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A Study on Comparative Efficacy of Teneligliptin and Metformin in Streptozotocin Induced Type 2 Diabetic Albino Rats

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Abstract

Introduction: The traditional anti diabetic drugs have several drawbacks in long term use. The approach of diabetes management today has shifted to include β-cell preservation, so as to delay the progression of type 2 diabetes. Teneligliptin, the newest DPP-4 (dipeptidyl peptidase-4) inhibitor helps to promote the Incretin effect and could be of benefit early in the treatment of type 2 diabetes to delay exhaustion of pancreatic islet function. In the absence of direct head-to-head comparative study, the position of Teneligliptin in the management of type 2 diabetes mellitus in comparison to other classes of anti-diabetic agents remains to be determined. This study is conducted to investigate the effect of Teneligliptin on fasting blood glucose level as well as comparative effectiveness with Metformin in Streptozotocin induced Type 2 diabetic albino rats.

Methods: Albino rats were divided into six groups of 6 rats in each group. Group A was non-diabetic given 1% Gum acacia. Group B, C and D were made diabetic by using Nicotinamide and Streptozotocin injection intra peritoneal and given 1% Gum acacia, Teneligliptin (0.72 mg/ 200 gram rats) and Metformin (18 mg/ 200 gram rats) respectively for the period of 42 days. Fasting Blood Glucose (FBG) levels were measured before induction of diabetes, 72 hrs after the induction, on day 0, 7th, 14th, 21st, 28th, 35th and 42nd day.

Results: In diabetic albino rats Teneligliptin normalized fasting blood glucose in fifth weeks and this effect is significant ($p<0.05$) with comparison to Metformin.

Conclusions: Efficacy of Teneligliptin in controlling fasting blood glucose is almost similar to Metformin. May be due to the fact that it improves beta cell function, promotes beta cell mass expansion and stimulate insulin biosynthesis and its release. It can be serves as an appropriate early in management of type 2 diabetes mellitus.

Keywords: Diabetes, Dipeptidyl peptidase–4 inhibitor, Metformin, Streptozotocin, Teneligliptin.

Introduction

Diabetes mellitus is one of the leading non-communicable diseases with the number of individuals suffering from this disease predicted to increase to 522 million worldwide by 2030. Globally, the disease is amongst the top ten causes of disability andaccounts for more than 4 million deaths per year and ~11% of total healthcare expenditure [1]. At present India is considered as the Diabetes capital of the World by World Health Organisation (WHO) [2]. Already approximately 3.5 crore population of India is diabetic and the value is likely to increase up to 5.2 crore by 2025, which will be the highest diabetic population worldwide [3]. Diabetes is a progressive disorder, management starts with lifestyle modification i.e. diet & exercise but eventually will require pharmacotherapy. The American Diabetes Association (ADA) recommended Metformin as the first line monotherapy for treating type 2 diabetes mellitus (T2DM) patients, especially those who are overweight [4]. Metformin does not cause insulin release but presence of insulin is essential for its action. In clinical scenario, Metformin therapy has been associated with gastrointestinal adverse effects, megaloblastic anaemia and lactic acidosis [5] [6]. The United Kingdom Prospective Diabetes Study (UKPDS) was the first to show that the combination of SU and Metformin resulted in a progressive decline in β-cell function and by 3 years up to 50% of diabetic patients may require an additional pharmacological agent to maintain the glycosylated haemoglobin (HbA1c) <7.0% [5][7].

