Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20160756

Research Article

Study to assess the role of bromocriptine in treatment of diabetes mellitus

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Received: 08 January 2016
Revised: 08 February 2016
Accepted: 09 February 2016

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ABSTRACT

Background: Bromocriptine is a dopamine D2 receptor agonist and a sympatholytic agent used very frequently in treatment of hyperprolactinemia, Parkinsonism and acromegaly. Its quick release formulation has been approved for treatment of type 2 diabetes mellitus as an adjunct to diet and exercise. This study evaluated the antihyperglycemic effect of quick release bromocriptine in alloxan induced diabetic rats.
Methods: 24 albino rats were taken and divided into four groups of six rats in each group. Diabetes was induced in three groups and one group was kept as a control group. After successful induction of diabetes, in remaining three group, first group was given no treatment second group was treated with bromocriptine and the third group was treated with metformin. Fasting blood sugar of all the groups were measured on day 1, 7, 14 and 28 of treatment.
Results: In this study both the treatment groups were found to have significant ($P<0.05$) antihyperglycemic effect. Further studies are needed to evaluate and compare antihyperglycemic effect and safety profile of bromocriptine with established antidiabetic drugs.
Conclusions: From this study, we concluded that individually both metformin and bromocriptine were effective in controlling hyperglycemia but metformin was better in achieving normal mean FBS. Further studies are required to ascertain the consistency in hypoglycemic effect of bromocriptine as well as its effect in lipid profile and cardiovascular outcomes. Study taking different doses of bromocriptine or with increasing the duration of study can elaborate its role in achieving proper glycemic control over time.

Keywords: Alloxan, Bromocriptine, Fasting blood sugar, Diabetes mellitus

INTRODUCTION

Type 2 Diabetes mellitus is resistance to insulin in various tissues like muscle, liver and adipose tissues which results in impairment of glucose uptake.[1] It is a disease linked to abnormal carbohydrate, protein and lipid metabolism, accounts for more than 90% of all cases of diabetes.[2,3]

According to International Diabetes Federation currently over 40 million diabetic patients are Indians and by year 2025 prevalence of diabetes in India will be 70 million.[4,5] This places India second only to China in terms of number diabetes population.[6] By the year 2025, India shall have the maximum number of diabetics in the world making it the "Diabetic capital of the world."[7] The prevalence of the disease is 2.4% in rural and 4.0 - 11.6% in urban population.[8]

Type-2 diabetes mellitus is a common chronic morbidity in the elderly.[9] 20% of the elder population suffers from type-2 diabetes mellitus in India.[10] This is attributed to various factors such as physical inactivity, rich food habits and sedentary life style leading to obesity.[11]

Since early 90s, a number of oral hypoglycemic drugs or their combinations are available for the management of type-2 diabetes mellitus and newer drugs are being approved regularly.[12] These drugs are commonly used for earlier and uncomplicated cases of diabetes mellitus and

play a role to delay the progression of hyperglycemic events while late and complicated cases of diabetes are managed with insulin therapy.[13] Traditionally sulphonylureases, and biguanides are very frequently used oral hypoglycemic drugs.[14]

Despite availability of various antidiabetic agents, research for the newer molecules is still continued. Many patients in their fight for control of hyperglycemia in long term receive multiple antidiabetic medicines and finally require insulin therapy. But eventually it also fails and resulting in life threatening hypoglycemia and sometimes excessive weight gain.[15,16] Uncontrolled hyperglycemia is causes micro vascular and macro vascular complications in diabetes.[17,18] Owing to the difficulty in achieving proper glycemic target.[19,20] And various comorbidities associated with diabetes like dyslipidemia, obesity and impaired renal function etc. there is a need to develop newer antidiabetic agents. Researchers are working tirelessly for other metabolic pathways involving systems such as brain, kidney etc., that also have contribution in metabolism and distribution of glucose in the body.

