International Research Journal of Medical Sciences _____ ISSN 2320 –7353
Vol. **2(1),** 7-10, January **(2014)** *Int. Res. J. Medical Sci.*

To evaluate the effect of Ranolazine on Post Prandial Plasma Glucose in patients of Type –II Diabetes Mellitus with Stable Angina as add on therapy

Budania Navin[1], Saharan Savita[2], Bhardwaj Vinod[3] and Sharma Priyamvada[3]
[1]Department of Pharmacology, S.H.K.M. Govt. Medical College, Mewat, Haryana, INDIA
[2]Department of Gynecology and Obstetrics,S.H.K.M. Govt. Medical College,Mewat, Haryana, INDIA
[3]Department of Pharmacology, S.N. Medical College, Agra, INDIA

Available online at: www.isca.in, www.isca.me
Received 19th September 2013, revised 30th December 2013, accepted 21st January 2014

Abstract

The study was aimed to evaluate the effect of Ranolazine on Post Prandial Plasma Glucose(PPPG) in patients of Type –II Diabetes Mellitus with Stable Angina as add on therapy. An open-labeled, randomized, controlled parallel group study was conducted from November 2009 to July 2011 in diagnosed patients of Type –II Diabetes Mellitus with Stable Angina attending the Medicine OPD, Cardiology OPD, Diabetic Clinic and admitted in Medical wards of S.N. medical College and Hospital, Agra. 80 willing patients were recruited on the the basis of inclusion and exclusion criteria. Four patients out of the selected eighty patients refused to take part in study after written consent. The remaining 76 selected patients randomly assigned in a1:1 fashion into 2 groups, Control group (Group 1): was on their regular therapy during the 8-week study period. Test group (Group 2): was on Ranolazine 500mg BD (orally) in addition to their regular therapy during the 8-week therapy. The PPPG measurement were done at baseline, repeated after 4 weeks and at the end of treatment(i.e at 8week). Data obtained were presented as mean ± standard deviation (SD). A statistical significance was reported at a two- tailed p value of <0.05. In group I Post Prandial Plasma Glucose (PPPG) concentration was 209.32 ± 15.85 mg/dl at 0 week, 211.11 ± 14.88 at 4 week and 209.01 ± 15.84 at the end of 8 week, whereas for group II, it was 212.37 ± 14.10 at 0 week, 202.61 ± 10.84 at 4 week and 202.47 ± 10.72 at the end of 8 week. There was decrease in PPPG in Group II and this decrease was statistically significant with P value < 0.05 in comparison to group I at end of 8 week after treatment. Ranolazine significantly reduced PPPG in patients of Type –II Diabetes Mellitus with Stable Angina as add on therapy in addition to their regular therapy. As this is a smaller study, larger studies are needed to show the definite effect of Ranolazine on PPPG.

Keywords: Ranolazine, PPPG, Type –II diabetes mellitus stable angina.

Introduction

The burden of Diabetes mellitus (DM) is increasing world widely and it is frequently associated with cardiovascular morbidity and mortality[1]. According to Centers for Disease Control Diabetes Surveillance System, 30% of individuals of age group 35- 64 years with DM have cardiovascular disease and this percentage increases with age[2]. In Presence of DM, cardiovascular diseases have poorer outcomes[1-4]. Postprandial hyperglycemia is an important risk factor for cardiovascular diseases progression in DM patients, as it has been found that postprandial hyperglycemia is more indicative of atherosclerosis than fasting glucose[5]. The conventional Antianginal drugs like, β-blockers and calcium Channel blocker, which are frequently used in diabetic patients with stable angina, have several safety concerns due to their prodiabetic effects[6].

Ranolazine, a novel oral antianginal agent, significantly reduces angina episodes in patients of stable angina[7-8]. In addition to this, Ranolazine has been shown lowering effect on HbA_{1c} in patients of CAD with diabetes in previous studies[9-10]. To best of our knowledge, no study has assessed the effect of Ranolazine on PPPG in patients of Type –II Diabetes Mellitus with Stable Angina. Therefore, the objective of the present study is to evaluate the effect of Ranolazine on PPPG in patients of Type –II Diabetes Mellitus with Stable Angina as add on therapy.

