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Study of Utilisation Pattern,Safety & Efficacy of Ranolazine in Patients of Coronary Artery Disease & Post AMI

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Introduction: *Ranolazine is an unique agent with antianginal activity that is independent of cardiovascular haemodynamics.It is a new drug with minimal or no significant post marketing safety & efficacy data in our region.On this background,*
the present study was undertaken to find out the utilisation pattern ,safety & efficacy of Ranolazine in patients of coronary artery disease in our tertiary care Hospital.
Methods*: Patients attending cardiology OPD, with evident of Coronary Artery Disease (i.e Angina/Acute Coronary Syndrome) & prescribed Ranolazine were included in the study.Episodes of Angina & nitrate consumption per week and TMT reports (Time to ST segment depression Time to Angina) of these patients were analysed to evaluate the efficacy of Ranolazine. Thorough clinical examination were done .Laboratory parameters were performed at each visit to find out any Adverse Drug Reaction associated with Ranolazine.*
Results: *In majority of patients(94%) in our study Ranolazine was used as add on therapy with other drugs in patients of Coronary Artery Disease. Significant reduction of angina episodes & improvement in exercise capacity was found in patients treated with Ranolazine as monotherapy or as add on therapy.No serious ADR /adverse drug interaction was found with Ranolazine treatement in our study.*
Conclusions: *Ranolazine is commonly used as add on therapy in our region .It is found to be quiet safe & effective in CAD cases both in Chronic Angina & Post MI Patients.*
Key Words:Ranolazine,Angina,Monotherapy,Nitrate,Coronary Artery Disease

I. Introduction

Chronic stable angina, a condition that impairs quality of life is associated with decreased life expectancy (1) Several new investigational drugs are being tested for the t reatment of chronic angina. Ranolazine was approved on January 27, 2006, by U.S FDA for use in patients with chronic angina who continue to be symptomatic on ß-blockers, calcium antagonists, or nitrates. Ranolazine ([(+) N- (2, 6-dimethylphenyl)-4 (2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazineacetamide dihydrochloride]) is an active piperazine derivative.(2) The mechanism of action of ranolazine is unknown. Initially, ranolazine was thought to exert its therapeutic efficacy primarily through partial inhibition of fatty acid oxidation (3, 4, 5, 6)

More recent evidence suggests that ranolazine reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current (I_{Na}). Myocardial ischemia produces a cascade of complex ionic exchanges that can result in intracellular acidosis, excess cytosolic Ca^{2+}, myocardial cellular dysfunction and if sustained, cell injury and death. Regulation of intracellular Na^+ homeostasis (ion channels, exchangers, transporters) during an episode of myocardial is a complex and the subject of some debate,but the rise in intracellular Na^+ is likely the result of several processes that include both the Na^+-H^+ exchanger and the nonactivating Na^+ channels (ie, late I_{Na}).(7,8)

The increase in intracellular sodium triggers an increase in the influx of calcium via the reverse mode of Na^+-Ca^{2+} exchanger, resulting in intracellular calcium overload. Increased intracellular Ca^{2+} results in increased left ventricular diastolic tension and the potential for compression of the vascular space and further reduction of nutrient coronary blood flow to the ischemic territory.(7,8) Thus, ranolazine is a relatively selective inhibitor for late I_{Na}. In isolated ventricular myocytes in which the late I_{Na} was pathologically augmented, ranolazine prevented or reversed the induced mechanical dysfunction, as well as ameliorate ventricular repolarization. (9, 10, 11, 12)

The effect of ranolazine on late I_{Na} is more pronounced in ischemic or failing myocytes . In patients with chronic angina and demand-induced ischemia, ranolazine has the potential to partially disrupt the consequences of cell hypoxia during transient myocardial ischemia by reducing excess late Na^+ influx, there by reducing calcium overload and ultimately reducing the concomitant increase in left ventricular wall tension.

