EFFICACY OF PIOGLITAZONE AS AN ADD ON DRUG WITH INSULIN, Glibenclamide AND METFORMIN IN PATIENTS WITH UNCONTROLLED TYPE 2 DIABETES MELLITUS

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SUMMARY

The aim of the study was to evaluate the clinical efficacy and safety of pioglitazone in patients with poorly controlled type 2 diabetes mellitus (DM), despite treatment with insulin and a combination of glibenclamide and metformin. Fifty-seven patients with type 2 DM, mean age 56.84 years and mean body mass index (BMI) 26.30 kg/m², were enrolled in this unicenter open label trial. They were given pioglitazone 30 mg/day in addition to previous treatment with insulin (≥30 units a day), glibenclamide (10 mg a day) and metformin (1000 mg a day) for a period of six months. Pioglitazone 30 mg/day, when added to insulin and the combination of glibenclamide and metformin, significantly decreased hemoglobin A1c at six months from a mean of 8.15%±0.24 to a mean of 7.17%±0.42 (p<0.0001) and fasting plasma glucose at six months from a mean of 209.3±32.43 mg/dl to 115.14±36.94 mg/dl (p<0.0001). Pioglitazone was well tolerated throughout the study period. Pioglitazone was found to improve glycemic control, when given as a fourth drug (quadruple drug therapy) in addition to insulin and the combination of glibenclamide and metformin in patients with type 2 DM. Foot edema and weight gain were common side effects. In a significant number of patients, insulin therapy could be stopped, and in the rest the dose of insulin and glibenclamide could be reduced.

INTRODUCTION

Chronic hyperglycemia in patients with type 2 diabetes mellitus (DM) occurs because of resistance to the action of insulin and decreasing insulin secretion. Insulin resistance is a prominent feature, if not the primary defect. In some of these patients, insulin-stimulated uptake of glucose is decreased by 60% to 80% (1). Patients with type 2 diabetes are often treated according to a stepped progression, starting with a regimen of nutrition and exercise, and progressing to sulphonylurea, metformin and acarbose alone or in combination. These therapies are often ineffective. The longer the diabetes has been present, the more likely the patients are to require insulin to control their hyperglycemia (2,3). Despite insulin treatment, often in high doses, hyperglycemia in these patients is not well controlled (2). In UKPDS (4), glycemic control deteriorated continuously, even in intensively treated patients with type 2 diabetes.

In order to reduce insulin dose in type 2 diabetes, various studies have been carried out using combination therapies with insulin and sulphonylureas (5,6), insulin and metformin (7,8) and insulin in combination with sulphonylureas and metformin (9-11). The insulin sparing effect of the two drugs, sulphonylurea and metformin, in addition to insulin was 62%, i.e., 1.5- to 2.0-fold effect achieved by the regimens combining either metformin alone or sulphonylurea alone with insulin (9-13).
Thiazolidinediones, a new class of oral antidiabetic agents, reduce hyperglycemia by decreasing insulin resistance in peripheral tissues (1,14). They act by binding to the peroxisome proliferator-activated receptor-γ (PPAR-γ) (15) and altering expression of the component that influences the insulin signaling and glucose transport systems (1). Glitazones, when added to previous insulin treatment, have improved glycemic control in patients with type 2 diabetes (16-18). In India, the experience with thiazolidinediones is limited, as troglitazone was never introduced for clinical use and rosiglitazone and pioglitazone have been introduced for the last two years.

The current trial was conducted to determine whether the addition of a glitazone, pioglitazone, could improve the glycemic control in patients with uncontrolled type 2 DM despite therapy with insulin combined with glibenclamide and metformin.

