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Original Research Article

Comparison of the efficacy and safety of Glimepiride and Glipizide as add-on therapy with metformin in patients of type 2 diabetes mellitus

Madhuri Chatterjee[1]*, Taruna Sharma[1], Anita Sharma[2], Juhi Kalra[1]

[1]Department of Pharmacology, [2]Department of Medicine, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun, Uttarakhand, India

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***Correspondence to:**
Dr. Madhuri Chatterjee,
Email: drmadhuri30@gmail.com

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder carrying an enormous burden of morbidity and mortality because of its characteristic complications, many of which are preventable with strict glycaemic control. Initial management of T2DM consists of non-pharmacological interventions; it those fail, an oral anti-diabetic drug, most typically metformin, is started. Combination therapy is initiated only when monotherapy fails to achieve glycaemic control. Glipizide and glimepiride, a second and a third generation sulphonylurea respectively, are the commonest drugs added to metformin when the latter fails to achieve euglycaemia on its own. Aims and Objectives of the study were to compare the efficacy and safety of glimepiride and glipizide as add-on therapy to metformin in patients of uncontrolled T2DM.
Methods: This prospective, observational and analytical study was conducted by the Department of Pharmacology among patients attending the Internal Medicine OPD of a tertiary-care hospital. Fifty patients were assigned to two groups of 25 patients each: Group A - Glimepiride + Metformin and Group B - Glipizide + Metformin. Patients were followed up for three months. Data were analysed by Student's t-test.
Results: There was a significant decrease in the HbA1c, FBS and 2h-PPBS in both groups. However there was no significant difference between the two groups during the three-month period of follow-up.
Conclusions: The combination of glimepiride and metformin is just as effective and safe as the combination of glipizide and metformin in patients not controlled on monotherapy with metformin.

Keywords: Metformin, Type 2 diabetes mellitus, Sulphonylureas

INTRODUCTION

Diabetes mellitus (DM) is a chronic, non-infectious metabolic disorder. The term covers several common metabolic disorders, all characterized by hyperglycemia resulting from defects in either insulin secretion or insulin action, or both. Diabetes mellitus is classified into Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), Gestational DM, and DM due to other causes; among these, T2DM is the commonest.[1,2] Regardless of differences in aetiopathogenesis, all kinds of DM can lead to several macrovascular and microvascular complications.[3]

Diabetic complications can be prevented to a significant extent by tight glycaemic control, which therefore remains the most important target of diabetes management. Euglycaemia can be achieved by both non-pharmacological and pharmacological means.[4] Among pharmaceutical interventions, metformin, a biguanide, remains the drug of first choice for the management of T2DM. The blood glucose-lowering action of metformin results primarily from a drop in hepatic glucose production, leading off from an amelioration of insulin resistance in the liver and muscles, and, to a lesser extent, in adipose tissue.[5]

Generally when metformin monotherapy fails to achieve glycaemic targets, the next step is to add a second oral agent, which can be either a sulphonylurea (SU) or an agent from any other anti-diabetic drug class.[6] SUs are the most preferred agents as add-on therapy to metformin

because they are efficacious, their effects are additive, and also because they are among of the cheapest drugs in our armamentarium.

All SUs stimulate insulin secretion by binding to a specific site on the K_{ATP} channel of pancreatic β-cells; their differences lie mainly in their pharmacokinetic characteristics.[7] Glipizide is a second-generation SU, while glimepiride is a third-generation member of the same class. By virtue of its distinctive interaction with its binding site, glimepiride inhibits the K_{ATP} channel to a lesser extent than does glipizide, and this has two important consequences: glimepiride is associated with a lower risk of hypoglycaemia than is glipizide and even if hypoglycaemia occurs with glimepiride, its duration is less than that caused by glipizide and other second-generation agents.[8] And among second-generation SUs, glipizide is associated with a lower risk of hypoglycaemia than other agents, although the advantage is not as marked as that with glimepiride.

Although both glipizide and glimepiride are commonly used in combination with metformin, there have been few head-to-head trials of these two drugs as add-on therapy to metformin. Therefore, we planned to undertake this study to compare the efficacy and safety of these two drugs as add-on therapy to metformin in patients of T2DM not controlled on metformin monotherapy.

METHODS

The study was conducted by the Department of Pharmacology in collaboration with the Department of Internal Medicine at a tertiary-care teaching hospital over a period of twelve months. The study protocol was approved by the Institutional Ethics Committee. Subjects were recruited from the patients attending the out-patient clinic of the Department of Medicine of the Himalayan Institute of Medical Sciences after taking informed and written consent.

Study design

Type of the study was prospective, observational, analytical study. Sample size was fifty subjects in two groups of 25 patients each. A minimum of 44 subjects were needed to rule out a mean difference of HbA1c of more than 0.5% between the two groups within 90% confidence intervals; however, the number of 50 was ultimately decided upon to accommodate the usual 15% subject attrition rate.

