Research Article

Hypoglycemic Effect of Various Formulations of Glimepiride and Glibenclamide by Alloxan Induced Hyperglycemia in Rats

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ABSTRACT

Diabetes mellitus (DM) is a common group of metabolic diseases associated with endocrine and metabolic disorders, which are mainly characterized by hyperglycemia, with a genetic predisposition. DM leads to abnormal metabolism of carbohydrates, fats and proteins, sometimes accompanied by the long-term complications of diabetes, including microvascular, macrovascular, and neuropathic disorders. DM affects human eyes, kidneys, hearts, nerves and blood vessels. According to previous reports, diabetes mellitus has become the third most serious threat to human health following malignant tumors and cardiovascular and cerebrovascular disease. This study examines the effect of various formulations of Glimepiride and Glibenclamide on alloxan induced mils and severe hyperglycemia relative to its route of administration. The animals were divided into 5 groups (n=6).Group I serves as normal or control where the group's normal blood glucose level was determined and Group II serves as diabetic control where it receives alloxan alone to induce hyperglycemia and the other groups like Group III & IV receives glimepiride and glibenclamide and the last Group V receives the formulation. The result of the study showed a significant decrease in the blood glucose level at 7th day and 10th day for the formulations F6 of Glimepiride and Q6 of glibenclamide.

Keywords: Diabetes mellitus, Glimepiride, Glibenclamide, Hyperglycemia, alloxan induced diabetes.

INTRODUCTION

The latest statistical data of the International Diabetes Federation (IDF) showed that at least 382 million people worldwide had diabetes in 2013. Compared with 371 million cases in 2012, the increasing rate reached 8.4 percent, and by 2025, the organization predicts that there will be 592 million cases. Moreover, IDF showed that there are 5.1 million deaths caused by this disease per year, or one death every 6 seconds. The expense for the treatment of diabetes is high: The global diabetes medical costs are $548 billion, accounting for 11% of the global medical expenditure, and this is likely to rise to $627 billion by 2035. It has become a heavy economic burden of the individual, family and society[1]. In China, 114 million people had diabetes in 2013, which means there is one Chinese patient for every three to four patients with diabetes mellitus in the world, and the amount of patients is expected to increase a few million per year. Therefore, research on the prevention and treatment of diabetes and its complications has become a major public health issue. Currently available therapies for diabetes include insulin and various oral hypoglycemic agents, such as sulfonylureas, biguanides, metformin, glucosidase inhibitors, troglitazone, *etc*[2].

In conventional therapy, insulin-dependent diabetes mellitus or type 1 is treated with exogenous insulin while the non-insulin-dependent diabetes mellitus or type 2 is treated with oral hypoglycemic agents[3]. However, these drugs have serious side effects. For example, sulfonylureas drugs may cause abnormal liver function and hypoglycemia and are also not recommended for pregnant women because of their teratogenic effects on the fetus[4].

A large dose of biguanide drugs can lead to gastrointestinal reactions, including nausea, vomiting, abdominal pain, diarrhea, and loss of appetite. Patients with lung, liver, and kidney diseases are prone to lactic acidosis after taking biguanide drugs. The other classes of antidiabetic drugs, such as insulin sensitizing agents, insulin antagonistic hormone inhibitors, gluconeogenesis inhibitors, insulin like growth factor, ISU (insulin) secretion, and traditional Chinese medicine preparations, including flavonoids, alkaloids and so on, are also not ideal. Therefore, the development of safer, more specific and more effective hypoglycemic agents is important for diabetes treatment[5].

Determination of Antidiabetic Activity of different doses of Glimepiride and Glibenclamide in Vivo (Alloxan Induced Diabetes)

The effects of the differently doses of Glimepiride and Glibenclamide on the fasting blood glucose levels of alloxan-induced diabetic rats are shown in the following tables. The administration of a single intraperitoneal injection of 50 mg/kg body weight of alloxan monohydrate induced diabetes in rats after 72 h. The fasting blood glucose levels in alloxan-induced diabetic rats were 21.83–27.01 mmol/L. The fasting blood glucose levels of the diabetic model rats were significantly higher than that of the normal control group. Different doses of Glimepiride and Glibenclamide have different hypoglycemic activities[6-9].

