Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20162456

Research Article

Ranolazine improves glucose and lipid homoestasis in streptozotocin induced diabetes mellitus in albino wistar rats

Sabreen Bashir*, H. L. Kalabharathi

Department of Pharmacology, JSS Medical College, JSS University, Mysuru, Karnataka, India

Received: 19 May 2016
Accepted: 13 June 2016

***Correspondence to:**
Dr. Sabreen Bashir,
Email: Sabreenbhat.sb@gmail.com

ABSTRACT

Background: Type 2 diabetes mellitus is one of the most common metabolic disorders at present with increasing incidence worldwide. The disease progresses with eventual multi-system involvement such as adverse cardiovascular outcomes. This necessitates pharmacotherapy which is able to retard disease progression, have a favourable cardiovascular profile in addition to stabilisation of glucose homeostasis. Ranolazine is an anti-anginal drug, which has been shown to reduce HbA1c in patients with CAD and diabetes in various clinical trials.
Methods: Albino wistar rats of either sex weighing 150-200 grams, bred in central animal facility of JSS Medical College were used for the study. The animals were randomly divided into three groups of six animals each. Diabetes was induced in all 3 groups of animals by injecting streptozotocin in a dose of 45 mg/kg. After 72 hours of STZ administration, rats with blood glucose levels greater than 250 mg/dl were selected for the study. Capillary blood glucose levels were measured on 0, 7th, 14th, 21st, 28th days. Blood lipid levels were measured at baseline and day 28.
Results: There was a persistent decrease in plasma glucose levels in the ranolazine treated animals during the study. Fasting plasma glucose levels were significantly lower in the ranolazine-treated group (206.3+12.74 mg/dl) compared with the vehicle group (437.8+34.03mg/dl) at 4 weeks. Ranolazine had a favourable effect on lipid profile when compared to the control (vehicle treated) animals.
Conclusions: Ranolazine improved glucose and lipid homeostasis in streptozotocin induced diabetic wistar rats. Further studies are needed to validate the findings and elucidate the exact mechanism.

Keywords: Ranolazine, Plasma glucose, Lipid profile, STZ induced diabetes

INTRODUCTION

Type 2 diabetes is characterized by elevated fasting and postprandial plasma glucose concentrations, which may either result from increased endogenous glucose production, decreased insulin-mediated muscle glucose disposal and inadequate pancreatic insulin secretion. It is also a risk factor for cardiovascular disease and frequently coexists with cardiovascular comorbidities, including dyslipidemia and hypertension, and thus is a significant predictor of cardiovascular mortality. The existing pharmacotherapy for type 2 diabetes consists primarily of sulfonylureas and metformin. Recent additions include thiazolidinedione's (TZDs), dipeptidyl peptidase IV (DDP IV) inhibitors, alpha glucosidase inhibitors, PPARγ agonists and SGLT II inhibitors (Gliflozins). These therapies provide reasonable glycaemic control but are unable to arrest the natural progression of diabetes or the eventual need for insulin. A number of new therapeutic agents are required to overcome the shortcomings of current therapies.

Ranolazine is a novel anti-anginal drug with proven cardiovascular safety profile. Ranolazine reduces myocardial ischemia by improving sodium-calcium homeostasis via inhibition of the late phase of the inward sodium current (late INa) during cardiac repolarization. In addition to its anti-anginal effects, ranolazine has been

shown to reduce HbA1c in patients with CAD and diabetes in various clinical trials. However the mechanism for its antidiabetic effect is unclear. Pre-clinical studies previously conducted suggest augmentation of glucose stimulated insulin secretion and reduction of glucagon secretion by modulation of Na channels. Inhibition of I Na by ranolazine may increase the concentration of intracellular ATP by lowering the consumption of ATP thereby inhibiting I KATP and causing depolarization of the cell followed by activation of calcium channels, increase in intracellular calcium concentration, and consequent increase in insulin release. Apart from augmented glucose stimulated insulin release it has a beta cell protective effect.[1]

Ranolazine, via blockade of NaChs expressed in pancreatic a-cells, inhibits their electrical activity and reduces glucagon release.[2]

