Beneficial Effects of Triple Drug Combination of Pioglitazone with Glibenclamide and Metformin in Type 2 Diabetes Mellitus Patients on Insulin Therapy

Vijay Panikar*, HB Chandalia, Shashank R Joshi***, Ami Fafadia+, C Santvana++**

Abstract

Background : The thiazolidinediones are a class of antidiabetes medication that enhance the actions of insulin in muscle, liver, and adipose tissue. Data have been lacking on their use in combination with both sulfonylurea and metformin among patients of type 2 diabetes who are on insulin therapy secondary to failure of routine oral hypoglycemic drugs in controlling their diabetes.

Objective: To determine the effects of pioglitazone in combination with sulphonylurea and metformin on diabetes control in patients being treated with insulin due to secondary failure of oral hypoglycemic agents.

Patients : One hundred and twenty-four consecutive type 2 diabetes patients (mean age, 57.13 years) attending four centres in Mumbai, who were being treated with insulin were selected. They were switched on to triple drug combination of glibenclamide 5 mg, metformin 500 mg and pioglitazone 15 mg along with insulin. Study participants were required to have type 2 diabetes mellitus for atleast 5 years. Patients were excluded if they had any of the following: serum creatinine concentration greater than 1.5 mg/dl, alanine aminotransferase (ALT) level more than two times the upper limit of normal, symptomatic angina, cardiac insufficiency or history of myocardial infarction.

Results: Pioglitazone 15 mg with glibenclamide 5 mg and metformin 500 mg, significantly decreased hemoglobin HbA_{1c} level from 11.5% to 7.32% ($P < 0.001$), average fasting blood glucose from 194.8 mg/dl to 124.06 mg/dl ($p < 0.01$), average post-prandial blood glucose from 256.24 to 162.32 mg/dl ($p < 0.01$). At 6 months, 43.35% of patients did not need to be continued on insulin. The total insulin requirement in 124 patients reduced by 71.81%. There were no significant side effects, liver enzymes were within acceptable levels, average weight gain was 2.23 kg, significant hypoglycemia was observed in 28 patients with two requiring hospitalisation, these patients were those who did not stick to follow-up schedules.

Conclusions : With proper patient selection, pioglitazone with glibenclamide and metformin can be safely used in patients receiving insulin with good results.

INTRODUCTION

Type 2 diabetes mellitus is characterised by the presence of insulin resistance with concomitant or eventual beta cell dysfunction. Resistance to insulin-stimulated glucose uptake is present in most patients with this disease.[1] Treatment is aimed at reducing blood glucose levels to normal or near-normal values.[2,3] Diet and exercise are the first treatments of choice for patients with type 2 diabetes mellitus. However, when they do not achieve adequate blood glucose[4] control initiation with oral antidiabetes therapy is then advocated.

First-line monotherapy typically begins with sulfonylurea (an insulin secretagogue) or metformin, which inhibits hepatic gluconeogenesis.[5] When monotherapy fails, these agents are frequently prescribed in combination.[6] However, when patients continue to experience suboptimal control on maximum doses of these drugs insulin therapy has to be initiated.[7,8]

*Department of Diabetes, Lilavati Hospital and KJ Somaiya Medical College. **Department of Diabetes, Jaslok Hospital, Breach Candy Hospital, ***Department of Diabetes, Lilavati Hospital and Department of Medicine, Grant Medical College; + Department of Diabetes, Lilavati Hospital'; ++Department of Medicine, KJ Somaiya Medical College and Hospital; Mumbai.
Received : 14.1.2003; Revised : 12.4.2003; Re-revised : 18.8.2003 ; Accepted : 12.9.2003

Thiazolidinediones are a class of peroxisome proliferator-activated receptor drugs that, unlike sulfonylureas and metformin, stimulate increased peripheral glucose disposal and reduce insulin resistance in the muscle, liver, and adipose tissue.[9-12] Studies have shown that pioglitazone used as monotherapy or in combination with sulfonylurea and metformin improves glucose control.[13-15] The addition of an insulin-sensitizing agent, such as pioglitazone, to complement the insulin-stimulatory and hepatic glucose-suppressive effects of sulfonylurea and metformin has been considered an attractive therapeutic alternative to insulin. However, the use of triple drug combination of pioglitazone, sulphonylurea and metformin in patients already on insulin therapy has not been studied. Whether a thiazolidinedione would be efficient at a stage of the disease when beta-cell secretion is failing[16] remains to be demonstrated.

