Co-administration of Glibenclamide and Amlodipine Induces Resistance to Hyperglycemic Treatment in Streptozotocin Induced Adapted/Non adapted Diabetic Rats

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Abstract
It is a well known fact that diabetes co-exist with hypertension. In fact studies have shown that about 65% of diabetics have hypertension. Amlodipine, a calcium channel blocker is a well known anti-hypertensive frequently prescribed, even in diabetes. Potassium adaptation combined with amlodipine has also been shown to reduce blood pressure. This research is geared towards assessing the effects of both amlodipine and potassium adaptation on diabetic rats treated with glibenclamide.

Diabetes was induced using streptozotocin in rats both potassium adapted and non-adapted, thereafter glibenclamide (5 mg/kg) alone and a combination of glibenclamide (5 mg/kg) and amlodipine (5 mg/kg) were administered orally.

The animals were separately kept in metabolic cages and their urine volume, levels of plasma glucose, plasma and urine creatinine/creatinine clearance, the lipid profile, plasma and urine electrolytes/urea were also determined 24 hours after drug administration.

The blood glucose levels of the diabetic rats treated with only glibenclamide was significantly (p<0.05) reduced however diabetic rats treated with both drugs were not lowered and had blood glucose levels significantly higher (p<0.05) than that of the untreated diabetic rats, and diabetic rats treated with only glibenclamide.

The results also shows the blood glucose of the potassium adapted diabetic group treated with both drugs to be significantly higher (p<0.05) than that of the normal diabetic rats treated with same drugs. The total cholesterol, HDL, uric acid, and creatinine clearance of the potassium adapted diabetic rats were also significantly lower (p<0.05) than that of the normal diabetic rats treated with both drugs. This study provides results that suggest that combining both drugs inhibits the ability of the oral hypoglycemic agent in lowering the blood glucose of diabetic rats.

Keywords: Diabetes mellitus; Diabetic rats; Potassium adaptation; Streptozotocin

Introduction
Diabetes mellitus is a disease/group of syndromes characterized by chronic hyperglycaemia. There is altered metabolism of lipids, carbohydrates and proteins and increased risk of complications from vascular disease. Diabetes is associated with many complications, such as increased risk of blindness, kidney failure, heart attacks, and stroke. It’s a well known fact that cardiovascular disease is a leading cause of both morbidity and mortality in diabetic patients [1].

Early detection and treatment helps to slow down or prevent the complications. Population studies have shown an inverse relation of potassium intake to blood pressure, the prevalence of hypertension, or the risk of stroke [2]. Studies have shown that increasing the potassium intake of hypertensive rats that were fed high-sodium diets lowered blood pressure, reduced the incidence of stroke and stroke-related death, and prevented cardiac hypertrophy, mesenteric vascular damage, and renal injury [3,4]. Both historically and currently, the most commonly used drugs are in the Sulfonylurea group, of which several members including glibenclamide and gliclazide are widely used. Sulfonylureas are useful in type 2 diabetes who are unable to achieve proper control with changes in diet alone. These hypoglycemic agents increase glucose stimulated insulin secretion by the pancreas i.e. they stimulate insulin release from pancreatic β cells and so lower blood glucose even in the face of insulin resistance. The acute administration of sulphonylureas to type 2 DM patients increases insulin release from the pancreas. They could also increase insulin levels by reducing hepatic clearance of the hormone [5].

Amlodipine is a calcium channel antagonist of the 1,4-dihydropyridine derivatives blocking potential operated calcium channels of the L-type. This anti-hypertensive is distinguished from other calcium channel antagonist by its prolong half life, gradual onset of action, resulting in a long lasting action of the drug [6]. Calcium channel blockers, lowers blood pressure by relaxing arteriolar smooth muscle and decreasing peripheral vascular resistance [7].

Amlodipine is frequently administered to diabetics with hypertension [1], hypertension have also been shown to resolve with potassium adaptation [8].

