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ORIGINAL ARTICLE

Controlling Hyperglycaemia Diabetes Mellitus Type-II: Bromocriptine Alone or in Combination with Metformin

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ABSTRACT

Background: Diabetes Mellitus is one of the leading cause of morbidity and mortality globally. According to WHO there is a steady increase in the number of diabetic patients annually. Maintenance of good glycaemic control in type 2 diabetic patients typically becomes progressively more difficult as the duration of disease lengthens due to decline in the capacity of the pancreatic beta cells for glucose stimulated insulin release, in the presence of insulin resistance. This study is conducted to observe the effect of metformin and bromocriptine individually and sub-therapeutic doses of these drugs when used as a combination therapy.

Objective: The objective of this study is to primarily investigate and then compare the antihyperglycemic effects of bromocriptine with metformin, also to see the combined effect of sub therapeutic doses of both these drugs.

Methodology: Random allotment of 24 albino male rats was done in four groups. Group 1 was kept as control. Alloxan monohydrate was given to group 2, 3 and 4 and diabetes was induced. Group 2 and 3 were treated with metformin (1.5mg/kg body weight) and bromocriptine (3 mg/kg body weight) respectively while group 4 was treated with sub therapeutic doses of metformin (1 mg/kg body weight) and bromocriptine (1.5 mg/kg body weight)both. Serum glucose levels were estimated at 1, 10, 20 and 30 days.

Results: Results showed that metformin reduces blood glucose level significantly where as bromocriptine also showed reduction of blood glucose level but not as significantly as metformin. However, the combination of metformin and bromocriptine showed much reduction in blood glucose level than metformin and bromocriptine used alone.

Conclusion: Bromocriptine and metformin when combined ameliorated blood guclose efficiently than given alone

Keywords: Diabetes mellitus, bromocriptine, metformin

INTRODUCTION

Diabetes mellitus is a multisystem metabolic disorder, which is an outcome of decreased carbohydrate metabolism in addition to increase metabolism of protein and fats.[1] Whether it is decreased carbohydrate metabolism or increase metabolism of fats or protein both are going to aggravate hyperglycaemia and triglyceride level in the body which leads to diabetes mellitus.[2,3]

Globally, Diabetes mellitus stands among one of the leading cause of morbidity and mortality.[4] It not only increases the misery of the patient but also affects the economy of the patient and the healthcare system, for which currently there is no solution.[5]

According to WHO there is a steady increase in the number of diabetic patients annually.[6] Research institution investigating this multisystem disorder are working to introduce a drug which shall not only control diabetes, but also limit its complications.[7]

It is difficult to achieve an ideal antidiabetic medicine which shall maintain the blood glucose level within desirable limits and decrease the risk factorsrelated to the disease and to the drug itself. It could be used alone or in combination with existing drugs and cost effectiveness. To achieve all such target, the success so far has been quite limited.[8]

Maintenance of good control of blood sugar among type 2 diabetics (T2DM) typically becomes progressively more difficult as the duration of disease lengthens due to decline in the capacity of the pancreatic beta cells for glucose stimulated insulin release, in the presence of insulin resistance.[9]

It was the year 2009, when bromocriptinemesylate got approval by FDA for the treatment of type-II diabetes which is , a dopamine D2 receptor agonist.[10,11]The therapeutic effect of Bromocriptine does not have a specific receptor involvement rather it acts by resetting dopaminergic and sympathetic tone within the CNS. Evidence suggest that bromocriptine is insulin sensitizer and promotes glucose utilization following meal.[12,13]

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This centrally acting anti-diabetic agent has a unique mode of action. It decreases insulin resistance and hepatic glucose production by increasing dopaminergic neurotransmission, through this mechanism it resets a new level in hypothalamus and which helps in improving insulin sensitivity. It increases a good control of glucose and reduces complications related to cardiovascular events.[14,15]

Objectives: To study the effect bromocriptine on blood glucose level.

- Compare the anti-glycaemic effect of the drug with metformin an already well known anti-hyperglycaemic drug.
- To study the sub therapeutic effect of bromocriptine and metformin when used in combination

Rationale: An ideal anti diabetic drug which achieve good glycaemic control with minimal complications is still awaited. Present study is an attempt to fulfil this gap

MATERIAL AND METHOD

Animals: 10-12 week aged albino rats, weighing 150-200 grams, purchased from university of veterinary and animal science for use in the current study. The animals are placed in appropriate cages where standard temperature was maintained.

