RANOLAZINE, A NEW ADDITION TO ANGINA TREATMENT
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ABSTRACT
Current therapies those alleviate angina frequency and increase the threshold at which demand-induced myocardial ischemic symptoms become evident include drugs (nitrates, β-blockers, calcium antagonists), exercise conditioning, enhanced external counterpulsation, and coronary revascularization. This review will focus on sustained-release ranolazine, a drug that reduces angina symptoms, with a mechanism of action different from that of currently available pharmacological therapies. Conventional oral dosage formulations are not ideally suited to ranolazine because the solubility of ranolazine is relatively high at the low pH that occurs in the stomach. Furthermore ranolazine also has a relatively short plasma half-life. The high acid solubility property of ranolazine results in rapid drug absorption and clearance, large and undesirable fluctuations in plasma concentration of ranolazine and a short duration of action, necessitating frequent oral administration for adequate treatment. Thus making it into an extended release formulation becomes the sole solution. Ranolazine is used in patients with chronic angina who continue to be symptomatic on β-blockers, calcium antagonists, or nitrates. Ranolazine blocks late inward sodium currents in cardiomyocytes. In the ischemic myocardium, late inward sodium currents contribute to an elevation in intracellular sodium, which leads to an increase in intracellular calcium through the sodium–calcium exchanger. Calcium overload in ischemic cells leads to impaired relaxation, which increases ventricular diastolic wall stress and end-diastolic pressure. This causes mechanical compression of the microcirculation within the wall of the ventricle, which impairs coronary blood flow during diastole and therefore worsens ischemia, particularly in the subendocardial regions. By blocking late inward sodium currents, calcium overload and diastolic wall stress are reduced, leading to improved coronary blood flow.

KEYWORDS: Ranolazine, Angina pectoris, Extended Release.

INTRODUCTION
Angina pectoris is chest pain ascribable to ischemia (a lack of blood, thus a lack of oxygen supply and waste removal) of the heart muscle, generally due to obstruction or spasm of the coronary arteries. Coronary artery disease, the principal cause of angina, is due to atherosclerosis of the cardiac arteries. The term descends from the Latin angina (“infection of the throat”), the Greek ankholē (“strangling”), and the Latin pectus (“chest”), and can therefore be translated as “a strangling feeling in the chest”. There is a feeble relationship between severity of pain and degree of oxygen deprivation in the heart muscle. There can be severe pain with little or no risk of a heart attack, and on the other hand heart attack can occur without pain. Worsening (“crescendo”) angina attacks, sudden-onset angina at rest, and angina lasting more than 15 minutes are symptoms of unstable angina (usually grouped with similar conditions as the acute coronary syndrome). As these may herald myocardial infarction (a heart attack), they require urgent medical attention and are generally treated as a presumed heart attack. Figure 1.

Types of angina
Stable angina
Also acknowledged as effort angina, this refers to the more common comprehending of angina related to myocardial ischemia. Typical presentations of stable angina is that of chest discomfort and associated symptoms precipitated by some activity (running, walking, etc.) with minimal or non-existent symptoms at rest. Symptoms typically abate several minutes following cessation of precipitating activities and reoccur when activity resumes.
Unstable angina
Unstable angina (UA) (also "crescendo angina;' this is a form of acute coronary syndrome) is defined as angina pectoris that changes or worsens. It has at least one of these three features:
1. it occurs at rest (or with minimal exertion), usually lasting >10 min;
2. it is severe and of new onset (i.e., within the prior 4–6 weeks); and/or
3. it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than before).

Microvascular angina
Microvascular Angina or Angina Syndrome X is characterized by angina-like chest pain, but has different causes. The cause of microvascular Angina is unknown, but it appears to be the result of poor function in the tiny blood vessels of the heart, arms and legs. Since microvascular angina isn't characterized by arterial blockages, it's arduous to recognize and diagnose, but its prognosis is excellent.