In contrast to earlier notion of tight glycaemic control, the approach of diabetes management today has shifted to include β-cell preservation, so as to delay the progression of type 2 diabetes. In addition to targeting glycaemia control, anti-diabetic drugs should ideally aim to minimize the risk of adverse outcomes such as weight gain and hypoglycaemia. An improved understanding of the pathogenesis of the disease and regulatory mechanisms involved in glucose homeostasis has resulted in the emergence of treatment strategies that target the gut-derived incretin hormones i.e. - glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [8]. Following release, GLP-1 and GIP are rapidly inactivated by dipeptidyl peptidase -4 (DPP-4). As a class, the efficacy of DPP4 inhibitor is well established. These agents have a convenient once daily regimen, body weight neutral effect and associated with a lower risk of hypoglycaemia [8] [9]. The gliptins do not appear to lead to secondary failure of the insulin-secreting β- cells of the pancreas and were shown to maintain the secretory capacity during the treatment [10]. A growing body of evidence indicates that they may slow the progress of the disease and increase β-cell mass and survival [11]. Among the gliptins, Teneligliptin is the newest, cheaper and its efficacy and safety is comparable to other gliptins – has been selected for this study. Owing to its pharmacodynamic, pharmacokinetic & pleiotropic benefits, Teneligliptin could be of benefit early in the treatment of type 2 diabetes and serves as an appropriate early in therapy to delay exhaustion of pancreatic islet function. In the absence of direct head-to-head comparative study, the position of Teneligliptin in the management of T2DM relative to other classes of anti-diabetic agents remains to be determined. Hence this study is taken up to investigate the effect of Teneligliptin on fasting blood glucose level as well as comparative effectiveness with Metformin in Streptozotocin induced diabetic albino rats.

Aims and Objectives:

To compare the efficacy of Teneligliptin and Metformin in streptozotocin induced Type 2 diabetic albino rats.

Materials and Methods

Animals:

Healthy male Wistar Albino rats were procured from authorized supplier from Kolkata and rats weighing between 150-250 grams were taken for the present study. The animals were kept in proper laboratory condition and acclimatized for the period of 2 weeks before using for the experiment and were fed with standard laboratory diet and water was given ad libitum.

Study design:

The entire experiment was carried out in Post graduate Laboratory of "Department of Pharmacology and Therapeutics, Rajendra Institute of Medical Sciences, Ranchi" after approval by the Institutional Animal Ethics Committee. The study was conducted over a period of 6 weeks. Fasting blood sugar before the initiation of study was within the range of 200- 250 mg/dl. Study animals were divided into four groups with six animals in each group and were kept in four appropriately labelled animal cages. The groups were normal control, diabetic control, diabetic with Teneligliptin, diabetic with Metformin. Animals in each cage were also labelled separately and colour coded with the help of permanent marker. Rats of each group were given different treatment orally once daily for 42 days in the morning hour at 09:30-10:30 am.

The details of groups were as follows (Table 1):

Group	Number of Rats	Drugs	Dose
A Normal Control (Non Diabetic)	6	*Vehicle* *Gum acacia 1%*	10 ml/kg body wt
B Diabetic control	6	*Vehicle* *Gum acacia 1%*	10 ml/kg Body wt
C Diabetic rats with Teneligliptin	6	Teneligliptin	40mg/70kg body Wt
D Diabetic rats with Metformin	6	Metformin	1000mg/70kg body wt

Drugs:

a) Streptozotocin 250 mg powder (SISCO Research Laboratories Pvt. Ltd., Maharashtra)

b) Teneligliptin 40 mg tablet (Tenglyn, Zydus Cadila)

c) Metformin 1000 mg tablet (Gyciphage, Franco Indian Remedies)

d) Nicotinamide 100 gm powder (Animed, Kolkata)

Dose calculation:

Dose of the drugs was calculated from the standard clinical human dose on the basis of surface area. Surface area ratio of 200g rat versus 70 kg man is 0.018. Thus human dose of the drug (for a 70 kg person) multiplied by 0.018 gives the value of the dose of that drug for 200g of rat. For 200 gram rat the dose of Teneligliptin and Metformin would be 0.72 mg and 18 mg respectively.

