EFFICACY OF ROSIGLITAZONE WITH GLIBENCLAMIDE AND METFORMIN COMBINATION IN TYPE 2 DIABETES

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ABSTRACT

The study was undertaken to evaluate the clinical efficacy and safety of rosiglitazone in patients with type 2 diabetes mellitus (DM) who were poorly controlled, despite optimum doses of glibenclamide and metformin. Ninety four patients with type 2 DM (mean age 51.2 years; mean body mass index (BMI) 25.54 kg/m^2) were enrolled in an open label trial. Patients were given rosiglitazone 4 mg twice a day in addition to glibenclamide and metformin, for a duration of six months.

Rosiglitazone 4 mg twice day, when added to glibenclamide and metformin, significantly decreased hemoglobin A_{1c} and fasting plasma glucose at six months from baseline, by - 0.94 % ($p < 0.0001$) and 81.95 mg/dl ($p < 0.0001$) respectively. Rosiglitazone was well tolerated throughout the study period. Rosiglitazone improved glycemic control when given as a third option drug in addition to glibenclamide and metformin in patients with type 2 DM and was well tolerated. Edema feet and weight gain were common side effects.

KEYWORDS: Peroxisome proliferator–activated receptor- γ (PPAR); Rosiglitazone; Thiazolidinedione; Type 2 diabetes mellitus; Triple drug therapy.

INTRODUCTION

Type 2 DM is often characterized by hyperglycemia as a result of increased insulin resistance and pancreatic β-cell dysfunction (1–3). Improved glycemic control is associated with reduction in long-term microvascular complications (4) and improved survival rates (5).

Monotherapy with sulphonylureas or biguanides is often insufficient to sustain glycemic control, indicating a need for a combination of these agents (6,7). However, many patients continue to experience sub optimal control, with ultimate recommendation to begin insulin injection therapy (8–10). Thiazolidinediones, a new class of oral antidiabetic agents, reduce hyperglycemia by decreasing insulin resistance in peripheral tissues (3,11). They act by binding to the peroxisome proliferator – activated receptor - γ (PPAR – γ) (12) and altering expression of component that influences insulin signaling and glucose transport systems (3).

Studies have shown that thiazolidinediones, used as monotherapy (13,14) or in combination with either sulphonylureas (15) or with metformin (16), improve glycemic control. However, in all these clinical situations, cheaper, safer and more effective alternatives are available. The addition of an insulin sensitizing agent troglitazone, to compliment the insulin stimulatory and hepatic glucose suppressive effects of sulphonylurea and metformin was tried as an attractive therapeutic alternative to insulin, before troglitazone was withdrawn from the market (17). The current trial was conducted to determine whether the addition of a thiazolidinedione, rosiglitazone, could decrease hemoglobin A_{1c} and fasting plasma glucose levels and delay or eliminate the need for insulin treatment in patients who did not achieve adequate glucose control, despite combined therapy with optimum doses of glibenclamide and metformin.

In India, the experience with thiazolidinediones is limited, as troglitazone was never introduced for clinical use and rosiglitazone and pioglitazone have been introduced only two years ago.

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PATIENTS AND METHODS

The efficacy of rosiglitazone was assessed in a unicentric open label trial. Indian men and women aged 40 – 70 years, BMI 22 – 35 Kg/m^2 with stable body weight and type 2 DM for at least over one year, with high HbA_{1c} levels of $\geq$ 8 % and FPG of $\geq$ 180 mg/dl, despite optimum doses of glibenclamide (15 mg per day) and metformin (1500 mg per day) for at least three months, were eligible for recruitment. Patients with clinically significant renal disease, New York Heart Association (NYHA) class III / IV coronary insufficiency or congestive heart failure, symptomatic diabetic neuropathy, past or present hepatic disease, ketonuria, active infections and women of child bearing potential were excluded. All subjects signed an informed consent before participation in the study. The institutional ethical committee approved the protocol. The study was conducted in accordance with the Declaration of Helsinki.

Patients who met the inclusion criteria were invited to participate in the study. At the beginning of the study, a complete history, physical examination, history of other pharmacological agents, blood pressure measurements, WHR and BMI were noted. A twelve lead ECG was recorded at baseline and after six months. Clinical chemistry was performed on fasting samples on Technicon, Ames, RA-50 Chemistry Autoanalyzer with strict quality control. Fasting plasma glucose was estimated at baseline and at each monthly visit by glucose oxidase method. Liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were estimated at baseline, at one month, two months and six months. HbA_{1c} was estimated at baseline and at three and six months by cation exchange resin method. Hematological parameters and serum creatinine were measured at baseline and at six months. At each monthly visit, physical examination was carried out. Body weight and history of adverse events were noted. Self-monitoring of blood glucose levels was encouraged. At the end of the study, body weight, BMI and WHR were recorded.

