CLINICAL TRIAL OF GLIMEPIRIDE COMPARED WITH GLIBENCLAMIDE FOR EFFICACY AND SAFETY IN TYPE 2 DIABETES MELLITUS IN JOS, NIGERIA

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ABSTRACT

Objective: The study was undertaken to compare the efficacy and safety of Glimepiride against Glibenclamide in the management of patients with type 2 DM in Jos, Nigeria.

Study design: An open, randomised controlled trial.

Setting: Diabetes Clinic of the Jos University Teaching Hospital, Jos, Nigeria.

Subjects: Seventy four type 2 diabetic patients were randomised to either Glimepiride or Glibenclamide for at least 12 weeks.

Measurements: Fasting plasma glucose (Primary outcome variable) and fasting plasma total cholesterol (TC), triglycerides (TG), HDL-cholesterol, and compliance (Secondary outcome variables) were the efficacy variables of interest. Adverse events and the laboratory variables of full blood count, liver function tests, electrolytes, urea, uric acid, and creatinine were the safety outcome variables.

Results: Satisfactory blood glucose control was achieved in the majority (88.7%) of patients on 1-6mg Glimepiride daily and 5 to 20mg Glibenclamide daily. The proportion of patients who had good blood glucose control was significantly higher in the Glimepiride-treated group (85.7%) than in the cohort treated with Glibenclamide (52.8%), $P<0.05$. Patients on Glimepiride had significantly lower mean plasma cholesterol, (total, LDL, HDL) and triglycerides post-trial than at baseline. Both drugs were metabolically inert and did not derange the haematological and/ or biochemical profiles of the patients. No side effects were observed and there was absence of hypoglycaemic episodes.

Conclusion: Glimepiride 1-6mg once daily and Glibenclamide 5-20mg daily are effective medications for Nigerians with type 2 DM.

Keywords: Diabetes mellitus, Glycaemic control, Glibenclamide, Glimepiride, Nigerians

INTRODUCTION

Diabetes mellitus (DM) is the commonest endocrine disease in Nigeria [1]. No fewer than 2.2% of Nigerians aged 15 years and above have DM [2].There are two major types of DM; type1 in which insulin is required for satisfactory control and survival, and type 2 in which satisfactory control is achievable by dietary regulation with or with out oral blood glucose lowering agents [3]. Type 2 DM is the commonest form and accounts for over 90% of our diabetic population in Nigeria.

Treatment in DM has the goal of restoring blood glucose to normal levels, avoiding acute symptoms and delaying or preventing late complications. The most widely used oral blood glucose lowering agents for the treatment of type 2 DM are the sulphonylureas (SU). The first of these to be introduced was Chlorpropamide, but the most widely used at the present time is Glibenclamide. The SU act mainly by stimulating insulin secretion by the pancreatic beta-cells (â-cells), thereby making target tissues more sensitive to insulin [3]. Glimepiride is a new second generation SU which has been extensively studied in many parts of the world. It had been shown in clinical trials to have no serious adverse effects within its therapeutic range [4,5]. Glimepiride has unique pharmacokinetic and

pharmacodynamic properties which may offer some advantages over Glibenclamide; having different binding sites at the â-cell and shorter interaction with the SU receptor [6, 7]. These properties give Glimepiride high efficacy in metabolic control of type 2 DM, with a rapid onset and a long duration of action allowing for a once daily dosage over the therapeutic range (1-8 mg) [4, 5]. In clinical trials, treatment with Glimepiride was observed to be associated with lower risk of hypoglycaemic events in newly diagnosed type 2 diabetic patients and in switch over type 2 diabetic patients when compared with Glibenclamide [8, 9].

Glimepiride is associated with insulin-saving effects in clinical trials. Lower fasting insulin levels and suppression of endogenous insulin release during physical exercise are properties associated with Glimepiride [9]. Moreover, Glimepiride has minimal interactions with the cardiovascular system [10]. Glimepiride does not interact significantly with cardiovascular ATP-dependent K^{+} channels in contrast to Glibenclamide and Gliclazide because of its pancreatic â-cell specificity (SU stimulate insulin release by inhibiting the ATP-dependent K^{+} channels in the â-Cells of pancreatic islet) [10, 11]. The vasoconstrictive effects of SU do not occur with Glimepiride therapy.

