



Comparative study of oral antidiabetic medications on the Rat Model

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Introduction: In recent times, comparing the effects of oral antidiabetic agents as monotherapy or in combination in controlling diabetes mellitus and other related complications has become increasingly apparent. The study examined the effects of acarbose (AC), pioglitazone (PGZ), and vildagliptin (VDG) on glycaemic control, as well as on biochemical indices in an alloxan-induced diabetic rat model. **Materials and Methods:** Adult Wistar rats were induced with diabetes through the alloxan monohydrate (100 mgkg⁻¹; i.v.) administration. Five (5) groups of rats were utilized (n=6); group 1 filled in as the normal control, group 2 filled in as diabetic control group 3, while 4 and 5 were the diabetic experimental groups that got 30 mgkg⁻¹day⁻¹ of AC, PGZ, and VDG. **Results:** The study analysed the effects of aspartate aminotransferase (AST), agents on blood glucose, low-density lipoprotein (LDL-C), alanine aminotransferase (ALT), high-density lipoprotein, total cholesterol (TC), alanine phosphatase, and triacylglycerol (TAG) activities. In diabetic rats administered AC ($P<0.05$), the result demonstrated [VDG ($P<0.05$) and PGZ ($P>0.05$)] marked decreases in the blood glucose levels. The serum TC, LDL-C, and TAG levels were significant in the AC ($P<0.05$) and VDG ($P<0.05$) groups, and were additionally decreased in every treated group, the serum TAG level was insignificantly ($P>0.05$) diminished in diabetic rats administered PGZ. Likewise, in every single treated group compared with the diabetic control group, ALP, AST, and ALT were significantly ($P<0.05$) reduced. **Conclusion:** The administration of AC, PGZ, and VDG displayed significant improvement in the biochemical indices altered during diabetic-related manifestations in the experimental subjects. However, VDG demonstrated superior anti-hyperglycaemic adequacy.

Keywords: Diabetes mellitus, Blood glucose, Alloxan, Lipoproteins, Liver enzymes

INTRODUCTION

Globally, there has been pervasiveness of diabetes mellitus, which is an unremitting metabolic issue (Alemu, 2015). All around the world, the commonness of the disease is around 200 million and is anticipated to rise to 522 million by the year 2030 (Danaei et al. 2011). In Nigeria, recent estimates indicate that about 2 million people are living with diabetes mellitus, which makes it a national health burden. As a result of the hyperglycaemia and its associated clinical sequelae, stabilisation of blood glucose is vitally important for diabetic patients (Van de Laar et al. 2005; Mai et al. 2007). This can be achieved through a healthy diet combined with exercise, and rational use of pharmacological agents directly targeted at optimising diabetes treatment. Typically, patients with diabetes mellitus utilise a wide assortment of antidiabetic medications (e.g., sulfonylureas, biguanides, meglitinides, thiazolidinediones, α -glucosidase inhibitors,

etc.) to accomplish better glycaemic control. These medications differ in their mechanism(s) of action and their long-run therapeutic results. In any case, about 70 % of the patients who are diagnosed to have diabetes mellitus do not accomplish satisfactory glycaemic control, and along these lines, have an expanded risk for creating micro- and macrovascular complications such as, dyslipidaemia, obesity, and oxidative stress, which results in premature mortality (Godinho et al. 2015). Acarbose, an orally available α -glucosidase inhibitor used as once *per day* dose regimen for the treatment for type 2 diabetes mellitus, has demonstrated a beneficial effect on glycaemic control. It decreases postprandial hyperglycaemia by significantly hindering the activity of the α -glucosidase compound at the intestinal brush-border, and in this way deferring hydrolysis and assimilation of complex carbohydrates, and consequently impedes the ingestion of glucose (He and Shi, 2014;

