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Study of the Effects of Pioglitazone Add-on to Sulfonylurea in Patients with Type 2 Diabetes Mellitus.

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Abstract:
Objective - To evaluate the efficacy and safety of combination of pioglitazone with sulfonylurea in the treatment of type-2 diabetes mellitus.
Methodology -Patients of Type-2 Diabetes Mellitus taking sulfonylurea 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 sulfonylurea was not altered throughout the study in any patient. Total forty one patients were taken in this study. Evaluation was carried out at 0, 30 days and on 90 days.
Results — At the end of 90 days, there were significant reductions from baseline in the levels of fasting blood glucose (176.53±20.86 vs 104.19±11.36 mg/dl, P<0.001), postprandial blood glucose (251.41±34.00 vs 169.07±15.56 mg/dl, P<0.001) and HbA1c (8.79±0.74 vs 7.43±0.42%, P<0.001) in all patients.
There were also significant reductions from baseline in the levels of Serum LDL (168.60±30.38 vs 154.24±22.02, p<0.01) and Serum Triglycerides (120.43±32.55 vs 111.07±29.71, p<0.01). There was also a significant elevation in serum HDL (48.12±9.04 vs 52.19±8.60, 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 – The combination of pioglitazone with sulfonylurea significantly improves levels of 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 level in this study.
Key words - Sulfonylurea, Pioglitazone, Type-2 diabetes mellitus.
Conflict of study – No conflict of study.

INTRODUCTION :

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia resulting from a defect in insulin secretion, insulin action, or both[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 combination of pioglitazone with sulfonylurea 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 sulfonylurea 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 sulfonylurea on serum lipid profile in patients with type-2 diabetes mellitus.
3. To Study the safety and tolerability of Pioglitazone in combination with sulfonylurea in patients with type-2 diabetes mellitus.

MATERIALS &METHODS:

This was an open non-comparative add on 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 April 2005 to August 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 sulfonylurea alone for more than three months were included in the 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 April 2005 to August 2006 of either sex aged 25-70 years. During the period of the study, forty one old patients of diabetes mellitus type-2, taking sulfonylurea 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 sulfonylurea 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 sulfonylurea was not altered throughout the study in any patient. Total forty one 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 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.

OBSERVATION & RESULTS:

In our study out of total 41patients the maximum number of patients i.e. 11 (26.83%) belonged to the age group of 51-55 years. The minimum number of patients i.e. 1 (2.43%) was in the age group 66-70 years. The mean age of patients was 51.341 ± 14.634 years (Table 1). These included 21 males (51.22%) and 20 females (48.78%). Male: Female ratio was 1.05:1.

Table No. 1. Age Distribution of Total Patients (n=41)

Age (Yrs.)	*Total No. of Patients*	*Percentage*
35-40	03	7.31
41-45	06	14.63
46-50	09	21.95
51-55	11	26.83
56-60	09	21.95
61-65	02	4.87
66-70	01	2.43

Out of 41 patients studied 13 patients (31.70%) had polyuria and 09 (21.95%) had polyphagia and 10 (24.39%) had polydipsia. Sensory symptoms were recorded in 05 (12.19%) patients, 04 (9.75%) patients complained of dimness of vision. The commonest symptom was polyuria, followed by polydipsia and polyphagia (Table-2).

Table No. 2. Distribution of Symptoms in all Patients (n=41)

Symptoms	*No. of Patients*	*Percentage*
Polyuria	13	31.70
Polyphagia	09	21.95
Polydipsia	10	24.39
Dimness of vision	04	09.75
Sensory symptoms	05	12.19

In total 41 patients, the range of baseline fasting blood glucose was 133-232 mg/dl and the mean was 176.536±20.860mg/dl. At the end of 30 days, the range of fasting blood glucose declined to 108-186 mg/dl and the mean was 129.902±17.563 mg/dl. At the end of 90 days, the range of fasting blood glucose dropped up to 92-142 mg/dl and the mean was 104.195±11.365 mg/dl. The decline was highly significant ($p<0.001$) and started as early as 30 days of treatment (Table-3).

