INTRODUCTION

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism and associated with absolute or relative deficiency of insulin secretion and/or insulin action.

Uncontrolled diabetes can lead to dreadful complications that cause physical, emotional and economical burden on the individual as well as on the society1. Type-2 diabetes is a progressive disease and its core defects are insulin resistance and beta-cell failure2.

The only effective way to avoid complications of diabetes is a good glycemic control, which in type-2 diabetes, can be achieved by oral hypoglycemic drugs. In the last few years new drugs have emerged targeting at better pharmacokinetic and low side effect profile. Among them have been various insulin sensitizers and Pioglitazone is one of them.

Pioglitazone is a relatively new drug. Pioglitazone has been demonstrated to provide clinically equivalent control of HbA1c in comparison with Metformin, traditionally the agent of choice for treatment of obese patients with type-2 diabetes6. Significantly greater reductions in fasting blood glucose have been observed with Pioglitazone compared with Metformin10. Use of this drug is quite limited despite its good tolerability and efficacy. Whereas, traditionally, metformin is used more in type-2 diabetics conventionally11.

Combining pioglitazone with metformin should enable additive clinical effects to be achieved through their different mechanisms of action 12. In patients with type 2 diabetes both the pioglitazone and metformin enhance insulin suppression of endogenous (hepatic) glucose production, increasing splanchnic and hepatic glucose utilization, and having a secondary effect on insulin resistance1. The metabolic effects of Metformin may be due to its ability to phosphorylate and activate AMP-activated protein kinase5. In obese patients with creatinine 1.5mg/dl, Metformin should be considered as initial therapy6. Pioglitazone, a thiazolidinedione, is a peroxisome proliferator-activated receptor agonist that affects regulators of carbohydrate and lipid metabolism7. Pioglitazone reduces insulin resistance by enhancing the action of insulin, thereby promoting glucose utilization in peripheral tissues, suppressing gluconeogenesis, and reducing lipolysis8. Pioglitazone with metformin significantly improves HbA1c, fasting blood glucose and postprandial blood glucose while producing beneficial effects on serum lipids in patients with type 2 diabetes with no evidence of drug-induced hepatotoxicity or drug-induced elevations of alanine aminotransferase levels in this study.

Key words - Metformin, Pioglitazone, Type-2 Diabetes Mellitus

OBJECTIVE - To evaluate the efficacy and safety of combination of pioglitazone with metformin in the treatment of patients with type 2 diabetes.

METHODOLOGY - Patients of Type-2 Diabetes Mellitus taking metformin for more than three months but diabetes not controlled as per blood glucose level assessment were additionally given pioglitazone starting from 15 mg OD before breakfast and gradually increased to 30 mg OD before breakfast as per blood glucose level assessment. The dose of metformin was not altered throughout the study in any patient. Total Sixty seven patients were taken in this study. Evaluation was carried out at 0, 30 days and on 90 days.

RESULTS – There were significant reductions from baseline in the levels of fasting blood glucose (180.02±22.44 vs 106.08±14.49 mg/dl, P<0.001), postprandial blood glucose (254.05±37.38 vs 169.07±16.48mg/dl, P<0.001) and HbA1c (8.86±0.65 vs 7.48±0.46%, P<0.001) in all patients. There were also significant reductions from baseline in the levels of Serum LDL (171.44±27.62 vs 156.23±20.38, p<0.01) and Serum Triglycerides (123.55±34.23 vs 113.64±31.18, p<0.01). There was also a significant elevation in serum HDL (48.04±9.87 vs 51.77±9.01, p<0.01).

But there were no statistically significant changes from baseline in terms of Serum ALT, AST, Alkaline Phosphatase, Total Serum Bilirubin, Blood Urea, Creatinine, Hemoglobin and body weight (BW) in all patients. The adverse effects were mild and not significant. Throughout the study, no patient had an alanine aminotransferase (ALT) value ≥3 times the upper limit of normal, a commonly used marker of potential liver damage. Thus, no evidence of drug-induced hepatotoxicity or drug-induced elevations in serum ALT was observed.

CONCLUSION - Pioglitazone with metformin significantly improves HbA1c, fasting blood glucose and postprandial blood glucose while producing beneficial effects on serum lipids in patients with type 2 diabetes with no evidence of drug-induced hepatotoxicity or drug-induced elevations of alanine aminotransferase levels in this study.

