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EFFECTS OF METFORMIN, GLIMEPIRIDE, SITAGLIPTIN AND THEIR COMBINATIONS ON BLOOD GLUCOSE LEVELS IN STREPTOZOTOCIN INDUCED DIABETES MELLITUS IN ALBINO RATS

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ABSTRACT

According to "The International Diabetes Federation", the number of people living with diabetes worldwide is expected to rise from 366 million in 2011 to 552 million by 2030. This equates to approximately three new cases every ten seconds or almost ten million cases per year. The International Diabetes Federation (IDF) reports a projected prevalence of 70 million patients in India by the year 2025, and the World Health Organization (WHO) estimates that India will have 80 million cases of diabetes by 2030. This places India second only to China in terms of number of people living with diabetes. Prevalence of Diabetes is increasing day-by-day in our country. The average cost of treating a diabetic in India has been estimated at 575 US Dollars or Rs.28750 annually in terms of direct costs, while, indirect costs like lost work-time, would account for another 100 US Dollars or Rs.5000 annually the greatest number of people with diabetes is between 40-59 years of age.

INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (PH, 1994). Several distinct types of Diabetes mellitus are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the Diabetes mellitus, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production (Genuth, 1982 and Macfarlane, 1991). The metabolic dysregulation associated with Diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. DM is the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness. It also predisposes to cardiovascular diseases (WHO, 1999). With an increasing incidence worldwide, Diabetes mellitus will be a leading cause of morbidity and mortality for the foreseeable future. Sitagliptin is an oral antidiabetic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class.

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This competitive inhibitor of the enzyme dipeptidyl peptidase 4 (DPP-4) prevents degradation of the incretins GLP-1, GIP and gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes, thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia) which is seen with some other oral hypoglycemic agents. Sitagliptin is used either alone or in combination with other oral anti-hyperglycemic agents (such as metformin or a thiazolidinedione) for treatment of diabetes mellitus type 2. It has fewer side effects (e.g., less hypoglycemia, less weight gain) (Herman *et al*., 2006 and Gadsby and Roger, 2009).

Aims and Objective

Sitagliptin is being evolved for the treatment of diabetes as monotherapy or in combination with other drugs. The aims and objective of this study was

- To evaluate the antidiabetic effect of Sitagliptin.
- To compare the antidiabetic effect of combination of Metformin and Glimepiride with that of Metformin and Sitagliptin combination.

MATERIALS AND METHODS

Healthy male wistar rats weighing between 150-250 grams were taken for the present study. The animals were kept in clean and dry cages, with 12 h: 12 h light-dark cycle at room temperature and humidity. They were acclimatized to the available housing condition and were fed with standard laboratory diet consisting of soaked black gram (Kala Chana) and water was given *ad libitum*. Arrangements were made to ensure regular cleaning of cages and disposal of excreta and urine. The cages were floored with a layer of saw dust for absorption of urine of rats. This was done because after induction of diabetes there would be excess of urination of rats. The whole experiment was conducted in accordance with ethical norms approved by Institutional Animal Ethics Committee (IAEC) Guidelines.

Drugs

- Sitagliptin (Januvia 100 mg tab) Merck Sharp and Dohme Limited.
- Metformin (Riomet 1000 mg tab) Ranbaxy Laboratories Ltd. Gurgaon (Haryana), India.
- Glimepiride (GLIMPID 2mg tab) Ranbaxy Laboratories Ltd. Gurgaon (Haryana), India.
- Streptozotocin (Zanosar 1gm powder) Pharmacia Healthcare Ltd. Mumbai.

Inclusion Criteria

1. All the animals used for the study were healthy and active in their cage.
2. Animals were male wistar rats.
3. Weight of the animal used was 150-250grams.
4. Fasting blood sugar before the initiation of study was within the range of 250- 350 mg/dl

Exclusion criteria

1. Diseased and inactive rats were excluded from the study.
2. Rats with weight less than 150 grams and above 250 grams were excluded from the study.
3. Rats with fasting blood sugar under 250 mg/dl and above 350 mg/dl were considered as improperly diabetic and excluded from the study.

The details of groups were as follows

There were five groups of six rats in each

Group	Number of Rats	Drugs	Dose
A Normal Control	6	*Vehicle Gum acacia 1%*	10ml/kg body wt
B Diabetic control	6	*Vehicle Gum acacia 1%*	10ml/kg body wt
C Sitagliptin	6	*Sitagliptin*	1.8mg
D Metformin+ Glimepiride	6	*Metformin+ Glimepiride*	18mg+.07mg
E Metformin + Sitagliptin	6	*Metformin + sitagliptin*	18mg+1.8mg