Material and Methods

An open-labeled, randomized, controlled parallel group study was conducted in the Department of Pharmacology in collaboration with other departments from November 2009 to July 2011 in diagnosed patients of Type –II Diabetes Mellitus with Stable Angina, attending the Medicine OPD, Cardiology OPD, Diabetic Clinic and admitted in Medical wards of S.N. medical College and Hospital, Agra.

The Institutional Ethical Committee approval was taken before starting the study. Written consent was obtained from all patients after detailed explanation of the study.

187 patients were screened of these, 80 willing participants were recruited on the basis of inclusion and exclusion criteria. Inclusion criteria: Patients of either gender in the age group of 30-70 years had a documented history of both Type –II Diabetes Mellitus and Stable Angina and treated with stable doses of drugs

for at least 3 months, Patients ready for therapy after knowing adverse effects of the test drug. Key exclusion criteria were: Acute coronary syndrome within 2 months, planning of coronary intervention during the study period, stroke or transient ischemic attack ≤ 6 months, uncontrolled hypertension, Significant hepatic impairment, Renal impairment, patients on Insulin Therapy, patients shows New York Heart Association functional class III-IV heart failure symptoms, Pregnant females, Nursing mother, Age <30 years and >70 years, prior treatment with Ranolazine, Patients with history of Torsades de pointes or QTc > 500 milliseconds and those receiving agents that are known to prolong QT_c interval and Patients currently on CYP3A inhibitors.

Four patients out of the selected eighty patients refused to take part in study after written consent. The remaining 76 selected patients on the basis of inclusion and exclusion criteria were randomly assigned in 1:1 fashion into 2 groups by computer generated randomization chart: Control group (Group 1): was on their regular therapy during the 8-week therapy. Test group (Group 2): was on Ranolazine 500mg BD (orally) in addition to their regular therapy during the 8-week therapy.

After selecting the patient, a detailed medical history and findings of clinical examination including demographic data were recorded in a Performa. After that all patients were subjected to investigations which include-Hb, TLC, DLC, ESR, Blood sugar, Weight of patient, SGPT/ SGOT, Serum creatinine, Urine analysis. The investigations were done at baseline, repeated after 4weeks and after end of treatment (i.e at 8week). Patients were followed at 4^{th} week and 8^{th} week. Each patient served its own control and patient's baseline values were compared with values after 4 weeks and 8 weeks. Concomitant medications were kept stable during the study period. Compliance to the therapy was monitored by receiving back the empty wrappers of the supplement at weekly follow-ups and telephonic communications.

After an overnight (8-12 hours) fast, in the morning patients were allowed to take their routine breakfast and after 2Hr, under aseptic conditions, venous blood sample was collected for the estimation of the 2Hr Post Prandial Plasma Glucose level. Post Prandial Plasma Glucose (PPPG) was measured by using modified Glucose Oxidase-Peroxidase method[11].

Statistical Analysis: All data obtained were presented as mean ± standard deviation (SD). All statistical tests were conducted at the 5% significance level. A two-tailed, un-paired student's t-test was used to test differences between control and test groups. The differences in observations before and after therapy in same group were studied using student's two-tailed paired t-test. A statistical significance was reported at a two- tailed p value of <0.05. All tests were done online at www.graphpad.com.

Results and Discussion

Results: All the 76 selected patients completed the study without any significant adverse drug reaction. As shown in table 1, the base line characteristics are similar among the groups. All patients were kept Concomitant medications stable during the study period.