The current study with triple drug therapy was undertaken to see the its effect in glycemic control in patients of type 2 diabetes mellitus who were already on insulin.

Methods And Materials

Patients : 124 consecutive type 2 diabetes patients (mean age, 57.13 years) males 58 and females 66 attending four centres in Mumbai, who were being treated with insulin were selected. They were switched on to triple drug combination of glibenclamide 5 mg, metformin 500 mg and pioglitazone 15 mg along with insulin, if they met the inclusion and exclusion criteria.

The criteria for inclusion/exclusion were:

1. Duration of type 2 diabetes mellitus of atleast five years and being treated with insulin were selected.
2. Patients with any cardiac abnormality, including history of symptomatic angina, cardiac insufficiency or history of myocardial infarction or an abnormal ECG were not included in the study.
3. Patients with known renal failure or increased serum creatinine levels >1.5 mg/dl were not included in the study.
4. Patients with SGOT/SGPT more than two times the upper limit of normal were not included in the study.
5. Patients having more than 60 ml alcohol/day were not included.

One hundred and twenty-four patients who met the inclusion criteria had their baseline ECG, fasting and post-prandial blood sugars, HbA_{1c}, SGOT, SGPT, creatinine and lipid profile were done. They were then treated with pioglitazone 15 mg/d and glibenclamide 5 mg, metformin 500 mg three times a day in addition to insulin. They were advised to repeat their plasma glucose every three weeks and report for follow-up. They were educated regarding hypoglycemia and were to report it telephonically if they experienced it before their follow-up date.

Fasting and postprandial plasma glucose level and biochemical measures of safety, including chemistry tests (SGOT, SGPT), hematologic tests, were performed at 3-week intervals throughout the study. Self-monitoring of blood glucose level was encouraged, if the patients had blood glucose monitors. At every follow-up as the plasma glucose levels reduced, the insulin doses were appropriately titrated and reduced. Some patients who experienced hypoglycemia before the follow-up date were telephonically instructed to reduce their insulin doses. Once the patient was off insulin, and continued to show a fall in plasma glucose levels, glibenclamide was periodically reduced. The pioglitazone and metformin was continued in full doses except in a few patients who could not tolerate full doses of metformin.

Repeat measurements of HbA_{1c} levels were done at three months and six months.

Results

One hundred and twenty-four patients who had complete records of follow-up and completed six months of triple drug therapy were analysed. Twenty eight patients experienced significant hypoglycemia with two requiring hospitalisation. These patients were those who did not stick to follow-up schedules. Most patients reporting hypoglycemia, at any time, reported only one occurrence.

Mean values for HbA_{1c}, fasting and postprandial glucose and insulin requirement decreased significantly from baseline during the course of therapy for six months. The combination therapy at the end of six months significantly increased the proportion of patients achieving treat-to-target HbA_{1c} levels compared to earlier therapy. The average HbA_{1c} in 124 patients was reduced from 11.5% to 7.32% a reduction of 36.35% ($p<0.001$). The average fasting plasma glucose levels reduced from 194.8 mg/dl to 124.06 mg/dl, a reduction of 36% ($p<0.01$). The average postprandial plasma glucose levels reduced from 256.24 mg/dl to 162.32 mg/dl, a reduction of 36.65% ($p<0.01$) (Fig. 1).

The total insulin being taken by 124 patients prior to starting triple drug therapy was 4194 units/day. After six months of therapy the requirement of insulin dropped to 1182 units/day, a reduction of 71.81%. Further in 55(43.35%) patients insulin therapy was totally discontinued (Fig. 2).