Patients were given fixed dose of rosiglitazone 4 mg twice a day for six months in addition to glibenclamide and metformin. During this study period no increase in doses of glibenclamide and metformin were allowed. However a decrease in glibenclamide dose was made, as suggested by Schwartz et al. (1), when patients had a fasting plasma glucose concentration below 90 mg/dl at one office visit, a concentration of 90 to 110 mg/dl on two consecutive office visits or a concentration of < 100 mg/dl on two consecutive days during self monitoring at home. Investigations like lipid parameters, serum insulin and C-peptide were not measured due to financial constraints. There was no control group with placebo therapy as the ethical committee did not feel it rational to keep the control group being exposed to hyperglycemia for six months.

At the end of the study, patients were classified as responders if the FPG was $\leq$ 110 mg/dl and HbA_{1c} $\leq$ 7.0% and rest were the non-responders.

Statistical Analysis: Statistical analysis was performed using Minitab Release 11.2, 1996 and Stata 7.0 statistical packages. Student 't' test was used to compare continuous variables (paired 't' test for paired data and two-sample 't' test for unpaired data). X^2 test was used for comparing categorical variables. Multiple logistic regression analysis was performed to determine the variables significantly associated with responders. 95% confidence interval (CI) and odd's ratio were computed whenever applicable. The analysis of efficacy was performed according to the intention–to-treat method and included all patients who received at least one dose of rosiglitazone and had at least one follow up visit. The last observation for patients was carried forward to impute missing values. The safety analysis also included all patients. Data are presented as mean $\pm$ SD. A p value < 0.05 was considered statistically significant.

RESULTS

Of the 94 subjects recruited, 85 subjects completed the study. Among those patients excluded, two withdrew because of lack of efficacy, four were lost to follow up, two withdrew because of edema feet and in one patient, rosiglitazone was withdrawn as his AST and ALT were raised after one month of therapy to three times of the normal values. Among those patients excluded, five were males and four were females.

Table 1: Baseline Characteristics (intention-to-treat population)

n	94
Age (years)	51.2 ± 7.6
Sex	
Male	38
Female	56
Duration of Diabetes (years)	5.62 ± 3.32
BMI (Kg./m²)	25.54 ± 3.12
WHR	0.92 ± 0.05
Body Weight (Kg.)	65 ± 10.6
Baseline Fasting Plasma Glucose (mg/dl)	199 ± 24.3
Baseline HbA_{1c} (%)	8.17 ± 0.2

Data are Mean ± SD

The clinical baseline characteristics at recruitment of the 94 subjects are summarized in table 1. There was a significant decrease in HbA_{1c} at six months compared with baseline from a mean 8.17% to 7.22%, 95% CI= 0.855 –1.032 ($p < 0.0001$) (Fig. 1). 48 patients (51.1%) achieved HbA_{1c} of ≤ 7 %. There was a significant decrease in fasting plasma glucose compared with baseline by 81.95 mg/dl, 95% CI= 4.15-4.95 ($P < 0.0001$), beginning at one month and reaching maximal effects at six months (Fig 1), 48 patients (51.1 %) achieved FPG ≤ 110 mg/dl at six months, and 46 patients (48.9%) patients could be classified as responders.

There was a significant increase in mean body weight by 2.12 kg ($p < 0.0001$) and mean BMI 1.12 kg/m² ($P < 0.0001$) at the end of the study. There was no significant change in waist to hip ratio ($p < 0.13$).

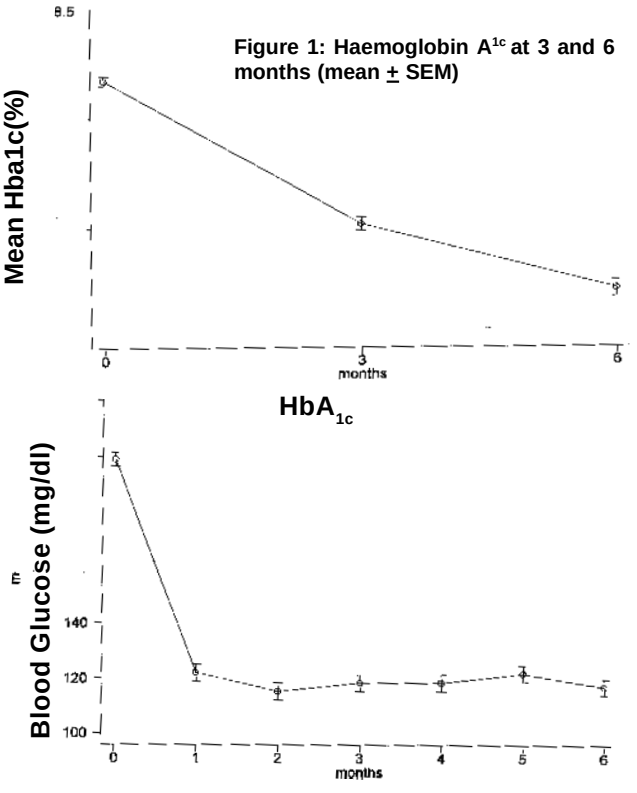
Rosiglitazone was well tolerated throughout the study. There was a slight drop, in hemoglobin and haematocrit values at six months, but the fall was not statistically significant. There were no clinically significant changes in the electrocardiograph recordings. Overall, 66% reported one or more adverse events during the study. The most common adverse events were flatulence 34 %, pain in legs 25.5%, constipation 19.1%, headache 17%, cough 12.8%, itching 11.7%, chest pain 7.4%, infections 2.1% These adverse events were not considered to be related to study medication. There were no significant changes in physical examination or electrocardiograph recordings in these patients.