Acute oral toxicity studies[10]

The acute oral toxicity studies of extracts were carried out as per the OECD guidelines, draft guidelines 423 adopted on 17th December 2001 received from CPCSEA, Ministry of social justice and empowerment, Govt. of India. Administration of the stepwise doses of different formulations of Glimepiride and Glibenclamide from 50 mg/kg b.w. up to the dose 5000 mg/kg b.w. caused no considerable signs of toxicity in the tested animals. One-tenth of the upper limit dose was selected as the level for examination of antidiabetic activity.

Analysis of blood sugar levels

Blood samples were collected from the tail vein after overnight fast at the intervals of 0, 2, 4, 8, 16, and 32 hrs[11]. The blood glucose level in the samples was estimated using One Touch Glucometer (Lifescan, Johnson & Johnson, California).

Experimental Design

The animals were divided in to seven groups and each group consisted of 6 rats.

1. Normal control (vehicle only)

2. Diabetic control (untreated rats)

3. Diabetic rats treated with Glibenclamide and Glimepiride 600µg/kg.

4. Formulations (F) of Glimepiride TDDS

5. Formulations (Q) of Gliemcalmide TDDS

Body Weight Measurement

Body weight was measured four times during the course of the study period (i.e., on, before alloxan induction (initial values), days 1, 4, 7 of the treatment period) [12-14], using a digital weighing scale obtained from KERN (EMB), Germany.

Statistical Analysis

The results of the study were subjected to one-way analysis of variance followed by Dunnett's t-test for multiple comparisons. Values with $P < 0.05$ were considered significant.

Table 1: Data showing physical parameters of glimepride transdermal patches

S. No	Formulation	Folding endurance	Thickness (mm)	Weight variation (gm)
1	F1	80±10.1	0.118±0.029	0.603
2	F2	50±12.2	0.103±0.023	0.612
3	F3	217±7.50	0.083±0.011	0.863
4	F4	227±6.39	0.100±0.017	0.637
5	F5	179±8.08	0.097±0.028	0.592
6	F6	189±7.90	0.089±0.012	0.672

Table 2: Data showing physical parameters of Glibenclamide TDDS patches

S. No	Formulation	Folding endurance	Thickness (mm)	Weight variation (gm)
1	Q1	100±9.0	0.108±0.078	0.599
2	Q2	150±11.6	0.113±0.032	0.621
3	Q3	200±7.3	0.093±0.011	0.785
4	Q4	207±6.0	0.116±0.019	0.675
5	Q5	169±8.76	0.123±0.029	0.524
6	Q6	205±7.92	0.119±0.019	0.512

RESULTS AND DISCUSSION

Table 3: Effect of Glimepiride and Glibenclamide on oral glucose tolerance test in normal rats

Sample	0min	30min	90min
Normal Control (5% Tween 80 + glucose (2g /kg)	81.33±1.874	164.33±2.301**	121.00±2.966**
Glibenclamide (600µg/kg) + glucose (2g /kg)	76.50±1.522	171.83±4.214**	106.16±4.316**
Glimepiride (600µg/kg) + glucose (2g /kg)	75.50±2.986	177.16±3.439**	155.33±3.018**

One-way ANOVA followed by Dunnett. s test. Values are expressed as mean ± SEM. **P<0.01as compared to normal control group.

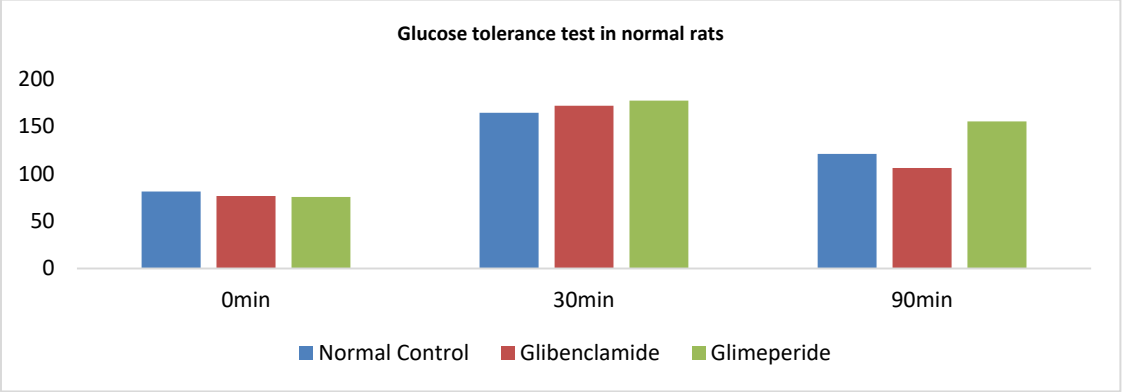

Figure 1: Glucose tolerance test in rats using Glimepiride and Glibenclamide

Table 4: Antidiabetic effect of Glimepiride and Glibenclamide formulations (F1-F6 & Q1-Q6)