Glimepiride and Glibenclamide are well-established oral blood glucose lowering compounds used in the treatment of type 2 DM. While Glibenclamide has been in use in Nigeria for many years now, Glimepiride has not been used in our local population. Because of the distinct advantages of Glimepiride from studies elsewhere, we decided to compare it with Glibenclamide, the most widely used oral anti-diabetic drug in Nigeria, with respect to efficacy and safety in the management of patients with type 2 DM.

MATERIALS AND METHODS

Study Design

This was an open, controlled, randomized, parallel group study comparing Glimepiride with Glibenclamide.

Patients

Patients of either sex with type 2 DM attending the out patient Diabetes Clinic of the Endocrinology Unit of Jos University Teaching Hospital were selected if they met the following criteria:

1. Newly diagnosed or known, previously treated type 2diabetics requiring treatment with oral hypoglycaemic agents (OHA),
2. Age 35-70 years,
3. Fasting blood glucose between 3.3-7.8 mmol/L for known diabetics on treatment,
4. Fasting blood glucose > 7.8 mmol/L for new patients,
5. Willingness to participate in the trial.

Excluded from the trial were patients with either of the following:

1. A history of primary or secondary failure of oral SU treatment,
2. History of hypersensitivity to SU or to drugs with similar chemical structure,
3. Pregnant or lactating women,
4. Serious life threatening concomitant disease,
5. Impaired renal function (serum creatinine > 140 μmol/L),
6. Severe complications of DM
7. Impaired hepatic function,
8. Severe mental ill health,
9. Unwillingness to participate in the trial,
10. Body-mass index (BMI) > 30kg/m^2.

Clinical procedure

Patients selected for the trial were randomized into treatment with either the test drug Glimepiride or the control drug (Glibenclamide). Equal number of patients were randomised to the test and control drug treatment groups.

On enrolment into the study, a detailed history was taken and all patients had full physical examination. In particular, information regarding the following were recorded: age, gender, body weight, height, previous history of diabetes, anti diabetic treatment, history of complications of diabetes, any concomitant disease, waist and hip circumferences.

New patients were stabilised on diet for two weeks after which the fasting plasma glucose (FPG) was repeated. Those with high FPG at this stage (> 7.8 mmo/L) were enrolled and randomised into either the test group or control group. Patients previously controlled

with an OHA with FPG in the inclusion range (3.3-7.8 mmol/L) were also enrolled into the study and randomised into either the test or control group.

The trial was divided into two phases:

(1) a titration phase and

(2) a maintenance phase.

Titration phase:

New patients commenced treatment with 1 mg Glimepiride or 2.5mg Glibenclamide once daily. Previously treated patients were started on Glimepiride or Glibenclamide at one dose step below the equivalent dose of the SU being taken previously as follows:

Glimepiride (mg)		Glibenclamide (mg)
2.5	-	1
5	-	2
10	-	3
15	-	4
20	-	6

During the titration phase which lasted 2-6 weeks, the patients were seen weekly. At each clinic visit a clinical assessment was undertaken and fasting plasma glucose (FPG) was measured. Patients with FPG levels between 3.3-7.8 mmol/L progressed to the maintenance phase at the same dose. Patients whose FPG levels exceeded 7.8 mmol/L had their SU doses raised to the next higher dose for the next week. This was continued until the FPG at the weekly visit was between 3.3-7.8 mmol/L or a peak dose of 20mg per day of Glibenclamide or 6mg per day of Glimepiride was reached. In such cases the patients were regarded as treatment failures. For FPG level below 3.3 mmol/L, the SU dose was reduced by one step.

Maintenance phase:

The daily dose of Glimepiride or Glibenclamide achieved during the titration phase was maintained. This phase lasted another 12 weeks during which patients were seen fortnightly. The maintenance dose was increased or decreased as the clinical situation in the judgement of the investigators warranted it. At the end of the maintenance phase the laboratory tests done at the beginning of the titration phase and clinical measurements were repeated. Drop-outs during the trial were not replaced.

Withdrawal criteria

Patients with the following were withdrawn from the study: frequent hypoglycaemic attacks, poor metabolic control, poor compliance defined as less than 80% of the medication taken or desire of the patient to withdraw.