Transient elevations, greater than 1.5 times the upper limit of normal in AST and ALT levels were not observed in any of the patients during the study except one. He was withdrawn from the study as his AST and ALT levels were raised three times the normal values. Eighteen patients (19.1%) experienced edema feet. No adverse changes in renal functions were evident during the study.

Symptoms associated with hypoglycemia were reported by ten patients (10.6%) patients. Most patients who reported hypoglycemia experienced only one episode. In two cases hospitalization was required with third party intervention and there was documented plasma glucose level of < 35 mg/l.

The mean dose of glibenclamide decreased at six months by 1.98 mg/day ($P < 0.0001$). In 9.6% of patients the dose of glibenclamide decreased by ≥ 50% and in one patient glibenclamide had to be completely stopped. There was no change made in the dose of metformin during the study.

Fig 1: HbA_{1c} and Fasting Blood Glucose Levels over Six Months



DISCUSSION

Our study provides evidence supporting the use of a thiazolidinedione, rosiglitazone in patients of type 2 DM with inadequate glycemic control, despite treatment with optimum doses of glibenclamide and metformin. The triple drug therapy method used in this study demonstrated early and sustained reductions in fasting glucose levels, followed more slowly by similar reductions in hemoglobin A_{1c} levels. Previous study using troglitazone as a third drug after sulphonylurea and metformin had shown similar glycemic efficacy (2).

In the present study, the sample studied was significantly hyperglycemic, as evident by the mean baseline hemoglobin A_{1c} level of 8.17% and mean fasting plasma glucose level of 199 mg/dl. A significant number of patients 51.1% achieved hemoglobin A_{1c} level of $\leq$ 7% and fasting plasma glucose of $\leq$ 110 mg/dl. The six-month duration of the study was intended to provide sufficient exposure to demonstrate the maximal therapeutic effect, as assessed by reduction in hemoglobin A_{1c} levels and fasting plasma glucose levels. Patients who did not meet these therapeutic goals despite the addition of rosiglitazone, eventually required the initiation of insulin therapy. 10.6% of patients treated with rosiglitazone during this study reported symptomatic hypoglycemia. Two patients had neuroglycopenia and required emergency treatment in the hospital with documented plasma glucose level of < 35 mg/dl. The incidence of reported hypoglycemia was evenly distributed over the entire six months, suggesting that hypoglycemic symptoms are not directly associated with the initiation of rosiglitazone therapy. Rosiglitazone is capable of reducing glucose levels when used in combination with an insulin secretagogue. Concurrent decrease in insulin secretagogue therapy is warranted when patients experience frank hypoglycemia or sustained reduction in plasma glucose levels. In the present study the mean dose of glibenclamide had to be decreased from 15 mg/day by 1.98 mg/day ($P < 0.0001$). In one patient glibenclamide had to be totally stopped by the end of the study, and in nine patients the dose of glibenclamide was decreased by $\geq$ 50%. Metformin doses were not altered.

We also tried to assess the responders and their relationship with the other clinical characteristics such as age, sex, duration of diabetes, body weight, BMI, WHR, baseline FPG and HbA_{1c}. However, we did not find any significant correlation of these clinical characteristics with responders except for significant association of responders with females. Among 38 males, 14 (36.8%) responded, while from 56 females 32 (57.1%) responded ($p < 0.05$). Our findings suggest that females were better responders than males. Similar findings have been reported by J. Patel et al. (3). They had also found that patients with BMI > 27 kg/m^2 responded better than those with BMI of < 27 kg/m^2.

