

Antihyperglycemic, Antihyperlipidemic and Cardioprotective Profile of Bromocriptine, Glibenclamide and Metformin Combination in Dexamethasone-induced Hyperglycemic Rats

¹Adejuwon Adewale Adeneye and ²Joseph Abayomi Olagunju

¹Departments of Pharmacology, ²Department of Medical Biochemistry, Faculty of Basic Medical Sciences, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria

Abstract: Objective: In recent years, attention has been drawn to the therapeutic usefulness of bromocriptine in the effective management of type 2 diabetes mellitus. The present study evaluates the effects of the oral treatments with 10 mg kg⁻¹ bromocriptine in combination with 1 mg kg⁻¹ glibenclamide, 20 mg kg⁻¹ metformin and glibenclamide/metformin combination on body weight, blood glucose, lipids and cardiovascular risk profile in dexamethasone-induced hyperglycemic male Wistar rats for 30 days. **Results:** The effects of these drug combinations on OGTT of the treated rats were also evaluated. Repeated daily dexamethasone injection for 30 days caused significant increases in the average body weight, blood glucose, triglycerides, total cholesterol, LDL-c, VLDL-c and cardiovascular risk indices in the treated Wistar rats. However, these increases were significantly attenuated in rats orally pretreated with bromocriptine and its various combinations. In addition, bromocriptine and its combinations significantly improved OGTT in the treated rats. **Conclusion:** Overall, results of this study suggest that the antihyperglycemic and antihyperlipidemic effects of the drug combinations were possibly mediated via improved glucose tolerance mechanism.

Key words: Bromocriptine, glibenclamide, metformin, anti-hyperglycemic, anti-hyperlipidemic, cardioprotective potentials

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases that is characterized by chronic hyperglycemia emanating from insufficient insulin production by the pancreatic β -cells (Type 1 DM) or insensitivity (or resistance) of the tissues to insulin action (Type 2 DM) with the latter being the more common type (Newman *et al.*, 1987; Amos *et al.*, 1997). Type 2 DM (T2DM) is often associated with obesity, sedentary lifestyle, advanced age, family history of diabetes, ethnicity, cigarette smoking and alcoholism (Poulsen *et al.*, 1999). Currently, there are more than 170 million diabetes sufferers worldwide and this figure is expected to double by the year 2030 (Wild *et al.*, 2004). The increasing prevalence of diabetes and its associated complications such as ischemic heart disease, neuropathy, retinopathy, cardiovascular accident and peripheral vasculopathy have made the disease a public health nightmare for not only its sufferers but also for health care providers (Murray and Pizzorno, 1998).

The effective management of diabetes mellitus usually involves multidisciplinary approaches which include lifestyle modification, physical therapy

(particularly for the obese/overweight patients), nutritional therapy and drug therapy. However, drug therapy for diabetes involves the use of insulin (of different forms based on the source and duration of action) and several classes of oral hypoglycemic agents such as insulin secretagogues (sulphonylureas: glibenclamide, meglitinides, etc.), insulin sensitizers (biguanides: metformin; thiazolidinediones: pioglitazone, rosiglitazone) which mediate their effects by augmenting insulin sensitivity of the skeletal and hepatic tissues, *alpha-glucosidase* inhibitors (e.g., acarbose, miglitol) which act by inhibiting intestinal glucose uptake and re-absorption, peptide analogues (exenatide, liraglutide and DPP-4 inhibitors) that increase GLP-1 serum concentration and slow down the gastric emptying (Adeneye, 2011).

Recent animal and human studies have reported bromocriptine to be effective in the management of T2DM (Cincotta *et al.*, 1991; Pijl *et al.*, 2000; DeFronzo, 2011). As such, bromocriptine was recently approved by the United State Food and Drug Administration for the clinical management of T2DM (Mahajan, 2009). Bromocriptine is believed to achieve good glycemic control in T2DM

subjects based on the observation that bromocriptine administered within 2 hours of awakening resulted in a reduction in postprandial plasma glucose levels due to enhanced suppression of hepatic glucose production without corresponding augmentation of insulin secretion or enhance insulin sensitivity in the skeletal muscles (Mahajan *et al.*, 2010). Bromocriptine is known to augment the low hypothalamic dopamine levels and inhibit excessive sympathetic tone within the central nervous system that is associated with awakening (DeFronzo, 2011; Mahajan *et al.*, 2010).