Study of Efficacy and Safety of Pioglitazone in Combination with Metformin in Patients with Type-2 Diabetes Mellitus

Neelesh Arya1, Ashutosh Chourishi2, SP Pandey3
1Department of Pharmacology, Gandhi Medical College, Bhopal, India
2Department of Pharmacology, R.D. Gardi Medical College, Ujjain, India
3Department of Pharmacology, NSCB Medical College, Jabalpur, India

Received 27-09-2011; Accepted 24-12-2011

pioglitazone, rather than metformin, improve insulin-mediated glucose uptake by muscle and fat over a wide range of insulin concentrations\(^1\).

In the present study, the effects of combination of pioglitazone with metformin in patients with type-2 diabetes mellitus were observed and compared with their baseline values. It has really helped to guide our treatment strategy in patients with type-2 diabetes mellitus.

**Aims and Objectives:**

1. To Study the efficacy of Pioglitazone in combination with metformin in reducing the levels of fasting blood glucose, postprandial blood glucose and glycosylated Hemoglobin (HbA1c) in patients with type-2 diabetes mellitus.
2. To Study the effect of Pioglitazone in combination with metformin on serum lipid profile in patients with type-2 diabetes mellitus.
3. To Study the safety and tolerability of Pioglitazone in combination with metformin in patients with type-2 diabetes mellitus.

**MATERIALS AND METHODS**

This was an open non-comparative step up dosing design trial carried out in Department of Pharmacology and Department of Medicine in Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur, M.P., India from March 2005 to July 2006. The study was approved by the Medical Ethical Committee of the NSCB Medical College Hospital Jabalpur. The study was performed in accordance with Good Clinical Practice guidelines. All patients provided written informed consent prior to any study-related procedures.

**Selection of Subjects:**

**Inclusion Criteria -**

1. All already detected patients of either sex who met the diagnostic criteria for Type-2 Diabetes Mellitus and were taking metformin alone for more than three months were included in the study.
2. Those patients who were willing to give informed consent prior to any study-related procedures.

**Exclusion Criteria -**

1. Women who were pregnant or breast-feed or at risk of pregnancy during therapy.
2. Patients who consume Alcohol or have drug dependency in the last six months.
3. Patients on ketoconazole, carbamazepine, levodopa, dopamine agonist, diuretic therapy or at risk for torsade de points.
4. Patients with history of hypersensitivity to pioglitazone or other thiazolidinedione derivatives.
5. Patients suffering from hepatic, renal, metabolic or neurological, gastrointestinal, hematological or psychiatric disorder.
6. Patients with clinically significant heart disease (including New York Heart Association III or IV cardiac status).
7. Patients with value for ALT/AST > 1.5 times upper limit of normal, alkaline phosphatase, total serum bilirubin > 1.2 times upper limit of normal or creatinine > 1.2 times upper limit of normal or fasting venous plasma glucose > 200 mg/dl or hemoglobin < 12 g/dl for men and <10 g/dl for women.
8. Patients with acute infection.
9. Patients unwilling to give informed consent or unable to comply with study procedure.

**Study Population:**

The study was carried out in the Medicine OPD from March 2005 to July 2006 of either sex aged 25-70 years. During the period of the study, 67 old patients of diabetes mellitus type2, taking metformin for more than three months, but Diabetes sub optimally controlled as per blood glucose level assessment, were registered to the Medicine department for our study who satisfied the inclusion and exclusion criteria.

**Methodology:**

Patients of Diabetes Mellitus Type-2 taking metformin for more than three months but diabetes not controlled as per blood glucose level assessment were additionally given pioglitazone starting from 15 mg OD before breakfast and gradually increased to 30 mg OD before breakfast as per blood glucose level assessment. The dose of metformin was not altered throughout the study in any patient. Total Sixty seven patients were taken in this study. Detailed Medical history with examination was done on each patient.

**Evaluation and Follow-up:**

Evaluation was carried out at 0, 30 days and on 90 days. Symptoms and detailed history of Diabetes mellitus as well as other concomitant diseases were noted at baseline visit. At baseline visit and after 30 days and 90 days, fasting Blood sugar and 2-hour Postprandial blood sugar was done and dosage of pioglitazone was adjusted accordingly without altering dose of metformin.