Table-1
Presents the baseline demographic characteristics and the background medication of the subjects who successfully completed the study

Baseline Characteristics and Concurrent medication at randomization	Group I (n = 38)	Group II (n = 38)	p value
Age	56.86 ± 8.081	57.73 ± 7.671	> 0.05
Sex	M = 68.42 %	M = 63.15 %	> 0.05
	F = 31.57 %	F = 36.84 %	> 0.05
Hypertension	84.21 % (32)	81.57 % (31)	> 0.05
Hyperlipidemia	68.42 % (26)	73.68 % (28)	> 0.05
Current smoker	28.94 % (11)	31.57 % (12)	> 0.05
Family History	15.78% (06)	18.42 % (07)	> 0.05
Previous myocardial infarction	15.78% (06)	13.15 % (05)	> 0.05
Previous percutaneous coronary intervention	7.89 % (03)	5.26 % (02)	> 0.05
Antiplatelet Drugs	97.36 % (37)	94.73 % (36)	> 0.05
Beta blocker	89.47 % (34)	92.10 % (35)	> 0.05
Sulfonylurea	78.94 % (30)	81.57 % (31)	> 0.05
Biguanide (metformin)	57.89 % (22)	55.26 % (21)	> 0.05
Statins	55.26 % (21)	55.26 % (21)	> 0.05
ACE inhibitors	36.84 % (14)	39.47 % (15)	> 0.05
Nitrates	28.94 % (11)	31.57 % (12)	> 0.05
Diuretics	13.15 % (05)	10.52 % (04)	> 0.05
Calcium channel blocker	7.89 % (03)	10.52 % (04)	> 0.05
Thiazolidinedione	2.63 % (1)	0 % (0)	> 0.05

Table-2
Comparison of changes in the PPPG between the two treatment groups

S. No.	Parameters	Group I (n = 38)			Group II (n = 38)		
		At 0 Wk	At 4 Wk	At 8 Wk	At 0 Wk	At 4 Wk	At 8 Wk
1.	PPPG (mg/dl) Mean ± SD	209.32 ± 15.85	211.11 ± 14.88	209.01 ± 15.84	212.37 ± 14.10	202.61 ± 10.84	202.47 ± 10.72
	p value In same group		t=0.5403 p >0.05	t=0.325 p >0.05		t=3.6685 p < 0.05	t=3.736 p < 0.05
	p value Between 2 groups	At 0 weeks t = 0.8859 p >0.05		At 4 weeks t = 2.8449 p < 0.05		At 8 weeks t = 2.107 p < 0.05	

As shown in table 2, in group I Post Prandial Plasma Glucose (PPPG) concentration was 209.32 ± 15.85 mg/dl at 0 week, 211.11 ± 14.88 at 4 week and 209.01 ± 15.84 at the end of 8 week, whereas for group II, it was 212.37 ± 14.10 at 0 week, 202.61 ± 10.84 at 4 week and 202.47 ± 10.72 at the end of 8 week. There was decrease in PPPG in group II and this decrease was statistically significant with P value < 0.05 in comparison to group I at end of 8 week after treatment.

Discussion: In our study, we have analyzed the effect of Ranolazine on PPPG in patients of Type –II Diabetes Mellitus with Stable Angina as add on therapy with their ongoing regular therapy. Patients were in the age group of 30-70 years of either sex in both groups. During study period there was negligible changes in PPPG concentration in group I but there was decrease in PPPG concentration in Ranolazine add on group. Ranolazine-treated group had significantly lower PPPG at 4 weeks compared with the control group and this effect persisted until the end of the study (8-week treatment).

High level of post prandial plasma Glucose is an important risk factor for cardiovascular diseases, as there is strong correlation between Post prandial plasma Glucose levels and the incidence of cardiovascular morbidity and mortality[12]. Many previous studies showed that increased mortality risk was much more closely associated with 2-h post–glucose load plasma levels than with fasting plasma glucose[13-15].

Mechanism by which Ranolazine lower PPPG is not clear but data from previous studies, suggests that Ranolazine may promote glucose-stimulated insulin secretion[16].

From our study findings we say that Ranolazine has additional beneficial effect in patients of type –II DM with stable angina due to its lowering effect on PPPG. In this context, Ranolazine is a promising choice for patients of Type –II Diabetes Mellitus with Stable Angina.

Conclusion

Ranolazine significantly reduced PPPG in patients of Type –II Diabetes Mellitus with Stable Angina as add on therapy in addition to their regular therapy, so in future it has wide scope in these types of patients. As this is a smaller study, larger studies are needed to show the definite effect of Ranolazine on PPPG.

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