Drugs and Chemicals: Alloxan, Dextrose, Bromocriptine Mesylate, metformin and Ether.

Instrument: Glucometer (ACCU-CHEK ACTIVE) with strips, and heparinized micro capillary tubes.

Procedure: Induction of Diabetes Mellitus: Rats were acclimatized for a period of 07 days before the start of the study. Study was stretched to a period of 30 days. Control group was separated. Albino rats were injected with freshly prepared alloxan in a dose of 150 mg/kg body weight. It was introduced subcutaneously. To counter hypoglycaemia rats were given 10% dextrose orally. Those rats which showed hyperglycaemia of 250mg/dl after 2-3 days were included in the study. This population of rats was divided into three groups each comprising of six animals each. The diabetic rats were given access to water,

normal diet, temperature of the cage was maintained keeping the conditions normal.

Group 1: Treated with 0.9ml of normal saline.

Group 2: Treatedorally with metformin 1.5mg/kg body weight.

Group 3: Treated orally with bromocriptine 3 mg/kg body weight.

Group 4: Treated orally with the low doses of bromocriptine (1.5 mg/kg body weight) and metformin (1 mg/kg body weight).

Sample collection and blood glucose estimation: Blood glucose level was determined with the help of glucometer on 01, 10th,20thand 30thdayrespectfully.

Statistical analysis: Standard Mean ± SD was determined to express results by repeated ANOVA test. The results of bromocriptine alone and of its combined effect with metformin were compared with the effect of metformin when given alone.

Duration of study: The study extended for 30 days, during which all rats were equally treated.

RESULTS

Group1 which served as control was treated with normal saline, during the study period it did not show any significant changes in the blood sugar levels.

Group 2, was treated with metformin 1.5 mg/kg body weight, during this study period of 30 days there was gradual reduction in the blood glucose levels, this is supported by the study conducted by Knowler WC, et al.[16]

At the start of study blood glucose level which was 280.41 mg/dl reduced to 160.1 mg/dl toward the end of 10 days and 106.1 at the end of 20 days and 94.9 toward the end of 30days.

Group 3, a study conducted by DeFronzo RAsupports the effect of bromocriptine in type-II diabetes. A steady fall in the blood sugar level of rats was observed among rats which were treated with Bromocriptine3 mg/kg body.[17] Level of 286.5 on 1st day was observed, toward 10 days' level of 232.11 was observed and toward the end of experiment level observed was 155.29 and 142.1 on 20 and 30th day of experiment when bromocriptinealone was used.

Ghosh A, et al and Goldman-Levine JD in two different studies supported the effect of combination therapy of metformin and bromocriptine in type-II diabetes. Group 4 which was given a combined therapy of sub therapeutic doses of bromocriptine1.5 mg/kg body weight and metformin 1mg/kg body weight.[18,19]A significantfall in the blood sugar level, which reduced from 259.01 mg/dl on 1stday to 136.2mg/dl on 10th day, 99.01 on 20th day and 92.1 on 30st day was observed. These finding are quiet close to the results of metformin 2.5 mg/kg body weight treated group-2.

Table-1: Sequential changes in blood sugar in all study group

Days	Group-1 Control group	Groups-2 Treated with metformin	Group-3 Treated with bromocriptine	Group-4 Treated with metformin and bromocriptine
Day 1	88.93+ 1.59	280.41+- 6.11	286.5+-5.91	259.01+-4.01
Day 10	91.5+4.07	160.1+-5.40	232.11+-5.01	136.2+-4.97
Day 20	84.9+3.19	106.1+-3.99	155.29+-7.01	99.01+-5.11
Day 30	91.1+3.88	94.9+-4.20	142.1+-5.21	92.1+-3.41