Ranolazine is found to decreases inflammatory mediators IL-1 beta, TNF-alpha and increases anti-inflammatory PPARy in cultured astrocytes.[3]

IL-1 has been implicated as immunological mediators that inhibits insulin secretion and induce beta cell destruction.[4]

PPAR-γ expressed in adipose tissue, is involved in adipose tissue differentiation and triglyceride synthesis. It is highly expressed in human islet endocrine cells both at mRNA and protein level. PPAR-γ agonists like thiazolidinedione's improve beta cell function & reduce insulin resistance. However, their use has dramatically decreased due to their potential untoward side effects. In view of these findings, we hypothesize that ranolazine if capable of decreasing inflammatory mediators like IL-1 and TNF alpha and increasing expression of PPAR γ, in adipocytes and pancreatic tissue can improve beta cell survival and insulin resistance respectively and serve as an alternative to thiazolidinedione's with a better safety profile.

METHODS

Albino wistar rats of either sex weighing 150-200 grams, bred in central animal facility of JSS Medical College were used for the study. The study was conducted after having received the approval for the study protocol by institutional animal ethical committee. The animals were randomly divided into three groups of six animals each and housed in polypropylene cages at an ambient temperature of 25±1ºC and 45-55% relative humidity, with a 12:12 hour light/dark cycle.

Chemical and drugs used in this study was distilled water: 10 ml/kg body weight per orally, glibenclamide 1.35 mg/kg body weight per orally, streptozotocin 45 mg/kg body weight i.p, ranolazine: 45 mg/kg

Inclusion criteria

- Animals weighing 150-200gms either sex
- Age 3-4 months
- Healthy rats with normal behaviour and activity.

Exclusion criteria

- Pregnant rats
- Diseased rats

Procedure

Diabetes was induced in all 3 groups of animals by injecting streptozotocin in a dose of 45 mg/kg.[5] A freshly prepared solution of STZ (45 mg/kg body weight) in 0.1 ml citrate buffer, pH 4.5 was injected intra-peritoneally in a volume of 1 ml/kg body weight to overnight fasted rats. After 72 hours of STZ administration, rats with blood glucose levels greater than 250 mg/dl were selected for the experiment. The study animals were provided with water and food ad libitum. Animals were given the following drugs for a period of 28 days.

CBG levels were measured on 0, 7th, 14th, 21st, 28th days.

- Group-1 (control): distilled water 10 ml/kg
- Group-2 (standard): glibenclamide 1.35 mg/kg
- Group-3 (test): ranolazine 45 mg/kg

Parameters observed

- Fasting blood sugar by capillary blood glucose method
- Blood lipid levels.

Statistical analysis

After collecting raw data, the values in all the groups were analysed by using one-way analysis of variance (ANOVA). Followed by post Hoc Tukey's test for comparison between groups. Results were presented as mean±SEM. For all the tests a 'P' value of 0.05 or less was considered for statistical significance.

RESULTS

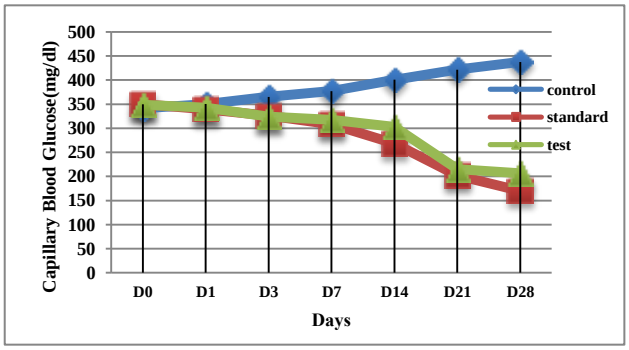

Figure 1: Capillary blood glucose levels from day 0 to day 28.

Table 1: Mean capillary blood glucose level in mg/dl on various days in study groups.

Groups	Day 0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
Control	341.2±24.64	350.3±24.45	*365.3±21.74	*377.2±22.83	*400.8±35.49	*421.7±32.64	*437.8±34.03
Standard	349.8±21.12	339.8±22.42	*326.2±22.45	*308.5±26.32	*268.2±26.39	*202.2±13.89	*169.8±13.3
Test	348.8±22.56	342.8±23.34	*324.5±22.77	*317.7±21.78	*303±18.19	*215.3±28.72	*206.3±12.74

n = 6, Values are expressed as Mean±SD. *p <0.05 indicates statistically significant value by one way ANOVA.