Glycosylated hemoglobin, CBC, ESR, Kidney function test, Liver function test, Lipid profile, ECG, X-ray chest (PA view) was done at baseline and after 90 days and were compared. Weight & B.P. was checked at every visit. The patients were followed upto 3 months (90 days).

**Key to Proforma**

- Patient's weight was recorded in kg.
- Height of the patients was recorded in centimeters.
- The patients were assessed for clinical improvement during the course and also the evidence of adverse effects was looked for.
- The presence of complications and other associated diseases were recorded and treated simultaneously.

**Goals of the Therapy:**

The patients with a fasting blood glucose of < 126 mg/dl and 2 hours postprandial of < 200 mg/dl were accepted and ideal if fasting blood glucose of < 100 mg/dl and 2 hours postprandial of < 140 mg/dl.

**Statistical analysis:**

Statistical analysis was carried out with appropriate statistical software. Descriptive statistics were used to summarize demographic and baseline characteristics. Mean and SD for fasting blood glucose, postprandial blood glucose and HbA1c was calculated for each visit. Student 'T' test was applied to compare means of fasting blood glucose, postprandial blood
In total 67 patients, the range of baseline 2-hour Postprandial blood glucose was 190–357 mg/dl and the mean was 254.059±37.388 mg/dl. At the end of 30 days, the range of 2-hour Postprandial blood glucose declined to 154-298 mg/dl and the mean was 202.388±30.416 mg/dl. At the end of 90 days, the range of 2-hour Postprandial blood glucose dropped up to 139-204 mg/dl and the mean was 169.074±16.487. The decline was highly significant ((p<0.001)) and started as early as 30 days of treatment (Table-4).

Table No. 5. Comparison of Glycosylated Hemoglobin Levels at Baseline and at the end of 90 days (n=67)

<table>
<thead>
<tr>
<th>Glycosylated Hemoglobin</th>
<th>Range</th>
<th>Mean</th>
<th>S.D.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.8-10.8</td>
<td>9.966</td>
<td>±0.658</td>
<td></td>
</tr>
<tr>
<td>90 days</td>
<td>6.8-8.4</td>
<td>7.486</td>
<td>±0.464</td>
<td>t = 5.631 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

In total 67 patients, the range of glycosylated hemoglobin was 7.8% to 10.8% and the mean was 8.861±0.658. At the end of 90 days the range of glycosylated hemoglobin was 6.8% to 8.4% and the mean was 7.486±0.464. The decline was highly significant ((p<0.001)) at the end of 90 days and showed excellent glycemic control (Table-5).

Table No. 6. Comparison of the Glycemic parameters, Lipid profile, Biochemical & Clinical characteristics at Baseline and at the end of 90 days in all patients (n=67)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>90 days</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosylated Hemoglobin</td>
<td>8.861±0.658</td>
<td>7.486±0.464</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (%)</td>
<td>5.631(p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum HDL (mg/dl)</td>
<td>48.044±8.872</td>
<td>31.776±9.013</td>
<td>t = 3.284 (p&lt;0.01)</td>
</tr>
<tr>
<td>Serum LDL (mg/dl)</td>
<td>171.447±27.628</td>
<td>154.238±20.382</td>
<td>t = 3.286 (p&lt;0.01)</td>
</tr>
<tr>
<td>Serum Triglycerides (mg/dl)</td>
<td>123.552±34.232</td>
<td>113.641±31.189</td>
<td>t = 3.291 (p&lt;0.01)</td>
</tr>
<tr>
<td>S. Alkaline Phosphatase (IU/L)</td>
<td>85.059±23.412</td>
<td>171.806±36.140</td>
<td>t = 1.464 (NS)</td>
</tr>
<tr>
<td>Total Serum Bilirubin (mg/dl)</td>
<td>0.931±0.141</td>
<td>1.065±0.143</td>
<td>t = 1.345 (NS)</td>
</tr>
<tr>
<td>Blood Urea (mg/dl)</td>
<td>30.716±5.896</td>
<td>31.059±6.383</td>
<td>t = 1.021 (NS)</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.756±0.154</td>
<td>0.779±0.168</td>
<td>t = 1.216 (NS)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.425±0.942</td>
<td>12.080±0.887</td>
<td>t = 1.336 (NS)</td>
</tr>
<tr>
<td>Weight (Kg.)</td>
<td>66.194±12.916</td>
<td>66.985±12.962</td>
<td>t = 1.442 (NS)</td>
</tr>
</tbody>
</table>

Data expressed as mean±SD. NS: not significant.