SUBJECTS AND METHODS

The efficacy of pioglitazone was assessed in a unicenter open label trial. Indian men and women aged 40-70 years, body mass index (BMI) 22-35 kg/m², with stable body weight and type 2 DM for at least over one year, high hemoglobin A1c (HbA1c) levels of ≥8% and fasting plasma glucose of ≥180 mg/dl were included. Patients who were poorly controlled despite combination treatment with glibenclamide (10 mg a day) and metformin (1000 mg a day) along with twice a day insulin therapy (≥30 units a day) for over 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 protocol was approved by the institution ethics committee. The study was conducted in accordance with the Declaration of Helsinki.

Patients who met the inclusion criteria were invited to participate in the study. In the beginning, a complete history and physical examination were carried out. A twelve lead electrocardiogram (ECG) was recorded at baseline and after six months. Clinical chemistry was performed on fasting samples on a Technicon Ames RA-50 chemistry autoanalyzer with strict quality control. Fasting plasma glucose was estimated at baseline and each monthly visit, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were estimated at baseline, one month, two months and six months, and HbA1c was estimated at baseline and three and six months. Hematologic parameters and serum creatinine were measured at baseline and six months. Self monitoring of blood glucose levels was encouraged.

Patients were given a fixed dose of pioglitazone 30 mg once a day for six months, in addition to insulin, glibenclamide and metformin. During the study period, no increase in the dosage of insulin, glibenclamide and metformin were allowed. However, a decrease in the dose of insulin and glibenclamide, if required, were made when patients had 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 (16). Investigations like lipid parameters and C-peptide were not performed due to financial constraints. There was no control group with placebo therapy as the ethics committee did not feel it rational to expose the control group to hyperglycemia for six months. At the end of the study, patients were classified as responders if fasting plasma glucose was ≤110 mg/dl and HbA1c ≤7.0%, and the rest were nonresponders.

Statistical analysis

Statistical analysis was performed using Minitab Release 11.2, 1996 and Stata 7.0 statistical packages. Student's t-test was used to compare continuous variables (paired t-test for paired data and two-sample t-test for unpaired data). The χ²-test was used to compare categorical variables. Multiple logistic regression analysis was performed to determine the variables significantly associated with responders. The 95% confidence interval (CI) and odds 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 pioglitazone 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 ± SD. A p value <0.05 was considered statistically significant.
RESULTS

Of the 57 subjects recruited, 52 subjects completed the study. Among the patients excluded, three were lost to follow up, one withdrew because of severe foot edema, and in one patient pioglitazone was withdrawn as he developed jaundice.

Clinical characteristics of the 57 subjects at recruitment are summarized in Table 1. There was a significant decrease in HbA1c at six months from a mean of 8.15% ± 0.24 to 7.17% ± 0.42 (p<0.0001) (Fig. 1); 30 (52.63%) patients achieved HbA1c ≤7%. There was a significant decrease in fasting plasma glucose at six months from a mean of 209.3 mg/dl ± 32.43 to 115.14 mg/dl ± 36.94 (p<0.0001), beginning at one month and reaching maximal effects at six months (Fig. 2); 24 (42.10%) patients achieved fasting plasma glucose of ≤110 mg/dl. There were 21 (36.84%) patients who could be classified as responders, who achieved both fasting plasma glucose ≤110 mg/dl and HbA1c ≤7%.

There was a significant increase in the mean body weight by 2.43 kg (p<0.0001) and BMI by 0.64 kg/m² (p<0.0005). There was no significant change in WHR. Pioglitazone was well tolerated throughout the study. There was a slight drop in hemoglobin and hematocrit values at six months but the fall was not statistically significant. There were no clinically significant changes in ECG recordings. Transient elevations greater than 1.5 times the upper limit of normal AST and ALT levels were not observed in any but one study patient. Nineteen (33.33%) patients experienced foot edema. No adverse changes in renal function were evident during the study. Symptoms associated with hypoglycemia were reported by 13 (22.80%) patients. Most patients who reported hypoglycemia experienced one episode. In two cases hypoglycemia was severe enough to require hospitalization with third party intervention, and there was a documented plasma glucose level <35 mg/dl.

