ORIGINAL RESEARCH PAPER

Pharmacology

A COMPARATIVE STUDY OF EFFICACY, SAFETY AND TOLERABILITY OF SITAGLIPTIN VERSUS GLIMEPERIDE IN PATIENTS OF TYPE-2 DIABETES MELLITUS INADEQUATELY CONTROLLED WITH METFORMIN ALONE.

KEY WORDS: Sitagliptin, Glimeperide, Metformin, Diabetes mellitus.

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ABSTRACT

The present study was designed to study the efficacy, safety and tolerability of sitagliptin in comparison with glimepiride in treatment of type 2 diabetes mellitus inadequately controlled with metformin alone. A total of 70 patients were included in the study out of which 35 patients were grouped in metformin plus glimepiride group and the rest 35 were grouped in the metformin plus sitagliptin group. This study was designed to evaluate the efficacy, safety and tolerability of sitagliptin in comparison with glimepiride as an add-on drug to metformin in type 2 diabetes mellitus as an objective. Both treatment groups were compared for the mean reduction in HbA1c from baseline to 18th week defined as a primary end-point. While mean reduction in fasting blood sugar and post prandial blood sugar from baseline to 18th week defined as secondary end point. Mean dose for the glimepiride group was 2.1 mg while 100 mg in sitagliptin group. Both treatments were successful in decreasing and improving HbA1c level over the course of the study. Mean HBA1C level at baseline in metformin plus glimepiride group was 8.31%. This was comparable (p=0.06) to metformin plus sitagliptin group in which the HbA1c at baseline was 8.56%. There was significant decrease in the HbA1c level in both the groups from baseline at the end of 18 week study period.

This study also shows that, patients treated with sitagliptin had a substantially lower rate of adverse drug reactions relative to those treated with glimepiride and experienced weight loss versus weight gain.

So, from the present study we conclude that metformin plus sitagliptin is as efficacious as previously well-established metformin plus glimepiride. This study also demonstrates that sitagliptin is better tolerated when compared to glimepiride in treatment of type 2 diabetes mellitus inadequately controlled with metformin alone and may provide effective alternative to glimepiride especially in those patients who are obese and are prone to develop hypoglycemia.

INTRODUCTION -

Diabetes mellitus (**DM**), commonly referred to as **diabetes**, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death.[1] Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.[2]

Several distinct types of diabetes mellitus (DM) are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycaemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.[3]

The prevalence of diabetes in adults has been increasing in the last decades. In 2015, there were 415 million people between 20 and 79 years of age with diabetes and this number was predicted to rise to 642 million by 2035. Type 2 diabetes accounts for almost 90% of all cases of diabetes worldwide[4].

Recent studies have shown that early intervention at pre-diabetes state and beta cell protection may improve the prognosis of diabetes [5,6]. The incretin response which contributes significantly to the insulin response in the healthy individuals, but is impaired in individuals with diabetes offers a target for development of agents that address many aspects of diabetes.[6,7] In response to a meal, glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) are released and, in turn, stimulate insulin and suppress glucagon release (both in a glucose dependent manner), delay gastric emptying, and increase satiety.[8-13] These incretins are rapidly degraded by Dipeptidylpeptidase (DPP)-4. Therapeutic agents that can block the DPP-4 enzyme (DPP4 inhibitor) can increase the endogenous GLP-1 levels and thus enhance the incretin action. Sitagliptin an oral and highly selective DPP-4 inhibitor represents a novel therapeutic approach for the treatment of patients with T2DM.[13]

Sulfonylurea drugs (e.g., glyburide, glipizide, and glimepiride) regulate glucose levels by stimulating insulin secretion by the pancreatic ß cell[14]. Combination of sulphonylureas with metformin is a well-established therapy for diabetes uncontrolled with monotherapy alone.