CURRENT TREATMENT
The goals of treatment are to alleviate the frequency of angina, increase longevity, and improve patient’s quality of life. Management of risk factors is an essential component of this therapy. The three classes of drugs commonly used for chronic angina include β adrenergic blocking agents, calcium channel blockers, and short- and long-acting nitrates. Each of these drug classes decreases cardiac workload and may increase coronary blood flow or improve its distribution and thus modify the imbalance between myocardial supply and demand. Although monotherapy is effective in some, the majority of patients require two or more antianginal agents to control their symptoms ¹. The choice of first-line treatment remains controversial because no single class of drug has demonstrated unequivocal superiority. Long-acting nitrates, β-adrenergic blocking agents, and calcium channel blockers, either alone or in combination, have been proven effective in reducing the frequency of angina. Sublingual nitroglycerin relieves episodes of angina and is also effective for short-term prophylaxis ². The effectiveness of oral nitrates or transdermal preparations is limited by the development of tolerance to their hemodynamic, antianginal, and anti-ischemic effects when administered in a dosing strategy designed to provide therapeutic plasma nitrate levels throughout 24 hours each day. In the absence of contraindications, β blockers are recommended as first-line treatment by the American Heart Association/American College of Cardiology guidelines particularly in patients with a previous
myocardial infarction because reduced mortality has been demonstrated in such cases\(^3,4\). Calcium channel blockers may be associated with unwanted side effects in angina patients with heart failure or abnormal left ventricular systolic function. For example, the Multicenter Diltiazem post-infarction trial findings suggest that in patients with left ventricular dysfunction, diltiazem increased the frequency of late-onset heart failure and cardiac events \(^5\). Whereas long-acting preparations have been better tolerated, flushing, headache, constipation, and peripheral edema continue to be problematic. The rate-lowering calcium channel blockers may also cause excessive bradycardia and heart block.

**DRUG PROFILE**
Ranolazine is a racemic mixture, chemically described as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy) propyl]-, (±)-. It has an empirical formula of C\(_{24}\)H\(_{33}\)N\(_3\)O\(_4\), a molecular weight of 427.54 g/mol, and the following structural formula: Figure 2.

![Figure 2](image)

Ranolazine is a white to off-white solid. Ranolazine is soluble in dichloromethane and methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water. (www.rxlist.com)

**PHARMACOLOGY AND MECHANISM OF ACTION**
Ranolazine blocks late inward sodium currents in cardiomyocytes. In the ischemic myocardium, late inward sodium currents contribute to an elevation in intracellular sodium, which leads to an increase in intracellular calcium through the sodium–calcium exchanger. Calcium overload in ischemic cells leads to impaired relaxation, which increases ventricular diastolic wall stress and end-diastolic pressure. This causes mechanical compression of the microcirculation within the wall of the ventricle, which impairs coronary blood flow during diastole and therefore worsens ischemia, particularly in the sub-endocardial regions. By blocking late inward sodium currents, calcium overload and diastolic wall stress are reduced, leading to improved coronary blood flow. Figure 3

Ranolazine 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 \(^6,7,8\). Therefore, it is not classified as a beta-adrenergic receptor blocker, calcium channel antagonist, or a vasodilator. Ranolazine is also believed to inhibit partially fatty acid oxidation resulting in a shift in substrate metabolism towards glucose during ischemia \(^8\). It is possible that other mechanisms may contribute to the antianginal effects of ranolazine. Unlike other antianginal drugs, such as beta-blockers and calcium-channel blockers, ranolazine has no clinically significant effect on heart rate or arterial pressure.
Figure 3: Increase in intracellular sodium concentration ([Na+]) in ischemic cardiac myocytes cause calcium (Ca2+) overload via the Na+-Ca2+ exchanger (NCX) leading to contractile dysfunction and cellular injury. A pathologically enhanced late Na+ current (late INa) contributes to the [Na+]i-dependent Ca2+ overload. Ranolazine, by decreasing the magnitude of the pathologically enhanced late INa, prevents or reduces Ca2+ overload and attenuates the accompanying deleterious consequences.