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The outcome of potassium adaptation on diabetics probably with hypertension, treated with a combination of amlodipine for the hypertension and an oral hypoglycemic agent such as glibenclamide for the diabetes is not known. Diabetes was induced with streptozotocin known to induce both type1 and type 2. It has been reported that in streptozotocin (STZ)-induced diabetes, hyperglycaemia leads to progressive insulin resistance of the peripheral tissues, which is typical of type 2 diabetes [7]. Also in the STZ-induced diabetic model there is selected destruction of pancreatic islet β-cells, however, some β-cells do survive since plasma insulin levels in the diabetic rats are about 22 % of that in normal, hence insulin secretion can be stimulated in the residual β-cells of these diabetic animals by glibenclamide [9].

Hence the form of diabetes induced in this study accounts for both type1 as well as type 2 who are frequently saddled with hypertension.

Experiments were thus designed with the following two objectives: firstly to investigate the effect of potassium adaptation on the lipid profile, blood glucose, electrolytes, creatinine and urea of diabetic and non diabetic rats treated with a combination of glibenclamide and amlodipine. Secondly to ascertain the outcome of combining both drugs.

Materials and Methods

Drugs and chemicals

Potassium Chloride (Wells Brand Nigeria), Total Cholesterol kit (Randox UK), Triglyceride kit (Randox UK), High density lipoprotein kit (Randox UK), Glucose oxidase kit (Randox UK), Streptozotocin (Sigma-Aldrich ,UK) prepared in a 0.1 M citrate buffer with a PH of 4.5, Glibenclamide (Smith Kline Beecham, UK ), Amlodipine (Dr Reddy’s Laboratories, UK ). Stock solutions of drugs were stored in a refrigerator at 4°C. All chemicals were of analytical reagent grade.

Animals

Wistar albino rats were obtained from the Animal house, Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin.

Animals were age and sex-matched and weighed between 200 and 300 g. They were allowed free access to water or a particular solution and fed on standard diet (Bendel feeds and flour mills Ewu feeds, Edo State). Depending on the group, animals were housed 5 in a cage with a 12 hr light-dark cycle. Approval for the work was obtained from the Faculty of Pharmacy Ethical Committee on the use of Animals for experiments.

Animals were handled according to the standard protocols for the use of laboratory animals. (National Institute of Health, USA: Public Health Service Policy on Humane care and use of Laboratory animals, 2002).

Potassium adaptation

The potassium adapted rats were given 0.75% KCL solution for 5 weeks in place of tap water [10].

Induction of diabetes

Experimental diabetes mellitus was induced using Streptozotocin (60 mg/kg I.P) which induces experimental diabetes mellitus in 2 to 4 days in a 0.1 M citrate buffer solution in normal and potassium adapted adult wistar rats [11]. The rats were treated immediately on discovery that they were diabetic. Diabetes was confirmed on the 3rd day, and treatment was commenced same day of diagnosis of diabetes.

Experimental protocols

Normal rats fasted over night (n= 15) were divided into 3 groups of 5 each. The 1st received normal saline, the 2nd, amlodipine (5 mg/kg) [6] and the 3rd group was given a combination of glibenclamide (5 mg/kg) and amlodipine respectively. Potassium adapted normal rats of 5 were placed in a group and given normal saline. Diabetic rats fasted over night were placed in 3 groups of 5 rats each. Normal saline, glibenclamide (5 mg/kg) and a combination of glibenclamide and amlodipine (5 mg/kg) were given to each group respectively.

The potassium adapted diabetic rats were also assigned into 3 groups of 5 rats each and given normal saline, glibenclamide (5 mg/kg) and a combination of glibenclamide and amlodipine (5 mg/kg) respectively. All administrations were done orally by an oro-gastric tube. Both drugs were administered together, and observation was for 24 hours. So the length of time was 24 hours following drug administration. 5 mg/kg of each of glibenclamide and amlodipine was used.

The animals were kept in metabolic cages separately. The 24 hour urine was collected and volume noted. Thereafter blood samples were collected via a cardiac puncture. This was introduced into lithium heparinized containers, centrifuged and the plasma withdrawn. The plasma obtained was used in assessing the levels of plasma glucose, plasma and urine creatinine, triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein and electrolytes (sodium, potassium, chloride and bicarbonate).