Table 2: Statistical analysis showing comparison of TC levels between different groups on day 1 and day 28.

Groups	Mean (mg%)+SD on 1st day	Mean (mg%)+SD on 28th day	Difference in TC levels
Control	119.33±10.78	212.5±8.11	93.17±2.67
Standard	106.6±7.76	100.6±7.89	6±0.13
Ranolazine	111.5±11.84	132.83±6.43	21.33±5.41

Table 3: Statistical analysis showing comparison of TG levels between different groups on day 1 and day 28.

Groups	Mean (mg%)+SD on 1st day	Mean (mg%)+SD on 28th day	Difference in TG levels
Control	101.33±14.34	210.16±14.46	108.83±0.12
Standard	109.5±14.55	101.83±5.34	7.67±9.21
Ranolazine	120.5±8.31	157.66±12.19	37.16±3.88

Table 4: Statistical analysis showing comparison of LDL levels between different groups on day 1 and day 28.

Groups	Mean (mg%)+SD on 1st day	Mean (mg%)+SD on 28th day	Difference in LDL levels
Control	127.83±10.14	213.66±9.11	85.83±1.03
Standard	111.33±9.89	114±10.75	2.67±0.86
Ranolazine	118.83±4.66	150.5±8.11	31.67±3.45

Table 5: Statistical analysis showing comparison of HDL levels between different groups on day 1 and day 28.

Groups	Mean (mg%)+SD on 1st day	Mean (mg%)+SD on 28th day	Difference in HDL levels
Control	37.33±5.2	27.16±4.26	10.17±0.94
Standard	42.33±3.07	44.66±3.61	2.33±0.54
Ranolazine	40.16±3.86	34.5±3.93	5.66±0.07

The control rats showed consistent hyperglycaemia and the standard drug showed persistent decrease in the blood glucose level from 1st to 28th day, while the test drug produced considerable decrease in blood glucose level up to 28th day when compared with the standard drug, as shown in Table 1 and Figure 1.

Lipid profile

Baseline blood lipid levels were measured and compared with the values taken at the end of the study i.e on day 28.

At the end of 28th day there was increase in the TC levels in all the groups. The raise in the TC levels was more with control group and least with standard. The test groups showed raise in TC levels and was statistically significant when compared to control. There was a considerably higher increase in triglyceride and LDL levels in control. The levels of both triglyceride and LDL increase was significantly less in the ranolazine treated group, which was comparable to the standard. There was significantly higher decrease in HDL level in control group. The fall in HDL was very minimal with standard and only a moderate decrease in HDL levels was found in ranolazine treated group.

DISCUSSION

Diabetes mellitus is one of the most commonly occurring metabolic disorders which co-exists which many other clinical conditions. It is a major risk factor for various cardiovascular disorders including Angina. Alterations in the concentration of major lipids like cholesterol, high density lipoprotein, low density lipoprotein and triglycerides could give useful information on the lipid metabolism as well as predisposition of the heart to atherosclerosis and its associated coronary heart diseases. Elevated levels of all lipids except the high density lipoprotein (HDL) are associated with increased risk ofatherosclerosis.[6]