Inzucchi, 2002). Pioglitazone, an agonist of peroxisome proliferator-activated receptor-gamma (PPAR) has a place with the thiazolidinediones (TZDs) class of oral anti-hyperglycaemic agents, which act by expanding insulin affectability and advancing glucose up-take and use in the liver, skeletal muscles, and adipose tissue (Cheatham, 2010; Chamberlain et al. 2017). Vildagliptin is an exceptionally viable medication for improving glycaemic control in the new class of antidiabetic agents for a broad scope of type 2 diabetic patients (Mathieu and Degrande, 2008). It is with the Dipeptidyl Peptidase-4 (DPP-4) inhibitors, which act by precisely hindering the dipeptidyl peptidase-4 enzyme, liable for glucose-subordinate insulinotropic peptide (GIP). Pancreatic islet α - and β -cells responsiveness to glucose, due to the activities increase levels of dynamic upgrades, there is an improvement in glucose-intervened insulin sessions and repressing wrong glucagon creation and smothers hepatic gluconeogenesis - they lower blood glucose concentration without causing hypoglycemia when utilized as a monotherapy (Ahrén and Foley, 2008; Cernea and Raz, 2011). The study investigated the impacts of Acarbose (AC), Pioglitazone (PGZ), and Vildagliptin (VDG) on the control of glycaemic levels and the different intricacies of diabetes mellitus utilising the alloxan-instigated diabetic model.

MATERIALS AND METHODS

Study Area

The study was carried out at the animal house section of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka between February 2016 and March, 2017.

Drugs and Chemicals

The active drugs, acarbose (Bayer Pharma, Germany), pioglitazone (Mega Pharma, India), and vildagliptin (Novartis Pharma, Nigeria) were utilised in the study. The cholesterol, triacylglycerol, low-thickness lipoprotein, high-thickness lipoprotein, ALP, ALT, and AST assay kits for the study were from Randox Diagnostics Ltd., United Kingdom. All other chemicals utilised were procured commercially.

Animals and Treatment

It was from the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, animal house that thirty (30) adult Wistar rats (100 – 160 g) were bought, with age roughly at ten weeks. The rats were kept up under temperature 20 ± 2 °C; relative humidity 55 ± 5 %; 12 h light/dull cycle (controlled environmental conditions). Free access to standard rat diets was permitted (indispensable feed), although the experiment strategies and tap water were not obligatory, but accessible.

The rats were separated into five (5) groups (n=6) as follows:

Group 1: Normal control

Group 2: Diabetic control (untreated)

Group 3: Received acarbose (AC); 30 mgkg⁻¹, p.o.

Group 4: Received pioglitazone (PGZ); 30 mgkg⁻¹, p.o.

Group 5: Received vildagliptin (VDG); 30mgkg⁻¹, p.o.

Induction of Diabetes

Before the induction of diabetes, baseline levels for glucose were determined. The rats had an overnight fast, but had access to water before the administration of alloxan monohydrate dissolved in physiological saline (ice cold) at a portion of 100 mgkg⁻¹ and the route of administration was intravenous. Collection of blood was from the tail vein of rats and set on the sensor pad of the glucometer strip previously embedded into the glucometer. After five days of stabilization, the animals were viewed as diabetic and utilised for the investigation when these animals have fasting blood glucose levels more prominent than 200 mgdL⁻¹. Blood glucose levels of the rats were resolved on days 0, 3, 7, and day 10 as the treatment went on for ten (10) days. The Accu-Chek® active blood glucose-checking meter and test strips were utilised for the measure, and every single animal test was affirmed.

Estimation of Biochemical Parameters

Through ocular puncture towards the end of the test time frame, blood samples (around 5mL) were collected with the guide of a non-heparinised capillary tube and transferred into clean sample bottles. In this manner, to acquire the serum segment, for 10 min, the samples were permitted to clump and centrifuged at 2000 revolutions *per* minute. The serum lipid profiles (absolute cholesterol, triacylglycerol, LDL, and HDL) was evaluated by the ultraviolet (UV) spectrophotometric technique (Pneumarthi et al. 2013; Pneumarthi et al. 2017). Through recently demonstrated strategies, the liver enzyme parameters activity was tested (Abou-Shoer, 2010; Jinda et al. 2020).

Statistical Analysis

Analysis of the data was done using ANOVA, employing a software programme, Statistical Package of the Social Sciences (SPSS, Version 18). The result was communicated at Mean $\pm$ SEM. Post-hoc Dunnett's test was used to evaluate the significant difference between the control and treated groups at a 95 % degree of significance. $P < 0.05$ was considered statistically significant.