Metformin, a commonly used oral hypoglycemic agent, both as monotherapy and in combination with other agents reduces elevated blood glucose levels by reducing hepatic glucose output and also by improving insulin resistance. Additionally, metformin has been reported to increase active GLP-1 concentrations by 1.5- to 2-fold following an oral glucose load in obese, non-diabetic subjects.[15] This effect on GLP-1 was not the result of inhibiting DPP-4 activity.[16,17]

Since sitagliptin and metformin lower glucose concentration through different but potentially complementary mechanisms, the initial combination of sitagliptin and metformin should provide effective potentially additive glycemic control.

MATERIALS AND METHODS

The present study was an institutional/ hospital based study conducted in Bhopal, the capital of Madhya Pradesh (MP), at Gandhi Medical College and associated Hamidia Hospital, an 885 bedded tertiary care hospital. This study was initiated after submitting the protocol and obtaining the approval of Institutional Review Board (IRB). The study was conducted in accordance with ethical principles originating from the Declaration of Helsinki and Good Clinical Practices, and in compliance with regulatory requirements. The drugs given to the study subjects were already well established and were in common use for treatment of diabetes mellitus.

STUDY DESIGN- It was an observational, open, comparative, and multiple follow up study.

STUDY SETTING- This study was carried out in Department of Medicine and Department of Pharmacology at Gandhi Medical

College and associated Hamidia Hospital, Bhopal (MP).

STUDY DURATION- This study was conducted for the period of 1 year duration from 15 December, 2014 to 14 December, 2015. Case collection was done during first 6 months of the study. Last 6 months were reserved for follow up, analysis and integration of the collected data and interpretation of results.

INCLUSION CRITERIA

1. Age 18 to 70 years.
2. Gender both male and female.
3. Patients with type 2 DM, who are using only metformin as antidiabetic agent at least for last 3 months and with inadequate glycemic control (HbA1c levels >7% and <10%) .
4. Who are willing to give written informed consent.

EXCLUSION CRITERIA

1. Patient with type 1 diabetes mellitus.
2. Patient who had previously been treated with sitagliptin or had previously been in a study using a DPP-4 inhibitor.
3. Alcoholic patients.
4. Pregnant and lactating females.
5. Females of childbearing age group planning pregnancy in recent future.
6. HIV positive patients.
7. Current participation in a weight loss program or is receiving weight loss medication.
8. Patient who had undergone a surgical procedure within the prior 4 weeks.
9. History of hypersensitivity to any of the investigational agents and other drugs of their class.
10. Patients with other systemic illness like Congestive cardiac failure, severe respiratory diseases, Renal insufficiency, Hepatic insufficiency and other terminal illnesses were excluded.

MATERIALS

1. Tablet Metformin 500 mg
2. Tablet Glimipiride 1 mg
3. Tablet Sitagliptin 100 mg

METHODOLOGY

The detailed semi-structured proforma and a validated consent form were designed as a tool for the case collection in consultation with the guide and co-guide for assessment of efficacy after interviewing the patients. The proforma was pretested on 20 patients and the necessary corrections were included. The investigator attended the outpatient department along with the physician. The treatment that was been given to the patients of type 2 diabetes mellitus was observed and two treatment groups were observed to have been existed already. These 70 patients after obtaining treatment from the treating physician, were included in the study by the investigator into two treatment groups after applying inclusion and exclusion criteria. Consecutive sampling procedure was followed and patients were included serially in two groups. Dose of sitagliptin was 100 mg per day and for glimepiride was 2 mg per day. Maximum permitted dose for sitagliptin was 200 mg/day and for glimepiride was 4mg/ day. If glycemic control was not reached then patient was excluded from the study and given further treatment for benefit of the patient. Dose of metformin was kept constant throughout study which was 500 mg twice a day and no other hypoglycemic agent was added. If subject was on some other medications for associated illnesses then doses of such drugs were kept constant during whole study period. Treatment was provided for the period of 18 weeks and patients were called for 3 follow ups at the end of 4, 12, 18 weeks. Baseline assessment was done by HbA1c level & Biochemical tests consisting of Blood urea, Serum creatinine, Liver Function Tests, CBC and Serum Amylase. At the time of follow up patient were evaluated for efficacy, safety and tolerability. Patients were enquired for the adverse events, if any, at each follow up and were documented.

