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A REVIEW ON RANOLAZINE AND TRIMETAZIDINE FOR ANGINA PECTORIS

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ABSTRACT

An imbalance between myocardial oxygen supply and demand leads to chronic stable angina pectoris. This blockage of the coronary arteries is fixed. For both patients and medical professionals, chronic angina pectoris poses a frequent and serious problem. The current medical paradigm tries to improve survival by reducing cardiovascular events (vasculoprotective), and/or to enhance quality of life by relieving ischemic symptoms (antianginal). For the treatment of chronic stable angina, Ranolazine and Trimetazidine are now approved.

KEYWORDS: Ranolazine, Trimetazidine, Antianginal, QT prolongation drugs.

INTRODUCTION

An important global source of illness and mortality is cardiovascular disease (CVD). Despite the fact that interventional treatments are used to treat the majority of CVD patients, a sizable portion still require medical therapy for symptomatic relief and prognosis.[1] A fixed atherosclerotic coronary plaque and an imbalance between myocardial oxygen supply and demand lead to chronic stable angina.[2] Chronic chest discomfort brought on by ischemic bouts brought on by stress is a symptom of stable angina pectoris, a form of coronary heart disease (CHD). The therapeutic goals are to reduce angina episodes, avoid myocardial infarction (MI), and prolong life.[3] However, routinely used medications like -

blockers and calcium channel blockers lower blood pressure in people whose resting pressures are frequently already low.[1]

Currently, stable chronic angina can be treated with Ranolazine.[2] Ranolazine has anti-ischemic and metabolic effects and selectively inhibits the late sodium current in myocytes.[4] Ranolazine, however, might be a first-line antianginal treatment for patients with Bradycardia or hypotension.[2] A potential medication that has minimal affects on blood pressure and heart rate is Ranolazine. Several cardiovascular problems, including ischemic heart disease, heart failure, and arrhythmias, have been linked to the use of this medication.[1] Utilizing cytoprotective metabolic drugs during ischemia, such as Trimetazidine, is a novel treatment strategy.[3] Trimetazidine (TMZ), an anti-ischemic metabolic drug, has been demonstrated to be effective in the treatment of angina, both when used alone and in combination. To make the drug schedule simpler, a new TMZ modified-release (MR) 80 mg formulation was created, which is to be given once daily (od), as opposed to twice daily (bid) for the currently existing TMZ MR 35 mg.[5]

RANOLAZINE

CLASS: Sodium channel blocker.

MOA: The anti-angina and anti-ischemic effects of Ranolazine, a piperazine derivative, are not known to have a specific mechanism of action. Ranolazine's anti-anginal and anti-ischemic effects are independent of changes in blood pressure or heart rate, and it has no adverse effects on myocardial workload. The inactivating portion of the sodium current (I(Na)) can be inhibited by Ranolazine at therapeutic doses, but it is unclear how this suppression relates to angina symptoms. The ventricular action potential is prolonged by Ranolazine inhibition of the fast inward rectifying current (I(Kr)).

USES

- Angina pectoris, chronic
- Atrial fibrillation; Prophylaxis
- Atrial fibrillation - Chemical cardio version; Adjunct

DOSE

Angina pectoris, chronic

The maximum advised dose of 1000 mg orally twice day after starting with 500 mg orally twice daily.

Atrial fibrillation; Prophylaxis

375 mg to 1000 mg orally twice daily

Atrial fibrillation - Chemical cardio version; Adjunct

1500 mg orally single-dose

ADVERSE REACTION

Common

Gastrointestinal: Constipation, Nausea.

Neurologic: Dizziness, Headache.

Serious

Cardiovascular: Prolonged QT interval, vasovagal syncope.

CONTRAINDICATION

- Simultaneous usage of CYP3A inducers like Rifampin, Rifabutin, Rifapentine, Phenobarbital, Phenytoin, Carbamazepine, and St. John's wort.
- The concurrent use of potent CYP3A inhibitors such Ketoconazole, Itraconazole, Clarithromycin, Nefazodone, Nelfinavir, Ritonavir, Indinavir, and Saquinavir.
- Hepatic cirrhosis.

DRUG INTERACTION[6]

Avoid using this medication with CYP 3A4 inducers (such as Phenytoin and Carbamazepine), strong inhibitors (such as Clarithyromycin and Azole antifungals), and QT prolonging drugs (Citalopram, Quetiapine, others).

PHARMACOECONOMICS[7]

Drug	Strength	Dosage Form	Cost ($)	Daily Usage On Average	The Average Cost of Daily Drug Usage($)	The Cost Of Treatment Course($)
Ranolazine	500mg 1000mg	Tablet	1.80	500mg twice daily	1.8 to 3.6	3 months:331 6 months:648

SAFETY

At any dose, Ranolazine had no clinically meaningful effects on blood pressure or heart rate during either rest or exercise. With higher doses, the incidence rate of side effects often rose. Dizziness, nausea, vomiting, constipation, headaches, and asthenia are some of the most

typical side effects of Ranolazine. The 1500 mg twice-daily dose is not advised for clinical use since it causes an increase in adverse events that is disproportionately greater than its increase in anti-angina efficacy.

A limited percentage of patients receiving less than 1000 mg of Ranolazine had postural hypotension and syncope, most likely as a result of taking other drugs at the same time that are known to enhance the plasma concentration of Ranolazine or to have a vasoactive effect. By commencing Ranolazine at a low dose (500 mg) and gradually raising the dose as necessary, this can be avoided. Ranolazine may have a minor impact on some laboratory measurements, including the eosinophil count, creatinine, hematocrit, and haemoglobin A1C in diabetic patients.