The prevalence of T2DM continues to rise at an alarming rate around the world, with even more people being affected by prediabetes. Although, the pathogenesis and long-term complications of T2DM are fairly well known, its treatment has largely remained challenging with only about half or less of the patients achieving the desired glycemic control (Nyenwe *et al.*, 2011). Thus, there is an urgent need for new therapies to effectively manage T2DM that will reduce both the fasting and postprandial glucose without attendant hyperinsulinemia, weight gain or hypoglycemia. In view of this need, the present study is designed at evaluating the possible therapeutic potential of bromocriptine/glibenclamide, bromocriptine/metformin and bromocriptine/glibenclamide/metformin combinations in the management of T2DM using dexamethasone-induced hyperglycemic rats as an animal model of T2DM. The choice of the doses of the drugs under investigation was made based on results of preliminary studies earlier conducted and previous literature (Adeneye *et al.*, 2010).

MATERIALS AND METHODS

Drugs and chemicals: Bromocriptine mesylate salt and glibenclamide salt (Sigma-Aldrich, St. Louis, U.S.A.), metformin (Glucophage[®], Merck Sante S.A.S, Lyon, France) and all other drugs used in the experiment were all of analytical grade.

Experimental animals: A total of thirty-six young adult male Wistar rats (weight range: 150-180 g) were obtained from the Department of Zoology, University of Ilorin, Kwara State, Nigeria, after ethical approval has been obtained from the Ethical Committee of Lagos State University College of Medicine, Ikeja, Lagos, Nigeria. The rats were acclimatized for 14 days, fed on standard rat chow and tap water *ad libitum*. The rats were housed in a standard rat cages in the Rat Colony of the Animal House, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria and maintained at standard laboratory conditions (12/12 h light-dark periodicity, temperature:

23-26°C as prescribed by the United States National Institute for Health in 1985. Five days prior to commencement of the experiment, rats were randomly divided into 6 groups of 6 rats per treatment group such that the weight differences within and between treatment groups do not exceed $\pm 20\%$ of the average weight of the rat population.

Drug treatment and experimental induction of insulin resistance diabetes mellitus: Single, daily oral treatments of the experimental rats with drugs are described below:

- Group I:** 10 mL kg⁻¹ of 0.9% normal saline water p.o.+1 mL kg⁻¹ of 0.9% normal saline water subcutaneous. This group served as the untreated control group
- Group II:** Pre-treatment with 10 mL kg⁻¹ of 0.9% normal saline water p.o. 1 h before subcutaneous injection with dexamethasone. This group served as the model control group
- Group III:** Oral pre-treatment with 10 mg kg⁻¹ of bromocriptine dissolved in 0.9% normal saline water
- Group IV:** Oral pre-treatment with 1 mg kg⁻¹ of glibenclamide+10 mg kg⁻¹ of bromocriptine both dissolved in 0.9% normal saline water
- Group V:** Oral pre-treatment with 20 mg kg⁻¹ of metformin+10 mg kg⁻¹ of bromocriptine both dissolved in 0.9% normal saline water
- Group VI:** Oral pre-treatment with 1 mg kg⁻¹ of glibenclamide+20 mg kg⁻¹ of metformin +10 mg kg⁻¹ of bromocriptine all dissolved in 0.9% normal saline water

One hour after pre-treatment all rats in the treatment groups II-VI were subcutaneously injected with 10 mg kg⁻¹ of dexamethasone sodium phosphate (Xasten[®], Yanzhou Xier Kangtai Pharmaceutical Company Limited, Jiuguan, Yanzhou City, Shandong Province, China). The treatments were usually conducted between 07:00-09:00 h for 30 days.

Measurement of body weight: Body weights of the treated rats were measured on the 1st, 15th and 30th day of the experiment with a mettle weighing balance (Mettler Toledo Type BD6000, Mettler-Toledo GmbH, Greifensee, Switzerland). The weight difference on the 15 and 30th day in reference to the initial weight per group was calculated.