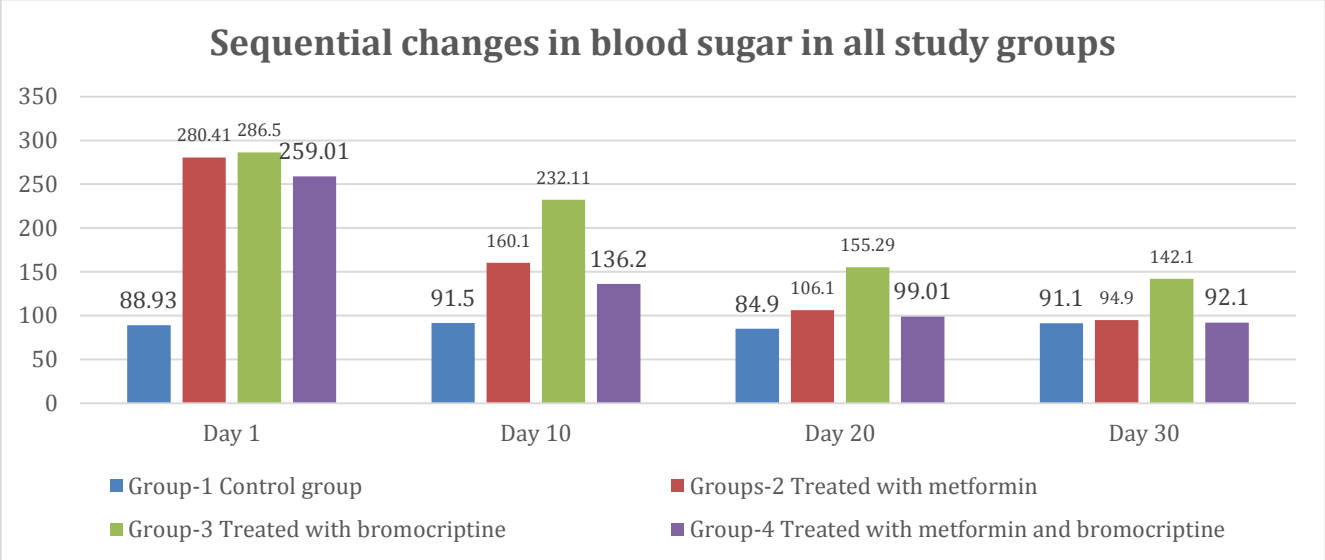

Figure-1

DISCUSSION

Group-1 which served as control doesn't showed any remarkable rise in the blood glucose level during the entire study, which is exhibited in table-1 and figure-1

Diabetic rats which were treated with metformin, bromocriptine and combination of low doses of metformin and bromocriptine showed variable reduction in the blood sugar level which are shown in table-1 and figure-1

In group-2 blood glucose showed significant reduction in the first two weeks (P<0.05) followed by mild reduction in the glucose level during the last 10 days this is supported in a study conducted by Association AD.[20]Group-3 also showed remarkable reduction in the blood glucose level, however, the reduction was more significant with metformin as compared with bromocriptine during first week.

During the second week greater reduction in blood glucose was observed with bromocriptine as compared with metformin than in the last 10 days (P>0.05) which is supported in a study by Inzucchi SE, et al.[14]

So far studies have shown that bromocriptine alone is not an effective medicine in controlling blood glucose as compared with metformin.

Group-4 where a combination of low doses of metformin and bromocriptine was used showed a significant fall in the level of blood glucose in comparison with the rest of the medicines alone. This was observed during the first and subsequent weeks is supported by Moon MK, et al in his study.[21]

During the third week the glucose level in the blood was maintained in the normal range. It was very close to the level of control group. This treatment was found to be far ahead than monotherapy in the form of metformin and bromocriptine for the

treatment of diabetes mellitus, Adeneye AA, Olagunju JA are in favor of our study.[22]

The graphical representation also shows that the glucose index in the control group was maintained within the range of normal level and was lower ($P<0.05$) than the diabetic rats. After first week of the experiment there was a fall in the glucose level in rats who were treated, whereas in untreated group there was an increase in the level of blood glucose.

Significant control was observed in rats who were given combination therapy of metformin and bromocriptine as compared to monotherapy of metformin and bromocriptine. It is also observed that toward the end of the experiment i.e. 30thday poor control of blood glucose was observed with bromocriptine than with combination therapy of metformin and bromocriptine.

CONCLUSION

Bromocriptine as a monotherapy shows a good control on the blood glucose level during the first week, during subsequent weeks its control becomes much poor.

Metformin shows better results in both halves of the study, its control on blood sugar is good in the first week which is maintained till third week of the experiment.

Combination therapy of metformin and bromocriptine shows better results during the start of the experiment during the 2nd week the values comes to normal level and are maintained till 21st day of experiment.

To conclude metformin along with bromocriptine shows better control of blood glucose than metformin and bromocriptine alone.

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