Table No. 3. Comparison of Fasting Blood Glucose Levels at Baseline, 30 days and 90 days in all Patients (n=41)

Fasting Blood Glucose	*Range*	*Mean*	*S.D.*	*P value*
Baseline	133-232	176.536	±20.860	
30 days	108-186	129.902	±17.563	t = 3.804 (p<0.001)
90 days	92-142	104.195	±11.365	t = 3.911 (p<0.001)

Table No. 4 - Comparison of Postprandial Blood Glucose Levels at Baseline, 30 days and 90 days in all Patients (n=41)

Post Prandial Blood Glucose	*Range*	*Mean*	*S.D.*	*P value*
Baseline	190-324	251.414	±34.003	
30 days	154-298	200.951	±27.789	t = 3.814 (p<0.001)
90 days	140-198	169.073	±15.567	t = 3.903 (p<0.001)

In total 41 patients, the range of baseline 2-hour Postprandial blood glucose was 190-324 mg/dl and the mean was 251.414±34.003 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

200.951±27.789 mg/dl. At the end of 90 days, the range of 2-hour Postprandial blood glucose dropped up to 140-198 mg/dl and the mean was 169.073±15.567. The decline was highly significant ((p<0.001)) and started as early as 30 days of treatment (Table-4).

In total 41 patients, the range of glycosylated hemoglobin was 7.8% to 10.8% and the mean was 8.790±0.744. At the end of 90 days the range of glycosylated hemoglobin was 6.9% to 8.4% and the mean was 7.434±0.425. The decline was highly significant ((p<0.001)) at the end of 90 days and showed excellent glycemic control (Table-5).

Table No. 5. Comparison of Glycosylated Hemoglobin Levels at Baseline and at the end of 90 days (n=41)

Glycosylated Hemoglobin	*Range*	*Mean*	*S.D.*	*P value*
Baseline	7.8-10.8	8.790	±0.744	
90 days	6.9-8.4	7.434	±0.425	t = 6.743 (p<0.001)

After treatment for 3 months with pioglitazone and sulfonylurea, there were significant reductions from baseline in the levels of Serum LDL (168.60±30.38 vs 154.24±22.02, p<0.01) and Serum Triglycerides (120.43±32.55 vs 111.07±29.71, p<0.01). There was also a significant elevation in serum HDL level (48.12±9.04 vs 52.19±8.60, 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).

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 with sulfonylurea given for 3 months to patients who controlled their type-2 diabetes by sulfonylurea alone resulted in a comparable mean HbA1c reduction of 1.35% from baseline. In addition, pioglitazone markedly reduced mean fasting blood sugar and mean postprandial blood sugar by 72.34 mg/dl and 82.34 mg/dl, respectively (Table No.-7).

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=41)

	Baseline	*90 days*	*P value*
Glycosylated Hemoglobin (%)	8.79 ±0.74	7.43±0.42	p<0.001
Serum HDL (mg/dl)	48.12±9.04	52.19±8.60	p<0.01
Serum LDL (mg/dl)	168.60±30.38	154.24±22.02	p<0.01
Serum Triglycerides (mg/dl)	120.43±32.55	111.07±29.71	p<0.01
Serum AST (IU/L)	29.57±7.24	45.58±8.31	NS
Serum ALT (IU/L)	33.34±4.45	46.78±9.34	NS
S. Alkaline Phosphatase (IU/L)	88.16±13.67	112.75±32.18	NS
Total Serum Bilirubin (mg/dl)	0.95±0.27	1.13±0.18	NS
Blood Urea (mg/dl)	29.68±3.89	30.06±2.83	NS
Serum Creatinine (mg/dl)	0.78±0.13	0.81±0.37	NS
Hemoglobin (g/dl)	12.12±0.98	12.34±0.76	NS
Weight (Kg.)	63.12± 2.31	63.49±2.41	NS

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

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

	After 30 DAYS	*After 90 DAYS*
Fasting Blood Glucose level	-46.634 mg/dl	-72.341 mg/dl
Post Prandial Glucose level	-50.463 mg/dl	-82.341 mg/dl
HbA_1C Level	---	-1.35 %
Triglyceride Level	----	-9.36 mg/dl
LDL Level	----	-14.36 mg/dl
HDL Level	----	+4.07 mg/dl

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 0.37 kg, probably due to the short treatment duration.

In summary, pioglitazone with sulfonylurea 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 sulfonylurea for 3 months had statistically significant mean decreases in the levels of HbA_{1c} (−1.35%), fasting blood glucose (-72.34 mg/dl) and postprandial blood glucose (-82.34 mg/dl) compared with baseline values ($P \leq 0.001$). There were significant mean changes in levels of triglycerides (-9.36 mg/dl), LDL (-14.36 mg/dl) and HDL (+4.07 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 in combination with sulfonylurea 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.

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