![Image](https://via.placeholder.com/150)

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![Image](https://via.placeholder.com/150)
Determination of blood glucose level

Glucose level in plasma was determined using the glucose oxidase method.

Determination of biochemical parameters

Total plasma cholesterol, high density lipoproteins, low density lipoproteins and triglycerides, including urea and creatinine were estimated in all groups of animals by collecting blood via cardiac puncture, 24 hours after drug/normal saline administration. Blood samples were introduced into lithium heparin tubes. The samples were then centrifuged at 5,000 rev for 15 minutes to obtain the plasma. The enzymatic method using the wet reagent diagnostic kit was used.

Determination of electrolytes in plasma and urine

Plasma and urine chloride were determined using the mercuric nitrate method, the principle of flame photometer was used in assessing the sodium and potassium levels, while the principle of acid titration was used in the determination of bicarbonates.

Statistics

Data are presented as the mean ± standard error of the mean (S.E.M) and n represents the number of rats per group. Comparisons were made where appropriate by One-way ANOVA (GraphPad Prism Software, UK, version 2.05a) with Tukey post hoc.

A value of p<0.05 indicates significant differences in all cases.

Results

Blood glucose

The blood glucose of the diabetic group (Figure 1) treated with both glibenclamide and amlodipine (217.7 mg/dl) was significantly not different from the untreated diabetic rats (223.5 mg/dl), this is in contrast to the diabetic rats that received only glibenclamide, where a significant reduction (p<0.05) was observed on treatment from 223.5 to 78.67 mg/dl. A blood glucose of 217.7 mg/dl for diabetic rats treated with both drugs is significantly higher than the 78.67 mg/dl obtained for diabetic rats treated with only glibenclamide.

The blood glucose of the potassium adapted diabetic group (288.23 mg/dl) treated with glibenclamide and amlodipine (257.5 mg/dl) and with only glibenclamide (277.5 mg/dl) was significantly higher (p<0.05) than that of the untreated diabetic rats (223.5 mg/dl) and diabetics treated with glibenclamide and amlodipine (217.7 mg/dl).

Creatinine clearance

The creatinine clearance of the potassium adapted diabetic group treated with glibenclamide and amiodipine was significantly lower (p<0.05) than that of the diabetics treated with glibenclamide and amiodipine (Figure 2). The creatinine clearance of the groups treated with glibenclamide and amiodipine separately were significantly lower (p<0.05) than that of the group treated with both glibenclamide and amiodipine.

Urine volume

The volume of urine of the potassium adapted diabetic rats treated

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with a combination of glibenclamide and amlodipine was significantly higher (p<0.05) than the potassium adapted group (Figure 3). Treatment with glibenclamide alone significantly lowered the urine volume of diabetic rats.

**Lipid profile**

The HDL of the potassium adapted amlodipine and glibenclamide combined treated group was significantly lower (p<0.05) than that of the potassium adapted group. The total cholesterol and HDL of the potassium adapted diabetic group treated with glibenclamide and amlodipine were found to be significantly lower (p<0.05) than that of the diabetic group treated with glibenclamide and amlodipine (Table 1).

**Electrolytes**

On the electrolytes (Table 2 and 3), the plasma bicarbonate for the

| Treatment | Total cholesterol (mg/dl) | HDL (mg/dl) | LDL (mg/dl) | Triglyceride (mg/dl) |
|-----------|--------------------------|-------------|-------------|----------------------|
| C (2ml/kg) | 61.81±3.52 | 28.59±3.42 | 22.86±2.47 | 75.20±10.93 |
| A | 65.78±2.27 *a | 51.55±0.27 **a | 6.89±1.25 **a | 46.07±1.31 **a |
| G | 66.51±6.44 *a | 20.41±2.78 | 45.84±5.92 b | 42.81±5.75 b |
| AG | 45.88±5.50 | 27.19±3.00 | 33.95±10.11 | 35.75±2.90 |
| K | 44.32±1.75 | 47.68±1.75 | 12.07±2.80 | 26.82±6.94 |
| KAG | 49.71±4.92 | 35.76±2.51 | 8.91±0.46 | 33.43±5.89 |
| D | 60.13±6.35 | 20.12±2.89 | 33.10±3.42 | 46.55±7.87 |
| DG | 71.84±2.83 | 75.38±8.46 | 7.97±2.27 | 34.20±8.11 |
| DGA | 50.74±4.95 | 33.34±2.15 | 12.45±3.19 | 52.81±4.03 |
| KDAG | 30.93±6.12 | 14.59±1.56 | 15.82±4.48 | 57.44±6.58 |

Values are mean ± SEM. (n=5 per group).

