Published in final edited form as:

Cardiovasc Revasc Med. 2012 ; 13(2): 141.e1–141.e5. doi:10.1016/j.carrev.2011.06.001.

Ranolazine for the treatment of refractory angina in a veterans population[☆]

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Abstract

Background—Pivotal ranolazine trials did not require optimization of conventional medical therapy including coronary revascularization and antianginal drug therapy prior to ranolazine use. This case series describes the use of ranolazine for the treatment of chronic stable angina refractory to maximal medical treatment in a veterans population.

Results—A total of 18 patients with a median age of 66 years were identified. All patients had prior percutaneous coronary intervention and/or coronary artery bypass graft surgery; 83% had three-vessel coronary artery disease, with left main disease present in 39% of patients. Prior to initiating ranolazine, antianginal use consisted of beta blockers (94%), long-acting nitrates (83%) and calcium channel blockers (61%). Median blood pressure (116.2/61.8 mmHg) and pulse (65 beats per min) were controlled. Median preranolazine angina episodes and sublingual nitroglycerin (SLNTG) doses per week were 14 and 10, respectively, with a Canadian Cardiovascular Society (CCS) angina grade of III–IV in 67% of patients. After initiation of ranolazine, median angina episodes per week and SLNTG doses used per week decreased to 0.7 and 0, respectively, with CCS grade of III–IV declining to 17%. Of the 18 subjects enrolled, 44% had complete resolution of angina episodes.

Conclusion—The addition of ranolazine to maximally tolerated conventional antianginal drug therapy post coronary revascularization was associated with decreases in angina episodes and SLNTG utilization and improvement in CCS angina grades. Ranolazine may provide an effective treatment option for revascularized patients with refractory angina.

Keywords

Ranolazine; Refractory angina; Drug therapy; Veterans Affairs

[☆]Author financial support (other than institution salary): Dr. Alvarez: Grant number: 5 KL2 RR024983-04; Principal Investigator: Packer, Milton; Project Title: North and Central Texas Clinical and Translational Science Initiative (KL2); Award Dates: 09/17/07-5/31/12.

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1. Background

Chronic angina affects approximately 10.2 million Americans and has detrimental effects on the quality of life of those it afflicts [1]. Current conventional medical therapy recommendations utilize coronary revascularization and antianginal drug therapy including beta blockers, long-acting nitrates and calcium channel blockers (CCB) [2]. Despite these therapeutic modalities, patients often continue to experience chronic refractory angina.

In 2006, ranolazine was approved for the adjunct treatment of chronic angina and subsequently approved as monotherapy in 2008 [3]. Ranolazine is a novel antianginal medication whose mechanism of action has not been fully elucidated [3]. However, ranolazine does exhibit its antianginal effect without significant changes in hemodynamics [3]. This unique feature is due to blockage of late sodium current. In ischemic myocytes, these channels increase intracellular sodium resulting in intracellular calcium overload. Intracellular calcium overload during diastole is believed to directly increase diastolic wall tension and perpetuate myocardial ischemia [3–5]. Thus, by blocking the late sodium current, ranolazine decreases angina through a different mechanism than conventional antianginal drug therapy.

Within our institution, prior to initiation of ranolazine therapy, patients must have ≥ 3 angina episodes per week and are prescribed maximally tolerated conventional antianginal drug therapy including beta blockers and CCB. Antianginal drug therapy is considered to be maximized if the blood pressure is <130/80 mmHg and the heart rate is <70 beats per min (bpm), unless limited by intolerable side effects. Additionally, patients must receive long-acting nitrate therapy unless not tolerated. These criteria innately select a refractory angina population that may benefit from the addition of this novel agent. We describe the use of ranolazine in patients identified at our institution meeting the above criteria and who had pre- and postranolazine angina symptoms documented.

2. Results

2.1. Population

A total of 18 patients were identified and are described in this case series. Preranolazine characteristics of those patients are listed in Table 1. All patients were white males with a median age of 66 years [interquartile range (IQR) 61–78]. Fifteen (83%) patients had a preexisting hypertension diagnosis. Prior to ranolazine, the median systolic blood pressure was 116.2mmHg (IQR 105.3–124.9), diastolic blood pressure was 61.8 mmHg (IQR 57.5–69.1) and heart rate was 65 bpm (IQR 61.5–68.9). Optimal hemodynamic control was maintained after ranolazine initiation, with resulting median systolic blood pressure of 115mmHg (IQR 105–123), diastolic blood pressure of 61 mmHg (IQR 56–68) and heart rate of 66 bpm (IQR 60–69). The rate–pressure product for each patient is reported in Table 2. The percentage of conventional antianginal drug therapy used was as follows: beta blockers 94% ($n=17$), CCB 61% ($n=11$) and long-acting nitrates 83% ($n=15$) (Table 1). Two or more conventional antianginal agents were used in 16 (89%) of the patients. Additionally, 94% of the patients were taking both HMG CoA reductase inhibitor (statin) and antiplatelet therapy,

and 78% were prescribed either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) prior to ranolazine use.

