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Original Research Article

Evaluation of Anti-Hyperglycaemic Effect of Ranolazine in Streptozotocin-induced Diabetic Rats

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Abstract

Title: Evaluation of the anti-hyperglycemic effect of Ranolazine in streptozotocin-induced diabetic rats.

Objectives: To evaluate the effect of the Anti-hyperglycemic property of Ranolazine in streptozotocin-induced diabetic adult albino rats.

Methods: After measuring the normal baseline blood sugar for 24 adult male albino rats weighing 150 to 200 grams by tail venipuncture method, Injection streptozotocin was injected intraperitoneally at a dose of 45mg/kg to all rats. Fasting B lood sugar was estimated 72 hours after streptozotocin injection and rats with blood sugar of more than 250mg/dl were considered for the study and were randomly divided into 4 groups (control, standard, test group 1 & test group 2) with six animals in eachgroup. Fasting blood sugar (FBS) was measured for all the animals on day1,3, 7,14, 21& 28 respectively. Cardiac puncture was done for all rats and blood samples were collected for estimation of Insulin on days 1 & 28. The results were finally tabulated and Statistical analysis was done using SPSS software.

Results: There was a statistically significant reduction in the blood glucose levels and a significant increase in serum Insulin levels in the animals of Test 1 & Test2 groups in comparison with the standard & control groups. ($p< 0.001$).

Conclusions: Ranolazine, an anti-anginal drug, has also got significant anti-hyperglycaemic properties and also increases the Insulin levels in streptozotocin-induced diabetic rats in comparison with the control rats. Hence, Ranolazine may help in the management of patients with type 2 diabetes mellitus (DM) by reducing glycaemic levels. As an added advantage, Ranolazine may also help to reduce the polypharmacy in patients with diabetes mellitus and angina thereby reducing the drug as well as disease-induced morbidity and mortality.

Keywords: Diabetes, FBS, Anti-hyperglycemic, Angina, ANOVA.

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Introduction

Diabetes mellitus is one of the chronic metabolic disease, characterized by 'too great emptying of urine', finds its place in antiquity through the Egyptian manuscripts dating

back to even 1500 B.C. Indian physicians had called it '***madhumeha'*** (honey urine) since it attracted ants [1]. Type 2 diabetes mellitus which is most common in adults,occurs when the body becomes resistant to insulin or doesn't make enough of insulin. The global diabetes prevalence in 2019 which was estimated to be 9.3% (463 million people), is projected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The prevalence of diabetes is higher in urban (10.8%) than rural (7.2%) areas, and in high-income countries (10.4%) than low-income countries (4.0%). One in two (50.1%) people living with diabetes are unaware of their clinical condition [2]. Chronic hyperglycemia is associated with relatively long-term macrovascular and microvascular complications that affects kidneys, nerves, eyes and has an increased risk for cardiovascular disease (CVD) [3]. Mortality rate due to MI is high (42%) among diabetics when compared to non-diabetics(15.4%) [4]. Diabetes is associated with 11.3% of global deaths from all causes [5]. Till now, multifactorial risk factor reduction (glycaemic control, smoking cessation, diet, exercise, aggressive blood pressure control, treatment of dyslipidaemia) is considered to be the most effective approach for prevention of macrovascular complications [6].

Ranolazine (piperazine derivative) an anti – anginal drug, has been found to be associated with significant reductions in the level of glycosylated haemoglobin (HbA1C) in previous animal studies [7]. Ranolazine treatment was shown to improve the beta cell function of the islets of pancreas, thereby increasing the levels of Insulin. Increased levels of Glucagon, increases the rate of glycogenolysis and gluconeogenesis thereby ultimately leading to increase in bothfasting glucose and PPG levels. Ranolazine inhibits the glucagon secretion from pancreatic α-cells by inhibition of their electrical activity via blockade of sodium channels (Nav1.3 isoform) [8]. Despite the availability of numerous anti-hyperglycemic agents, the advantage of Ranolazine is that, this single drug can be used to treat both diabetes as well as angina, reducing the intake of multiple drugs referred to as polypharmacy, thereby reducing the drug as well as disease induced morbidity and mortality.

With this background, this study was undertaken to evaluate the effect of Anti-hyperglycemic property of Ranolazine in streptozotocin induced diabetic rats.

Aim and objectives

To evaluate the effect of Antihyperglycemic property of Ranolazine in adult albino rats.

