Research Article

STUDY OF THE EFFECTS OF PIOGLITAZONE MONOTHERAPY IN NEWLY DIAGNOSED PATIENTS OF TYPE 2 DIABETES MELLITUS

Dr. Neelesh Arya[1], Dr. Ashutosh Chourishi[2]*, Dr. S. P. Pandey[3]
1. M.D. Assistant Professor, Department of Pharmacology, Gandhi Medical College, Bhopal, India.
2. M.D. Associate Professor, Department of Pharmacology, R.D. Gardi Medical College, Ujjain, India.
3. M.D. Professor, Department of Pharmacology, NSCB Medical College, Jabalpur, India.
*Corresponding author's E-mail: dr_chourishi@yahoo.co.in

Accepted on: 04-02-2012; **Finalized on:** 20-03-2012.

ABSTRACT

The aim of this study was to evaluate the efficacy and safety of pioglitazone in the treatment of newly diagnosed patients with type 2 Diabetes Mellitus. Patients of Type-2 Diabetes Mellitus who were on diet control alone but diabetes not controlled as per blood glucose level assessment, were given pioglitazone starting from 15 mg OD before breakfast and gradually increased to 30 mg OD before breakfast as per blood glucose level assessment. Total fourteen patients were taken in this study. Evaluation was carried out at 0, 30 days and on 90 days. At the end of 90 days, 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 (264.85±46.32 vs 170.50±18.23 mg/dl, P<0.001) and HbA1c (8.92±0.27 vs 7.17±0.22%, P<0.001) in all patients. There were significant reductions from baseline in the levels of Serum LDL (179.85±24.56 vs 162.85±17.84, p<0.01) and Serum Triglycerides (141.85±33.58 vs 131.21±31.26, p<0.01). There was also a significant elevation in serum HDL level (48.64±9.88 vs 52.21±8.03, 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. Pioglitazone monotherapy 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 serum ALT levels in this study.

Keywords: Pioglitazone, Type-2 diabetes mellitus, fasting blood glucose, postprandial blood glucose, HbA1c.

INTRODUCTION

Type 2 diabetes is a heterogeneous disorder characterized by insulin resistance, that is, reduced insulin action at the level of the liver, adipose tissue and skeletal muscle as well as a progressive beta-cell defect[1,2]. It is an endocrine disorder, more than 100 million (6% of the population) of people world-wide are affected inspite of enormous facilities available to control its growth[3]. Type 2 diabetes is caused by two primary metabolic defects: progressive pancreatic β-cell dysfunction and insulin resistance[4].

Uncontrolled diabetes can lead to dreadful complications that cause physical, emotional and economical burden on the individual as well as on the society[5].

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 was introduced into clinical practice in 1999. Both sulfonylurea and pioglitazone have positive effects on patients of type-2 diabetes mellitus. Sulfonylureas are the most widely used drugs for the treatment of type 2 diabetes. Sulfonylureas stimulate endogenous insulin secretion via their action at the KATP channel in the plasma membrane of pancreatic b-cells[6] and effectively decrease HbA1c levels by between 0.8% and 2.0%[7].

In animal models of diabetes, pioglitazone reduced the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states[8,9].

Pioglitazone, a thiazolidinedione, is a peroxisome proliferator-activated receptor agonist that affects regulators of carbohydrate and lipid metabolism[10]. Pioglitazone reduces insulin resistance by enhancing the action of insulin, thereby promoting glucose utilization in peripheral tissues, suppressing gluconeogenesis, and reducing lipolysis[11].

In the present study, the effects of pioglitazone monotherapy in newly diagnosed 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 monotherapy 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 monothetrapy on serum lipid profile in patients with type-2 diabetes mellitus.
3. To Study the safety and tolerability of Pioglitazone monothetrapy in patients with type-2 diabetes mellitus.

MATERIALS AND METHODS

This was an open non-comparative drug trial carried out in the 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 newly detected patients of either sex who met the diagnostic criteria for Type-2 Diabetes Mellitus and who were on diet control alone, included in this study.
2. Those patients who were willing to give consent for the treatment.

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 pointes.
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 < 12g/dl for men and <10g/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, fourteen new patients of diabetes mellitus type-2, who were on diet control alone, 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 who were on diet control alone but diabetes not controlled as per blood glucose level assessment were given pioglitazone starting from 15 mg OD before breakfast and gradually increased to 30 mg OD before breakfast as per blood glucose level assessment. Total fourteen 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 Post prandial blood sugar was done and dosage of pioglitazone was adjusted accordingly without altering dose of sulfonylurea.

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 glucose and HbA1c values at baseline and at each subsequent visit. Drop in fasting blood glucose, postprandial blood glucose and HbA1c was calculated between baseline and last follow up visit i.e. after three months of treatment. All results were expressed as mean with their standard deviation (mean=SD). A p value of < 0.05 was considered significant.

RESULTS

In our study out of total 14 patients, the maximum number of patients i.e. 6 (42.85%) belonged to the age group of 56-60 years. There was no patient in this group belonging to age group of 35-40 years and age group 66-70 years. The mean age of patients was 53.71 ± 12.19 years (Table 1). These included 08 males (57.14%) and 06 females (42.86%). Male: Female ratio was 1.33:1.