The significant weight gain observed in the present study may be attributed to increased adipocyte differentiation (4,5), fluid retention (4,6) or increased appetite (7). Despite increase in body weight and BMI no significant differences in waist to hip ratio were observed, suggesting that rosiglitazone treatment leads to increased energy storage in the subcutaneous adipocytes (8). In type 2 DM, weight gain is usually associated with worsening of insulin resistance and deterioration in glycemic control. In the present study, six months of rosiglitazone treatment was associated with weight gain of 2.11 kgs. Despite the weight gain, there was an improvement in glycemic control. Improved glycemic control, despite weight gain, has been reported with other thiazolidinediones, including rosiglitazone (3,9). Binding of thiazolidinediones to the PPAR-γ receptor causes preadipocytes to differentiate into mature small adipocytes and induces lipogenesis, explaining the increase in body weight (5,10). Although PPAR-γ receptors are present in visceral adipose tissue in humans, they do not seem to be activated by thiazolidinediones (11). It is the increased visceral fat that is associated with increased insulin resistance and cardiovascular risk (8,12). The rosiglitazone associated weight gain is associated with increased subcutaneous fat and a simultaneous decrease in visceral abdominal fat, as has been reported by Kelly et al. (13). Thus explaining the improvement in insulin sensitivity and glycemic control despite weight gain. In the present study, the weight gain in 9.6% patients was $\geq$ 5 kgs; the maximum being 6 kgs in 7.4%. In 20.2% of patients there was no weight gain. None of the patients lost any weight during the study period. The long-term effects, of the increased body weight, on metabolic and cardiovascular outcomes remain to

be determined. It is therefore, very important, to emphasize diet therapy and exercise in patients with type 2 DM being treated with thiazolidinediones. The small decreases in hemoglobin and haematocrit levels have been described with rosiglitazone therapy which may relate to plasma volume expansion derived from fluid retention and haemodilution (14). However, we did not find any statistically significant decrease in hemoglobin or haematocrit at six months from baseline. Edema feet were found to be common side effect of thiazolidinedione therapy and are attributed to fluid retention (4,6). In the present study, 18 (19.1%) patients experienced edema feet; two patients withdrew (both females) from the study because of disturbing pedal edema.

We did not find any significant hepatotoxicity with rosiglitazone therapy except in one patient who developed a rise in ALT and AST enzymes, three times the normal values, within one month of initiation of rosiglitazone and the drug had to be withdrawn. The serum enzymes returned to normal after one month of withdrawal of rosiglitazone. There was no rise in serum bilirubin level. However, a repeat challenge dose of rosiglitazone was not given. It is therefore mandatory to monitor AST and ALT closely in all patients receiving rosiglitazone.

Patients with type 2 diabetes mellitus are often treated according to a stepped progression regime, starting with a regimen of nutrition counseling and exercise and progressing to monotherapy with a sulphonylurea, metformin, or acarbose. As hyperglycemia worsens, combinations of oral agents are often required. When a combination of a sulphonylurea and metformin cannot achieve the treatment goals, insulin injections need to be initiated (15, 16).

Previous studies have shown that thiazolidinediones used as monotherapy (3, 17) or in combination with either sulphonylurea or metformin (18), improve glycemic control. However, in all these clinical situations, cheaper, safer and more effective alternatives are available.

Our study shows that a thiazolidinedione (rosiglitazone) is effective and well-tolerated when used as a third option drug with sulphonylurea (glibenclamide) and metformin. The addition of rosiglitazone may thus offer an alternative to insulin for patients with inadequate glycemic control despite treatment with a glibenclamide and metformin. As a result, a proportion of such patients may be able to reach target levels of hemoglobin A_{1c} and fasting plasma glucose levels. However, how long the improvement in the glycemic control lasts, needs to be evaluated by long term studies.

In a six months short trial, we have found rosiglitazone to be safe drug. However a more fundamental concern is that these PPAR– γ receptor agonists have far–ranging and unpredictable effects, extending well beyond those considered therapeutically desirable and including effects upon cell differentiation in many tissues (19). Their long-term consequences are therefore not known. In contrast, we have decades of experience with extensive use of sulphonylureas and metformin. It is therefore rational to use thiazolidinediones as a third option drug for type 2 diabetes rather than making it the first option drug.

It was earlier thought that it is indeed rather illogical to introduce thiazolidinediones in the later stages of clinical course of type 2 DM when there is significant β-cell dysfunction (20) and therefore it was suggested that these agents might be tried much earlier in the clinical course of type 2 DM, perhaps with combination of metformin (21). Our study has shown that rosiglitazone is effective even in later stages of clinical course of type 2 diabetes.

Our experience shows that rosiglitazone is effective in improving the glycemic control when added to a combination of glibenclamide and metformin in type 2 DM. In a significant number of patients the insulin therapy can be postponed with reduction in doses of glibenclamide. It is a relatively safe drug, but edema feet and weight gain are its unpleasant side effects. Rosiglitazone is a valuable addition to currently available oral antidiabetic agents.

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