Oral glucose tolerance test: After an overnight fast on the 30th day of the experiment, the Fasting Blood Glucose (FBG) levels of rats in all the treatment groups were determined using the glucose monitoring system. Half-an-hour afterwards, a 3 h oral glucose tolerance test was

conducted in all the drug-treated rats with 3 g kg⁻¹ of D-Glucose (British Drug House, Poole, U.K.) using the method of Sepici *et al.* (2004). The blood glucose levels were monitored at every 30 min over 3 h period and the blood levels compared relative to the basal values at 0 min.

Bioassay: Whole blood was collected by tail tipping method at between 07:00 and 09:00 h as described by Adeneye and Adeyemi (2009) and FBG was determined by glucoseoxidase method of Trinder (1969) using a One Touch Basic Blood Glucose Monitoring System® (Life Scan Inc., Milpitas, California, U.S.A.). The blood glucose monitor was calibrated and validated at the beginning of, midway into and at the end of the experiment.

Following the oral glucose tolerance test, the rats were fasted overnight for 14 h. At between 07:00 h and 09:00 h, the overnight fasted rats had their blood samples collected directly from the retro-orbital plexus under light inhaled diethyl ether anaesthesia. Blood samples were collected into plain sample bottles and allowed to clot at room temperature for 4 h before they were centrifuged using Uniscope Laboratory Centrifuge (Model SM 902B, Surgifriend Medicals, England, U.K.) at 10,000×g at the same temperature for 20 min to separate the sera. Serum TG, TC and HDL-c were assayed using standard diagnostic test kits (Randox Laboratories, Crumlin, U.K.) on Automated Clinical System (Synchron Clinical System®, model: CX5 PRO) (Beckman Coulter Inc., Galway, Ireland). Serum LDL-c was estimated using Friedlwann's equation:

$$LDL-c = \{TC - [(HDL-c) + (TG/5)]\}$$

Serum very low density lipoprotein cholesterol fraction (VLDL-c) concentration was calculated by deduction of the sum of HDL-c and LDL-c concentrations from that of TC.

Statistical analysis: Data were expressed as mean±SEM of six observations. Statistical analysis was done using two-way analysis of variance followed by post-hoc test, Student-Newman-Keuls test on SYSTAT 10.6. Statistical significance were considered at p<0.05 and p<0.001.

RESULTS

Effect of bromocriptine, glibenclamide and metformin combination on body weight of treated rats on the 1st, 15 and 30th day: Table 1 shows the effect of the 30 days of oral treatments with the different drug combinations on the body weight of the treated rats. Oral treatment with

dexameth as one alone was associated with significant (p<0.05, p<0.001) weight gain pattern in the Group II rats on the 15 and 30th day, respectively, when compared with untreated control (Group I) values. However, this pattern of weight gain was significantly attenuated (p<0.05) in rats treated with bromocriptine-treated, bromocriptine/glibenclamide, bromocriptine/glibenclamide/metformin combination-treated groups and most significantly (p<0.001) in bromocriptine/metformin combination-treated group when compared to Group II values on the 15 and 30th day (Table 1).

Effect of bromocriptine, glibenclamide and metformin combination on blood FBS on the 1st, 15 and 30th day:

Figure 1 illustrates the effect of oral treatment with bromocriptine and its combinations with glibenclamide and metformin on the fasting blood glucose concentrations of treated rats on the 1st, 15 and 30th day of their treatments. Daily subcutaneous injection with 10 mg kg⁻¹ of dexamethasone was associated with significant (p<0.05 and p<0.001) increases in the FBG levels on the 15 and 30th day, respectively when compared with the basal FBG levels and Group I values on the 15 and 30th day (Fig. 1). However, with oral pre-treatments with bromocriptine only, bromocriptine/glibenclamide, bromocriptine/metformin and bromocriptine/glibenclamide/metformin combinations, there was a significant (p<0.05 and p<0.001) attenuation in the FBG levels on the 15 and 30th day when compared to Group II values on these days, respectively (Fig. 1).

