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THE EFFECT OF SINGLE DRUG THERAPY VERSUS COMBINATION DRUG THERAPY IN INDIAN POPULATION WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Their complimentary mechanisms of action suggest that a combination of pioglitazone hydrochloride and metformin may have clinically beneficial effects in the treatment of patients with type 2 diabetes. This study was undertaken to assess the safety and efficacy Pioglitazone, metformin in patients with type 2 diabetes mellitus. Pioglitazone, metformin lower HbA1c and fasting plasma glucose in patients with type 2 diabetes. We compared the effects of these two drugs, used as monotherapy and in combination. This was a 24-weeks, observational, open-ended, open-label study. Patients were receiving once-daily pioglitazone 30 mg, metformin 1000 mg and combination of pioglitazone 30 mg with metformin 1000 mg. Patients receiving combination had statistically significant mean decreases in HbA1c and fasting plasma glucose (FPG) levels compared with monotherapy. The incidence of adverse events was similar in all groups. 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, combination of pioglitazone with metformin significantly improved HbA1c and FPG levels, with positive effects on serum lipid levels compared with metformin and pioglitazone alone and no evidence of drug-induced hepatotoxicity. These effects were maintained for >24 weeks.

Key words: Metformin, Pioglitazone, Combination drug therapy, Type 2 diabetes mellitus

INTRODUCTION

It is known that 3 major metabolic abnormalities contribute to the development of hyperglycemia in type 2 diabetes mellitus: impaired insulin secretion in response to glucose, increased hepatic glucose production, and decreased insulin-stimulated glucose uptake in peripheral tissues. The latter abnormalities are due primarily to insulin resistance [1]. "The mechanism is not fully understood, but reducing insulin resistance, or increasing insulin sensitivity, appears to improve glucose and lipid metabolism. The crude prevalence rate of diabetes in urban areas is about 9% and the prevalence in rural areas has also increased to around 3% of the total population. If one takes into consideration that the total population of India is more than 1000 million then one can understand the sheer numbers involved. Taking an urban-rural population distribution of 70:30 and an overall crude prevalence rate of around 4%, at a conservative estimate, India is home to around 40 million diabetics.

Metformin has been widely used worldwide for >30 years, although it has been available in the United States only since 1995. This agent, which sensitizes hepatic and peripheral tissues to insulin, inhibits hepatic gluconeogenesis and may inhibit hepatic glycogenolysis, has become an important part of the therapeutic armamentarium against type 2 diabetes mellitus, used alone or in combination with other antidiabetic drugs [2-4]. Pioglitazone hydrochloride is a member of the thiazolidinedione class, also referred to as insulin sensitizers. This drug class has a mechanism of action that involves binding to nuclear peroxisome proliferator-activated receptor gamma.

Dose-related improvements in hyperglycemia, hyperinsulinemia, and hypertriglyceridemia have been shown in animal models of type 2 diabetes mellitus after administration of pioglitazone; blood glucose levels in normoglycemic animals were not affected [5,6]. The antihyperglycemic effect of pioglitazone appears to be related to its ability to enhance insulin sensitivity, which increases the efficacy of insulin. Although metformin alters insulin sensitivity, the reduction of insulin resistance by metformin occurs by other mechanisms. Therefore, their complimentary mechanisms of action suggest that the combination of pioglitazone and metformin might have clinically beneficial effects in the treatment of patients with type 2 diabetes. The purpose of the present observational, openlabel study with an was to assess the efficacy and tolerability of pioglitazone 30 mg given once daily in combination with metformin in patients with type 2 diabetes that had been poorly controlled with metformin therapy alone.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria to be eligible for this multicenter study, patients have a body mass index of 25 to 45 kg/m2. Patients have a age between 35-65 years at screening, patients had to have a glycated hemoglobin [HbA1c, value more than 7%. (Based on American Diabetes Association guidelines for initiating combination therapy in patients with type 2 diabetes (American Diabetes Association, 2000)] and a fasting glucose level more than 125 mg/dL. Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were patients with impaired liver function, impaired kidney function, or anemia. Patients with unstable cardiovascular conditions or cerebrovascular conditions within 6 months of study enrollment were excluded. Each patient gave written informed consent, and study protocol was approved by independent ethics committee before any patient entered the study.