CYP3A4 is principally responsible for the liver's role in the metabolism of Ranolazine, thus people who take other medications known to interact with it or have liver disease should use caution. Ranolazine may accumulate in patients with hepatic impairment because of this. Furthermore, careful dose titration is necessary because Ranolazine is primarily excreted via the kidneys. While it is totally in patients with mild to moderate renal impairment. Patients with severe renal impairment should not use it.

EFFICACY

Multiple clinical trials evaluated the effectiveness of the immediate-release version of Ranolazine for the treatment of chronic angina. The prolonged formulation of Ranolazine did not show any benefit in this population when used to treat acute coronary syndrome without ST-elevation.

With additional anti-anginal medications, Ranolazine alone improved the treadmill exercise performance. The favourable effects of Ranolazine, i.e., it reduced angina episodes by about 1 per week and it increased exercise duration by nearly 24-34 s at trough concentrations, first appeared to be limited when Ranolazine was taken with other anti-angina medicines. Ranolazine is therefore indicated for the treatment of persistent angina either alone or in combination with other medications.[8]

GUIDELINES

The Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease was released in 2012 by the American College of Cardiology Foundation and the

American Heart Association. If individuals with stable ischemic heart disease were unable to take b-blockers at safe dosages, Ranolazine was advised (Class of recommendation IIa, Level of Evidence B).

With no proof that it improves prognosis, the 2013 European Society of Cardiology guidelines propose Ranolazine as one of the medications for second-line symptomatic treatment of angina (Class of recommendation IIa and Level of Evidence B).

Finally, in 2009, the Canadian Cardiovascular Society published a position paper on the treatment choices for those with refractory angina pectoris. Ranolazine was given a weak recommendation under the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system for patients who were unable to tolerate the recommended doses of conventional antianginal drugs.[9]

TRIMETAZIDINE

CLASS: Fatty acid oxidation inhibitor.

MOA: Trimetazidine inhibits a drop in intracellular ATP levels, which ensures the appropriate operation of ionic pumps and transmembrane sodium-potassium flow while maintaining cellular homeostasis by conserving energy metabolism in cells subjected to hypoxia or ischaemia. Trimetazidine prevents long-chain 3-ketoacyl-CoA thiolase from oxidising fatty acids, which promotes glucose oxidation. Energy produced by glucose oxidation in an ischemic cell requires less oxygen than energy produced by beta-oxidation. Increased glucose oxidation potentiates cellular energy activities and preserves healthy energy metabolism during ischaemia.

USES

Acute kidney injury, Angina pectoris, Cardiac dysrhythmia, Cardiac syndrome X.

DOSE

Oral route

Angina pectoris

Treatment of exertional angina with 20 milligrammes of trimetazidine taken orally three times per day has been successful.

ADVERSE EFFECTS

Gastric burning, Dizziness, Muscle cramps, Parkinsonism.[6]

CONTRAINDICATION

Patients with tremors, restless legs syndrome, Parkinsonism symptoms, and other movement problems are not recommended to take Trimetazidine.[10]

PHARMACOECONOMICS[7]

Drug	Strength	Dosage Form	Cost (□)	Daily Usage On Average(□)	The Average Cost of Daily Drug Usage(□)	The Cost Of Treatment Course(□)
Trimetazidine	20mg 35mg	Tablet	16.5	35mg once daily	16.5	165

EFFICACY OF TRIMETAZIDINE

In terms of reducing angina attacks and enhancing exercise parameters, Trimetazidine was just as effective as Propranolol (120–160 mg/day) and Nifedipine (40 mg/day). Patients whose therapy with Diltiazem, Nifedipine, Propranolol, Indolol, Oxprenolol, or long-acting nitrates had failed experienced an improvement in anginal frequency and symptoms after using Trimetazidine. Additionally, Trimetazidine performed better as a propranolol adjunct than Isosorbide dinitrate (30 mg/day). Trimetazidine does not impair heart function and is therefore not contraindicated in any situation, although having an efficacy that is comparable to that of beta-blockers and calcium antagonists. Use of Trimetazidine as a monotherapy or supplementary therapy for the symptoms of stable angina pectoris is safe and effective. To find out whether Trimetazidine will reduce death rates, longer-term trials are required.[6]

COMPARSION OF RANOLAZINE AND TRIMETAZIDINE[6,11,12]

GENERIC NAME	RANOLAZINE	TRIMETAZIDINE
USES	Angina pectoris, chronic Atrial fibrillation; Prophylaxis Atrial fibrillation - Chemical cardioversion; Adjunct	Acute kidney injury, Angina pectoris, Cardiac dysrhythmia, Cardiac syndrome X
DOSE	500mg -1000mg twice daily	20mg, 35mg
CLASS	Sodium channel blockers	Fatty acid oxidation inhibitor
ADVERSE EVENT	**Common** **Gastrointestinal:** Constipation, Nausea **Neurologic:** Dizziness, Headache **Serious** **Cardiovascular:** Prolonged QT interval, Vasovagal syncope	Gastric burning, Dizziness, Muscle cramps, Parkinsonism
METABOLISM	Hepatic and intestinal; rapid and extensive, mainly via cytochrome CYP3A and to a lesser degree by CYP2D6	Orally absorbed, Partly metabolized
EXCRETION	Renal excretion: 75%; less than 5%	Largely excreted in urine

	unchanged Fecal excretion: 25%; less than 5% unchanged	
DRUG INTERACTION	Rifampin, Rifabutin, Rifapentine, phenobarbital, phenytoin, carbamazepine,	–
HEPATIC IMPAIRMENT	Moderate	_

CONCLUSION

Two effective medications for treating angina are Ranolazine and Trimetazidine. As early as six weeks, Ranolazine is effective to Trimetazidine in managing the angina symptoms. While both medications are useful for treating anxiety and generalised systemic musculoskeletal pain, Ranolazine's effectiveness is more pronounced.

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