Reduction in diastolic left ventricular wall tension would decrease myocardial oxygen requirements in marginally ischemic myocytes and has the potential to reduce vascular compression, allowing more coronary blood flow to the affected area. It has weak calcium channel antagonist activity.(13)

Thus, its mechanism of action to alleviate angina is different from the currently available drug classes that affect heart rate, inotropic state, or hemodynamic state or increase coronary blood flow. At usual dosage ranolazine does not have a clinically significant effect on resting or exercise heart rate or blood pressure.(3,14)

Hence this study was undertaken to assess the safety & efficacy of ranolazine in patients of chronic stable angina

Study Site & Study Period

This study was conducted in the department of Pharmacology & Cardiology from MARCH 2008 to April 2010.

Ethical Issues

The study protocol was approved by the IEC (Institution ethical committee) of S.C .B Medical College, Cuttack.

Study Design

It was an open level, prospective, observational study to evaluate the utilisation pattern,safety profile and efficacy of Ranolazine in patients of Coronary Artery Disease.

The protocol was approved by the institutional ethics committee and written informed Consent was obtained from each patient.Detail clinical history & physical findings were recorded.Patients were devided in to two groups

Group A- Patients presented with Chronic Stable Angina for first time were considered for ranolazine monotherapy.

Group B- Patients of Chronic stable angina already on antianginal drug but continued to have angina receive Ranolazine as add on therapy. These patients were taking nitrates ,betablockers,&calcium channel blockerse either alone or in combonation.Ranolazine was given in a dose of 500mg twice a day to both groups of patients. All the patients were followed up monthly for 3 months & there after every 3 months for 1yr. Episodes of angina&nitrate consumption per week and adverse reactions, were recorded in all group of patients ,before starting of therapy & during follow up,particularly at 3 months of therapy as subjective evidence of efficacy. All patients were exposed to stress test.

(Treadmill test-TMT) At start of therapy and at 3 months of therapy.During TMT total exercise time ,time to 1mm ST segment depression and time to angina were noted as objective evidence and assessed at baseline & at 3 months of therapy.

II. Methodology

The patients attending cardiology OPD with features of Coronary artery Disease were evaluated thoroughly by clinical Examination & Laboratory investigation with complaints of symptoms of Ishemic Heart Disease were thoroughly evaluated by detailed clinical examination (enrolled in to the study) and broadly divided into 2 Groups.

Patient selection

Inclusion criteria

Patients of Coronary Artery Disease attending cardiology OPD during the above period were included in the study

Exclusion criteria

Patients were excluded if they had class IV (NYHA) congestive heart failure, Active Acute Myocarditis, Pericarditis,hypertrophic cardiomyopathy,or uncontrolled Hypertension, Patients with a history of torsades de pointes,those receiveing agents known to prolong the QTc interval or who had a QTc interval measurement >500ms.

Study design

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(Treadmill test-TMT) At start of therapy and at 3 months of therapy.During TMT total exercise time ,time to 1mm ST segment depression and time to angina were noted as objective evidence and assessed at baseline & at 3 months of therapy.

III. Result

Mean angina frequency & mean nitrate consumption decreased from 5.2± 2.1 episodes per week to 2.6± 0.9 at 3 months and Mean nitrate consumption per week 2.2± o.7 to 1.5±0.5 in at 3 months Ranolazine monotherapy group (Group-A) . In Group B(Ranolazine add on therapy) Mean angina episodes decreased from 4.1± 1.8 to 1.9±0.7 at 3months and mean nitrate consumption per week 1.7±0.5 to 1.1±0.03 at 3 months.