End points

Fasting plasma glucose (Primary outcome variable) and fasting plasma total cholesterol (TC), triglycerides (TG), HDL-cholesterol, compliance (Secondary outcome variables) were the efficacy variables of interest. Adverse events and the laboratory variables full blood count, liver function tests, electrolytes, urea, uric acid, and creatinine were the safety outcome variables.

Case record form (CRF)

All information collected in the course of the trial were recorded in the case record forms specially prepared for the trial. Any intercurrent illness and the treatment given were properly documented in the case record forms.

Adverse events

All adverse events volunteered by the patient or detected by the investigator were recorded in the CRF in detail as well as action taken on them. Serious adverse events were to be handled as in the sponsor's instruction to investigators.

Ethics

The study was undertaken in accordance with the principles laid down in the Declaration of Helsinki and approved by the Ethics Committee of the Jos University Teaching Hospital. The requirement of Good Clinical Practice was adhered to at all times. After verbal and written information regarding the aim and methods of the study had been given and explained in the language most comfortable to the patients, all those who participated in the study gave full consent before recruitment.

Data analysis

The patients' CRF were examined and relevant variables contained in them were extracted for statistical analysis. The statistical package, EPI- Info version 2.2.1

was used for data entry. All tests were two-sided with a significant level of 0.05. Chi-square was used to compare proportions (Fisher exact was used for cells less than 5) and the Student t-test to compare group means. The laboratory test values measured before and at the end of the study were compared using Wilcoxon's matched pairs signed- rank test within each treatment group.

RESULTS

A total of seventy four (74) Patients were randomised (37 to each treatment group) to participate in the trial. Overall, 71 patients (95.9%) completed the trial. Three patients (2 from the test group and 1 from the control group) could not progress to the maintenance phase. Newly diagnosed patients constituted 8 (10.8%) of the population (5 in the Glimepiride treated group and 3 in the Glibenclamide treated group respectively).

Baseline clinical and laboratory characteristics

The mean age of the test group was similar to that of the control group; 51.7 ± 9.2 vs. 52.6 ± 7.7 years, respectively, p >0.05 (Table 1). Similarly there were no significant differences between the two groups with respect to body weight, body mass index (BMI) and waist to hip ratios (WHR). There were no statistically significant differences in the mean baseline fasting plasma glucose (FPG) concentrations and other laboratory tests of the patients in both treatment groups.

Outcome measure and efficacy of the drug

The comparison of the pre and post-treatment values of the fasting plasma glucose (FPG) concentrations (Primary variable) and Secondary laboratory efficacy variables of the patients in the Glimepiride and Glibenclamide groups are shown in Table 2. In the Glimepiride-treated group, there was significant improvement of the post treatment FPG, mean (± SD) 5.4 (± 1.4) mmol/L over the pre-treatment value of 6.8 (± 2.4) mmol/L (p< 0.001). There was no statistically significant difference in the pre-and post-treatment mean FPG levels of the Glibenclamide treated group (6.6 ± 2.0 and 6.6 ± 1.7 mmol/L respectively, p > 0.05). The mean of lipid profile of the Glimepiride-treated patients decreased significantly post treatment compared to the pre treatment values (p<0.05). In the Glibenclamide treated patients a slight and insignificant reduction of the mean levels of total cholesterol, TG, and LDL - cholesterol was observed (p > 0.05). The control group also had an insignificant increase in their mean HDL level (2.38 ± 0.42 mmol/l) post-treatment compared to the pre-treatment values, (2.24 ± 1.15 mmol/l), p > 0.05. There were no statistically significant differences in the pre-and-post treatment values of the clinical variables of weight, BMI and WHR in both treatment groups (p > 0.05).

The distribution of the glycaemic status of the patients at the end of the trial by drug treatment is shown in Table 3. Overall, 69.0% of the patients had good glycaemic status (FPG < 7.0 mmol/L). Thirty patients (85.7%) in the Glimepiride treated group that completed the trial had FPG levels less than 7.0 mmol/L. This was significantly higher than the corresponding 52.8% in the Glibenclamide-treated patients ($X^2 = 9.03$, $p < 0.01$). Only 2 patients (5.7%) of the Glimepiride treated group had FPG greater than 7.8 mmol/L at the end of the trial, compared to 16.7% in the Glibenclamide-treated group.