Bromocriptine is a dopamine D2 receptor agonist and sympatholytic agents.[21] Till few years back it was used for treatment of Parkinson's disease, acromegaly and hyperprolactinemia. In 2009, the bromocriptine quick release was approved by FDA as an adjunct to diet and exercise to improve glycemic control.[22,23] The concept of using bromocriptine for treatment of hyperglycemia came while correlating the metabolic pathways of migratory birds with hibernation theory of circadian neuroendocrine rhythm.[10] It was proposed that during winter hibernation, animals put a lot of weight by rendering the body with insulin resistant/glucose intolerant state to conserve glucose and lipids for energy production. This is achieved by decreasing the dopaminergic activity of hypothalamus.

Similar theory when applied to humans leads to the hypothesis relating development of obesity and insulin resistance to an adaptation for survival in times of famine.[24] Circadian neuroendocrine rhythms are mediated by dopaminergic and serotonergic activity also plays a major role in the development of changes in insulin sensitivity and regulates the seasonal alterations in body composition, body weight, no seasonal obesity and insulin resistance.[25-27] Bromocriptine through its inhibitory effects on serotonin turnover in brain reverses many of the metabolic pathways linking obesity with diabetes mellitus.[28] In some studies, when bromocriptine was administered systemically or into the cerebral ventricle during the early morning there was reduced endogenous (hepatic) glucose production and reversed the insulin resistance in animals.[25-27,29] In another study in obese nondiabetic women there was reduction in mean plasma glucose, free fatty acid (FFA) and triglyceride levels with bromocriptine.[30] Also in an open-label study in obese patients with type 2 diabetes, bromocriptine administration resulted in improved glycemic control, reduced and reduced the need for oral hypoglycemic agents.[31]

With this background the study was performed to assess the blood sugar lowering effect of bromocriptine in alloxan induced diabetic rats.

METHODS

The experiment was carried out in "Department of Pharmacology, Rajendra Institute of Medical Sciences, (RIMS) Ranchi". Study was conducted in accordance with ethical guidelines approved by Institutional Animal Ethics Committee (IAEC) of RIMS, Ranchi, Jharkhand, India.

Healthy male wistar rats weighing between 150-225 grams were taken for the 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 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. As excessive urination in diabetic rats was expected under the effect of diabetes, cages were floored with a layer of saw dust for absorption of urine of rats.

Drugs used were

1. Alloxan monohydrate (10 g) powder, from Sigma Aldrich Chemicals Private Limited (Bangalore).
2. Metformin (Tab. Gluconorm 500 mg) - from Lupin pharmaceuticals.
3. Glucomind (Tab. Bromocriptine mesylate 0.8 mg quick release) - from Lupin pharmaceuticals.

Selection criteria for animals

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 150-225 grams.

Methodology

Total twenty four male wistar rats were used for the study. All the animals were acclimatized for one week before the initiation of the study. Then rats were divided into four groups with six rats in each group. One group consisted nondiabetic rats and other three groups had hyperglycemic rats i.e. with fasting blood sugar 250 - 400 mg/dl that were randomly divided into three groups B, C, D.

Group A rats were nondiabetic, served as a normal control and were given 0.9% normal saline.

Group B rats were diabetic and were given 0.9% normal saline, served as diabetic control group.

Group C rats were diabetic and were treated with metformin (9mg/200g body weight, p.o.)

Group D rats were diabetic and were treated with bromocriptine (0.03mg/200g body weight, p.o.)

Estimation of fasting blood sugar

Rats were kept deprived of food overnight and were allowed free access to water. Blood samples were collected from the tail of rat and fasting blood glucose was measured with the help of Glucometer before the induction of diabetes as well as on days 1, 7, 14 and 28 of the study.

Statistical analysis

All the data were expressed as mean ± SD. Statistical analysis of data was carried out by Graph pad software. Results were considered significant if P<0.05.