* p<0.0001, ** p<0.05 significantly different from the control, *** p<0.05 significantly different from the diabetic group treated with glibenclamide and amlodipine, **** p<0.05 significantly different from the potassium adapted group and ***** p<0.05 significantly different from the normal group treated with amlodipine and glibenclamide.

C: Control (normal saline group)
A: Normal group treated with amlodipine
G: Normal group treated with glibenclamide
AG: Normal group treated with both amlodipine and glibenclamide
K: Potassium adapted group
KAG: Potassium adapted treated with both glibenclamide and amlodipine
D: Diabetic group
DG: Diabetic group treated with glibenclamide
DGA: Non-adapted diabetic group treated with both glibenclamide and amlodipine
KDAG: potassium adapted diabetic group treated with both amlodipine and glibenclamide

**Table 1:** Effect of potassium-adaptation on the lipid profile of normal and streptozotocin-induced diabetic rats treated with amlodipine (5 mg/kg) and glibenclamide (5 mg/kg).

| Plasma electrolytes (mmol/l) | Treatment | Na⁺ | K⁺ | HCO₃⁻ | Cl⁻ |
|-------------------------------|-----------|-----|-----|-------|-----|
| C (2ml/kg) | 139.0±2.08 | 4.8±0.15 | 26.2±1.16 | 104.3±1.50 |
| A | 142.8±2.15 | 5.0±0.24 | 21.2±1.86 *a | 102.4±1.17 |
| G | 142.0±1.14 | 4.5±0.18 | 26.8±0.74 | 105.4±3.32 |
| AG | 143.8±1.56 | 4.6±0.22 | 27.2±0.86 | 106.0±1.79 |
| K | 146.0±1.09 b | 5.3±0.36 | 24.4±0.40 | 105.2±1.49 |
| KAG | 144.6±1.78 | 4.6±0.16 | 25.0±0.55 | 105.8±1.74 |
| D | 140.8±1.08 | 4.6±0.12 | 24.2±0.54 *a | 103.4±1.78 |
| DG | 145.6±2.11 | 5.0±0.28 | 25.4±1.63 *a | 103.4±1.78 |
| DGA | 142.0±1.38 | 4.8±0.07 | 24.2±0.50 | 105.6±1.57 |
| KDAG | 145.4±1.87 | 4.6±0.22 | 24.6±0.88 | 107.0±1.00 |

Values are mean ± SEM. (n=5 per group).

* p<0.05 significantly different from the control, ** p<0.05 significantly different from the diabetic group treated with glibenclamide and amlodipine, *** p<0.05 significantly different from the potassium adapted group and **** p<0.05 significantly different from the normal group treated with amlodipine and glibenclamide.

C: Control (normal saline group)
A: Normal group treated with amlodipine
G: Normal group treated with glibenclamide
AG: Normal group treated with both amlodipine and glibenclamide
K: Potassium adapted group
KAG: Potassium adapted treated with both glibenclamide and amlodipine
D: Diabetic group
DG: Diabetic group treated with glibenclamide
DGA: Non-adapted diabetic group treated with both glibenclamide and amlodipine
KDAG: potassium adapted diabetic group treated with both amlodipine and glibenclamide

**Table 2:** Effects of potassium-adaptation on plasma electrolytes of normal and streptozotocin-induced diabetic rats treated with amlodipine (5 mg/kg) and glibenclamide (5 mg/kg).
amiodipine group was significantly different (p<0.05) from the control and amiodipine and glibenclamide treated groups. Urine potassium for the potassium adapted diabetic group treated with glibenclamide and amiodipine combined were significantly higher (p<0.05) than that of the diabetic group treated with glibenclamide and amiodipine combined.