RESULTS

Effects of Acarbose, Pioglitazone and Vildagliptin on Blood Glucose Levels

The blood glucose levels, when compared with the

Normal Control (NC) group, were significantly ($p < 0.05$), higher in the Diabetic Control (DC) group. The blood glucose levels, when compared with the diabetic control, was significantly ($p < 0.05$) decreased by the oral administration of VDG (30 mg kg^{-1}) and AC (30 mg kg^{-1}) on days 3, 7 and 10. It was observed that when compared with diabetic control, there was an insignificant ($p > 0.05$) decrease in the blood glucose levels of diabetic rats administered PGZ (30 mg kg^{-1}) Fig 1.

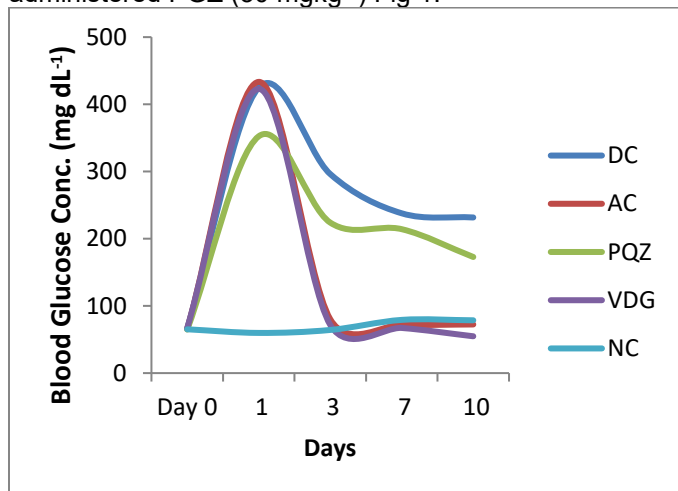


Figure 1: The Effect of Acarbose, Pioglitazone, Vildagliptin on Blood Glucose Levels of Hyperglycaemic Rats

The result showed that there was significant blood glucose level reduction ($p < 0.05$) across the different test samples from day three (3). Acarbose showed the most consistent and significant blood glucose reduction followed by the VDG.

Effects of Acarbose, Pioglitazone, and Vildagliptin on Serum Lipid Profile

It was observed that total cholesterol (TC), triacylglycerol (TAG), and low-density lipoprotein cholesterol (LDL-C) concentrations in the diabetic control group (DC) were significant ($p < 0.05$), and when compared with the normal control, they were higher with an accompanying reduction in the high-density lipoprotein (HDL-C) concentration. The result demonstrated a marked decrease in the TC, TAG, and LDL-C concentrations, when compared with the diabetic control group in diabetic rats administered 30 mg/kg , p.o. of AC, PGZ, and VDG separately. Correspondingly, there was a significantly ($p < 0.05$) higher HDL-C concentration in diabetic rats administered 30 mg kg^{-1} , p.o. of AC, PGZ, and VDG. In general, in TAG centralisation of diabetic rats administered pioglitazone (30 mg kg^{-1}), a non-significant ($p > 0.05$) decrease was observed.

Effects of Acarbose, Pioglitazone and Vildagliptin on Liver Marker Enzymes

There was a significant ($p < 0.05$) expanded degrees

of serum ALP, ALT, and AST in the diabetic control group when compared with the normal control. The alloxan-actuated height in these liver marker catalysts was significantly ($p < 0.05$) decreased by the oral treatment with VDG (30 mg kg^{-1}), PGZ (30 mg kg^{-1}), and AC (30 mg kg^{-1}).

Effects of Acarbose, Pioglitazone, and Vildagliptin on Body Weight

At the end of the experiment in the diabetic control group, when compared with the normal control, a reduction (16.9 %) was observed in the body weight and of the diabetic rats orally administered AC (30 mg kg^{-1}), PGZ (30 mg kg^{-1}), and VDG (30 mg kg^{-1}), with an increase by 3.7, 3.8 and 1.9 % respectively (Fig. 2-3).