Of the 35 Glimepiride-treated patients, 25 (71.4%) completed the trial on 1-2mg daily dose. Five patients were on the maximum dose of 6mg Glimepiride daily, out of whom two had FPG> 7.8 mmol/L at the end of the trial. Thirteen (36.1%) of 36 patients on Glibenclamide required 2.5-5mg daily dose; while the majority of these patients (52.8%) required 10mg daily dose of Glibenclamide at the end of the trial. These differences were statistically significant, $X^2 = 8.90$, $p < 0.001$.

Drug compliance

Overall, no unused tablets were returned by the patients in both treatment groups throughout the duration of the trial. None of the patients in either treatment group stopped treatment on account of any side effect or adverse reaction.

However, one female patient, aged 65 years misplaced 6 tablets of 4 mg Glimepiride between the 4th and 5th maintenance visits and was drug-free during the period. She was then moved to the maximum dose of 6mg Glimepiride daily following a grossly elevated

FPG. She eventually had a FPG level >140mg/dl on the last visit of the trial.

Adverse events and withdrawals

There was no report of any serious adverse event among the 74 patients that were involved in the trial. Similarly, no history of adverse reaction was elicited from the patients. There was also no report of symptoms of hypoglycaemia from any patient. The lowest FPG level measured was 3.5 mmol/L on the last visit and the patient was asymptomatic.

There were no significant differences in the pre-and post-trial laboratory tests results of the patients in both treatment groups (p-values in all cases >0.05) as shown in Table 4.

Table 1. Patient characteristics at baseline

Parameter	Glimepiride group (n=35)	Glibenclamide group (n=36)
Clinical		
Age, years	51.7 ± 9.2	52.6 ± 7.7
Sex, m/f	23/12	16/20
Weight, kg	70.6 ± 11.9	70.3 ± 10.2
BMI, kg/m^2	25.7 ± 3.05	26.4 ± 2.2
WHR	0.92 ± 0.06	0.93 ± 0.05
Duration of DM, years	2.5 ± 2.2	3.4 ± 3.7

There were no significant differences between the groups when these parameters were compared using the Chi-square and student t test where appropriate.

Table 2 Comparison of patients pre-and post-trial efficacy variables

Parameter	Treatment group	Period		p-value
		Pre-trial (mean ± SD)	Post-trial (mean ± SD)	
FPG (mmol/L)	Glimepiride	6.8 ± 2.4	5.4 ± 1.4	< 0.001
	Glibenclamide	6.6 ± 2.0	6.6 ± 1.7	> 0.05
Total cholesterol (mmol /L)	Glimepiride	5.10 ± 1.14	4.32 ± 1.00	< 0.01
	Glibenclamide	4.71 ± 1.18	4.66 ± 0.73	> 0.05
Triglyceride (mmol/L)	Glimepiride	1.59 ± 0.71	1.25 ± 0.54	< 0.05
	Glibenclamide	1.47 ± 0.71	1.47 ± 0.61	> 0.05
HDL cholesterol (mmol/l)	Glimepiride	2.40 ± 1.02	2.33 ± 0.59	< 0.05
	Glibenclamide	2.24 ± 1.15	2.38 ± 0.42	> 0.05
LDL - cholesterol (mmol/l)	Glimepiride	1.98 ± 0.81	1.52 ± 0.71	< 0.05
	Glibenclamide	1.76 ± 1.18	1.61 ± 0.61	> 0.05