**OBJECTIVES IN DEVELOPING EXTENDED RELEASE FORMULATION**

Conventional oral dosage formulations are not ideally suited to ranolazine because the solubility of ranolazine is relatively high at the low pH that occurs in the stomach. Furthermore ranolazine also has a relatively short plasma half-life. The high acid solubility property of ranolazine results in rapid drug absorption and clearance, large and undesirable fluctuations in plasma concentration of ranolazine and a short duration of action, thus necessitating frequent oral administration for adequate treatment (www.freepatentsonline.com, www.drugs.com). There is therefore a need for administering ranolazine in an oral dosage form once or twice daily that provides a drug delivery system which control the release profile and inhibit rapid release of the drug from the formulation during its residence in the stomach (where the pH is below about 4.5) and which promotes the release of a therapeutic amount of drug from the dosage form in the lower gastrointestinal tract (where the pH is generally greater than about 4.5).

**PHARMACOKINETICS**

Exposure to ranolazine is not affected by food. Oral bioavailability is in the range of 30% to 55%. Plasma protein binding (mainly to α1-acid glycoprotein) is 65%. The cytochrome P450 (CYP) 3A4–mediated pathway accounts for the majority of ranolazine biotransformation. Additional pathways include metabolism by CYP2D6 (10% to 15%), glucuronidation (<5%), and excretion of unchanged ranolazine by the kidneys (<5%). Three phase I metabolites (CVT-2512, CVT-2514, CVT-2738) and phase II metabolite of ranolazine in plasma occur at concentrations >1% of the parent compound. The 4 most abundant metabolites in plasma have elimination half-life periods of 6 to 22 hours. At least 11 metabolites have been identified with a plasma disposition in humans >1% relative to ranolazine. Ketoconazole, a potent competitive reversal inhibitor of CYP3A isoenzymes, increases...
ranolazine exposure at steady state 2.5 to 4.5 fold on average. The metabolite to ranolazine area under the curve from time 0 to 12 hours (AUC$_{12}$) ratio decreased 5.6-fold, 2.1-fold, and 4.6-fold for CVT-2512, CVT-2514, and CVT 2738, respectively. Adverse events, generally mild to moderate, but occasionally intolerable, such as headache, dizziness, and nausea, are significantly increased with the concomitant administration of ketoconazole 200 mg twice daily to ranolazine 1000 mg twice daily. Average increase in plasma ranolazine concentrations is 1.2-fold at steady state after paroxetine, a potent inhibitor of the CYP2D6 enzyme system. Clearance of ranolazine is reduced by renal insufficiency and moderate hepatic impairment. Ranolazine C$_{\text{max}}$ at steady state is 1.7 to 2 fold greater in patients with moderate to severe renal insufficiency (<30 mL/min), resulting in significant increase in C$_{\text{max}}$ from time 0 to 12 hours (AUC$_{12}$) compared with healthy subjects (>81 mL/min) [10]. A 10 to 15 mm Hg increase in mean diastolic blood pressure was observed in 6 patients with severe renal insufficiency on ranolazine 500 mg twice daily. In 8 subjects with moderate hepatic impairment (Child-Pugh grade B), ranolazine C$_{\text{max}}$, AUC$_{12}$, and C$_{\text{trough}}$ were increased by 51% ($P<0.01$), 76% ($P<0.001$), and 123% ($P<0.001$) compared with healthy subjects [11]. In 8 subjects with mild hepatic impairment (Child-Pugh grade A), ranolazine pharmacokinetics were not significantly altered. There are no apparent gender differences in ranolazine pharmacokinetics, nor are pharmacokinetics significantly altered by diabetes mellitus or heart failure (in the absence of renal insufficiency). Ranolazine clearance decreases modestly with age.