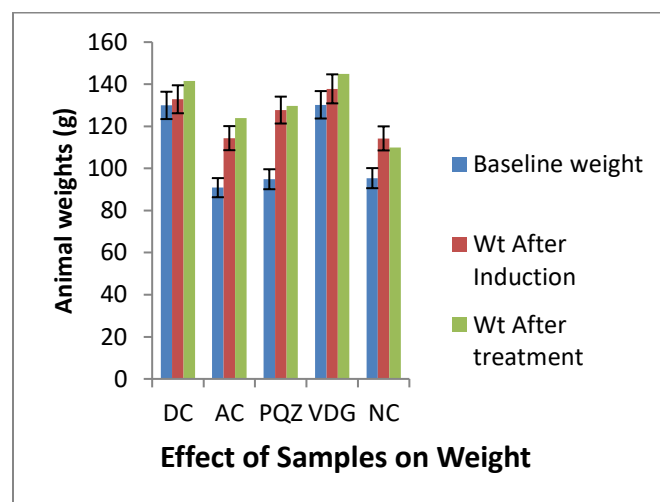


Figure 2: Effect of Samples on the Weight of Animals

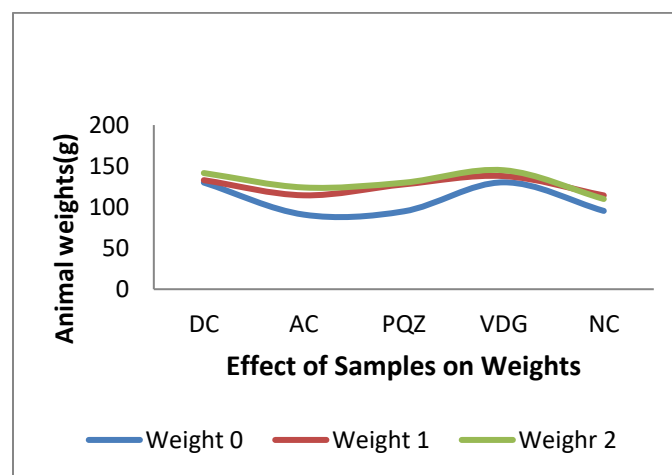


Figure 3: Effect of Samples on the Weight of Animals

Data were expressed as mean $\pm$ SEM ($n=6$). $=^*p < 0.5$ when compared with Normal Control (NC) and Diabetic Control (DC) respectively. Weight 0 is the baseline or initial weight before the commencement of the study, Weight 1 is the weight after induction while weight 2 is the weight of animals after treatment with the samples

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder with devastating consequences on the sufferer. It is characterised by an elevated blood glucose concentrations due to a relative or absolute deficiency of insulin from the β -cells of the pancreas. The pathological sequelae can be worrisome with very high mortality around the world. In the study, through the injection of alloxan monohydrate (100 mg kg^{-1} , iv.), diabetes was prompted in rats. Alloxan is a beta cytotoxin, that produced marked hyperglycemic impact by destroying the insulin-secreting β -pancreatic cells, bringing about decreased endogenous insulin discharge. Also, insulin inadequacy prompts different metabolic aberrations in particular dyslipidemia, renal, and cardiovascular complications. Reliable with literature, the administration of alloxan mainly expanded the Blood Glucose Level (BGL), which means diabetic condition. Following the administration of AC and VDG when compared with the diabetic control group, the higher BGL in alloxanized rats diminished significantly ($p < 0.05$). Vildagliptin acts by expanding β - and α -cell affectability to glucose, thus subsequently decreasing blood glucose concentrations by upgrading the impacts of 'incretins' (Ahrén and Foley, 2008). As seen in the result, AC and VDG exhibited a significant impact on glucose-lowering potential. Interestingly, when compared with the diabetic control group, an insignificant ($p > 0.05$), decrease in blood glucose level was produced by PGZ (Islam et al. 2016). Islam et al. (2016) detailed that in diabetic rats administered PGZ, there was a significant decrease in blood glucose levels. A potential purpose behind this distinction was the brief time of the study. A more grounded impact may have been found in a drawn-out time of examination. Through the improvement of insulin sensitivity, oral antidiabetic drugs that improve metabolic control in patients with type 2 diabetes are thiazolidinediones (for example, pioglitazone), otherwise known as glitazone, and they are agonists for the peroxisome proliferator receptor gamma (Hauner, 2002). Diabetes mellitus is related to a significant change in lipid and lipoprotein profiles; in this way, a perfect treatment for diabetes mellitus should favorably affect the lipid profile, notwithstanding offering great glycaemic control (Azizi et al. 2014; Salemi, 2016). The Triacylglycerol (TAG), Total Cholesterol (TC) and Low-Density Lipoprotein (LDL) levels are significantly ($p < 0.05$) increased in the diabetic condition in rats and significantly ($p < 0.05$) decreased the High-Density Lipoprotein (HDL) level compared with the control group. Some of the conceivable explanations of higher centralization or concentration of serum cholesterol in diabetes could be ascribed to diminish muscular exercise or restraint of cholesterol catabolism because of diabetes-actuated dyslipidaemia (Wong and Cheung, 2013). The outcome in diabetic rats administered AC, PGZ, and VDG showed a marked decrease in the TC, TAG, and LDL levels individually. It