SOURCE OF DATA - Patients diagnosed as type 2 DM coming in Medicine OPD of Gandhi Medical College and associated Hamidia Hospital, Bhopal (MP).

TYPE OF DATA - Both qualitative as well as quantitative data were assessed for the outcome assessment

STATISTICAL ANALYSIS

At the end of the present study, the data collected were compiled using Microsoft Excel Worksheet and processed by using appropriate statistical software. The collected data was analysed statistically using paired t test and student t test. A *p-value* of less than 0.05 was considered to be statistically significant.

OUTCOME ASSESSMENT

1. PRIMARY ENDPOINT:

a) Change from baseline at 18 weeks in HbA1c.

2. SECONDARY ENDPOINT:

a) Change from baseline at 18 weeks Fasting Blood Sugar level.
b) Change from baseline at 18 weeks Post Prandial Sugar level.

3. SAFETY ENDPOINT: Any reported adverse event.

OBSERVATIONS AND RESULTS -

The present study was evaluated under the following heads:

1. Baseline Demographic data: It includes
- Age and gender of the patients (Table 1)
2. Assessment of efficacy of metformin plus glimepiride and metformin plus sitagliptin:
- Comparison of mean HbA1c in both groups (Table 2)
- Comparison of mean fasting blood sugar (Table 3)
- Comparison of mean post prandial blood sugar (Table 4)
3. Assessment of safety and tolerability of metformin plus glimepiride and metformin plus sitagliptin.
- Comparison of change in mean weight (Table 5)
- Comparison of Adverse drug reactions reported in each treatment group (Table 6)

TABLE 1 - AGE WISE DISTRIBUTION OF PATIENTS

Age (inYear)	Metformin + Glimepiride Treated Group (n = 35)			Metformin + Sitagliptin Treated Group (n = 35)			TOTAL (n = 70)			
	M	F	T	M	F	T	M	F	T	%
20-30	1	2	3	1	0	1	2	2	4	05.7
31-40	2	7	9	1	3	4	3	10	13	18.6
41-50	7	7	14	4	12	16	11	19	30	42.9
51-60	3	4	7	3	5	8	6	9	15	21.1
61-70	1	1	2	6	0	6	7	1	8	11.4
Total	14	21	35	15	20	35	29	31	70	100

M =No. of Males; F =No. of Females; T= Total no. of patients; % = Percentage p value >0.05

Table 1 shows that majority of the patients in both groups, belongs to 41-50 years (42.9%) followed by 51-60 years (21.1%).

TABLE 2 -COMPARISON OF MEAN HbA1c IN BOTH GROUPS

Duration	Metformin Plus Glimepiride Treated Group (n=32)	Metformin Plus Sitagliptin Treated Group (n=33)	p value
Baseline	8.31	8.56	0.06
18 weeks	7.42	7.75	0.07
P Value	0.0001	0.0001	

** P < 0.05 significant when compared to baseline values.*
Values represented as Mean±SD

Table 2 shows comparison of mean reduction of HbA1c. It was observed that mean reduction in HbA1c level at 4, 12 and 18 weeks, respectively from baseline was significant in both Metformin + Glimepiride Treated Group & Metformin + Sitagliptin Treated Group. However, The difference between the two groups was not statistically significant.

TABLE 3 -COMPARISON OF MEAN FASTING BLOOD SUGAR

Duration	Metformin + Glimepiride Treated Group (n = 32)	Metformin + Sitagliptin Treated Group(n = 33)	P value
Baseline	186.34±58.09	194.54±48.24	0.4
4 Weeks	147.06±39.88	161.72±41.9	0.2
12 Weeks	131.3±24.64	129.48±26.16	0.7
18 Weeks	109.9±17.69	112.3±.15.58	0.6

Values represented as Mean±SD
** p < 0.05 significant when compared to baseline values.*

Table 3 shows comparison of mean reduction of Fasting Blood Sugar Level. It was observed that mean reduction in Fasting blood sugar level at 4, 12 and 18 weeks, respectively from baseline was significant in both Metformin + Glimepiride Treated Group & Metformin + Sitagliptin Treated Group. However, difference between the two groups was not statistically significant.