Table 1: Age Distribution of Total Patients (n=14)

Age (Yrs.)	Total No. of Patients	Percentage
35-40	00	00
41-45	02	14.28
46-50	03	21.42
51-55	02	14.28
56-60	06	42.85
61-65	01	7.14
66-70	00	00

Out of 14 patients studied 05 patients (35.71%) had polyuria and 04 (28.57%) had polyphagia and 03 (21.42%) had polydipsia. Sensory symptoms were recorded in 01 (07.14%) patients and 01 (07.14%) patients complained of dimness of vision. The commonest symptom was polyuria, followed by polyphagia and polydipsia (Table-2).

Table 2: Distribution of Symptoms in all Patients (n=14)

Symptoms	No. of Patients	Percentage
Polyuria	05	35.71
Polyphagia	04	28.57
Polydipsia	03	21.42
Dimness of vision	01	07.14
Sensory symptoms	01	07.14

In total 14 patients, the range of baseline fasting blood glucose was 133-247 mg/dl and the mean was 180.02±22.44 mg/dl. At the end of 30 days, the range of fasting blood glucose declined to 108-186 mg/dl and the mean was 133.73±20.10 mg/dl. At the end of 90 days, the range of fasting blood glucose dropped up to 92-153 mg/dl and the mean was 106.08±14.49 mg/dl. The decline was highly significant (p<0.001) and started as early as 30 days of treatment (Table-3).

In total 14 patients, the range of baseline 2-hour Postprandial blood glucose was 202-357 mg/dl and the mean was 264.85±46.33 mg/dl. At the end of 30 days, the range of 2-hour Postprandial blood glucose declined to 168-289 mg/dl and the mean was 210.92±36.09 mg/dl. At the end of 90 days, the range of 2-hour Postprandial blood glucose dropped up to 142-204 mg/dl and the mean was 170.50±18.23. The decline was highly significant (p<0.001) and started as early as 30 days of treatment (Table-4).

Table 3: Comparison of Fasting Blood Glucose Levels at Baseline, 30 days and 90 days in all Patients (n=14)

Fasting Blood Glucose	Range	Mean	S.D.	P value
Baseline	133-247	180.029	±22.447	
30 days	108-186	133.731	±20.103	t = 3.784 (p<0.001)
90 days	92-153	106.089	±14.490	t = 3.812 (p<0.001)

Table 4: Comparison of Postprandial Blood Glucose Levels at Baseline, 30 days and 90 days in all Patients (n=14)

Post Prandial Blood Glucose	Range	Mean	S.D.	P value
Baseline	202-357	264.857	±46.332	
30 days	168-289	210.928	±36.098	t = 4.816 (p<0.001)
90 days	142-204	170.50	±18.239	t = 4.918 (p<0.001)

In total 14 patients, the range of glycosylated hemoglobin was 8.4% to 9.3% and the mean was 8.92±0.27. At the end of 90 days the range of glycosylated hemoglobin was 6.9% to 7.6% and the mean was 7.17±0.22. The decline was highly significant (p<0.001) at the end of 90 days and showed excellent glycemic control (Table-5).

Table 5: Comparison of Glycosylated Hemoglobin Levels at Baseline and at the end of 90 days (n=14)

Glycosylated Hemoglobin	Range	Mean	S.D.	P value
Baseline	8.4-9.3	8.921	±0.273	
90 days	6.9-7.6	7.178	±0.224	t = 7.146 (p<0.001)

Table 6: Comparison of the Glycemic parameters, Lipid profile, Biochemical & Clinical characteristics at Baseline and at the end of 90 days in all patients (n=14)

	Baseline	90 days	P value
Glycosylated Hemoglobin (%)	8.92 ±0.27	7.17±0.22	p<0.001
Serum HDL (mg/dl)	48.64±9.88	52.21±8.03	p<0.01
Serum LDL (mg/dl)	179.85±24.56	162.85±17.84	p<0.01
Serum Triglycerides (mg/dl)	141.85±33.58	131.21±31.26	p<0.01
Serum AST (IU/L)	29.45±6.47	31.59±8.78	NS
Serum ALT (IU/L)	37.53±3.67	39.67±8.22	NS
S. Alkaline Phosphatase (IU/L)	95.34±10.68	98.45±16.15	NS
Total Serum Bilirubin (mg/dl)	0.91±0.14	1.09±0.32	NS
Blood Urea (mg/dl)	29.23±4.67	30.12±3.78	NS
Serum Creatinine (mg/dl)	0.80±0.16	0.83±0.24	NS
Hemoglobin (g/dl)	12.09±0.86	12.38±0.55	NS
Weight (Kg.)	61.15± 5.23	61.46±3.58	NS

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

After treatment for 3 months with pioglitazone, there were significant reductions from baseline in the levels of Serum LDL (179.85±24.56 vs 162.85±17.84, p<0.01) and Serum Triglycerides (141.85±33.58 vs 131.21±31.26, p<0.01). There was also a significant elevation in serum HDL level (48.64±9.88 vs 52.21±8.03, 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 6).