ELECTROPHYSIOLOGICAL PROPERTY OF RANOLAZINE

Ranolazine significantly inhibits the rapidly activating component of the delayed rectifier or I$_{Kr}$ with potency (i.e., IC$_{50}$) of 12 μmol/L. The IC$_{50}$ for ranolazine inhibition of late I$_{Na}$ is ≥6 μmol/L. The parent compound inhibits late I$_{Na}$ and I$_{Kr}$ equipotently at the low end of the therapeutic range but inhibits late I$_{Na}$ more potently at the high end. The net effect is to prolong the action potential duration (APD) of epicardial and endocardial cells, in which late I$_{Na}$ is relatively small, but to abbreviate or produce little change in the APD of the M cells, in which late I$_{Na}$ is more prominent. The most abundant ranolazine metabolite is present at a plasma concentration of 30% to 40% that of the parent compound. Four of the metabolites produce a weak inhibition of I$_{Kr}$ (40% to 50% at a concentration of 50 μmol/L) in canine cardiac myocytes. The IC$_{50}$ values for I$_{Ks}$ inhibition by the 11 metabolites tested were all >50 μmol/L. All 11 metabolites were found to inhibit late I$_{Na}$ by 12% to 57% at a concentration of 10 μmol/L. Because the metabolites inhibit late I$_{Na}$ more potently than I$_{Ks}$, they are likely to produce less of a reduction in the net outward current than the parent compound and are unlikely to contribute to QT interval prolongation.
Ranolazine in Heart failure

In an isolated ventricular myocyte canine heart failure model, the delayed or incomplete inactivation of late I_{Na} of the sodium channel contribution was substantially augmented. Ranolazine inhibits the late I_{Na} current and significantly improves left ventricular performance in experimental models of heart failure. Sabbah et al measured hemodynamics before and 40 minutes after an intravenous dose of 0.5 mg/kg of ranolazine followed by a continuous infusion of 1.0 mg/kg per hour in a canine model of heart failure induced by intracoronary microembolization to produce an average ejection fraction of 27%. Results in 13 experimental dogs were compared with those obtained in 8 normal healthy dogs. Ranolazine significantly decreased left ventricular end-diastolic pressure and increased left ventricular ejection fraction (27% versus 36%; P<0.001), peak LV +dP/dt (1712 versus 1900 mm Hg/s; P=0.001), and stroke volume (20 versus 26 mL) in the absence of any effects on heart rate or blood pressure. In normal dogs, there was no effect on indices of left ventricular function. The study was limited by the absence of blinding and a placebo control. In subsequent experiments from the same laboratory, Chandler et al reproduced these findings and determined that the improvement in left ventricular performance was not associated with an increase in myocardial oxygen consumption (MVO_{2}) compared with an intravenous infusion of dobutamine that improved left ventricular performance to a similar extent but was associated with a significant increase in MVO_{2} requirements. In subsequent studies from the same laboratory in which a chronic canine heart failure model was used, pre/post 3-month comparison of oral ranolazine compared with placebo demonstrated decreased left ventricular end-diastolic pressure, negative LV −dP/dt, and left ventricular circumferential wall stress and increased deceleration time of early mitral inflow velocity. In a study of 15 patients with prior myocardial infarction (average ejection fraction 35%) who received an intravenous ranolazine infusion (200 or 500 μg/kg), regional function was assessed in ischemic, infarcted, and normal left ventricular segments. Global left ventricular function was not changed significantly after ranolazine infusion; left ventricular ejection fraction was 37% after dosing (P=NS). However, ranolazine was associated with a significant increase in peak filling rate and regional wall lengthening during the isovolumic relaxation phase in ischemic left ventricular segments, suggesting evidence of improved regional diastolic function.

DRUG INTERACTION

Ketoconazole, a potent inhibitor of CYP3A4, increases ranolazine exposure at steady state 2.5–4.5-fold on average. This increase in ranolazine plasma concentration typically contributes to an increase in adverse effects such as headache, dizziness, and nausea. Diltiazem, in doses of 240 mg/day or greater, is a more moderate inhibitor of CYP3A4 and increases ranolazine plasma concentrations approximately 1.5-fold. Ranolazine is also a weak inhibitor of CYP3A4 and CYP2D6. Simvastatin plasma concentrations are increased less than 2-fold after ranolazine, but a significant increase in creatine kinase level, clinical myositis, or elevated liver function test results have not been noted for patients taking statins in ranolazine clinical trials. Paroxetine, a potent inhibitor of CYP2D6, produces an increase in steady-state ranolazine plasma concentrations of 1.2-fold.