Mean body weight at baseline and 6 months was 68.04 kg and 70.27 kg, (2.23 kg), respectively.

Triple drug therapy was well tolerated throughout the study. No patients withdrew from the study because of elevated ALT levels. Symptoms associated with hypoglycemia were reported by 28 patients with two requiring hospitalisation. No patient required intervention other than a snack or beverage. Many reports of hypoglycemic symptoms were associated with missed meals. No clustering of hypoglycemic events was associated with the start of therapy; instead, the incidence rates were fairly evenly distributed over the course of the study.

Discussion

Patients with type 2 diabetes mellitus are often treated according to a stepped progression, starting with a regimen

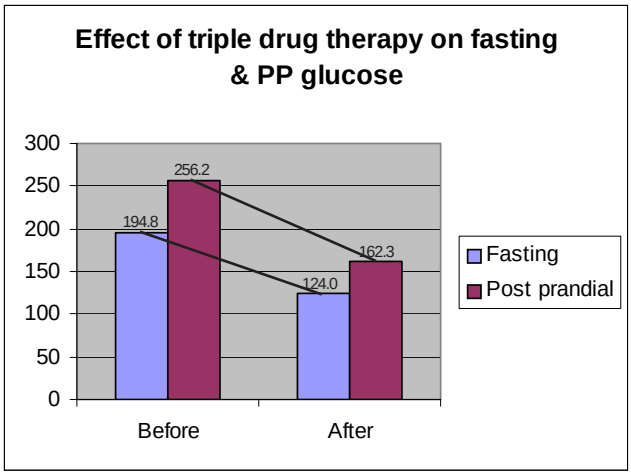

Fig. 1 : Effect of triple drug therapy on fasting and PP glucose

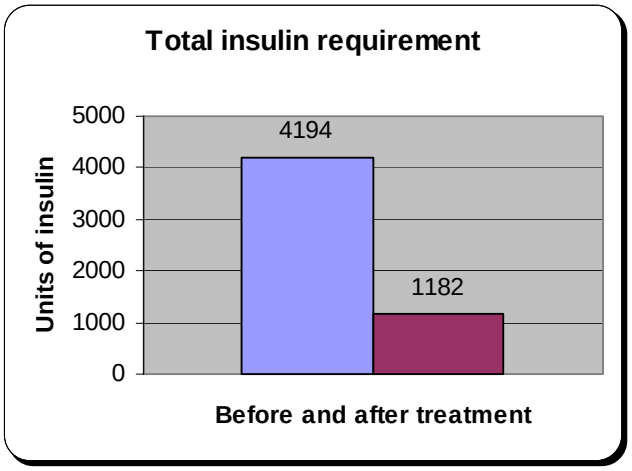

Fig. 2 : Effect of triple drug therapy on total insulin requirement

of nutrition counseling and exercise and progressing to monotherapy with a sulfonylurea, metformin, or acarbose. As hyperglycemia worsens, combinations of oral agents are often required. When a combination of a sulfonylurea and metformin cannot achieve the treatment goals, insulin injections must be initiated.[2,3]

Addition of an insulin-sensitizing agent, such as pioglitazone, to complement the insulin-stimulatory and hepatic glucose-suppressive effects of sulfonylurea and metformin has been considered an attractive therapeutic alternative to insulin. The triple drug combination could work synergistically in reducing insulin resistance, thereby reducing the requirements of insulin significantly. However, the use of triple drug combination of pioglitazone, glibenclamide and metformin in patients already on insulin therapy has not been studied. Our study provides evidence, supporting use of a triple drug therapy of glibenclamide 5 mg, metformin 500 mg and pioglitazone 15 mg in patients of type 2 diabetes as a therapeutic means of improving glycemic control in patients with inadequate glycemic control despite treatment with insulin.

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 HbA_{1c} levels. Inclusion criteria were specifically designed to test the effects of triple drug therapy in patients on insulin therapy, patients with cardiac or renal compromise were strictly not included.