Patient selection Type 2 DM patients of either sex and ≥18 years of age, which were not controlled on maximum tolerated dose of metformin, were included in the study. Patients with complications of DM, as well as a history of congestive heart failure, chronic liver disease, renal disease, and tuberculosis, were excluded from the study, as were pregnant and lactating women.

Patients were divided into two groups. Drugs were prescribed according to physicians' discretion. Group A (n=25) patients received glimepiride (1-4mg) with metformin in maximum tolerated dose, while Group B (n=25) patients received glipizide (2.5-10mg) with metformin in maximum tolerated dose.

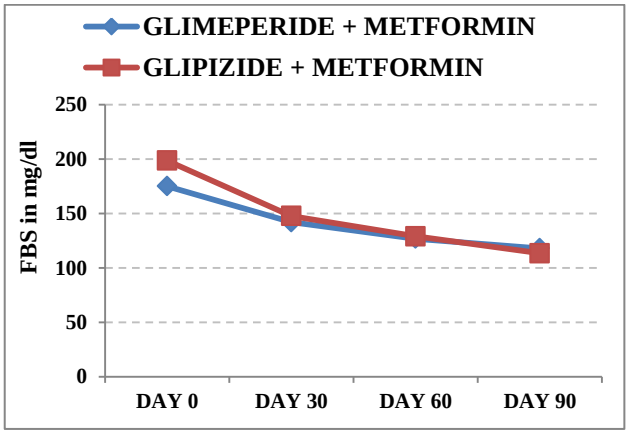
Demographic details and history were recorded at the time of recruitment; a detailed physical examination was done at the same time. Body Mass Index (BMI) and waist-hip ratio (WHR) were determined for all patients and recorded with above-mentioned details in the same case-recording form. FBS, 2h-PPBS, and HbA1c were tested on the day of recruitment along with other baseline parameters.

Follow up Patients were followed up every month for three months. Body weight, FBS and 2h-PPBS were measured on every monthly visit. Patients were questioned about adverse drug effects and drug compliance on every visit. HBA1c was tested again at the end of three months.

Data management and statistical analysis

Data were entered in Microsoft Excel 2010 sheets, and transferred to SPSS19 for analysis. The treatment groups were compared and results were analysed by appropriate statistical tests. The comparison of HbA1c and BMI in the same group was done with the paired t-test, while intergroup comparison was done with the unpaired t-test. Repeated measurements of FBS and PP2BS were tested using repeated measures ANOVA. A p-value <0.05 was considered significant.

RESULTS



Group A (Glimepiride + Metformin)
Mean values of FBS in mg/dl

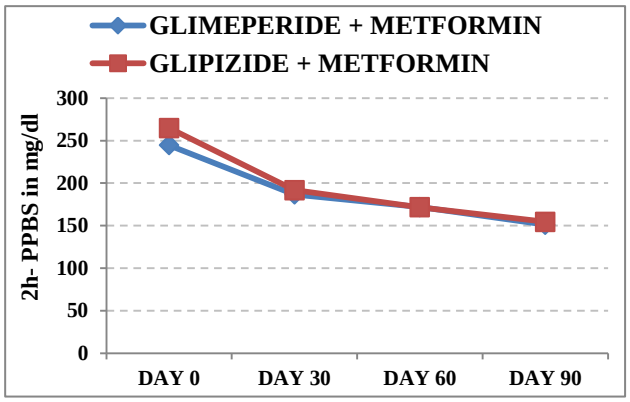
Day 0	Day 30	Day 60	Day 90
175.08	141.92	126.82	117.92

Group B (Glipizide + Metformin) Mean values in mg/dl

Day 0	Day 30	Day 60	Day 90
198.68	147.76	128.96	113.44

Figure 1: Changes in FBS in treatment groups.

Fifty-two percent of patients were female, and 48% had a family history of diabetes. Fasting blood sugar, 2-h PPBS and HbA1c were above the normal range in both the groups even after treatment with maximum tolerated doses of metformin.