Ranolazine's interaction with P-glycoprotein also contributes to additional drug interactions. Verapamil, in doses of 360 mg/day or greater, is an inhibitor of P-glycoprotein; the drug increases absorption of ranolazine and contributes to a 2.3 fold increase in ranolazine plasma concentrations. Ranolazine increases digoxin concentrations 1.4 to 1.6-fold at trough and approximately 2-fold at peak plasma concentrations, most likely through competition for intestinal and renal P-glycoprotein. Drugs that are known to increase the QTc should not be used with ranolazine. Since agents known to prolong QTc were excluded from the major clinical trials with ranolazine, the true impact of this type of drug interaction is unknown.

SIDE EFFECTS

Nervous system

Nervous system side effects include dizziness (6.2% to 11.8%) and headache (5.5%). Nervous
system reactions that are rare (0.5% or less), but potentially medically important, include hypoesthesia, paraesthesia, and tremor. Additional side effects have included confusional state.

**Gastrointestinal**
Gastrointestinal side effects include constipation (4.5% to 10.9%), nausea (4.4% to 5.6%), and diarrhea (3.8%). Other, less common reactions (less than 2%) include abdominal pain, dry mouth, and vomiting.

**Cardiovascular**
The variable blood levels attained after a given dose of ranolazine result in a wide range of effects on QTc. At Tmax following repeat dosing at 1000 mg twice a day, the mean change in QTc is about 6 msec. However, in 5% of the population with the highest plasma concentrations, the prolongation of QTc is at least 15 msec. The relationship between ranolazine plasma level and QTc is linear over a concentration range up to 4 fold greater than the concentrations produced by a dosage of 1000 mg twice a day, and this relationship is not significantly affected by age, weight, gender, race, heart rate, congestive heart failure NYHA class, or diabetes. In subjects with hepatic impairment, the relationship between plasma level of ranolazine and QTc is much steeper. During a long-term safety study (ROLE program) involving patients with chronic angina (n=746), there were no treatment discontinuations due to QTc prolongation and no episodes of Torsades de Pointes were reported. Cardiovascular side effects occurring in less than 2% of patients have included palpitations, bradycardia, hypotension, orthostatic hypotension, and syncope. ECG abnormalities have included dose- and plasma concentration related increases in the QTc interval, reductions in T wave amplitude, and notched T waves.

**General**
In general, a higher incidence of adverse events has been reported in elderly patients 75 years or older than in younger patients. In general, long-term therapy with ranolazine is well tolerated in high-risk patients. During a long-term safety study (ROLE program) involving patients with chronic angina (n=746), more than two years after initial dosing, 76.7% of patients remained on therapy and 9.7% discontinued ranolazine due to adverse effects. In this study, age (greater than or equal to 64 years) was associated with increased adverse effects related withdrawals.

**Renal**
Renal side effects include small, reversible elevations in serum creatinine and BUN levels. These elevations occur without evidence of renal toxicity. Renal failure has been rarely (less than 0.5%) reported.

**Metabolic**
Metabolic side effects have been minimal. Ranolazine does not appear to significantly affect triglyceride or blood glucose levels; however, diabetes has been reported as an adverse effect. In contrast, in patients with diabetes, ranolazine has produced a dose-related reduction in glycosylated hemoglobin (HbA1c).

**Respiratory**
Respiratory side effects have included cough (6%) and dyspnea (4.3%). Pulmonary fibrosis has been rarely (less than 0.5%) reported.

**Musculoskeletal**
Musculoskeletal side effects include back pain (4.8%) and arthralgia (4.4%).

**Hematologic**
Hematologic side effects include anaemia (4.6%). Additional side effects have included thrombocytopenia, leukopenia, and pancytopenia (less than 0.5%).