Preparation of testing materials:

1. Nicotinamide

The dose of Nicotinamide for this study was 120mg/kg. It means for a 200 gm rat the dose of Nicotinamide would be 24 mg. Thus 2400 mg of Nicotinamide was dissolved in 100 ml of normal saline to have strength of 24 mg/ml. Now during diabetes induction the dose of Nicotinamide was adjusted according to the body weight of the rat.

2. Preparation of streptozotocin

Streptozotocin (250mg) was bought from SISCO Research Laboratories Pvt. Ltd., Maharashtra. Since Streptozotocin is highly sensitive to temperature, it was used within 15-30 minute after preparing the solution and as it is stabilized at pH 4-4.5, the citrate buffer is taken for preparation of solution. For inducing of moderate type 2 diabetes the dose of streptozotocin is 60 mg/kg. It means for 200 mg of rat 12 mg of Streptozotocin is required. For this purpose 250 mg of Streptozotocin dissolved in 20.8 ml of 0.1 M citrate buffer (pH of 4.2). As a result 1 ml buffer solution contained 12 mg Streptozotocin. Now during diabetes induction dose was adjusted according to the body weight of the rat.

3. Preparation of teneligliptin

The tablet was powdered and a uniform suspension was made by using 1% gum acacia. 72 mg Teneligliptin was dissolved in 100 ml of 1%gum acacia solution to have strength of 0.72 mg/ml. Now during feeding by gavage tube the volume of Teneligliptin solution was adjusted according to the body weight of the individual rat.

4. Metformin

The tablet was powdered and a uniform suspension was made by using 1% gum acacia. 1000 mg Metformin was dissolved in 50 ml of 1% gum acacia solution to get strength of 20 mg/ml. During feeding by gavages tube the volume of Metformin solution was adjusted according to the body weight of the individual rat.

Induction of type 2 diabetes mellitus: [12]

Diabetes was induced by freshly prepared single intraperitoneal injection of Streptozotocin in the dose of 60 mg/kg and Just 15 minutes before the Streptozotocin injection, Nicotinamide was injected intraperitoneally in a dose of 120 mg/kg with help of A 26 gauge needle with 1 ml syringe to the rats of group B, C and D. After intraperitoneal injections animals were allowed to drink 5% glucose solution overnight to overcome Streptozotocin induced hypoglycemia.

Confirmation of diabetes:

The fasting blood glucose level was measured after 72 hours of Streptozotocin injection for confirmation of diabetes. The rats having blood glucose level between 200-250 mg/dl were selected for the study. The diabetic animals were allowed free access to tap water, standard laboratory diet and were kept at appropriate laboratory condition. Though diabetes was confirmed after 72 hours of induction, Teneligliptin and Metformin were started on 8th day of induction and this day was considered as day '0' of the study and the treatment continued for 42 days. The blood samples were collected from all groups before induction of diabetes, after 72 hrs of diabetic induction and on day 0, 7th, 14th, 21st, 28th, 35th and 42nd day to determine the blood sugar level by glucose oxidase method by means of glucometer (Contour TS).

Statistical Analysis [13]

Statistical analysis of data was carried out by employing analysis of variance (ANOVA). Post hoc analysis was done by using Tukeys HSD (honestly significant difference) test. For intergroup comparison data were analyzed with the help of SPSS version 22 software. The data was tested at 5% and 1% level of significance.

Results

Table 2 gives sequential changes in FBS in the all groups on day 0, 7, 14, 21, 28, 35 and 42. Values are expressed in mean ± standard deviation. Figure-1 gives the graphic representation of the same. Group B rats (diabetic control) shows very high FBS that increase as the day progresses during the entire treatment period. Rats in Group C (Teneligliptin) and group D (Metformin) respectively shows progressive decrease in FBS level from day 7 to 42.