Table 7: Changes of Mean value from Baseline

	After 30 Days	After 90 Days
Fasting Blood Glucose level	-46.298 mg/dl	-73.94 mg/dl
Post Prandial Glucose level	-53.929 mg/dl	-94.35 mg/dl
HbA_1C Level	---	-1.74 %
Triglyceride Level	----	-10.64 mg/dl
LDL Level	----	-17.00 mg/dl
HDL Level	----	+3.57 mg/dl

DISCUSSION

Thiazolidinedione, a new class of oral antidiabetic drug have been studied extensively in patients with type 2 diabetes. Pioglitazone can improve blood glucose and plasma lipoprotein by modulating the transcription of genes that play key roles in carbohydrate and lipid metabolism[12]. Pioglitazone has been shown to enhance insulin sensitivity in the peripheral organs and liver, resulting in improved glycemic control in patients with type 2 diabetes as monotherapy or in combination with other antidiabetic agents[13,14]. It 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 sulfonylureas[14,15]. In our study, pioglitazone given for 3 months to patients who suboptimally controlled their type-2 diabetes by diet control alone resulted in a comparable mean HbA1c reduction of 1.74% from baseline. In addition, pioglitazone markedly reduced mean fasting blood sugar and mean postprandial blood sugar by 73.94 mg/dl and 94.35 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 diabetes[16]. 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%, respectively[14,15]. 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 rare[17]. 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 0.31 kg, probably due to the short treatment duration.

In summary, pioglitazone 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 for 3 months had statistically significant mean decreases in the levels of HbA_{1c} (−1.74%), fasting blood glucose (-73.94 mg/dl) and postprandial blood glucose (-94.35 mg/dl) compared with baseline values ($P \leq 0.001$). There were significant mean changes in levels of triglycerides (-10.64 mg/dl), LDL (-17.00 mg/dl) and HDL (+3.57 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.

From the assumption described in results and discussion the present study concludes that, in the patients with type 2 diabetes mellitus, pioglitazone monotherapy significantly improved HbA_{1c} and fasting and postprandial blood glucose levels, with positive effects on serum lipid levels and no evidence of drug-induced hepatotoxicity.

REFERENCES

1. Bergman RN, Finegood DT, Kahn SE. The evolution of beta-cell dysfunction and insulin resistance in type 2 diabetes. Eur J Clin Invest (32Suppl 3):2002; 35-45.
2. Boden G. Pathogenesis of type 2 diabetes. Insulin resistance. Endocrinol Metab Clin North Am 30:2001; 801-815.
3. Datta A. and Deb L., Diabetes Mellitus its possible pharmacological evaluation techniques and naturotherapy, Int. J. of Green pharmacy, 2006, 15-28.
4. Defronzo R. A., Pharmacologic Therapy for Type 2 Diabetes Mellitus, Ann. Intern. Med., 131 (4), 1999. 281-30.
5. Iqbal F. Global epidemic of Diabetes Mellitus-an overview. Proceedings Shaikh Zayed Postgrad Med Inst 17:2003; 99-106.
6. Lebovitz HE. Oral therapies for diabetic hyperglycemia. Endocrinol Metab Clin North Am 30: 2001; 909–33.
7. Luna B, Feinglos M. Oral agents in the management of type 2 diabetes mellitus. Am Fam Physician 2001; 63: 1747–567.Stumvoll M, Häring HU. Glitazones: clinical effects and molecular mechanisms. Ann Med 34:2002; 217–24.

8. Sugiyama Y, Taketomi S, Shimura Y, Ikeda H, Fujita T: Effects of pioglitazone on glucose and lipid metabolism in Wistar fatty rats. *Arzneimittel-Forschung Drug Res* 40: 1990, 263–267.

9. Kemnitz JW, Elson DF, Roecker EB, Baum ST, Bergman RN, Meglasson MD: Pioglitazone increases insulin sensitivity, reduces blood glucose, insulin, and lipid levels, and lowers blood pressure, in obese, insulinresistant rhesus monkeys. *Diabetes* 43:204–211, 1994

10. Stumvoll M, Häring HU. Glitazones: clinical effects and molecular mechanisms. Ann Med 34:2002; 217–24.

11. Miyazaki Y, Mahankali A, Matsuda M. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 87:2002; 2784–91.

12. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. Drugs 63:2003; 1373-1405.

13. Rendell MS, Glazer NB, Ye Z. Combination therapy with pioglitazone plus metformin or sulfonylurea in patients with Type 2 diabetes: influence of prior antidiabetic drug regimen. J Diabetes Complications 17:2003; 211-217.

14. Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type2 diabetes mellitus:a randomized, placebo-controlled study. Am J Med 111:2001; 10-17.

15. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 23:2000; 1605-1611.

16. Syvanne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. Lancet 350(Suppl 1):1997; SI20-SI23.

17. May LD, Lefkowitch JH, Kram MT, Rubin DE. Mixed hepatocellular-cholestatic liver injury after pioglitazone therapy. Ann Intern Med 136:2002; 449-452.

****