The mean dose of insulin decreased during the study from 35.51 ± 9.93 units per day to 20.0 ± 9.6 units/day at six months (p<0.0001). The frequency of insulin injections decreased from a mean of 2.05 ± 0.22/day to 1.18 ± 1.05/day (p<0.0001). In 24 (42.10%) patients insulin had to be totally stopped. The mean dose of glibenclamide significantly decreased from 10.35 ±1.29 to 9.47±1.69 mg/day (p<0.0005). In six (10.52%) patients the dose of glibenclamide decreased

| Table 1. Baseline characteristics (intention-to-treat population) |
|-----------------|-----------------|
| **N**           | 57              |
| **Age (yrs)**   | 56.84 ± 7.81    |
| **Sex**         |                 |
| Male            | 21              |
| Female          | 36              |
| **Diabetes duration (yrs)** | 9.75 ± 5.47   |
| **BMI (kg/m²)** | 26.30 ± 4.15    |
| **WHR**         | 0.92 ± 0.08     |
| **Body weight (kg)** | 65.11 ± 11.79  |
| **Fasting plasma glucose (mg/dl)** | 209.3 ± 32.43 |
| **HbA1c (%)**   | 8.15 ± 0.24     |

Data are mean ± SD

Figure 1. Decrease in mean HbA1c (%) (mean ± SEM)

Figure 2. Decrease in mean fasting plasma glucose (mean ± SEM)
by ≥50%. There was no change in the dose of metformin during the study.

DISCUSSION

In the present study, the study sample was significantly hyperglycemic, as evident by the mean baseline HbA1c level of 8.15% and fasting plasma glucose level of 209.3 mg/dl. A significant number of patients (n=30; 52.63%) achieved HbA1c level of ≤7%. Similarly, 24 (42.1%) patients achieved a fasting plasma glucose of ≤110 mg/dl. The 6-month duration of the study was intended to provide a sufficient exposure to demonstrate the maximal therapeutic effect, as assessed by reduction in the HbA1c and fasting plasma glucose levels. Our study has provided evidence supporting the use of pioglitazone as an add on drug in type 2 diabetes patients with inadequate glycemic control despite the treatment with insulin and combination doses of glibenclamide and metformin. The quadruple drug therapy used in the study demonstrated early and sustained reductions in fasting glucose levels, followed more slowly by similar reductions in HbA1c levels. A previous study using troglitazone as a third drug after sulphonylurea and metformin showed similar glycemic efficacy (19).

In this study, ten (22.8%) patients treated with pioglitazone reported symptomatic hypoglycemia. Two patients had neuroglycopenia and required emergency treatment. The incidence of reported hypoglycemia was evenly distributed over the entire 6-month study period, suggesting that hypoglycemic symptoms are not directly associated with the initiation of pioglitazone therapy. Pioglitazone therapy can lead to hypoglycemic episodes when used in combination with insulin or insulin secretagogue. Concurrent decrease in insulin doses and insulin secretagogue therapy is warranted when patients experience frank hypoglycemia or sustained reduction in plasma glucose levels. In the present study there was a significant reduction in the insulin requirement as well as in the frequency of insulin injections, and a decrease in the mean dose of glibenclamide. Insulin therapy had to be totally stopped in 24 (42.10%) patients, and the addition of pioglitazone led to insulin sparing by 56.32%.

We also tried to assess the responders and their relationship with other clinical characteristics such as age, sex, duration of diabetes, body weight, BMI, WHR, baseline fasting plasma glucose and HbA1c. However, we did not find any significant correlation of these characteristics with responders except for a significant association of responders with female sex (p<0.005). The excess of adipose tissue in females could be the possible explanation. Similar findings have been reported by Patel et al. (20). They also found that patients with BMI >27 kg/m² responded better than those with BMI <27 kg/m².