Treatment	Fasting Blood Glucose Level(mg/dl)			
	Basal Value	4th Day	7th Day	10th Day
Normal Control	90.46±3.80	92.82±2.92	92.32±1.73	88.29±3.24
Diabetic Control (vehicle)	293.8±5.27	286.91±5.05	291.8±5.41	289.41±9.75
Alloxan + Glimepiride (10mg/kg)	285.86±6.92	205.25±7.06	183.18±6.35	178.13±6.20
Alloxan + Glibenclamide (10mg/kg)	291.76±4.79	277.76±5.65	266.23±8.19	255.42±7.71
Alloxan + F1	284.48±5.32	258.23±6.66	255.85±9.97	252.06±9.19
Alloxan + F2	248.48±5.02	232.43±4.32	230.25±3.36	222.56±9.19
Alloxan + F3	274.28±5.72	253.23±6.32	240.25±3.14	233.42±4.39
Alloxan + F4	244.16±6.16	240.23±7.54	233.32±3.14	230.42±4.39
Alloxan + F5	263.42±3.19	260.53±6.66	257.43±6.76	250.24±8.19
Alloxan + F6	244.12±6.27	230.23±7.54	229.44±7.12	225.24±3.12
Alloxan + Q1	287.13±5.27	285.43±6.54	279.21±7.42	275.34±4.12
Alloxan + Q2	282.12±7.45	280.13±4.14	279.33±6.64	275.12±3.34
Alloxan + Q3	277.42±8.12	274.63±7.13	273.53±5.43	270.44±7.32
Alloxan + Q4	287.23±6.75	282.43±5.35	280.13±4.46	270.44±6.32
Alloxan + Q5	275.45±3.27	271.21±5.65	270.15±7.81	268.42±4.12
Alloxan + Q6	245.54±6.47	243.11±7.23	240.14±8.21	238.62±4.12

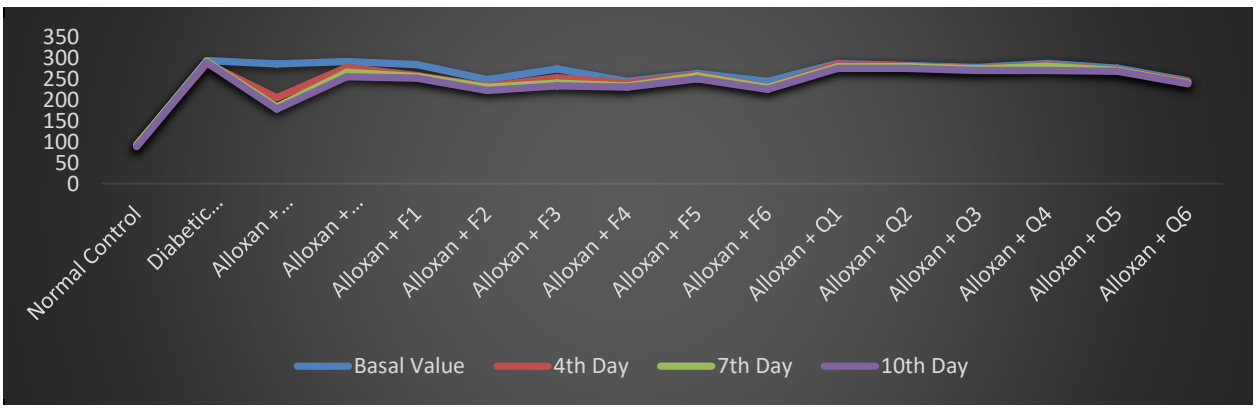

Figure 2: Antidiabetic effect of Glimepiride and Glibenclamide formulations (F1-F6 & Q1-Q6)

The animals were divided into 5 groups (n=6).Group I serves as normal or control where the group's normal blood glucose level was determined and Group II serves as diabetic control where it receives alloxan alone to induce hyperglycemia and the other groups like Group III & IV receives glimepiride and glibenclamide and the last Group V receives the formulation. The result of the study showed a significant decrease in the blood glucose level at 7^{th} day and 10^{th} day for the formulations F6 of Glimepiride and Q6 of glibenclamide.

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