Study Design: The 24-week, prospective, open, observational study during which patients received their usual dosage of metformin 1000 mg in combination with pioglitazone 30 mg or metformin 1000 mg or pioglitazone 30 mg alone for 24 weeks. The dose of metformin was not adjusted, except at the investigator's discretion in response to findings of hypoglycemia. To eliminate the effect of change in body weight and isolate the effect of pioglitazone, patients were asked to adhere to an individualized weight-maintenance diet. Concomitant use of lipid-lowering medications was allowed, provided the patient had been taking a stable dose for 24 weeks and the regimen was continued without alteration throughout the study. If patients had been receiving prior antidiabetic medication in addition to metformin, they were required to discontinue.

Efficacy and safety measurements: HbA1c was measured at baseline, after 12 and 24 weeks. Secondary efficacy end points included changes in FPG and lipid profiles [total cholesterol (TC), HDL, low density lipoprotein cholesterol (LDL), TG]. Adverse events (AEs), laboratory tests, blood pressure, and weight were determined throughout the study.

Safety and Tolerability Assessment: The safety profile was assessed based on the results of laboratory testing and adverse events elicited by general questioning. All patients who were received study medication were included in the safety assessment. Adverse events were summarized in terms of frequency counts and percentages of patients reporting adverse events (coded on the basis of modified World Health Organization Adverse Reaction Terminology). Laboratory values were summarized in terms of changes from baseline and the number of patients having laboratory values outside the normal range or markedly abnormal values.

Statistical Analysis: Descriptive statistics were used to summarize demographic and baseline characteristics. The comparability of the treatment groups was assessed using a 2-way analysis of variance for continuous variables (eg, age). All efficacy variables were assessed for changes from baseline. Observed HbA1c and FPG values at each time point were used for the efficacy analysis.

All the results will be express as mean ± standard deviation (S.D.). Data will be analyzing using ANOVA followed by Dunnet´s-test. $P < 0.05$ consider as statistically significant.

RESULTS

Of 210 patients recruited (age range, 30-60 years) and were treatment with metformin in combination with pioglitazone or metformin or pioglitazone alone. There were no significant differences in demographic characteristics (Table I) or baseline lipid levels (Table II) between treatment groups. Two hundred five patients (77.62%) completed the study. Reasons for withdrawal loss to follow-up (5/210) [2%].

Glycemic Control: Table 1 A shows the mean change in HbA1c from baseline over the course of the study in all patients. At all time points at which HbA1c was measured, the metformin, pioglitazone alone group showed statistically significant mean increase in HbA1c from baseline, compared with significant mean decreases in the pioglitazone + metformin group ($P < 0.05$). At all time points, differences in HbA1c between the 3 groups statistically significantly favored pioglitazone + metformin ($P < 0.05$). Figure 1A shows the mean change in FPG from baseline over the course of the study in all patients. At all time points at which FPG was measured, the metformin, pioglitazone alone group showed statistically significant mean increase in FPG from baseline, compared with significant mean decreases in the pioglitazone + metformin group ($P < 0.05$). At all time points, differences in FPG between the 3 groups statistically significantly favored pioglitazone + metformin ($P < 0.05$).

Tolerability Assessment: Overall rates of adverse events were similar between the metformin in combination with pioglitazone, metformin, pioglitazone alone groups. The incidence of individual adverse events was generally ~5% in all. Most events were considered mild or moderate. The incidence of adverse events commonly associated with metformin therapy, such as diarrhea, nausea, and epigastric discomfort. No patient had alanine aminotransferase (ALT) values that increased to 3 times the upper limit of normal during the study. There were no cases of jaundice and no evidence of drug-induced hepatotoxicity or drug-induced elevations in ALT.