RESULTS

As shown in Table 1, mean FBS of group A and group B were 89.33±1.63, 92.66±4.08, 85.16±3.20, 90.66±3.77 and 260.16±9.04, 280.33±2.94, 294.83±2.13, 298.66±7.03 on day 1, 7 ,14 and 28 of the study respectively. This showed that there was progressive increase in mean FBS over the entire study duration and the diabetes was maintained in the entire study period in group B rats. This can be inferred that high mean FBS in group B was not associated with dietary factors, as all the rats were provided with similar laboratory diet.

Table 1: Comparison of mean FBS in Group A Vs Group B.

	Gr A	Gr B	p value
	Mean ± SD	Mean ± SD	
Day 1	89.33±1.63	260.16±9.04	< 0.001
Day 7	92.66±4.08	280.33±2.94	< 0.001
Day 14	85.16±3.20	294.83±2.13	< 0.001
Day 28	90.66±3.77	298.66±7.03	< 0.001

As shown in Table 2, mean FBS in group C and group D rats were 278.33±6.08, 159.66±5.39, 105.5±4.08, 95.50±4.18 and 284.83±6.01, 231.16±4.875, 156.16±6.91, 141.37±5.20 on day 1, 7, 14 and 28 of the study respectively. Thus both the study groups showed progressive decrease in the values of mean FBS and the values were statistically significant (p <0.001) on day 1, 7, 14 and 28 of the study.

Table 2: Comparison of mean FBS in Group C Vs Group D.

	Gr C	Gr D	p value
	Mean ± SD	Mean ± SD	
Day 1	278.33±6.08	284.83±6.01	> 0.05
Day 7	159.66±5.39	231.16±4.875	< 0.001
Day 14	105.5±4.08	156.16±6.91	< 0.001
Day 28	95.50±4.18	141.37±5.20	< 0.001

On comparing group A with group C rats in As shown in Table 3, it was found that mean FBS was statistically significant (p <0.001) for day 1, 7 and 14 while it was insignificant (p >0.05) for day 28 of the study. So metformin was able to decrease the mean FBS of diabetic rats to the extent of the normal nondiabetic mean FBS value on 28th day of study as the difference was not significant (p >0.05) on day 28 of study.

Table 3: Comparison of mean FBS in Group A Vs Group C.

	Gr A	Gr C	p value
	Mean ± SD	Mean ± SD	
Day 1	89.33±1.63	278.33±6.08	< 0.001
Day 7	92.66±4.08	159.66±5.39	< 0.001
Day 14	85.16±3.20	105.5±4.08	< 0.001
Day 28	90.66±3.77	95.50±4.18	> 0.05

On comparing group A with D rats in as in Table 4 it was found that mean FBS values were statistically significant (p <0.001) for day 1, 7 and 14 while it was insignificant (p >0.05) for day 28 of the study. So here bromocriptine also, like metformin, was able to decrease the mean FBS of diabetic rats to the extent of the normal nondiabetic value on 28th ^{day} of study as the difference was not significant (p >0.05) on day 28 of study. However mean FBS on day 28 for bromocriptine treated diabetic rats was much higher than that for metformin treated diabetic rats.

Table 4: Comparison of mean FBS in Group A Vs Group D.

	Gr A	Gr D	p value
	Mean ± SD	Mean ± SD	
Day 1	89.33±1.63	284.83±6.01	< 0.001
Day 7	92.66±4.08	231.16±4.87	< 0.001
Day 14	85.16±3.20	156.16±6.91	< 0.001
Day 28	90.66±3.77	141.37±5.20	> 0.05

On comparing group B with group C rats in As shown in Table 5, it was found that mean FBS of group B rats on day 1, 7, 14 and 28 of the study respectively were statistically significant (p <0.001). Thus there is significant reduction in mean FBS of diabetic rats with metformin treatment.

Table 5: Comparison of mean FBS in Group B Vs Group C.

	Gr B	Gr C	p value
	Mean ± SD	Mean ± SD	
Day 1	260.16±9.04	278.33±6.08	< 0.001
Day 7	280.33±2.94	159.66±5.39	< 0.001
Day 14	294.83±2.13	105.5±4.08	< 0.001
Day 28	298.66±7.03	95.50±4.18	< 0.001

On comparing group B with group D rats in Table 6, it was found that mean FBS of group B rats on day 1, 7 ,14 and 28 of the study respectively were statistically significant (p <0.001). Here also bromocriptine was successful in reducing the mean FBS of diabetic rats significantly.