Group A (Glimepiride + Metformin)
Mean values of 2h- PPBS in mg/dl

Day 0	Day 30	Day 60	Day 90
244.76	186.64	171.88	151.08

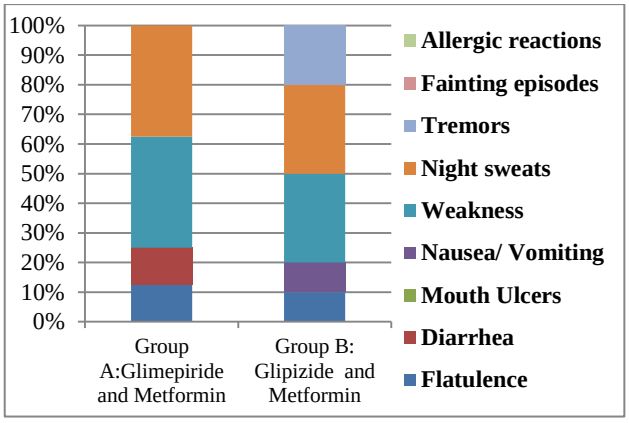
Group B (Glipizide + Metformin)
Mean values of 2h-PPBS in mg/dl

Day 0	Day 30	Day 60	Day 90
264.88	191.76	171.60	154.52

Figure 2: Changes in 2-hour post prandial blood sugar in the treatment groups.

Fasting blood sugar and 2h-PPBS came down after four weeks of combination therapy in both study groups and continued to decrease thereafter throughout the duration of the study. The reduction in fasting blood sugar over the 12-week study period was significant both in the glimepiride group ($p < 0.0004$) and the glipizide group ($p < 0.0001$). The decrease in 2-hr post-prandial blood sugar over 12 weeks was also significant at $P < 0.0001$ in both the study groups.

In summary, there was a significant change in FBS and 2-hour PPBS in both in the glimepiride group and the glipizide group, but there was no significant difference between these two groups.



Group A: Glimepiride + Metformin Group B: Glipizide +Metformin

Figure 3: Adverse effects.

Table 1 Demographic profile of patients in groups A and B.

	Group A (N=25)	Group B (N=25)
Sex distribution (F/M)	13 / 12	13 / 12
Family history of diabetes	11 / 25	11 / 25
Age (years)	52.52±9.74	55.72±9.25
BMI (kg/m²)	25.75± 5.72	24.69± 4.12
Waist:hip ratio, female	0.918±0.064	0.930±0.089
Waist:hip ratio, male	0.943±0.057	0.959±0.042
FBS (mg/dl) - Day 0	175.08±60.34	198.68±79.97
2-h PPBS (mg/dl) - day 0	244.76±73.63	264.88±90.48
HbA1c (%) - day 0	9.028±1.40	9.152±1.58

Note 1 Group A got glimepiride + metformin; Group B got glipizide + metformin
Note 2 All continuous variables expressed as mean±SD

Table 2: Sequential change of FBS and 2-hPPBS (mg/dl) during the study period in both groups.

		Day 0	Day 30	Day 60	Day 90	p-value
Group A	FBS	175.08±61.58	141.92±42.82	126.82±40.73	117.92±36.90	<0.0004
	PP_2BS	244.76±75.15	186.64±45.12	171.88±82.99	151.08±37.38	<0.0001
Group B	FBS	198.68±81.61	147.76±44.53	128.96±40.46	113.44±34.41	<0.0001
	PP_2BS	264.88±92.34	191.76±57.71	171.60±53.89	154.52±51.07	<0.0001

Note 1 All values expressed as mean±SD
Note 2 Data analyzed with repeat measure ANOVA

Table 3: Change in FBS, PP2BS, and HbA1c from day 0 to day 90 in group A.

	Day 0	Day 90	Difference	p-value
FBS (mg/dl)	175.08±60.34	117.92±36.90	57.04±23.54	<0.0003
2h-PPBS (mg/dl)	244.76±73.63	151.08±37.38	93.68±36.25	<0.0003
HbA1C (%)	9.028±1.40	7.51±1.35	1.518±0.05	<0.0001

Note 1 All values expressed as mean±SD; Note 2 Data analyzed with paired t–test

Table 4: Change in FBS, PP_2BS, and HbA1c from day 0 to day 90 in group B.

	Day 0	Day 90	Difference	p-value
FBS (mg/dl)	198.68±79.97	113.44±34.41	85.24±45.56	<0.0004
2h-PPBS (mg/dl)	264.88±90.48	154.52±51.07	110.36±39.41	<0.0001
HbA1C (%)	9.152±1.58	7.62±1.70`	1.532±0.12	<0.0005

Note 1 All values expressed as mean±SD
Note 2 Data analyzed with paired t–test

Table 5: Comparing groups for reduction of key variables between day 0 and day 90.

	Group A	Group B	p value
FBS (mg/dl)	28.12%	36.63%	0.09
PP_2BS (mg/dl)	34.67%	38.53%	0.23
HbA1c (%)	16.76%	17.03%	0.44
BMI (kg/m²)	00.07%	00.33%	0.34

Note 1 Group A got glimepiride + metformin, while Group B got glipizide + metformin
Note 2 All values refer to the decline of the respective variable from Day 0 to Day 90, as a percentage of its value on Day 0
Note 3 p value in the last column pertains to the significance of the difference between the reductions in appropriate parameters between Group A and Group B
Note 4 Data analyzed with unpaired t–test

Table 6: Possible drug-related adverse effects in both study groups.