Total exercise duration ,time to 1mm ST segment depression and time to angina increased from 396 ,254 & 345 seconds at baseline to 466sec($p<0.01$), 381sec ($p<0.01$)&438sec($p<0.01$) at 3 months in Ranolazine monotherapy group & from 466 sec 312sec&414 sec at baseline to 478 sec ($p<o.05$),336 sec($p<0.05$) 449 sec($P<0.05$)sec at 3 months in Ranolazine add on therapy groups respectively. Patients with more severe angina had better treatment effect.No serious adverse drug reaction / adverse drug interaction was found with Ranolazine treatment in our study. Ranolazine was well tolerated.

Table-1 (Utilization Pattern Of Ranolazine) n=64

MONOTHERAPY(n=4) 6%	ADD ON THERAPY (n=60) 94%	
	CHRONIC ANGINA	POST MI
4 (6%)	18 (28 %)	42 (66 %)

In our study Ranolazine was used predominantly (94%) as add on therapy & most commonly in post MI patients (65%).

Table-2 Adverse Drug Reaction Of Ranolazine (n= 64)

ADVERSE DRUG REACTION	PERCENTAGE(%)
Serious ADR (either requiring dose reduction or withdrawal)	NIL
Minor ADR	No of pts
Nausea	1(1.5%)
Mild constipation	2(3.1%)
Dizziness	2(3.1%)
Total	5 (7.8%)

In one patient slight increase in AST (2 times raised 80 meq/l)(no jaundice billirubin with in normal limit) did not require with drawal or dose reduction of the drug. (In Ranolazine as add on therapy group after one year use of Ranolazine)

Table-3 Symptoms In Patients Groups Ranolazine Monotherapy (n=4)

Symptoms	At baseline	At 3 months	% Reduction
Mean angina episodes per week	5.2 ± 2.1	2.6 ±0.9	50%
Mean nitrate consumption per week	2.2±0.7	1.5±0.5	47%

Ranolazine Add On Therapy (n=60)

Symptoms	At base line	At 3 months	%Reduction
Mean angina episodes per week	4.1±1.8	1.9±0.7	54%
Mean nitrate consumption per week	1.7± 0.5	1.1±0.3	35%

Shows the presence of symptoms in different group of patients, at baseline and at 3 months.

(Table-4 Shows Stress Test (Tmt) Finding In Patients Groups Parameters In Trade Mill Test (Tmt)

	Group A (n=4)			Group B (n=60)		
	TED insecs	TSD Insecs	TAO insecs	TED insecs	TSD insecs	TAO insecs
Baseline	396	254	345	466	312	414
3months	466	381	438	478	336	449
P value	<0.001	<0.01	<0.05	<0.05	<0.05	<0.05

TED-Total exercise duration TSD-Time to ST segment Depression TAO Time to angina onset

In both the groups total exercise duration ,time to 1mm ST segment depression and time to angina onset improved at 3 months compared to that with baseline

Statistical analysis

All values were expressed as mean ±SEM .The data obtained through careful observation were analysed using students t-test.P value less than 0.05($p<0.005$) was considered statistically significant.

IV. Discussion

Ranolazine has shown efficacy as an antianginal drug when used alone.(3) and when used as a part of combination therapy regimen with conventional doses of other agents.(14)

As monotherapy (MARISA) ranolazine has been effective to reduce angina frequency and improve exercise performance in patients with stable CAD.(3)

The present study result also shows significant reduction in anginal episodes & improvement in exercise capacity,demonstrated by improvement in different exercise parameters like total exercise duration ,time to 1mm ST segment depression and time to angina onset.

In combination therapy (CARISA) addition of ranolazine with conventional doses of Amlodipine (5mg),atenolol(50mg) or Diltiazem(180 mg) improved total exercise time,time to imm ST segment depression and time to onset of angina in patients with symptomatic Chronic stable angina.

The present study results also demonstrable decrease in angina episodes,decrease in nitrate consumption & improvement in exercise parameters in add on(combination) therapy group.

V. Summary and conclusion

Ranolazine is commonly used as add on therapy in our region .It is found to be quite safe & effective in CAD cases both in chronic angina & post angina patients.

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