Materials and methods

This interventional animal experimental study was conducted over a period of 6 months at the Central animal house, Madurai Medical College, Madurai, after obtaining clearance from Institutional Animal Ethical Committee.

Materials

Oral feeding tube, Tab. Ranolazine, Diethyl ether, Syringes, Blood collection tubes coated with anticoagulant, Glucometer, Glucose strips, Rat insulin ELISA Kit, Drop jar, Cotton, Distilled water, Inj. Streptozotocin.

Animals

24 adult male albino rats weighing 150 to 200 grams, inbred in Central animal house, MaduraiMedical College, Madurai were used for the study. The animals were dividedinto 4 groups with 6 rats in each group. They were allowed standard diet (pellet feed) with tap water ad libitum. To prevent infection adequate hygiene was maintained.

Streptozotocin

Streptozotocin manufactured by Sisco Research Laboratories Pvt. Ltd was used for inducing diabetes in the albino rats.

Glibenclamide

Glibenclamide 5 mg tablet, manufactured by Sanofi aventis (trade name- daonil) was used for this study. Tab. Glybenclamide was made soluble in distilled water and was given at a dose of 1mg/kg oral od.

Ranolazine

Ranolazine available as 500mg tablet, manufactured and sold as Ranexa was made soluble in distilled water and was given at 2 different doses to 2 different groups - 45mg/ kg & 90 mg//kg oral od.

Blood sample collection

0.2 ml of blood was collected from the rats by tail venipuncture method, using a 22G needle for blood sugar estimation & for estimation of serum insulin, 2 ml of blood was collected by cardiac puncture method.

Glucose Estimation Method

Glucometer was used to measure the blood sugar with a glucose oxidize enzyme-specific strips. Insulin estimation method: By using rat insulin ELISA Kit (manufactured by Novus Biologicals Ltd.), serum insulin level was measured in rat blood sample.

Methodology

Theblood glucose was estimated for all the rats by tail venipuncture method and only the rats with normal baseline blood sugar was taken for study. All the rats received Injection streptozotocin intraperitoneally at a dose of 45mg/kg. Blood sugar was estimated 72 hours after streptozotocin injection, and the rats with blood sugar of more than 250mg/dl were considered to be diabetic and were taken for the study. The diabetic rats were divided into 4 groups (control, standard, test group 1 & test group 2) with six animals in each group. Fasting blood sugar was measured for all the animals on day1,3, 7,14, 21& 28 respectively. The cardiac puncture was done for all rats and blood samples were collected for estimation of insulin on day 1 & 28. The results were finally tabulated, and Statistical analysis was done based on ANOVA test and the level of significance were done between the group.

Results and Discussion

Results obtained from this study is tabulated as below.

Table 1: Blood glucose levels: (mean ±SD)

Groups	1st Day	3rd Day	7th Day	14th Day	21th Day	28th Day
Control	425.33 ±21.85	413.5 ±19.10	407.33 ±18.92	408 ±15.67	405.83 ±15.31	407 ±16.54
Standard	419.83 ±71.68	263.5 ±21.85	172.83 ±17.03	158.6 ±11.97	126.5 ±17.59	117.16 ±16.91
Test- 1	486 ±95.09	304.5 ±36.87	140.16 ±9.04	132 ±7.79	113.66 ±14.94	101.66 ±11.77
Test - 2	468.5 ±111.02	229 ±30.26	127.5 ±8.93	119.83 ±8.42	100.66 ±10.25	89.16 ±12.68

All the animals in the control group had elevated blood sugar levels with no change in Insulin levels. Blood glucose levels were under control for the animals in the control group with no change in Insulin levels. Animals in the Test group I had reduced blood glucose levels with slight increase in Insulin levels. Animals in the Test group II had reduced blood glucose levels with significant increase in Insulin levels.

Table 2: Serum Insulin levels in diabetic rats- mIU/ml -Day1& 28

S. No	1st Day (mean ±SD)	28th Day (mean ±SD)
Control	1.26 ±0.15	1.4 ± 0.12
Standard	1.5±0.45	1.8 ± 0.11
Test- 1	1.32±0.13	1.88 ±0.36
Test - 2	1.3±0.22	2.17 ± 0.17

From this study it was found that there was a significant reduction in the blood glucose levels and a significant increase in serum insulin levels in Test 1 & Test 2 in comparison with the standard & control group. Statistical analysis showed no significant difference in the baseline values. There was a significant difference between test 1 and test 2 groups and standard groups (p value of 0.001). Finally, the Post hoc analysis showed more statistical difference in the test group 2 >test group 1 > standard rats in comparison with the control group rats. The results were found to be statistically significant with p value of 0.001.