Side effect	Group A	Group B
Weakness / fatigue	3 / 25	3 / 25
Night sweats	3 / 25	3 / 25
Tremors	0 / 25	2 / 25
Flatulence	1 / 25	1 / 25
Diarrhea	1 / 25	0 / 25
Nausea / vomiting	0 / 25	1 / 25
Oral ulcers	0 / 25	0 / 25
Fainting episodes	0 / 25	0 / 25
Allergic reactions	0 / 25	0 / 25

Note 1 Group A got glimepiride + metformin, while Group B got glipizide + metformin
Note 2 All values refer to the number of patients who had the respective adverse effect out of all 25 participants in each group

DISCUSSION

Mean glycosylated haemoglobin levels at the onset of the present study were 9.028±1.40% and 9.152±1.58% in the glimepiride and glipizide groups respectively. These are similar to the mean HbA1c level of 9.2±1.3 % in the study cohort of Mohan V et al.[9] Our findings are also close to the mean HbA1c level of 9.4±2.0 % reported by Duckworth W et al. in a study of patients with uncontrolled diabetes mellitus.[10]

Forty-four percent of patients in the glimepiride group and 52% of those in the glipizide group achieved HbA1c levels below 7% after 12 weeks of therapy in our study. These values closely approximate that of 44% patients who reached HbA1c <7% after 12 months of treatment in the study by Gonzalez.[11] In the study of Gonzalez, patients were treated with escalating doses of metformin and glimepiride in fixed dose combinations until euglycaemia was achieved; this is in contrast to the present study in which patients continued to receive the same doses of metformin and SUs for the 12-week duration of the study.

In the present study, 52% of patients in the glipizide plus metformin group attained HbA1c <7%, a figure that is comparable to that found in the study by Nauck MA et al.[12]

HbA1c decreased by 1.5% ± 0.05% in the glimepiride plus metformin group in the present study. This is similar to the 1% reduction seen after glimepiride treatment in the Lead 2 trial.[13] The glimepiride plus metformin group had a 1.6% reduction of HbA1c in the study by Santos et al; this is the same as that seen by us in our glimepiride plus metformin group.[14]

The mean decline in HbA1c in our glipizide plus metformin group was 1.5±0.12%, which is comparable to that noted by Goke B et al. in their study on the same two drugs in combination.[15] In their study, patients whose HbA1c was ≥9%, achieved a reduction of 1.72% at the end of therapy; this is more than what was found in our study. The difference can be explained partly by the greater dose of glipizide used in the latter study, and partly by their longer period of follow-up. The ADA-EASD guidelines state that SUs combined with metformin can reduce HbA1c levels up to 2%.[7] In the present study, both the groups showed a decline of HbA1c that approached this ideal target.

The combined mean FBS of both our groups was 186.5±70.61mg/dl, while the combined mean 2-h PPBS was 254.82±82.05 mg/dl. This is comparable to that seen in the study conducted by Charpentier et al.[16] In both our groups, target FBS was reached within 12 weeks of starting combination therapy, and the reduction was statistically significant at p <0.05. The percentage change in FBS from baseline to the end of therapy was 28.12 in the glimepiride and 36.63 in the glipizide groups respectively; however, with a p value of 0.09, this difference between glimepiride and glipizide was not statistically significant, a finding that is in keeping with those on combinations of other sulphonylureas and metformin.[11]

The percent change in 2-h PPBS was 34.67 in the glimepiride plus metformin and 38.53 in the glipizide plus metformin groups. At p=0.23, this difference was not significant, and is comparable to that seen in the two studies by Santos and Gonzalez.[11,14]

Few adverse events were observed in this study, with no significant difference in rates between the glimepiride plus metformin (32%) and the glipizide plus metformin (40%) groups. In a study by Charpentier et al, patients on glimepiride plus metformin suffered a 31% incidence of adverse effects; this is practically the same as that seen by us in patients on a combination of the same two drugs.[16] The proportion of our patients experiencing adverse effects while on glipizide and metformin (40%) is comparable to that reported in the study by Nauck et al.[12] None of our patients suffered from unconsciousness or required admission to hospital. None of them had correlated with blood sugar estimation during the brief periods of hypoglycemic symptoms like tremor, sweating and near fainting. No patients in our study discontinued or changed the treatment due to adverse events. The study drug groups were similar with respect to their safety profiles.

CONCLUSION

In the present observational study glimepiride and glipizide as add-on therapy to metformin showed reduction in fasting blood sugar, 2h-Post prandial blood sugar and HbA1c. It can be concluded that glipizide and glimepiride when added to metformin cause reduction in glycaemic parameters. They do not cause severe hypoglycemia if used judiciously. The limitation of this study was the small sample size and short duration.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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