Table 6: Comparison of mean FBS in Group B Vs Group D.

	Gr B	Gr D	p value
	Mean ± SD	Mean ± SD	
Day 1	260.16±9.04	284.83±6.01	< 0.001
Day 7	280.33±2.94	231.16±4.875	< 0.001
Day 14	294.83±2.13	156.16±6.91	< 0.001
Day 28	298.66±7.03	141.37±5.20	< 0.001

On comparing group C with group D rats as in Table 2, it was found that value of mean FBS on day 1 was statistically not significant (p>0.05). On further treatment on day 7, 14 and 28 of the study the differences were statistically significant (p<0.001). This was also observed that reduction in mean FBS was more on day 7 in group C as compared to group D and the final value of mean FBS i.e. on day 28 was more in group D than in group C and the difference was statistically significant.

So metformin showed rapidity in action to reduce hyperglycemia as well as it was able to achieve normoglycemia more efficiently as compared to bromocriptine. The maximum effect of bromocriptine was seen on second week and final value at the end of treatment was at high-normal value. Final result suggested that bromocriptine alone was not superior to metformin as a monotherapy in treatment of alloxan induced diabetic rats.

Figure gives the graphic representation of mean FBS values during the study period. As shown in the graph, mean FBS during the entire study period in group A was maintained at a constant level with minor fluctuations and this value was significantly (P <0.001) lower than rats of group B. In control group B, the mean FBS was very high and this was not only maintained but also progressively increased on 1st, 7th, 14th, and 28th day of study. In groups treated with drugs on 7th, 14th and 28th day of study, there was a progressive decrease in mean FBS while in untreated group, mean FBS increased continuously. Mean FBS on 7th day of study indicated that the decrease in FBS was more in group C while in group B there was moderate decrease in mean FBS. After 14th day of treatment, mean FBS in group C comes to near normal values whereas in group D though the value of mean FBS was lesser than the 7th day mean FBS but still it was at higher level. At the end of study i.e. on 28th day, mean FBS in group C was maintained at near normal level but FBS in group D remained at high normal level.

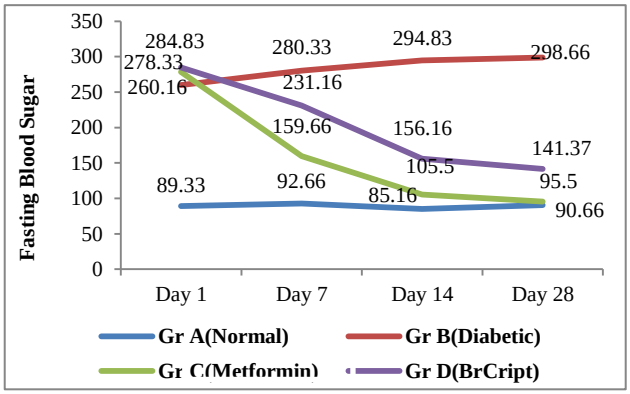

Figure 1: Mean FBS values during the study period (consolidated).

DISCUSSION

Use of "Bromocriptine quick release" as an antihyperglycemic agent is a new approach in the treatment of diabetes. Most of the traditional antidiabetic agents work by either increasing the insulin secretion from pancreas, or by increasing peripheral utilization of glucose by increasing the sensitivity of peripheral tissues to insulin while the target for bromocriptine is hypothalamic dopamine pathway. So the problems with traditional agents like weight gain, hypoglycemia and later on progressive beta cell failure etc are well addressed with the use of bromocriptine. Earlier, study conducted by Kamath V, et al proposed the possible mechanism of action of bromocriptine in hyperglycemia and hyperlipidemia.[30] Further studies by Luo S, et al, established the central action of bromocriptine with intracerebroventricular administration of bromocriptine lead to improvement of glucose tolerance and insulin tolerant state in hamsters.[28] Our study also was in coherence with the finding of previous studies with bromocriptine and there was improvement in glucose tolerance as indicated by significant lowering of mean FBS in allox an induced diabetic rats, treated with early morning dose of bromocriptine.