Urine bicarbonate of the glibenclamide alone and amiodipine alone treated groups were significantly different (p<0.05) from the group given a combination of both drugs.

**Creatinine and urea**

Table 4 shows the effect of potassium adaptation on both the creatinine and urea (plasma and urine) of diabetic rats treated with a combination of amiodipine and glibenclamide. The creatinine (plasma and urine) of the potassium adapted group treated with a combination of amiodipine and glibenclamide were significantly higher (p<0.05) than that of the non-treated potassium adapted group. The plasma creatinine of the amiodipine treated group was significantly higher (p<0.05) than those of the control and glibenclamide and amiodipine

| Treatment | Na⁺ (mmol/l) | K⁺ (mmol/l) | HCO₃⁻ (mmol/l) | Cl⁻ (mmol/l) |
|-----------|-------------|-------------|----------------|-------------|
| C (2ml/kg) | 247.8±11.21 | 33.9±2.89   | 22.5±4.33      | 53.2±5.98   |
| A          | 234.0±18.08 | 26.7±4.54   | 54.4±6.61      | 42.4±7.32   |
| G          | 123.6±3.90  | 35.8±1.45   | 19.6±2.12      | 32.5±6.20   |
| AG         | 227.0±10.02 | 34.4±2.75   | 30.2±2.06      | 54.4±5.50   |
| K          | 223.0±30.98 | 26.6±2.70   | 70.4±6.17      | 39.6±7.39   |
| KAG        | 236.4±10.6  | 35.6±2.35   | 34.2±2.15      | 61.6±6.49   |
| D          | 124.8±5.08  | 34.0±2.52   | 9.0±1.73       | 49.6±3.82   |
| DG         | 199.4±13.18 | 34.9±3.54   | 59.8±5.06      | 41.0±7.13   |
| DGA        | 216.4±21.75 | 19.4±1.59   | 28.4±1.21      | 46.8±7.39   |
| KDGA       | 237.0±9.32  | 31.9±1.94   | 28.4±1.21      | 60.4±3.76   |

Values are mean ± SEM. (n=5 per group).

| Treatment | Creatinine (mmol/l) | Urea (mmol/l) |
|-----------|---------------------|---------------|
| plasma    | urine               | plasma        | urine         |
| C (2ml/kg) | 0.21±0.03           | 2.67±0.62     | 9.27±0.37     | 785.8±116.90 |
| A          | 0.65±0.12           | 5.52±1.39     | 5.22±1.68     | 469.39±62.26 |
| G          | 0.21±0.02           | 2.37±0.46     | 7.57±0.55     | 545.93±69.92 |
| AG         | 0.11±0.09           | 3.19±0.45     | 6.61±1.16     | 237.74±45.50 |
| K          | 0.09±0.01           | 1.77±0.13     | 9.44±0.42     | 336.41±49.71 |
| KAG        | 0.35±0.12           | 6.37±0.90     | 9.39±1.09     | 251.92±23.39 |
| D          | 0.26±0.03           | 2.64±0.46     | 11.23±0.49    | 473.33±51.56 |
| DG         | 0.08±0.13           | 4.56±0.84     | 7.94±0.51     | 276.96±48.85 |
| DGA        | 0.23±0.02           | 3.98±0.44     | 11.62±1.67    | 392.77±23.46 |
| KDGA       | 0.19±0.01           | 1.57±0.24     | 8.47±0.69     | 499.13±59.10 |

Values are mean ± SEM. (n=5 per group).

Table 4: Effects of potassium-adaptation on creatinine and urea of normal and streptozotocin induced- diabetic rats treated with amiodipine (5 mg/kg) and glibenclamide (5 mg/kg).
combined treated groups. However treatment of the potassium adapted diabetic with glibenclamide and amlodipine produced a significant decrease (p<0.05) in the urine creatinine in comparison with the diabetic group treated with both drugs.

Discussion

Streptozotocin is known to induce both type 1 and 2 diabetes. At the dose level (60 mg/kg) used for induction, there is selective destruction of beta cells. However there are still a few beta cells unaffected which can still be stimulated by glibenclamide, hence the use of glibenclamide in this work. In situations of type 1 DM induction, there is an eventual progression to type 2 DM, because of the progressive insulin resistance that develops with time [9]. Both type 1 and 2 DM have similarity in complications. In both cases, complex and multifactorial metabolic changes often lead to damage and function impairment of organs most importantly the cardiovascular system [11].