Lipid profiles: Lipid changes after pioglitazone or metformin or pioglitazone + metformin combination treatment are shown in table no. 2. The mean percentage changes in triglycerides, TC, HDL, LDL from baseline to end of study (week 24) are shown in Table II. The pioglitazone + metformin group had a statistically significant mean percentage decrease in triglycerides compared with baseline and compared with the pioglitazone and metformin group ($P < 0.05$). Lipid changes after pioglitazone or metformin treatment are shown in table no. 2. At wk 24, estimated mean TG levels were approximately 54.6 mg/dl lower than baseline in the pioglitazone group compared with decreases of 26.9 mg/dl in the metformin group and 65.8 mg/dl lower than baseline in the pioglitazone + metformin group a difference that was statistically significant ($P \leq 0.001$). HDL significantly increased by 6 mg/dl in the pioglitazone group compared with 2.4 mg/dl in the metformin group and increased by 7 mg/dl than baseline in the pioglitazone + metformin group a difference that was statistically significant ($P \leq 0.001$). LDL increased by 10.6 mg/dl in the pioglitazone group compared with 4.8 mg/dl in the metformin group and 10.2 mg/dl increased than baseline in the pioglitazone + metformin group, and TC increased by 9.4 mg/dl in the pioglitazone group compared with 4.7 mg/dl in the metformin group 4.8 mg/dl increased than baseline in the pioglitazone + metformin group.

Weight changes: Mean body weight in the pioglitazone group increased by 1.9 kg, With metformin, there was a decrease in mean body weight by 2.7 kg and with pioglitazone + metformin was a decrease in mean body weight by 2.5 kg.

DISCUSSION

The Diabetes Control and Complications Trial 17 showed that strict control of blood glucose levels can prevent development of the complications of diabetes, including neuropathy, retinopathy, and nephropathy. Furthermore, the United Kingdom Prospective Diabetes Study demonstrated that type 2 diabetes is a progressive disorder and that once marked fasting hyperglycemia has developed, glycemic control will continue to decline. These data highlight the need for regular reassessment and adjustment of therapeutic regimens to maintain the desired level of glycemic control in patients with type 2 diabetes. Results of the present study showed that pioglitazone 30 mg was effective in reducing both HbA1c and FPG when administered in combination with metformin, with statistically significant reductions in FPG observed by week 4 ($P < 0.05$). Decreases in HbA1C a long-term marker of glycemic control, were statistically significant compared with pioglitazone and metformin alone ($P < 0.05$) at all measurement points (12, and 24 weeks). If maintained, responses of this order may be sufficient to delay the onset or slow the progression of complications of type 2 diabetes mellitus [8,9].

Patients with uncontrolled type 2 diabetes mellitus often have dyslipidemia characterized by elevated triglyceride levels and decreased HDL levels [10-12]. In this study, pioglitazone + metformin had a beneficial effect on the lipid profile, with decreased triglyceride levels and increased HDL levels, and no significant differences in TC and LDL compared with pioglitazone and metformin. Pioglitazone + metformin was generally well tolerated. The incidence of adverse events was similar between groups. All reported cases were considered mild to moderate. A small decrease in mean body weight was observed in patients treated with pioglitazone +

metformin during the study; however, the decrease was generally associated with improvements in glycemic control (ie, decreases in HbA1c). Finally, no evidence of drug-induced hepatotoxicity or ALT elevation or cases of jaundice was observed in this study.