Type 2 Diabetes mellitus is characterized by insulin resistance withprogressive reduction of pancreatic β-cell function [8]. Ranolazine directly improves the glycemic control in type 2 diabetes mellitus patients. From the previous studies, it was observed that the patients on sulfonylureas or Insulin have more risk of developing angina. Due to increased prevalence of glucose impairment in patients with coronary artery disease, we need a better understanding of the relationship between glucose-lowering drugs and angina [09]. Ranolazine could treat chronic angina and also lowers the blood glucose levels. Studies by Fanaroff A C *et al.*, has shown that in diabetic patients with chronic angina, with incomplete revascularization after percutaneous intervention, ranolazine's effect on glucose control and angina at 6 months was proportionate to baseline HbA_{1c}, but the effect on angina dissipated by 12 months [9].

At molecular level, ranolazine targets either nutrient-induced insulin secretion pathway or influence GLUT receptors that are involved in glucose transport into the cells. Ranolazine treatment improves the beta cell function of the islets of pancreas. It was also found that Ranolazine-treated mice had healthier islet morphology and significantly higher number beta cell mass when compared with the vehicle group.

Ranolazine also causes an increased glucose-stimulated insulin secretion in humans and rat islets. B. Bhowmik *et al.*, has shown that in animal models of diabetes, ranolazine has reduced postprandial and basal glucagon levels too, thus leading to reduced hyperglycaemia, confirming that the glucose-lowering effects of ranolazine could have been mediated by blockade of sodium channels in the alpha-cells of pancreas [10].

From the above results, it was confirmed that Ranolazine has significant anti hyperglycemic effect in streptozotocin induced diabetic rats. Ranolazine, an anti-anginal drug, also increases the Insulin levels in streptozotocin induced diabetic rats in comparison with the control rats.

Hence, Ranolazine may help in the management of patients with type 2 diabetes mellitus (DM) by reducing the glycemic levels. As an added advantage, Ranolazine may also help to reduce the polypharmacy in patients with diabetes mellitus and angina thereby reducing the drug as well as disease induced morbidity and mortality.

References

1. R. Lakhtakia, The History of Diabetes Mellitus, Sultan Qaboos Univ Med J. Aug. 2013;13(3): 368–370.
2. Diabetes Canada Clinical Practice Guidelines Expert Committee, Z. Punthakee, R. Goldenberg, and P. Katz, Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, Can. J. Diabetes. Apr. 2018; 42(Suppl 1): S10–S15
3. Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of Diabetes, Prediabetes and metabolic syndrome. Diabetes Canada Clinical practice guidelines expert committee; Can J Diabetes. 2018: April; 42-Suppl: 1: S10 -5.
4. J. B. Cole and J. C. Florez, Genetics of diabetes mellitus and diabetes complications, Nature Reviews Nephrology. May 2020; 1-14.
5. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org; last accessed on November 23, 2022
6. Diabetes Canada Clinical Practice Guidelines Expert Committee, Z. Punthakee, R. Goldenberg, and P. Katz, Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, Can. J. Diabetes., Apr. 2018; 42(Suppl 1): S10–S15.
7. R. Pathak and M. B. Bridgeman, Dipeptidyl Peptidase-4 (DPP-4) Inhibitors in theManagement of Diabetes, P T., Sep. 2010;35(9):509-513.
8. B. C. Simes and G. G. MacGregor, Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A Clinician's Guide, Diabetes Metab Syndr Obes, Oct. 2019; 12:2125-2136.
9. Fanaroff AC, James SK, Weisz G, Prather K, Anstrom KJ, Mark DB et al., "Ranolazine after incomplete percutaneous coronary revascularization in patients with versus without diabetes mellitus: RIVER -PCI Trial. J Am Coll Cardiol.2017 May 9 ; 69(18): 2304 -13.
10. B. Bhowmik et al., Serum Lipid Profile and Its Association with Diabetes and Prediabetes in a Rural Bangladeshi Population, Int J Environ Res Public Health., Sep. 2018; 15(9).