Effect of bromocriptine, glibenclamide and metformin combination on OGTT on the 30th day:

Oral administration of 3 g kg⁻¹ of D-glucose as a single bolus to Group II rats was associated with an increasing significant (p<0.05, p<0.001) rise in the postprandial blood glucose levels at between 30 and 90 min, peaking at 60 min

Table 1: Effect of repeated oral bromocriptine, glibenclamide and metformin combinations pretreatment on body weight of dexamethasone-treated rats

Treatment groups	Average body weight (g)		
	1st day	15th day	30th day
I	161.50±31.11	185.33±33.59	207.33±37.86 ^a
II	170.17±27.53	217.50±24.55 ^a	240.83±22.77 ^b
III	172.83±20.69	185.67±13.66	162.00±09.36
IV	163.17±15.64	174.83±14.35	155.67±07.23
V	161.33±22.51	110.83±06.62 ^c	93.17±09.30 ^c
VI	159.83±17.78	175.33±24.09	160.83±30.00

^{a,b}Represent significant increases at p<0.05 and p<0.001, respectively when compared to initial body weight on the 1st day while ^crepresents a significant decrease at p<0.05 when compared with initial body weight on the 1st day

Table 2: Effects of bromocriptine, glibenclamide and metformin combinations on serum lipids and cardiovascular risk indices

Groups	TG	TC	HDL-c	LDL-c	VLDL-c	AI	CRI
I	94.83±6.830	86.33±4.560	45.83±3.50	21.53±1.80	18.97±1.37	0.46±0.04	1.89±0.06
II	162.00±16.00 ^b	147.33±15.33 ^b	29.17±6.56 ^f	85.77±6.30 ^b	32.40±3.20 ^b	3.09±0.43 ^b	5.25±0.56 ^b
III	110.17±6.890 ^c	103.33±7.670 ^c	55.00±5.33 ^h	26.30±1.20 ^d	22.03±1.38 ^d	0.48±0.02 ^d	1.89±0.05 ^d
IV	101.00±5.000 ^c	91.17±5.830 ^d	52.50±4.17 ^h	18.47±3.78 ^g	19.70±1.33 ^d	0.36±0.09 ^d	1.73±0.10 ^d
V	86.83±6.780 ^d	80.17±7.220 ^e	49.17±4.50 ^h	13.67±4.49 ^g	17.33±1.38 ^d	0.29±0.10 ^e	1.64±0.12 ^e
VI	73.17±12.17 ^e	64.00±12.00 ^e	42.50±9.17 ^g	6.87±1.87 ^e	14.63±2.43 ^e	0.17±0.05 ^e	1.52±0.08 ^e

^{a,b}Represent significant increases at p<0.05 and p<0.001, respectively when compared to Group I values while ^{c,d} and ^e represent significant decreases at p<0.05, p<0.01 and p<0.001 when compared with Group II values. ^frepresents a significant decrease at p<0.001 when compared to Group I values while ^g and ^h represent significant increases at p<0.05 and p<0.001 respectively, when compared to Group II values

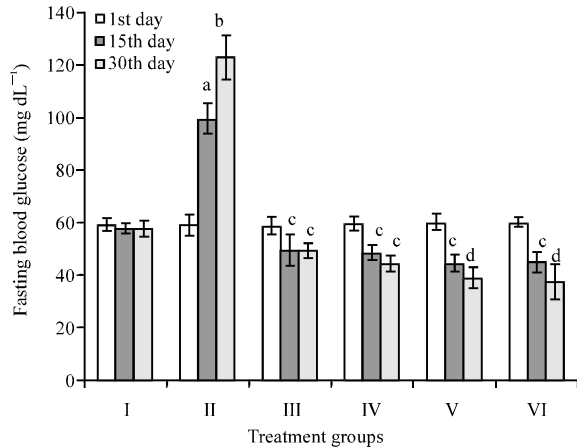


Fig. 1: Effect of bromocriptine, glibenclamide and metformin combinations on FBG levels in dexamethasone-treated rats, ^a and ^b represent significant increases at p<0.05 and p<0.001, respectively, when compared to initial FBG on day 1 while ^c and ^d represent significant decreases in FBG values at p<0.05 and p<0.001, respectively, when compared to Group II FBG values on the 15 and 30th day