The 71.81% reduction in total insulin dose, paralleled the reductions in glucose and HbA_{1c}. These findings suggest that the triple drug therapy is quite effective in improving insulin-mediated glucose utilization through increased insulin sensitivity.

The patients gained 2.23 kg, which may be explained in part by a decrease in glycosuria secondary to improved glycemic control and resultant caloric retention.

Pioglitazone and glibenclamide are also known to contribute to weight gain.

Twenty-eight patients reported occurrences of symptomatic hypoglycemia with two requiring hospitalisation. This happened in patients who did not stick to follow-up schedules as advised. Pioglitazone is capable of reducing glucose levels when used in combination with an insulin secretagogue and metformin, timely decrease in concurrent insulin therapy is warranted to avoid severe hypoglycemia or sustained activity-limiting hypoglycemic episodes.

With respect to hepatic events, the SGOT/SGPT levels showed marginal variations but never enough to warrant discontinuation of therapy as none of the patients had levels greater than 2.5 times the normal. Our study shows that a thiazolidinedione, pioglitazone, is effective and well tolerated when used in combination with sulfonylurea and metformin. The addition of a pioglitazone may thus offer an alternative to patients with inadequate glycemic control despite treatment with full doses of a sulfonylurea and metformin with or without insulin. As a result, a good proportion of such patients may be able to reach target levels of HbA_{1c}.

An important limitation of the study is to analyse the beta-cell reserve by estimating the c-peptide status. This subset is being seperately studied in another ongoing study. It appears that these patients were started on early insulin when probably either they had an adequate beta-cell reserve or after insulin therapy their beta-cell function had improved. It also highlights that either insulin or insulin sensitizers both may induce beta-cell rest in clinical situation.

REFERENCES

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-607.
2. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 1999;22(Suppl 1):S32-S41.
3. Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, *et al.* 1998 clinical practice guidelines for the management of diabetes in Canada. Canadian Diabetes Association. *CMAJ* 1998;159(Suppl 8):S1-29.

4. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 1995;310:83-8.
5. Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. *Diabetes Reviews* 1998;6:89-131.
6. Trischitta V, Italia S, Raimondo M, Guardabasso V, Licciardello C, Runello F, *et al*. Efficacy of combined treatments in NIDDM patients with secondary failure to sulphonylureas. Is it predictable? *J Endocrinol Invest* 1998;21:744-7.
7. Lardinois CK. Type 2 diabetes: glycemic targets and oral therapies for older patients. *Geriatrics* 1998;53:22-3.
8. Johnson M, Krosnick A, Carson P, McDade AM, Laraway K. A retrospective chart review of uncontrolled use of metformin as an add-on therapy in type 2 diabetes. *Clin Ther* 1998;20:691-8.
9. Piegelman BM. PPAR-: adipogenic regulator and thiazolidinedione receptor. *Diabetes* 1998;47:507-14.
10. Maggs DG, Buchanan TA, Burant CF, Cline G, Gumbiner B, Hsueh WA, *et al*. Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;128:176-85.
11. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, *et al.* Efficacy and metabolic effects of metformin and troglitazone in type 2 diabetes mellitus. *N Engl J Med* 1998;338:867-72.
12. Yu JG, Kruszynska YT, Mulford MI, Olefsky JM. A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients. *Diabetes* 1999;48:2414-21.
13. Tan MH. Current treatment of insulin resistance in type 2 diabetes mellitus. *Int J Clin Pract Suppl* 2000;113:54-62.
14. Boyle PJ, King AB, Olansky L, Marchetti A, Lau H, Magar R, Martin J. Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus : a retrospective review of randomly selected medical records. *Clin Ther* 2002;24:378-96.
15. Lebovitz HE. Differentiating members of the thiazolidinedione class: a focus on safety. *Diabetes Metab Res Rev* 2002;18(Suppl2):S23-9.
16. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 1988;37:667-87.