Table 3. Comparison of patients pre and post trial laboratory parameters

Parameter	Treatment group	Period	
		Pre-trial (mean ± SD)	Post-trial (mean ± SD)
Total Proteins (g/L)	Glimepiride	76.19 ± 7.55	73.46 ± 7.3
	Glibenclamide	75.50 ± 5.90	74.81 ± 5.80
Albumin (g/L)	Glimepiride	38.65 ± 5.01	39.51 ± 3.98
	Glibenclamide	38.19 ± 4.33	38.97 ± 3.64
Alkaline Phosphatase (IU/L)	Glimepiride	49.14 ±20.06	47.51 ±22.31
	Glibenclamide	56.65 ±31.60	55.75 ±19.87
SGOT (IU/L)	Glimepiride	9.70 ± 4.70	10.49 ± 6.5
	Glibenclamide	12.30 ± 7.50	11.67 ±10.23
SGPT (IU/L)	Glimepiride	7.43 ± 3.66	9.94 ±11.70
	Glibenclamide	9.03 ± 5.40	8.67 ± 6.70
Urea (mmo/L)	Glimepiride	4.47 ±1.27	4.12 ±1.27
	Glibenclamide	4.75 ±1.35	4.47 ±0.97
Creatinine (μmol/L)	Glimepiride	84.35 ±26.77	85.03 ±20.48
	Glibenclamide	89.32 ±20.73	84.50 ±15.11
Uric acid (mmol/L)	Glimepiride	280.05 ± 82.07	269.86± 76.47
	Glibenclamide	255.49 ± 70.28	285.39± 69.95
PCV (%)	Glimepiride	41.5 ± 7.9	44.1 ± 2.8
	Glibenclamide	42.9 ± 3.5	42.9 ± 3.2
WBC x 10^9/ μL	Glimepiride	4046 ± 2305.2	3701 ± 1926.8
	Glibenclamide	4195.5 ± 2335.9	3770 ± 1966.2

There were no significant differences between the groups when these parameters were compared (P-Value were all greater than 0.05).

DISCUSSION

This clinical trial compared the efficacy and tolerability of Glimepiride and Glibenclamide in Nigerian Patients with type 2 DM. The mean value of the fasting plasma glucose improved significantly in the Glimepiride-treated group of patients at the end of the trial, while in the cohort that received Glibenclamide the mean value post-trial compared to the baseline, was not significantly different. Both drugs were effective in maintaining normal plasma glucose levels in the subjects, but Glimepiride appeared to be more effective, particularly at lower doses. The proportion of patients who had good glycaemic status was significantly higher in the Glimepiride treated group (85.7%) than in the Glibenclamide-treated

group (52.8%). At completion of the trial 94.3% of the Glimepiride-treated patients and 83.3% of the Glibenclamide-treated patients had fasting plasma glucose levels below 7.8 mmol/L. Seventy one point four percent (71.4%) of Glimepiride-treated patients required 1 to 2mg daily dose for maintenance of control, while the majority of the Glibenclamide treated patients (86.1%) required 5 to 10mg daily dose. This observation had been noted in many studies done elsewhere [4 - 9]. In these studies Glimepiride was observed to provide better blood glucose control than Glibenclamide at lower doses.

The post trial plasma lipid profile (mean total cholesterol, triglycerides, LDL - cholesterol and HDL - cholesterol) fell significantly from the baseline values in the Glimepiride-treated patients, whereas no significant difference was observed in these parameters in the cohort on Glibenclamide, although both groups had similar pre trial clinical and laboratory test features. This observation is interesting because it is widely accepted that monotherapy with SU may result in visceral fat accumulation and dyslipidaemia [12]. Clinical characteristics (weight, body mass index, hip and waist circumferences and waist - to hip ratios) remained similar to baseline values at completion of trial in both treatment groups.

In this study both Glimepiride and Glibenclamide were well tolerated and there was no incidence of hypoglycaemia. The most well documented side effect of the SU is hypoglycaemia which is observed in many studies to be worse with the older SU like Chlorpropamide and Glibenclamide. Some studies have however, observed the absence or low- risk of hypoglycaemia while using newer second generation SU [8, 9, 13]. In a particular study [13], a prospective trial of risk factors for SU-induced hypoglycaemia in type 2 DM, the second generation SU Gliburide and Glipizide were compared and no episode of hypoglycaemia was observed and fasting was well tolerated among elderly patients (mean $\pm$ SD age, 65.1$\pm$5.7 years). Therefore, old age should not be considered a contraindication to newer generation SU. Although hypoglycaemia was not reported in this study, there is evidence from many studies of its danger particularly with the older SU [9, 12]. Laboratory tests, electrolytes, urea, uric acid and haematological indices remained similar to baseline values, when tested post trial.

CONCLUSION

In conclusion, Glimepiride at 1-6mg daily produced good glycaemic control in majority of patients. Good glycaemic control was achieved in the Glibenclamide group at doses of 5-20mg daily. Glimepiride use was observed to be associated with lowering of plasma cholesterol (TC, HDL, and LDL) and triglycerides. Side effects were not encountered. Therefore, Glimepiride 1-6mg taken once daily as monotherapy is an effective and well tolerated medication for Nigerian patients with Type 2 DM.

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