Table 2: Level of Fasting Blood Glucose (Mean ± Standard Deviation) of All the Groups throughout the Study Period.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Gr. A (Normal Control)	81.50 ± 4.09	82.67 ± 2.42	81.17 ±3.54	82.33 ± 3.78	82.17 ±4.26	81.33 ±4.59	81.83 ±2.93
Gr. B (Diabetic Control)	230.50 ± 4.18	236.67 ± 7.23	245.67 ±6.19	247.33 ± 5.20	251.67 ± 3.33	253.83 ±6.71	253.00 ±5.10
Gr. C (Teneligliptin)	230.83 ± 7.36	209.83 ± 4.96	173.33 ±3.88	155.00 ± 9.44	120.17 ± 6.62	97.50 ± 4.76	82.33 ± 2.25
Gr. D (Metformin)	230.00 ± 7.59	212.17 ± 4.17	179. 67 ±7.15	162.17 ± 2.32	128.67 ± 6.59	107.17 ± 5.27	92.67 ± 4.50

Figure 1: Showing changes in FBS in all groups on 0, 7th, 14th, 21st, 28th, 35th & 42nd day.

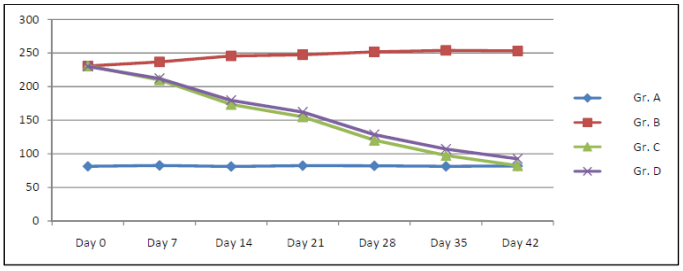
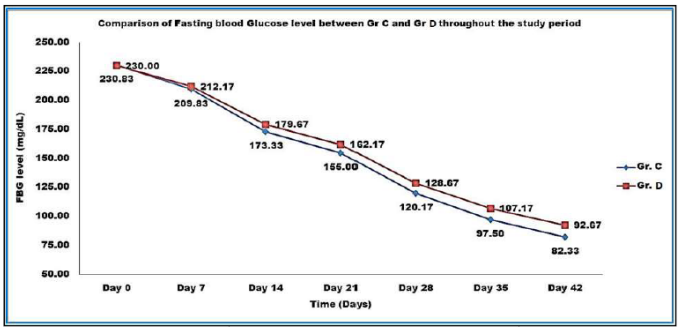


Table 3 compares the FBS in Teneligliptin and Metformin treated group. FBS values between groups C & D were significant on day 35 and 42 ($p<0.05$). Figure 2 depicts the graphic representation of FBS values; Slope of graph indicates the rate of fall in FBS during study period. It is clear from the graph that the rate of fall of FBS was more in 35th week and 42nd week in group C in comparison to group D.

Table 3: Comparison of Fasting blood Glucose level and Gr D throughout the study period.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Gr. C	230.83 ± 7.36	209.83 ± 4.96	173.33 ± 3.88	155.00 ± 9.44	120.17 ± 6.62	97.50 ± 4.76	82.33 ± 2.25
Gr. D	230.00 ± 7.59	212.17 ± 4.17	179. 67 ± 7.15	162.17 ± 2.32	128.67 ± 6.59	107.17 ± 5.27	92.67 ± 4.50
Mean Difference	0.83	2.33	6.33	7.16	8.50	9.66	10.33
Significance	0.99	0.95	0.22	0.21	0.053	0.017	0.00

Figure 2: depicts the graphical representation of FBG of group C& group D throughout the study period.