**Hypersensitivity**
Hypersensitivity side effects include angioedema and eosinophilia (less than 0.5%).

**Psychiatric**
Psychiatric side effects include post marketing reports of hallucinations.

**Dermatologic**
Dermatologic side effects include angioedema, pruritis and rash.

**CLINICAL TRIALS**
**Erica study**
In this placebo controlled study, 565 patients were randomized to receive a 1 week loading regimen of 500 mg Ranexa or placebo twice daily, followed by a 6 week regimen of 1000 mg ranolazine or placebo twice daily, in combination with 10 mg amiodipine once daily. Trial data showed that ranolazine significantly decreased frequency of
angina attacks (mean 3.3 attacks per week, vs. 4.3 for placebo; p=0.028) and need for intervention treatment with nitroglycerin (mean 2.7 doses per week, vs. 3.6 for placebo; p=0.014). The drug was seen to have higher efficacy in male patients.

**Carisa study**

This placebo controlled study enrolled 823 patients, who received one of two twice daily doses of Ranexa (750 mg or 1000 mg) or placebo, in combination with continued background therapy (50 mg atenolol, 5 mg amlodipine, or 180 mg diltiazem CD). Trial data yielded a significant increase in modified Bruce treadmill exercise tolerance (p<0.05) and time to angina onset (p<0.05) at both peak (4 hours post dose) and trough (12 hours post dose) drug plasma concentrations. Both doses significantly reduced angina frequency (750 mg: 2.5 attacks/week; 1000 mg: 2.1 attacks/week; vs. 3.3 attacks/week for placebo; p=0.006 and p<0.001, respectively) and nitroglycerin intervention (750 mg: 2.1 doses/week; 1000 mg: 1.8 doses/week; vs. 3.1 doses/week for placebo; p=0.016 and p<0.001).

**Merlin-timi 36 trial**

As previously discussed, the CARISA, and ERICA trials provided evidence regarding the efficacy and short-term safety of ranolazine SR. Myocardial Infarction (MERLIN-TIMI) 36 trial was designed and conducted with the express goal of addressing these issues. Patients in the MERLIN trial (6560 patients) were randomly assigned in a double-blinded fashion to placebo or ranolazine as a 200-mg intravenous bolus followed by an 80-mg/hour infusion for a minimum of 12 hours and a maximum of 96 hours. Patients assigned to ranolazine then began to receive oral ranolazine 1000 mg twice/day and the placebo group received oral placebo (median follow-up 348 days). Patients with severe renal insufficiency had their infusion dose reduced to 40 mg/hour. The initial intravenous dosing regimen was designed to quickly achieve therapeutic ranolazine plasma concentrations similar to those seen in the CARISA trials with 1000 mg orally twice/day (about 2500 ng/ml). Patients were evaluated for clinical end points every 4 months, and an exercise tolerance test was conducted at 8 months after randomization. A digital continuous electrocardiographic Holter monitor was applied to patients at the time of randomization and remained in place for 7 days, including after hospital discharge.

**CONCLUSION**

Ranolazine is a selective inhibitor of the late I_{Na} current. This relatively unique mechanism of action merits further study in cardiovascular conditions in which the late I_{Na} is amplified such as heart failure, acute and chronic myocardial ischemia, certain types of cardiac sodium channel gene mutations, and ventricular and supraventricular arrhythmias. Other conditions such as left ventricular diastolic dysfunction with preserved systolic function and skeletal muscle ischemia (intermittent claudication) should also be considered for study.

Ranolazine should be used in combination with amlodipine, β-blockers, or nitrates. It should not be used as an alternative to β-blocker therapy in patients otherwise eligible for this form of therapy unless future studies demonstrate an indication. The therapeutic dose range of 500 to 1000 mg twice daily is generally well tolerated, with constipation, nausea, asthenia, and dizziness being the most common adverse events reported (<7% excess frequency compared with placebo). The maximum recommended dose of ranolazine is 1000 mg twice daily. Ranolazine should be reserved for patients who have not achieved an adequate response with other antianginal drugs because ranolazine is known to prolong the QT interval.

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