Comparing the Efficacy and Safety Profile of Sitagliptin Versus Glimepiride in Patients of Type 2 Diabetes Mellitus Inadequately Controlled with Metformin Alone

Swati Srivastava*, GN Saxena**, P Keshwani***, Ritesh Gupta†

Abstract

Objective: To compare the efficacy and safety of sitagliptin and glimepiride in treatment of patients with type 2 diabetes mellitus inadequately controlled with metformin alone.

Research design and methods: In an 18 week, randomized parallel group interventional trial, 50 subjects who were only on metformin as antidiabetic agent, with inadequate glycemic control, were randomized to either sitagliptin 50/100mg or glimepiride 1/2 mg per day. Dose of drugs was adjusted after 4 weeks if glycemic control was not reached.

Results: At 18 weeks both groups (sitagliptin and glimepiride) produced significant (P<0.001) reduction in HbA1C (-0.636% and -1.172% respectively), with 12% patients in sitagliptin group and 36% patients in glimepiride group achieving target HbA1C. Reduction was also significant (P<0.001) in both groups in FPG (-15.49mg and -29.84mg respectively) and 2HPPG (-34.28mg and -44.83mg respectively). Sitagliptin group showed net decrease in body weight by 0.102kg whereas glimepiride group showed net increase in body weight by 0.493 kg. Incidence of hypoglycemia was 4% in sitagliptin group and 8% in glimepiride group.

Conclusion: In this study addition of sitagliptin and glimepiride to metformin monotherapy, produced significant improvement in glycemic control. Benefits were more with glimepiride in comparison to sitagliptin. Sitagliptin was well tolerated, with lower risk of hypoglycemia than glimepiride, and produced weight loss as compared to weight gain with glimepiride.

Introduction

Type 2 diabetes is a progressive disease characterised by impaired beta cell function, and reduced insulin sensitivity and secretion. Despite good compliance to treatment, the glycaemic control of type 2 diabetes deteriorates progressively. Analysis from the United Kingdom Prospective Diabetes Study (UKPDS)5 demonstrated that after 3 years of longitudinal follow up, only 50% of the initial cohort could achieve the target haemoglobin A1C (HbA1C) control of <7% while the remaining 50% required the addition of a second drug for diabetes control. By the time of nine years, 75% of patients required multiple therapies to achieve the target HbA1C control. Hence newer treatment options and combination therapies which sustain glycemic control with lesser adverse effects like hypoglycemia and weight gain are being evaluated. Recent studies have shown that early intervention at prediabetes stage5-7 and beta cell protection may improve the prognosis of diabetes.

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 4 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.5-8 These incretins are rapidly degraded by Dipeptidyl peptidase (DPP)-IV. Therapeutic agents that can block the DPP-4 enzyme (DPP4 inhibitor) can increase the endogenous GLP-1 levels and thus enhance the incretin action.9 Sitagliptin an oral and highly selective dipeptidyl peptidase-4 inhibitor represents a novel therapeutic approach for the treatment of patients with type 2 diabetes.

Metformin, a commonly used oral antihyperglycemic 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, nondiabetic subjects.10 This effect on GLP-1 was not the result of inhibiting dipeptidyl peptidase-4 activity.11,12

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 control13. Combination of sulphonylureas with metformin is a well established therapy for diabetes uncontrolled with monotherapy alone.

The prevalence of type 2 diabetes particularly in the Indian subcontinent is increasing enormously over the recent years. For the physicians to be able to use these new drugs for pharmacotherapy, clinical trials which evaluate the efficacy and safety of these drugs are important. In India there is dearth of data regarding results of use of DPP-4 inhibitors in the Indian population. In the present study we compared the efficacy and safety profile of sitagliptin and glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone.
Materials and Methods

The study population was selected from patients attending Medical Outpatient Department, SMS Hospital, Jaipur who satisfied the inclusion criteria. The study was carried out between August 2008 and October 2009. The study design and protocol was reviewed and approved by Research Ethics Committee of SMS Hospital.