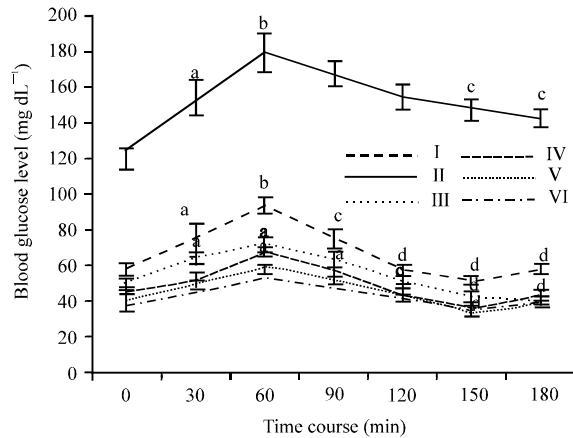


Fig. 2: Effect of bromocriptine, glibenclamide and metformin combinations on the OGTT of dexamethasone-treated rats, ^a and ^b represent significant increases at p<0.05 and p<0.001, respectively, when compared to FBG at 0 min while ^c and ^d represent significant decreases in FBG values at p<0.05 and p<0.001, respectively, when compared FBG values at 60 min

(Fig. 2). This was followed by a non-significant (p>0.05) fall in the blood glucose levels up to 180 min postprandial (Fig. 2). However, in Groups III-V rats, oral glucose administration was associated with a significant (p<0.05) rise in blood glucose levels at between 30 and 60 min and then a significant steady, time-dependent fall (p<0.05, p<0.001) in postprandial glucose levels at between 90 and 180 min (Fig. 2). Similar pattern of postprandial glucose changes was recorded for the Group I rats. In Group VI rats, there was no significant (p>0.05) alterations in the postprandial blood glucose levels until at 120-180 min when there was a significant (p<0.05) fall in the postprandial glucose levels (Fig. 2).

Effect of bromocriptine, glibenclamide and metformin combinations on serum lipids and cardiovascular risk indices on 31st day: Table 2 also shows the effect of the different drug combinations on the serum TG, TC, HDL-c,

LDL-c and VLDL-c as well as AI and CRI. Chronic subcutaneous treatment with 10 mg/kg/day with dexamethasone resulted in significant (p<0.001) increases in the serum TG, TC, LDL-c and VLDL-c levels as well as AI and CRI values. The dexamethasone treatment also resulted in a significant (p<0.001) decrease in HDL-c level. However, chronic oral pre-treatments with bromocriptine, bromocriptine/glibenclamide, bromocriptine/metformin and bromocriptine/glibenclamide/metformin combinations significantly (p<0.05, p<0.001) reversed the effects of dexamethasone treatment on the measured lipid parameters and cardiovascular risk indices (Table 2).

DISCUSSION

Bromocriptine [(5 α)-2-bromo-12'-hydroxy-5'-(2-methylpropyl)-3',6',18-trioxo-2'-(propan-2-yl)ergotaman], is a semi-synthetic ergoline derived centrally-acting dopamine D₂ receptor agonist. It is widely used in the