Ranolazine is an FDA approved drug used in the treatment of chronic angina. In the present study we demonstrated the effect of ranolazine on blood glucose and lipid levels in streptozotocin treated albino wistar rats. Ranolazine was found to lower the blood glucose levels consistently over the period of 28 days (Table 1). The improvement in the various parameters of lipid profile was considerably found in the test group when compared to the control. In this study, plasma glucose and total cholesterol increased ($p<0.05$) in streptozotocin-induced diabetic rats. Streptozotocin is a naturally occurring product produced by streptomyces achromogenes which has been extensively used to induce diabetes for various diabetes studies in laboratory animals. Streptozotocin is observed to cause a massive reduction of the β- cells of the islets of Langerhans and induce hyperglycaemia. STZ has been reported to be capable of generating reactive oxygen species resulting in oxidative stress and cell death. The elevation in the serum glucose level and decline in serum insulin level of diabetic control animals may be attributed to the specific destruction of beta cells by STZ which produces the hormone insulin for normal glucose homeostasis. Hyperlipidemia is a recognized complication of DM characterized by elevated levels of cholesterol, triglycerides and phospholipids and changes in lipoprotein composition. One of the major pathogenesis of lipid metabolism disturbances in diabetes is the increased mobilization of free fatty acids from adipose tissue and secondary elevation of free fatty acid level in the blood due to insulin deficiency or insulin resistance. The excessive lipolysis in diabetic adipose tissue may lead to increased free fatty acids in circulation which enter the liver and are esterified to form triglycerides. The fatty acid compositions of various tissues are altered in both experimental and human diabetes. The improvement in the plasma glucose in ranolazine treated animals was statistically significant when compared to animals treated with the standard drug glibenclamide. Glibenclamide is a Sulfonylurea which is one among the most commonly used drugs in the treatment of diabetes mellitus. A reduction in total cholesterol, triglycerides and LDL was found in the ranolazine treated rats when compared to animals treated with streptozotocin alone (Tables 2, 3, 4). Reduction of blood cholesterol protects against the risk of cardiovascular diseases.

Limitations of the study were other parameters of glucose homeostasis such as Hba1c, plasma insulin, were not measured. Islet cell morphology before and after treatment with the test drug was not studied. Alterations in PPAR gamma expression in adipocytes were not studied.

CONCLUSION

Our results were consistent with the earlier studies where ranolazine reduced blood glucose levels. In addition ranolazine also exhibited a favourable effect on the blood lipid profile. Hence ranolazine by its capability of lowering plasma glucose and significant improvement in the lipid profile may prove to be a beneficial drug in treating the patients of chronic angina with co-existing diabetes mellitus. Effect of ranolazine on PPAR gamma expression in adipocytes if proved may confer this drug an additional benefit in improving lipid homeostasis and cardiovascular outcomes.

ACKNOWLEDGEMENTS

The Authors would like to thankful to the department of pharmacology, Central Animal Facility, JSS medical College, JSS University for the support and technical assistance.

Funding: The project was majorly self-funded with assistance from department of Pharmacology, JSS Medical College, JSS University.
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ning Y, Zhen W, Fu Z, Jiang J, Liu D, Belardinelli L, et al. Ranolazine increases beta-cell survival and improves glucose homeostasis in lowdose streptozotocin-induced diabetes in mice. J Pharmacol Exp Ther. 2011;337(1):50-8.
2. Dhalla AK, Yang M, Ning Y, Kahlig MK, Krause M, Rajamani S, et al. Luiz blockade of Na+ channels in pancreatic a-cells has antidiabetic effects. Diabetes. 2014;63:3545-56.
3. El Amrani FB, Guerra S, Aldasoro M. Anti-inflammatory and antioxidant effects of ranolazine in primary culture in primary cultured astrocytes. Crit Care. 2014;18(1)447-50.
4. McDaniel ML, Kwon G, Hill JR, Marshall CA, Corbett JA. Cytokine in Islet Inflammation and Diabetes. Exp Biol Med. 1996;221(1):24-32.
5. Zhang M, Xiao-Yan LV, Li J, Zhi-Gang XU, Li C. The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat. Exp Diabetes Res. 2008;2008:704045.
6. Prohp TP, Onoagbe IO, Joel P. Plasma glucose concentration and lipid profile in streptozotocin-induced diabetic rats treated with extracts of triplochiton scleroxylon K. Schum. International Journal of Analytical Pharmaceutical and Biomedical Sciences. 2012;1(1):22-9.
7. Dhanush KB, Suguna R, Satyanarayana ML. Serum insulin levels and lipid profiles of streptozotocin induced diabetic wistar rats. J Ind Vet Assoc. 2012;10(2):22-5.

Cite this article as: Bashir S, Kalabharathi HL. Ranolazine improves glucose and lipid homoestasis in streptozotocin induced diabetes mellitus in albino wistar rats. Int J Basic Clin Pharmacol 2016:5:1477-80.