Patients with type 2 DM, aged more than 18 years, who were using only metformin as antidiabetic agent at least for last 3 months and with inadequate glycemic control (hbA1c levels >7% and <10%) were eligible to participate. Those with type 1 Diabetes, evidence of cardiac failure, evidence of hepatic or renal insufficiency or other terminal illnesses were excluded.

The study design was a randomized parallel group interventional trial. The subjects received one of the two study drugs in addition to ongoing metformin therapy.

50 subjects were included in the study. Informed consent was taken. Baseline blood investigations consisting of FPG, 2HPPG and HbA1C were done. Also biochemical tests consisting of Blood urea, Serum creatinine, liver function tests, CBC and ESR were conducted. All investigations were performed at SMS Hospital Laboratory.

Subjects were allocated randomly by computer generated random number table to one of the two groups. Group A subjects received sitagliptin and Group B subjects received glimepiride.

Table 1 : Efficacy end point

<table>
<thead>
<tr>
<th>Group</th>
<th>Group A (n=25)</th>
<th>Group B (n=25)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12week</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>8.280±0.418</td>
<td>7.784±0.423</td>
</tr>
<tr>
<td>2HPPG (mg/dl)</td>
<td>264.60±17.196</td>
<td>240.27±15.384</td>
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Results

Starting dose of sitagliptin was 50/100mg per day and for glimepiride was 1/2 mg per day. Dose of drugs was adjusted after every 4 weeks if glycemic control was not reached. Maximum permitted dose for sitagliptin was 200 mg/day and for glimepiride was 4mg/ day. Dose of metformin was kept constant throughout study and no other antihyperglycemic 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.

Data of biochemical parameters were recorded at baseline, 12 weeks and 18 weeks of therapy. The collected data was analysed statistically using paired t test and student t test.

Study End Points

The efficacy end point was change from baseline at 18 weeks of hbA1c, FPG, 2hPPG levels. change of Bm I from baseline to 18 weeks was noted. Safety and tolerability were assessed throughout the study (Table 1). Monitoring for adverse experiences, physical examinations, vital signs, body weight, ECG, laboratory measurements comprising routine hematology, serum chemistry and urinanalysis were performed. Adverse experiences of special interest included hypoglycemia.

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Subjects were allocated randomly by computer generated random number table to one of the two groups. Group A subjects received sitagliptin and Group B subjects received glimepiride.
The mean 2HPPG reduction in sitagliptin group was 34.28±6.07mg/dl and in glimepiride group was 44.83±6.47mg/dl (Figure 3).

On analysis of comparative effect of the two different treatment modalities on HbA1C, FPG and 2HPPG in our study, the mean difference in these values was statistically significant more in glimepiride group than in sitagliptin group (P<0.001).

The mean values of BMI decreased in sitagliptin group by -0.039 Kg/m² whereas the mean BMI increased in glimepiride group by +0.184Kg/m² (P=0.01) (Table 1).

During the study period we observed 3 episodes of hypoglycemia, 1 in sitagliptin group and 2 in glimepiride group.

**Discussion**

The incretins have emerged as important targets in the modern management of type 2 diabetes mellitus. New medications manipulating the incretin system are being considered. New guidelines on the management of type 2 diabetes mellitus were published by the National institute for Health and Clinical Excellence (NICE) which included DPP-4 inhibitors as an alternative or additional oral hypoglycemic drug as second or third line therapy.

Our study evaluated the efficacy of sitagliptin and its comparison with glimepiride as an additional therapy in patients uncontrolled with metformin monotherapy.

Sitagliptin added to metformin significantly improved the glycemic control. The HbA1C levels showed a net reduction of -0.63±0.09% at 18 weeks. Similar results were observed by Charbonnel B et al who studied the efficacy of sitagliptin added to ongoing metformin therapy in patients with type 2 DM inadequately controlled with metformin alone. At 24 weeks sitagliptin led to -0.65% reduction in HbA1C levels as compared to placebo.

In a study of sitagliptin monotherapy by Vishwanath Mohan, Yang W et al, sitagliptin reduced mean HbA1C by -1% at 18 weeks. Goldstein Barry J. et al reported placebo subtracted A1C change from baseline, -0.83% for sitagliptin 100mg, -1.57% for combination of sitagliptin 100mg and metformin 1000mg. Aschner P. et al examined the efficacy of sitagliptin as monotherapy. They concluded that 100 and 200 mg sitagliptin produced significant placebo-subtracted reduction in A1C (-0.79% and -0.94% respectively).