clinical management of hyperprolactinemia-associated dysfunctions, neuroleptic malignant syndrome, acromegaly and Parkinson disease (Mahajan, 2009; Mahajan *et al.*, 2010). Bromocriptine mesylate is also indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (Parker and Schimmer, 2010). It may also be used either as monotherapy or as adjunctive therapy to metformin or any of the sulfonylureas but not for T1DM or diabetic ketoacidosis treatment (Parker and Schimmer, 2010). Since its approval for the treatment of T2DM in 2009 by the USFDA, bromocriptine mesylate under the trade name Cycloset® (VeroScience LLC, Tiverton, RI 02878, USA) has been reported to improve glycemic control and reduce HbA_{1c} by approximately 0.5% (Cincotta *et al.*, 1991; Pijl *et al.*, 2000; Kerr *et al.*, 2010). Although, the exact mechanisms of its glycemic control remains unclear but bromocriptine has been reported to inhibit glucose-stimulated insulin secretion by direct activation of the α_2 -adrenergic receptors in INS-1E beta cells in *in vitro* studies (De Leeuw van Weenen *et al.*, 2010). Similarly, metformin (N,N'-dimethylimidodicarbonimidic diamide) is an oral biguanide drug which is widely used as an antihyperglycemic in the management of T2DM (Bailey and Turner, 1996; Wu *et al.*, 2008). Metformin lowers blood glucose by stimulating fatty acid oxidation, glucose uptake and non-oxidative metabolism while reducing lipogenesis and gluconeogenesis without inducing hyperinsulinemia unlike glibenclamide (a sulfonylurea) which attains glycemic control primarily by inducing hyperinsulinemia (Powers and D'Alessio, 2010). Metformin is currently the most commonly used oral anti-hyperglycemic agent for the management of T2DM and is generally accepted as the first-line treatment for this condition (Powers and D'Alessio, 2010).

In this study, hyperglycemia and dyslipidemia were induced in the rats by repeatedly injecting the rats with 10 mg/kg/day of dexamethasone subcutaneously, dexamethasone being a potent diabetogenic agent (Adeneye *et al.*, 2010). These dexamethasone-induced derangements in blood glucose and lipids were attenuated by daily oral pretreatment with 10 mg kg⁻¹ of bromocriptine alone and in combinations with glibenclamide and metformin, indicating the therapeutic potential of bromocriptine and its drug combinations in this respect. However, the homeostatic effects of bromocriptine combinations with glibenclamide, metformin and glibenclamide/metformin on the blood glucose and lipids appear to be more than with bromocriptine alone. Similarly, bromocriptine and its various combinations significantly improved the OGTT pattern suggesting that euglycemia was possibly achieved via improved oral

glucose tolerance mechanism. This observation appears to be in concordance with what has previously been reported for metformin (Powers and D'Alessio, 2010; Stumvoll *et al.*, 1995).

Another remarkable observation in this study is the significant reductions in the average body weight, AI and CRI values. Obesity has been reported to be closely related to T2DM and weight reduction forms an important integral part of T2DM management, particularly, in obese diabetic patients (Norris *et al.*, 2004). Bromocriptine like other centrally acting appetite suppressants (e.g., sertraline, sibutramine, etc.) induce weight loss by centrally inhibiting the activity of the hunger center in the hypothalamus (Norris *et al.*, 2004). Usually, drugs that enhance body weight and cardiovascular risk indices are known to increase risk of atherosclerosis-related heart diseases while drugs that lower them have the opposite effects (Ginsberg, 2000; Adeneye *et al.*, 2010). The fact that bromocriptine and its various combinations significantly lowered the weight gain pattern and cardiovascular risk indices strongly suggests that these drug combinations possess the therapeutic potential of preventing/ameliorating the development of atherosclerosis-related heart diseases. Again, this observation is similar to what has been reported for metformin (Stumvoll *et al.*, 1995; Evans *et al.*, 2006).

CONCLUSION

Overall, results obtained from this study showed the therapeutic potentials of bromocriptine and its various combinations in T2DM management. However, for these combinations to form the mainstay of T2DM in the near future there is need for the clinical studies of these drug combinations in human subjects.

ABBREVIATIONS

AI	= Atherogenic index
CRI	= Coronary risk index
DM	= Diabetes mellitus
DPP-4	= Dipeptidyl peptidase IV
FBG	= Fasting blood glucose
GLP-1	= Glucagon-like peptide type 1
HbA _{1c}	= Glycosylated hemoglobin
HDL-c	= High density lipoprotein cholesterol
LDL-c	= Low density lipoprotein cholesterol
OGTT	= Oral glucose tolerance test
p.o.	= <i>Peros</i>
sc.	= Subcutaneous route
TC	= Total cholesterol
T1DM	= Type 2 diabetes mellitus

T2DM = Type 2 diabetes mellitus
TG = Triglyceride
USFDA = United States Food and
Drug Administration
VLDL-c = Very low density lipoprotein
cholesterol

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