The advent of hypoglycemic drugs that modulate lipids has focused attention on the potential benefits of these compounds on diabetic lipoprotein abnormalities. This study was sufficiently powered to show superiority for either compound for effects on lipids. Pioglitazone treatment reduced TG levels and increased HDL, nearly double the improvements with metformin. TGs, although not independent risk factors for coronary heart disease (CHD), induce adverse modifications in other lipoproteins [11]. Additionally, high TG levels may produce a procoagulant state that may further increase cardiac risk; hence, pioglitazone may confer an additional therapeutic effect [12]. However, the quantitative contribution of low HDL to CHD risk is difficult to assess. Nonetheless, low HDL signals the presence of other lipoprotein abnormalities, especially small LDL particles and increased very low density lipoprotein cholesterol levels, and a larger rise in HDL may reflect CHD risk reduction. A decrease in LDL levels by metformin cannot be overlooked and may represent a benefit of metformin even though the effects on other lipid parameters were not as potent. In contrast to metformin, which reduced LDL and TC, pioglitazone increased LDL, an effect that has been attributed to a shift from small dense particles to larger, potentially less atherogenic particles, and which may be secondary to the substantial TG lowering [13]. TGs have been shown to be strong predictors of CHD events in patients with low (as is the case in the population in this study) compared with higher LDL levels, and the effect of pioglitazone on TG levels is potentially more significant [14,15].

CONCLUSIONS

In this study, pioglitazone in combination with metformin was effective and well tolerated in patients with type 2 diabetes. Our report compares the effect of pioglitazone with metformin (as monotherapy and combination therapy) on HbA1c, fasting plasma glucose and lipid profile in patients with type 2 diabetes. In combination treatment, pioglitazone and metformin both improve glycemic control (HbA1c and FPG) more effectively than single drug treatment.

The positive effect of this combination on dyslipidemia and possibly beta-cell function may provide additional benefit in reducing the known risks for complications of the disease.

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Table 1- Patients detail and baseline characteristics of the study population

	Metformin (1000 mg)	**Pioglitazone (30 mg)**	**Metformin+Pioglitazone (1000 mg + 30 mg)**
Age (years)	54±10.8	57±8.9	52±11.6
Sex			
Male	55.4±11.2	58.6±8.6	54.6±7.6
Female	53.5±10.2	55.2±9.6	49.2±9.6
BMI (kg/m2)	32.5±4.3	30.6±6.2	32.5±5
HbA1c (%)			
No. of patients	70	70	70
Least squares mean ± SD			
Baseline	10.95±1.47	10.92±1.48	10.98±1.35
After 24 weeks	8.76±1.47	8.70±1.43	7.92±1.53
% Change from baseline	-20	-20.23	-27.86
FPG (mg/dl)			
No. of patients	70	70	70
Least squares mean ± SD			
Baseline	222.32±18.64	223.39±18.77	224.65±19.25
After 24 weeks	171.42±11.59	170.85±10.86	160.35±18.56
% Change from baseline	-22.89	-23.51	-28.62

Table -2 Lipid Level of the study population

	Metformin (1000 mg)	**Pioglitazone (30 mg)**	**Metformin+Pioglitazone (1000 mg + 30 mg)**
Triglycerides, mg/dL			
No. of patients	70	70	70
Least squares mean ± SD			
Baseline	161.6±9.5	160.6±9.2	168.4±8.5
After 24 weeks	134.7±5.0	106.4±5.2	102.6±9.7
% Change from baseline	-16.65	-33.74	-39.1
HDL, mg/dL			
No. of patients	70	70	70
Least squares mean ± SD			
Baseline	44.7±2.1	45.6±1.9	47.6±2.8
After 24 weeks	47.1±2.1	51.6±2.5	54.6±1.9
% Change from baseline	5.34	13.15	14.71
LDL, mg/dL			
No. of patients	70	70	70
Least squares mean ± SD			
Baseline	124.5±3.0	123.6±3.8	125.6±4.2
After 24 weeks	119.7±2.7	134.2±2.9	135.8±3.8
% Change from baseline	-3.81	8.57	8.1
TC, mg/dL			
No. of patients	70	70	70
Least squares mean ± SD			
Baseline	198.2±7.4	199.5±6.8	197.5±7.5
After 24 weeks	193.5.5±7.7	208.9±7.9	202.3±8.1
% Change from baseline	-2.3	4.71	2.4

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

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