was hypothesized that all classes of oral antidiabetic drugs have a vast lipid-lowering effect alongside glycaemic control effect (Pavithra and Chaitanya, 2025). The changes in TC, LDL, and HDL levels in diabetic rat administered AC, PGZ, and VDG was in concurrence with the discovered (Jalalvand et al. 2015; Ogunlana et al. 2017). In contrast, the changes seen in the TAG level in diabetic rats administered PGZ was opposite to the findings of the previous authors (Islam et al. 2016). This activity on the lipid profile proposes that AC, PGZ, and VDG have some cardiovascular defensive effects, notwithstanding their antidiabetic activities. Their advancement of the use of glucose, and thus discouraged mobilization of fats, could be said to be the reason for this.

Further, increased oxidative pressure in diabetics may prompt hepatic insult, which brings about the release of ALP, ALT, and AST. These enzymes are usually found in enormous amounts where they assume a significant role in the digestion of amino acids in the liver. These enzymes spill into the blood due to hepatic injury (Aulbach and Amuzie, 2017; Ogunlana et al. 2017). In the study, raised exercises of serum ALP, ALT, and AST, pointers of impeded liver capacity were observed in the diabetic control group, which affirms the hepatic insult. Strangely, comparative reports have demonstrated elevated exercises of serum ALP, ALT, and AST in diabetic animals. This asserts oxidative stress, characterized by the increased bioavailability of reactive oxygen species (ROS), and thus assumes a primary role in hepatic injury during diabetic manifestation. In general, following the oral administration of AC, PGZ, and VDG, the study observed significant ($p < 0.05$) decreases in the activities of these enzymes compared with the diabetic control group. This proposes that AC, PGZ, and VDG, notwithstanding their antidiabetic properties, may have a protective effect against diabetes-instigated hepatic dysfunction in the animals.

The result of the animal's mean body weights after the test showed that, with diabetic and control groups, there was a significant reduction in the body weights. As a result of the increased loss of muscle proteins, the characteristic loss of body weight is pathognomonic of induction of diabetes with alloxan (Harris, 2005). The administration of AC, PGZ, and VDG to alloxan-induced diabetic rats turned around weight reduction. This might be ascribed to the enhancement of glucose usage by the peripheral tissues (e.g., liver and muscles).

CONCLUSIONS

The study showed that acarbose and vildagliptin were more effective in decreasing blood glucose concentrations than pioglitazone. AC, PGZ, and VDG demonstrated significant improvement in the biochemical indices adjusted during diabetic-related indications, and thus demonstrated antidiabetic effect in the *trio* medications. These agents also, protected against diabetes-instigated complications in alloxan-induced

diabetic rats. They possessed both hyperglycaemic potential and protective effects against diabetes-induced dysfunctions in the animals, but acarbose had peak activity followed by vildagliptin, and pioglitazone (i.e., AC>VDG>PGZ). The study, therefore, suggests that all the three medications can be used in managing oxidative stress caused by chronic hyper-glycaemia, with acarbose standing out. More research is, nonetheless, needed to validate the outcomes.

Supplementary Materials

The supplementary material / support for this article can be found online: www.journals.viamedica.pl; www.e-enm.org.

Author Contributions

Conceptualization, supervision of bench work, and manuscript preparation, P.N.; Co-supervision, T.A. and A.E.; Bench work, C.E.; Data analysis *cum* proof reading of manuscript, C.N. and B.O. All the authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

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Data Availability Statement

All of the data is included in the article.

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Conflicts of interest

The authors declare that there was no conflicts of interest in the study.

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