Amlodipine, a calcium channel blocker is a well known anti-hypertensive frequently prescribed, even in diabetes mellitus [6]. Hence in this work, both drugs (amlodipine and glibenclamide) were administered at the same time to ascertain the exact type of drug-drug interaction that could exist between both classes of drugs and possibly provide data on the effects of such a combination on the biochemical parameters investigated.

The blood glucose of diabetics treated with both amlodipine and glibenclamide was not lowered on treatment as seen from the result, however for the diabetic group that received only glibenclamide, interestly a significant reduction in the blood glucose level was noted, which showed that the hyperglycemia, responded to treatment with glibenclamide alone, as evident by the lowering of the blood glucose [12], this is opposed to what was observed for the diabetic group given a combination of glibenclamide and amlodipine, where resistance to treatment and hence persistent hyperglycemia was observed. This simply means that for a patient with both conditions (diabetes and hypertension), there has to be a reasonable time interval between the administration of both drugs or possibly replace glibenclamide with another suitable oral hypoglycemic agent like metformin or vice versa.

Hence both drugs should not be taken concomitantly as indicated by the persistent high blood glucose observed on treatment of the diabetic rats with both drugs. In fact the blood glucose of the diabetic rats treated with both drugs (amlodipine and glibenclamide) was not significantly different from the untreated diabetic rats. It seems that the administration of amlodipine interfere the effects of glibenclamide on hyperglycemia.

A further increase in the blood glucose was noted for the potassium adapted diabetics treated with both amlodipine and glibenclamide suggesting induction of hyperglycemia by potassium adaptation. Potassium adaptation may increase the open state of the potassium channels and may be increasing potassium conductance in the β-cells of the islets of langerhans, inhibiting membrane depolarization, calcium influx through voltage sensitive channels and hence insulin release [13].

A significant increase in the plasma creatinine on treatment with amlodipine for the non adapted was noticed. A rise may thus indicate marked damage to functioning nephrons and renal disease [14]. This means more creatinine been filtered into the blood which possibly indicates an increase in the GFR [13]. Amlodipine seems to have the ability to increase the creatinine clearance in comparison with the control and the combination of amlodipine and glibenclamide. The implication of this is that possibly amlodipine has an influence on renal function, most likely on the GFR and thus glomerular function [15].

The co-administration of both drugs also significantly lowered the HDL values in comparison with those that were adapted and not treated, and those given glibenclamide alone. It can simply be inferred that the presence of amlodipine could be responsible for this decrease noticed.

Low concentrations of HDL (below 40 mg/dl for men, below 50 mg/dl for women) increases the risk for atherosclerotic diseases [16]. Hence HDL values of diabetics on amlodipine will have to be monitored for this reason.

The potassium adapted diabetic group treated with both drugs had significantly higher potassium values, though the other electrolytes were higher, this was not significant when compared with the non-adapted diabetics treated with both drugs. Obviously, the presence of adaptation to potassium accounts for the higher potassium values noted. Treatment with amlodipine alone significantly lowered the plasma bicarbonate and increased the urine bicarbonate in comparison with the control. Bicarbonates acts as a buffer to maintain normal levels of acidity in blood and other fluids, increased levels are a sure sign of metabolic alkalosis and compensated respiratory acidosis [17].

Higher levels of bicarbonate in the urine are a pointer to the fact that calcium channel blockers may be saddled with the side effect of compensated respiratory acidosis in patients receiving it. Hence the electrolytes of such a hypertensive patient will have to be monitored to avert this possibility.

This study provides results that suggest that combining both amlodipine and glibenclamide inhibits the ability of the oral hypoglycemic agent in lowering the blood glucose of diabetic rats. The administration of amlodipine and glibenclamide to the diabetic group induced resistance to treatment with glibenclamide alone. Secondly with potassium adaptation, a further increase in the blood glucose of diabetic rats non responsive to treatment was observed.

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