2.2. Cardiovascular history

All patients had a history of coronary revascularization prior to ranolazine therapy. Fifteen (83%) had three-vessel coronary artery disease, with left main disease also present in seven of those patients. Three (17%) patients had a left ventricular ejection fraction <40% (Table 2).

2.3. Effectiveness

Prior to ranolazine initiation, the respective number of median angina episodes per week and sublingual nitroglycerin (SLNTG) doses used per week were 14 (IQR 7–21) and 10 (IQR 0.5–21). Following the initiation of ranolazine, median angina episodes per week and SLNTG doses used per week decreased to 0.7 (IQR 0–12) and 0 (IQR 0–3), respectively. Of the 18 subjects reported, 12 (67%) had a >80% decline in angina frequency, with eight (44%) attaining complete resolution of angina episodes. Of the 14 patients with documented SLNTG use, 10 experienced a reduction in SLNTG use; six of these patients reported no SLNTG use with ranolazine. Fig. 1 and Fig. 2 illustrate the improvement in pre- and postranolazine angina episodes and SLNTG use.

Additionally, prior to ranolazine, 12 (67%) patients had a grade III or IV on the Canadian Cardiovascular Society (CCS) angina grading scale; only three (17%) had a CCS grade III or IV on therapy, two of which were nonresponders. None of the patients had an increase in CCS grade while prescribed ranolazine. Individual patient CCS grades are noted in Table 2.

Three patients had no response to ranolazine therapy (Table 2). Each of these patients were prescribed ranolazine 500 mg twice a day without further dose escalation for the following reasons: moderate cytochrome P450 3A4 drug interaction (case 5), successful repeated coronary revascularization performed (case 14) and patient preference (case 15).

3. Discussion

Ranolazine has been reported to reduce myocardial ischemia, increase exercise tolerance and decrease self-reported angina episodes in several studies [6–8]. Two previous pivotal trials, the Combination Assessment of Ranolazine in Stable Angina (CARISA) and the Efficacy of Ranolazine in Chronic Angina (ERICA), combined ranolazine with conventional antianginal drug therapy, but did not require optimization of conventional therapy prior to initiating ranolazine [7,8]. Thus, it was unclear whether ranolazine would be effective in combination with maximally tolerated conventional medical therapy in refractory angina patients, including those who had previously undergone coronary revascularization.

This case series reports improvements in angina frequency and SLNTG use after the addition of ranolazine to previously revascularized patients refractory to maximally tolerated conventional medical therapy. A key difference of this case series vs. CARISA and ERICA was the requirement that all patients have optimized hemodynamic control as tolerated prior to initiation of ranolazine [7,8]. Optimal hemodynamic control was achieved using at least

two conventional antianginal medications in 16 (89%) patients in this case series. This prescribing pattern of maximizing conventional antianginal drug therapy followed by ranolazine may be a more clinically relevant approach to refractory angina management.

Additionally, 67% of patients experienced a baseline frequency of angina episodes per week that was greater than that reported by either the CARISA [750-mg dose: 4.3 ± 5.3 (mean $\pm$ S.D.); 1000-mg dose: 4.5 ± 5.4] or ERICA (5.6 ± 0.2 ; trimmed mean $\pm$ standard error) trial [7,8]. This lends support to the effectiveness of ranolazine in a more severely symptomatic patient. These findings are consistent with a trend found in the ERICA trial that revealed that ranolazine may be more effective in patients with higher baseline angina frequency [8].

3.1. Limitations

There are several limitations to this case series. All patients were white males, limiting the ability to generalize these data to other population groups. Additionally, the number of patients reported in this case series was small. Also, patients with clinically significant hepatic impairment and those receiving strong cytochrome P450 3A4 inhibitors or inducers were excluded from using ranolazine per institutional criteria due to limited safety data in these populations. Therefore, extrapolation of these data to patients within these groups should be done so with caution. Finally, the determination of efficacy was reliant on patients' subjective recall of their angina symptoms and SLNTG use, which leaves the case series vulnerable to recall bias.

4. Conclusion

This report demonstrates that the addition of ranolazine to maximally tolerated conventional medical therapy in refractory angina patients, post coronary revascularization, was associated with decreases in both angina frequency and SLNTG utilization as well as improvements in CCS angina grades. Ranolazine may add another effective option in the management of patients with severely symptomatic refractory angina. Larger, prospective studies are necessary to further validate these results.