TABLE 4 -COMPARISON OF MEAN POST PRANDIAL BLOOD SUGAR

Duration	Mean Post Prandial Blood Sugar		p value
	Metformin + Glimepiride Treated Group (n = 32)	Metformin + Sitagliptin Treated Group (n = 33)	
Baseline	261.9±67.92	287.27±62.04	0.12
4 weeks	213.5±55.03	234.51±49.01	0.11
12 weeks	179.34±25.04	184.75±38.26	0.8
18 weeks	159.21±15.96	162.6±.16.42	0.9

P < 0.05 significant when compared to baseline values.
Values represented as Mean±SD

Table 4 shows comparison of mean reduction of Post Blood Sugar Level. It was observed that mean reduction in Posting blood sugar level at 4, 12 and 18 weeks, respectively from baseline was significant in both Metformin + Glimepiride Treated Group & Metformin + Sitagliptin Treated Group. However, the difference between the two groups was not statistically significant.

TABLE 5 COMPARISON OF CHANGE IN WEIGHT

Duration	Metformin plus Glimepiride Group (n=32)	Metformin plus Sitaliptin Group (n=33)
Baseline	64.59+7.9	62.06+7.02
18 weeks	66.06+8.02	60.57+6.66
P value	0.0008	0.0001

p value < 0.05(significant).Weight in kgs

Table 5 shows comparison of change in mean weight in both treatment groups. At base line, both groups were comparative with p value=0.17. However significant weight gain (+1.46 ± 2.24Kgs) was observed that in metformin plus glimepiride group. While in metformin plus sitagliptin group significant weight reduction (-1.48±1.92 Kgs) was observed.

TABLE 6 COMPARISON OF ADVERSE DRUG REACTIONS REPORTED IN EACH TREATMENT GROUP

Adverse Drug Reaction	Metformin Plus Glimepiride Treated Group (n=32)	Metformin Plus Sitagliptin Treated Group (n=33)		
	Number of case	%	Number of case	%
Headache	2	6.25	3	9.09
Abdominal Pain	2	6025	2	6.06
Nausea	4	12.5		
Vomiting	2	6.25	1	3.03
Hypoglycemia	1	3.125	0	0.00
Total	11	34.3	8	24.2

P value < 0.05(significant).

Table 6 shows that comparatively higher number of adverse drug reactions were observed in metformin plus glimepiride treated Group (34.3%) compared to metformin plus sitagliptin treated group (24.2%). However, difference between the two treatment groups was not statistically significant (P > 0.05).

DISCUSSION AND CONCLUSION

Overall, the present study that was designed to study the efficacy and safety of sitagliptin in comparison with glimepiride in treatment of 2t6.06ype 2 diabetes mellitus inadequately controlled with metformin alone. The present study demonstrated that metformin plus sitagliptin is as efficacious as previously well-established metformin plus glimepiride. The present study also demonstrated that both metformin plus sitagliptin and metformin plus glimepiride are safe and well tolerable for use in T2DM patients. However, metformin plus sitagliptin had a better safety profile as compared to metformin plus glimepiride and is better tolerated; however the difference was not clinically and statistically significant.

The present study also demonstrated that both metformin plus sitagliptin and metformin plus glimepiride effectively reduced both fasting blood sugar and post prandial sugar as well as HbA1C in T2DM patients. Lastly, taking into consideration the factors like the similarity of the therapeutic effect of metformin plus sitagliptin and metformin plus glimepiride and ease of administration of once a daily dose of sitagliptin, it seems that sitagliptin is a better alternative to glimepiride in treatment of T2DM. But, when the cost factor comes into play, glimepiride becomes better choice for the patients who can't afford the drug.

In Conclusion, Sitagliptin may provide effective alternative to glimepiride especially in those patients who are obese and are prone to develop hypoglycaemia.

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