There are some clinical trials to study the role of bromocriptine in type 2 diabetes mellitus like one conducted by De Fronzo, et al, and other by Cincotta AH, et al, both studies observed improved glucose tolerance in type 2 diabetes mellitus on treatment with bromocriptine quick release.[21,25] Another study by Cincotta AH, et al observed lipid lowering and glycemic controlling effect of bromocriptine. Gaziano JM, et al observed improved

glycemic control and cardiovascular outcomes with bromocriptine treatment in diabetic patients.[23] Scranton, et al, observed role of bromocriptine in improving glycemic control in diabetic patients who were failed to improve with metformin/sulfonylurea combination therapy.[32] In all these studies, bromocriptine quick release was administered at the morning within two hrs of awakening thus this early morning action of bromocriptine is supported by our study.

In our study there was a lag period in the antihyperglycemic effect of bromocriptine as the mean FBS in bromocriptine treated group was reduced by 53 mg/dl, 75 mg/dl and reduction in mean FBS in metformin treated group was 119 mg/dl and 54 mg/dl from baseline values on 7th and 14th day respectively. So in first week there was lag in response to treatment with bromocriptine while in later weeks the response was rapid as there was greater decrease in mean FBS. This finding was comparable to study conducted by Ramteke, et al and this may be attributed to the complex central action of bromocriptine through neural circuits and related to its effects on regulation of hypothalamic circadian rhythm.[33]

Bromocriptine is relatively safe and it meets all the USFDA cardiovascular safety guidelines, use results in 40% reduction in cardiovascular end points.[23] It had also benefitted remarkably the patients of type 2 diabetes mellitus with dyslipidemia, obese patients, depressed patients with limited mobility and patient with profound insulin resistance.[34] But still the use of quick release bromocriptine in diabetes has not gained much popularity and despite having novel mechanism of action, it is very much underutilized. The reason for this are multifaceted as lack of sensitization among physicians, poor understanding of its indications in co-morbidities and drug interaction, possible side effects as well as large number of existing antidiabetic armamentarium hinders and discourages the use of bromocriptine among diabetologists.[35]

Bromocriptine quick release is used in treatment of type 2 diabetes in the dose of 0.8-1.8 mg per day in early morning within two hour of awakening. This dose of bromocriptine is 2 to 3 fold lower than dose used for treatment of hyperprolactinemia and 10 to 20 fold lower than that used for treatment of Parkinson's disease at these low doses, bromocriptine seldom shows any adverse effects and overall safety and tolerability for most of the individuals are very much encouraging.[36,37]

CONCLUSION

The present animal study was a small study as regards to the number of animals included, the dose, and duration of the study was also fixed. Results of the study concluded that individually both metformin and bromocriptine were effective in controlling hyperglycemia but metformin was better in achieving normal mean FBS. Further studies are required to ascertain the consistency in hypoglycemic effect of bromocriptine as well as its effect in lipid profile and cardiovascular outcomes. Study taking different doses of bromocriptine or with increasing the duration of study can elaborate its role in achieving proper glycemic control over time.

This study was conducted on fasting rats, so further study is needed to evaluate its effect on post prandial blood sugar. Thus this study opens the scope for animal studies involving large number of animals, as well as human clinical trials to evaluate its role in diabetes, hyperlipidemia and cardiovascular outcomes.

ACKNOWLEDGEMENTS

We are sincerely thankful to the faculty members and animal house staff of department of pharmacology, RIMS, Ranchi, for their constant support and encouragement during and after the study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Pathak AK, Kumar S, Kumar M, Dikshit H. Study to assess the role of bromocriptine in treatment of diabetes mellitus. Int J Basic Clin Pharmacol 2016;5:423-8.