Ranolazine: A review of its use in chronic stable angina pectoris. *Drugs*. 2006;66(5):693–710.

22. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: A randomized controlled trial. *JAMA*. 2004;291(3):309–316.
23. US Food and Drug Administration. Available from: http://www.fda.gov/ohrms/dockets/ac/03/briefing/4012B2_01_Action%20Letter.pdf. Accessed April 4, 2007.
24. Penman AD, Eadie J, Herron WJ, Reilly MA, Rush WR, Liu Y. The characterization of the metabolites of ranolazine in man by liquid chromatography mass spectrometry. *Rapid Commun Mass Spectrom*. 1995;9(14):1418–1430.
25. Herron WJ, Eadie J, Penman AD. Estimation of ranolazine and eleven phase I metabolites in human plasma by liquid chromatography-atmospheric pressure chemical ionisation mass spectrometry with selected-ion monitoring. *J Chromatogr A*. 1995;712(1):55–60.
26. Jerling M, Abdallah H. Effect of renal impairment on multiple-dose pharmacokinetics of extended-release ranolazine. *Clin Pharmacol Ther*. 2005;78(3):288–297.
27. Arnold SV, Morrow DA, Lei Y, et al. Economic impact of angina after an acute coronary syndrome: Insights from the MERLIN-TIMI 36 trial. *Circ Cardiovasc Qual Outcomes*. 2009;2(4):344–353.
28. Arnold SV, Morrow DA, Wang K, et al. Effects of ranolazine on disease-specific health status and quality of life among patients with acute coronary syndromes: Results from the MERLIN-TIMI 36 randomized trial. *Circ Cardiovasc Qual Outcomes*. 2008;1(2):107–115.