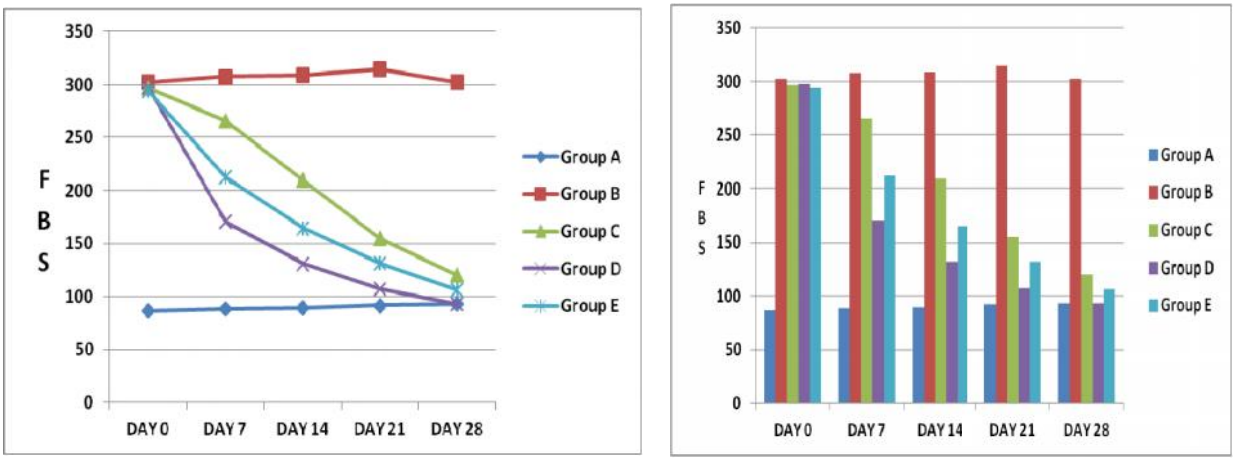
Statistical Analysis

Statistical analysis of data was carried out by employing analysis of variance (Snedecor and Cochran, 1967). One way ANOVA test was used to compare the effect of drugs on different group the effect. Tukey's HSD test was used for post-hoc analysis of significant overall differences. Tukey's HSD (honestly significant difference) test or the Tukey's-Kramer method, is a single- step multiple comparison procedure and statistical test. It is used in conjunction with an ANOVA to find means that are significantly different from each other. Tukey's test compare the means of every treatment to the mean of every other treatment; that is, it applies simultaneously to the set of all pair wise comparisons.

Table 1. Showing sequential changes in FBS in all groups on 0, 7th, 14th, 21st and 28th day. All the values are expressed in mean± standard deviation

	Group A	Group B	Group C	Group D	Group E
Day 0	86.50±1.72	302.50±8.758	297±4.427	298.00±5.967	293.83±4.665
Day 7	88.83±1.72	307.50±6.285	266.00±4.336	170.67±3.327	212.50±8.758
Day14	89.67±1.86	309.00±5.06	209.83±4.956	131.00±3.742	164.67±5.989
Day21	91.83±2.14	314.33±4.926	155.00±9.445	107.50±6.745	131.17±5.231
Day28	93.17±4.07	302.67±4.28	120.17±6.617	93.50±4.889	106.17±4.834

Table 1 (Master Chart)



CONCLUSION AND DISCUSSION

- Combination of glimepiride and metformin significantly reduces the fasting blood sugar level and has fast onset of action in comparison to other groups.
- Sitagliptin has significant effect in lowering of fasting blood sugar in diabetic rats but this effect only become significant after 7 days.
- Combination of Sitagliptin and metformin also has significant effect in lowering of fasting blood sugar in diabetic rats and its effect also become significant after 7 days but in comparison to sitagliptin it achieve lower level of FBS.
- Combination of Sitagliptin and metformin and Sitagliptin have slower onset of action and take more time to achieve euglycemic level of FBS in comparison to combination of glimepiride and metformin.

Overall decrease in FBS was highest in group D and it was also the most rapid fall. Although it appears as the best group but this pattern of blood glucose lowering can give rise to hypoglycemic episodes and can be fatal, which is highly undesired. Group C shows consistent fall but overall decrease is less, which may not be desirable in cases of severe hyperglycemia. Group E shows good overall decrease in FBS, almost near the value of group D, yet its fall is consistent like group C. Hence from above discussion it seems that Group E can be considered as the most desirable group. Table 1 gives sequential changes in FBS in the all groups on day 0, 7, 14 21and 28.Values are expressed in mean ± standard deviation. Figure 1 gives the graphic representation of the same. It is apparent from the table that fasting blood sugar in group A rats vary between 86 to 93 mg per dl.

This is the normal FBS level for rats and this serves as the target level to achieve good glycemic control. Group B rats were diabetic control that given only vehicle as a treatment. This group shows very high FBS that increase as the day progresses during the entire treatment period. Rats in Group C, D and E, were treated with Sitagliptin alone, combination Metformin and Glimepride and combination of Sitagliptin and metformin respectively shows progressive decrease in FBS level from day 7 to 28.

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