HbA1C net reduction in glimepiride group in our study was 1.17±0.25%. Lead 2 trial study showed a reduction of 1% in HbA1C with glimepiride therapy. Ferrannini et al in a 52 week long study demonstrated a decrease of 0.53% in HbA1C levels with glimepiride therapy.

The FPG values in sitagliptin treated group in our study showed a statistically significant net reduction of -15.48±2.42mg%. After 18 weeks of therapy, Aschner P et al noted treatment difference versus placebo in FPG change from baseline of 17.1mg% (for 100mg sitagliptin) and 21.3 mg% (for 200 mg sitagliptin). Charbonnel et al, at 24 weeks, showed a placebo subtracted least square mean reduction from baseline of FPG by -25.4mg% with 100mg sitagliptin. Goldstein et al found statistically significant reduction with sitagliptin in FPG levels with additive reduction in patients with coadministration group.

The glimepiride treated group showed net reduction in FPG values by 29.8±4.5mg%. Similar results were reported by LEAD 2 trial demonstrating a decrease of 20.52 mg% in FPG in a 52 week study.

We found a net reduction of -34.28mg/dl in 2HPPG levels in sitagliptin group. In the study by Aschner P et al, sitagliptin 100 and 200mg significantly decreased 2HPPG values (placebo subtracted) -46.7 and -54.1 respectively. Goldstein et al showed clinically meaningful reductions in 2HPPG compared to placebo, in sitagliptin therapy. Charbonnel et al also found significant decrease (P<0.001) in 2HPPG levels with sitagliptin therapy.

The glimepiride treated group also showed significant reduction in 2HPPG levels. The net reduction was of 44.8mg% noted in this group. Significant net reduction in 2HPPG was also found by Baustin et al in a 14 week study with glimepiride.

Evaluating the effect of sitagliptin on bodyweight, mean body weight decreased by 0.102 kg in the sitagliptin group. Aschner et al observed that after 24 weeks of treatment, sitagliptin had a neutral effect on body weight relative to baseline. Charbonnel et al also reported a weight neutral effect of the drug in their study.

BMI increased in glimepiride treated cases by 0.18±0.06kg/m² (0.493 kg) which was statistically significant. LEAD 2 study demonstrated an increase of 1kg in mean weight with glimepiride therapy.

Hypoglycemia is a matter of great concern with anti hyperglycemic agents. Our study demonstrated no statistically significant difference in hypoglycemia between the sitagliptin and glimepiride groups. Sitagliptin added to metformin showed a 4% hypoglycemia whereas metformin plus glimepiride group had 8% incidence of hypoglycemia. Nauck M A et al reported a 4.9% incidence of hypoglycemia in patients taking sitagliptin and metformin and 32% incidence of hypoglycemia in patients taking glipizide and metformin.

**Conclusion**

In this study, both treatment groups, sitagliptin and glimepiride, when added to metformin in previously uncontrolled diabetes patients, produced clinically meaningful reduction in HbA1C, FPG and 2HPPG from baseline. The reduction in these values were more in glimepiride group than in sitagliptin group. Greater proportion of patients achieved HbA1C target with glimepiride group than with sitagliptin group.

Consistent with overall complimentary mechanisms of action, essentially additive efficacy of sitagliptin and metformin was observed for HbA1C, FPG and 2HPPG. The additive effect on glycemic improvement was more with glimepiride as compared to sitagliptin when added to metformin alone.

Increased body weight observed with OHA is generally an undesired effect. BMI decreased in sitagliptin treatment group whereas BMI increased in glimepiride treated cases.

Both group treatment modalities were generally well tolerated in this study. Despite marked improvement in glycemic control, there was a low incidence of hypoglycemia. Incidence of hypoglycemia was lower in sitagliptin group than in glimepiride group.

**References**


9. Vanessa WS Ng, Alice PS Kong. Dipeptidyl Peptidase (DPP)-IV Inhibitor: A Novel class of Oral Anti-hyperglycemic Agents