The significant weight gain observed in the present study may be attributed to increased adipocyte differentiation (21,22), fluid retention (21,23) or increased appetite (24). Improved glycemic control, despite weight gain, has been reported with thiazolidinediones (20,25-27). Thiazolidinediones associated weight gain is due to increased subcutaneous fat and a simultaneous decrease in visceral abdominal fat, as reported by Kelly et al. (28). In the present study, weight gain in 10 patients was ≥5 kg, maximum 13 kg in two patients. In 19 patients there was no weight gain. There was no weight loss in any of the study patients during the study period. Small decreases in hemoglobin and hematocrit levels have been described with pioglitazone therapy, which may relate to plasma volume expansion derived from fluid retention and hemodilution (29). However, we did not find any statistically significant decrease in hemoglobin or hematocrit at six months from baseline. Foot edema was found to be a common side effect of thiazolidinedione therapy and is attributed to fluid retention (21,23). In the present study, 19 (33.33%) patients experienced foot edema. One female patient withdrew from the study because of disturbing pedal edema.

We did not find any significant hepatotoxicity with pioglitazone therapy, however, one patient developed jaundice within one month of starting pioglitazone and the drug had to be withdrawn. This 40-year-old male was further investigated, his sonography was normal and hepatitis markers for hepatitis A, B, C were negative. His hepatitis E IgM value was significantly raised. The patient made an uneventful recovery in two months, with return of serum bilirubin, alkaline phosphatase and ALT, AST values to normal. It was thought to be a case of viral hepatitis (HEV), a common infection in India (30,31), rather than a pioglitazone induced hepatitis. Yet, the challenge dose of pioglitazone was not given.

Patients with type 2 DM are often treated according to a stepped progression, 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 (32,33). However, most patients with type 2 DM who are treated with insulin remain uncontrolled despite the increase in insulin doses (2).

Our study showed that pioglitazone was effective and well tolerated when used as a fourth drug with sulphonylurea (glibenclamide), metformin and insulin. The addition of pioglitazone reduced the requirement of insulin and glibenclamide. As the result, a proportion of such patients treated with quadruple drug therapy were able to reach target HbA1c ≤7.0% and fasting plasma glucose levels ≤110 mg/dl. Insulin therapy had to be discontinued in 24 (42.10%) patients, and in the rest the insulin dosage was significantly reduced.

Previous studies have shown that thiazolidinediones, used as monotherapy (26,34) or in combination with either sulphonylureas (35), metformin (36) or insulin (17-19), improve glycemic control in type 2 DM. However, in all these clinical situations, less expensive, safer and more effective alternatives are available.

Although in this short, 6-month trial we found pioglitazone to be a safe drug, its longterm consequences are not known (37). In contrast, we have decades of experience with the extensive use of sulphonylureas and metformin. It is therefore rational to use thiazolidinediones either as a third drug for type 2 DM, after sulphonylurea and metformin, or a fourth drug in patients on insulin and combination of sulphonylurea and metformin, rather than making it the first option drug in therapy of type 2 DM.

It was earlier thought that it is indeed rather illogical to introduce thiazolidinediones in later stages of the clinical course of type 2 DM, when there is a significant β-cell dysfunction (38). It has therefore been suggested that these agents might be tried much earlier in the clinical course of type 2 DM, perhaps in combination with metformin (39). Our study has shown that pioglitazone is effective even in later stages of the clinical course of type 2 DM and can be an add on drug for uncontrolled type 2 DM, administered along with insulin and a combination of sulphonylurea and metformin.

CONCLUSION

Our study has shown that pioglitazone is effective in improving the glycemic control when added to a combination of insulin, glibenclamide and metformin in type 2 DM. In a significant number of patients, insulin therapy could be stopped and in the rest the dosage of insulin and glibenclamide could be reduced. Pioglitazone is a relatively safe drug, but foot edema and weight gain are of great concern to both the patient and the treating physician. Pioglitazone is a valuable addition to the currently available oral antidiabetic agents.

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