After treatment for 3 months with pioglitazone and metformin, there were significant reductions from baseline in the levels of Serum LDL (171.447±27.628 vs 156.238±20.382, p<0.01) and Serum Triglycerides (123.552±34.232 vs 113.641±31.189, p<0.01). There was also a significant elevation in serum HDL level (48.044±8.872 vs 51.776±9.013, p<0.01). But there were no statistically significant changes from baseline in terms of Serum ALT, AST, Alkaline Phosphatase, Total Serum Bilirubin, Blood Urea, Creatinine, Hemoglobin and body weight (BW) in all patients (Table No. 6).

Table No. 7: Changes of Mean value from Baseline.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After 30 DAYS</th>
<th>After 90 DAYS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Blood Glucose level</td>
<td>46.299mg/dl</td>
<td>37.94 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Prandial Glucose level</td>
<td>-51.871mg/dl</td>
<td>-44.985 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1C Level</td>
<td>---</td>
<td>1.375%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides Level</td>
<td>---</td>
<td>0.911 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL Level</td>
<td>---</td>
<td>1.209 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL Level</td>
<td>---</td>
<td>3.72 mg/dl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

Pioglitazone have been studied extensively in patients with type 2 diabetes. The clinical effects of pioglitazone, both as
monotherapy or in combination therapy with metformin, can decrease fasting and postprandial blood glucose levels. It can also reduce HbA1c values by 1–2% from baseline, which is comparable to the effectiveness of metformin and sulfonylureas14,15. In our study, pioglitazone with metformin given for 3 months to patients who sub optimally controlled their type 2 diabetes by metformin alone resulted in a comparable mean HbA1c reduction of 1.37% from baseline. In addition, pioglitazone markedly reduced mean fasting blood sugar and mean postprandial blood sugar by 73.94 mg/dl and 84.985 mg/dl, respectively (Table No.-7). These results showed a similar effectiveness on glycemic control to that shown in the majority of the published literature.

Dyslipidemia is a well-established risk factor for the atherogenic process in type 2 diabetes16. Insulin resistance syndrome and type-2 diabetes are associated with a characteristic pattern of lipid abnormalities, namely, increased small, dense LDL particles, elevated plasma TG and low HDL levels. In type 2 diabetes, it was reported that pioglitazone lowered fasting TG levels and increased HDL by approximately 9-20% and 5-10%, respectively14,15. Our study showed that there were significant effects of pioglitazone on the lipid profile, with reduction of TG and elevation of HDL levels.

The most frequently reported adverse events of pioglitazone are weight gain and peripheral edema. Other adverse events include myalgia and a transient rise in creatine phosphokinase, while nonfatal hepatic dysfunction is rare17. Our patients did not have elevated ALT or AST or peripheral edema during the 3-month treatment period. In our patients, body weight was insignificantly increased by an average of 0.79 kg, probably due to the short treatment duration.

In summary, pioglitazone with metformin appears to be a safe and tolerable antidiabetic agent that not only enhances insulin sensitivity to reduce fasting glucose parameters, but also attenuates postprandial blood glucose.

CONCLUSION

Patients receiving pioglitazone and metformin for 3 months had statistically significant mean decreases in the levels of HbA1c (-1.37%), fasting blood glucose (-73.94 mg/dl) and postprandial blood glucose (-84.985 mg/dl) compared with baseline values ($P \leq 0.001$). There were significant mean changes in levels of triglycerides (-9.911 mg/dl), LDL (-15.209 mg/dl) and HDL (+3.732 mg/dl) compared with baseline values ($P \leq 0.01$). The adverse events were mild and not significant. Throughout the study, no patient in either treatment group had an alanine aminotransferase (ALT) value ≥3 times the upper limit of normal, a commonly used marker of potential liver damage. Thus, no evidence of drug-induced hepatotoxicity or drug-induced elevations in serum ALT was observed.

In this study in patients with type 2 diabetes mellitus, pioglitazone in combination with metformin significantly improved HbA1c and fasting and postprandial blood glucose levels, with positive effects on serum lipid levels and no evidence of drug-induced hepatotoxicity.

REFERENCES


Source of support: Nil
Conflict of interest: None Declared