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Figure 1.
Change in angina episodes per week with ranolazine therapy.

Figure 2.
Change in SLNTG doses per week with ranolazine therapy.

Table 1

Preranolazine patient characteristics

Characteristic	<i>n</i> =18
Age, median (IQR), years	66 (61–78)
Male, no. (%)	18 (100)
White, no. (%)	18 (100)
Past medical history, no. (%)	
Hypertension	15 (83)
Diabetes mellitus	10 (55)
PCI or CABG prior to study	18 (100)
Vitals prior to ranolazine therapy, median (IQR)	
Systolic blood pressure, mmHg	116.2 (105.3–124.9)
Diastolic blood pressure, mmHg	61.8 (57.5–69.1)
Heart rate, bpm	65 (61.5–68.9)
Antianginals, no. (%)	
Beta blocker	17 (94)
Metoprolol tartrate (<i>n</i> =10)	
Metoprolol succinate (<i>n</i> =5)	
Carvedilol (<i>n</i> =2)	
Calcium channel blocker	11 (61)
Amlodipine (<i>n</i> =7)	
Felodipine (<i>n</i> =3)	
Diltiazem (<i>n</i> =1)	
Long-acting nitrate	15 (83)
Isosorbide mononitrate (<i>n</i> =10)	
Isosorbide dinitrate (<i>n</i> =3)	
Nitroglycerin patch (<i>n</i> =2)	
Two or more antianginals	16 (89)
Other medications, no. (%)	
Statin	17 (94)
Rosuvastatin (<i>n</i> =7)	
Simvastatin (<i>n</i> =6)	
Pravastatin (<i>n</i> =4)	
Antiplatelet	17 (94)
Aspirin plus clopidogrel (<i>n</i> =13)	
Aspirin (<i>n</i> =3)	
Clopidogrel (<i>n</i> =1)	
ACE inhibitor or ARB	14 (78)
Lisinopril (<i>n</i> =12)	
Enalapril (<i>n</i> =1)	
Valsartan (<i>n</i> =1)	

CABG=coronary artery bypass graft; PCI=percutaneous coronary intervention.

Table 2

Clinical information for 18 patients treated with ranolazine

Case	Age	Ranolazine dose (mg; twice a day)	Time to follow-up evaluation (days)	Left main disease	Number of coronary vessel territories involved	LVEF <40%	Rate–pressure product		CCS angina grade		Angina episodes per week		SLNTG use per week		Corrected QT	
							Pretherapy	Posttherapy	Pretherapy	Posttherapy	Pretherapy	Posttherapy	Pretherapy	Posttherapy	Pretherapy	Posttherapy
1	79	500	20	Yes	3	No	7.1	10.9	III	II	56	5	-	-	445	455
2	65	500	14	No	3	No	8.0	7.7	II	I	21	1	21	3	433	408
3	56	1000	70	No	3	No	6.6	6.2	IV	II	7	0	21	0.3	-	443
4	78	500	49	No	2	Yes	8.3	6.4	II	I	3	0.3	4	0	408	389
5	67	500	35	No	3	No	7.7	8.2	III	III	14	14	14	14	402	444
6	87	1000	49	No	3	No	8.4	7.8	III	I	14	0	14	0	-	412
7	67	1000	106	No	3	No	8.6	8.0	IV	II	7	0	0.5	0	-	415
8	69	1000	63	No	3	Yes	6.0	5.7	IV	III	21	12	63	18	413	421
9	60	500	18	Yes	3	No	6.0	6.5	II	I	14	0	14	0	-	414
10	62	500	45	Yes	3	No	7.5	6.8	II	I	3	0	6	0	414	467
11	74	1000	84	No	3	No	10.2	10.0	III	I	105	0	0	0	-	409
12	62	500	133	Yes	3	Yes	6.7	7.2	III	II	21	4	-	-	444	434
13	85	500	28	Yes	3	No	7.0	8.1	II	II	3	2	-	-	-	450
14	49	500	12	Yes	3	No	6.7	6.4	III	III	14	14	0	0	435	494
15	64	500	42	No	3	No	7.9	7.7	III	II	14	14	0	0	-	419
16	78	500	42	No	2	No	6.7	6.7	II	I	7	0	1	0	436	398
17	80	500	92	No	2	No	7.7	7.3	III	I	14	0	-	-	403	417
18	56	1000	28	Yes	3	No	6.6	7.5	IV	II	56	28	42	21	454	407

LVEF=left ventricular ejection fraction; therapy=ranolazine.