Discussion

Type 2 Diabetes mellitus is a metabolic disorder characterized by insulin resistance as well as β-cell dysfunction and is often associated with obesity. The insulin secreting pancreatic β-cell is central to the aetiology of diabetes. It is generally accepted that diabetes results when there is an inadequate functional mass of β-cells [14]. In face of insulin resistance the pancreatic β-cells tries to compensate for the increased metabolic demand by expanding their mass and enhancing insulin secretion but with progression of disease there is progressive deterioration in β-cell mass and function. The disease appears at a later stage and results from the progressive deterioration of β-cell mass and function [15]. Consequently, new approaches for diabetes treatment should aim at the preservation and the expansion of pancreatic β-cell mass. In the present study, Streptozotocin induced diabetic albino rat, a model of type 2 diabetes, was used to evaluate the effects of treatment with Teneligliptin (40 mg) on Fasting blood glucose and comparing its effect with Metformin (1000 mg). To observe the effect of Teneligliptin on Fasting blood glucose of Diabetic Albino Rats, various intergroup comparisons were made. Comparison between diabetic rats treated with Teneligliptin and Metformin is depicted in Table 2, Table 3; Figure 1 and figure 2. Our results show statistically significant 'P' value (<0.05) on day 35 & day 42 between these two groups. At the end of 42 days study, our results revealed that oral hypoglycaemic effect

of Teneligliptin has shown quite promising role in glycaemia control. A study on Zucker fatty rats done by Fukuda-Tsuru S et al. [16] showed that Teneligliptin improves postprandial hyperglycaemia and Dyslipidemia after single and repeated administrations. Hironori Nakagami et al. [17] showed that Treatment with Teneligliptin significantly improved hyperglycaemia and Insulin resistance, as evidenced by an oral glucose tolerance test and homeostasis model assessment for insulin resistance in SHRcp rats. Study done by Yoshinobu Nakamaru et al. comparing Teneligliptin Monotherapy and combination with other oral hypoglycaemic agents showed improved side effect profile for Teneligliptin in comparison to sulfonylurea and Metformin but equally effective HbA1c lowering results after 1 year [18]. In another animal study done by Pospisilik J. A. et al. [19] showed that DPP-4 inhibitor treatment in diabetic animal models stimulated beta-cell survival, facilitated islet neo-genesis, enhanced insulin biosynthesis. A critical appraisal of evidence done by van Genugten R. E. Et al. [11] stated that in humans with T2DM, DPP-4 inhibitors have demonstrated improvement of beta cell function both in the fasting and postprandial status and these beneficial effects were sustained in studies with duration up to 2 years. From above findings and previous literatures it is clear that in long term Teneligliptin shows similar effect as Metformin. Metformin improve peripheral insulin resistance and decrease fasting and random blood glucose and also it does not cause hypoglycaemia. But it does not devoid of troublesome side effects like severe gastrointestinal upset, lactic acidosis and megaloblastic anaemia. Teneligliptin in long term use has similar efficacy like Metformin in controlling fasting blood glucose level and has pleiotropic effect like beta cell protection as well as beta cell proliferation, increase insulin sensitivity, improves endothelial dysfunction and also devoid of any worrisome side effect like other conventional oral hypoglycaemic agent. The newer approach of type 2 diabetes mellitus management not only focuses on the control of blood glucose and HbA1c but the overall improvement of pancreatic endocrine function, improvement of metabolic profile along with reversal of disease progression. In this regard the therapeutic profile of Teneligliptin can prove itself as an upcoming superior agent as monotherapy or combination therapy in treatment of diabetes mellitus.

Conclusion

With the available data from the current study and related literature it can be concluded that on long term use, efficacy of Teneligliptin in controlling fasting blood glucose is almost similar to Metformin. So it can be serves as an appropriate early in therapy of type 2 diabetes mellitus. Hence, the present investigation warrants further studies to find out the relevance of this result in human beings and also the further studies are required at molecular level to know the exact impact on pancreatic beta cell function and further progression of the disease.

Limitations

1) In order to properly evaluate the effect of Teneligliptin on diabetic animal model, the db/db mice model would have been better option.

2) Effect of Teneligliptin on blood sugar could have been more properly evaluated if postprandial glucose and HbA1C level was measured.

3) Effect of Teneligliptin on beta cell mass and function could have been more properly evaluated using homoeostasis model assessment (HOMA) indexes.

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